NOTE TO USERS

A cost-effectiveness and cost-utility study of lung transplants

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Abstract

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Introduction: Lung recipients are faced with life-threatening complications which may impede in reaching an acceptable overall clinical and HRQOL level. Furthermore, the reported costs associated with the rigid follow-up care and expensive drug regimen raises the question whether this intervention is cost-effective.

Objectives: To determine the incremental cost-effectiveness (C/E) and cost-utility (C/U) of lung transplantation (L-Tx) according to the health system perspective.

Methods: A C/E and C/U analysis of L-Tx was carried out on 124 patients accepted unto the Quebec L-Tx waiting list (1997-2001). Survival was presented in mean life years (LY). HRQOL and utility were assessed using the SF-36 and standard gamble; they were studied cross-sectionally and longitudinally on a group of patients. Utility was used in the computation of the QALY. The economic impact of L-Tx was based on direct medical costs for 3 time periods: the waiting list, the transplant procedure and post-transplant phase. In the incremental C/E and C/U ratio, the costs for the procedure and follow-up care were compared to those during the waiting list, which served as an estimate for costs without transplantation. Estimates were modeled beyond the study period based on registry data. Simulating different person-time experiences during the waiting time (1 to 6 years) and post-transplant phase (1 to 8 years) tested key assumptions. Costs were based on provincial and national data and were discounted at a rate of 5%.

Results: The estimates were based on the 1,090.0 and 1,421.5 person-months contributed by the cohort (N=124) to the waiting list and post-transplant phase

(N=91), respectively. The mean LYs and QALYs gained were 0.57 (95% CI: 0.36-0.78) and 0.62 (95% CI: 0.36-0.78), respectively. HRQOL was higher on average for all domains in lung recipients versus candidates. Utility scores were also higher in recipients as compared to candidates: 0.76 (95% CI: 0.69, 0.83) versus 0.17 (95% CI: 0.12, 0.22). The estimated total average cost per patient without Tx was $15,015 or $1,708 (95% CI: $1,327 - $2,090) per month. The L-Tx program induced an additional screening cost of $9,622 per patient. The average cost of a transplant procedure was $49,314 (95% CI: $39,216 - $69,465). The average post-Tx follow-up cost per patient per month in the first, second, third and fourth year was $2,804 ($1,840 - $3,792), $1,643 ($1,090 - $2,291), $1,749 ($804 - $2,690) and $971 ($768 - $1,175), respectively. The estimated C/E and C/U of the L-Tx program were $302,160 per LY and $245,149 per QALY gained, respectively. These estimates reflect the dynamics of the Montreal L-Tx program with respect to admission policies, organ availability and donor selection as well as the success rate of the L-Tx team with the procedure and follow up care. Modeling survival and costs beyond the study yielded C/E and C/U estimates in the range of $62,074 per LY and $72,278 per QALY gained. Case scenarios yielded varying C/E and C/U estimates.

Conclusion: L-Tx is a costly intervention, which improves, on average, HRQOL and utility. It confers a survival benefit to few patients but for a long period of time. The C/U of L-Tx is better than the C/E ratio because L-Tx improves the quality of survival. A longer follow-up however would improve the C/E ratio.

Résumé

Introduction: Chez certains patients, une transplantation pulmonaire (TP) peut prolonger la survie et améliorer la qualité de vie. Cependant, ce traitement est grevé de complications parfois mortelles en cas de rejet du greffon ou d'infections. De plus, les coûts associés à l'intervention et au protocole de suivi sont très élevés. Il est donc légitime de se poser la question du rapport coût-efficacité (C/E) et coût-utilité (C/U) de cette intervention. Comme objectif, on a évalué les ratios C/E et C/U de la TP selon la perspective du système de santé.

Methods: Une analyse C/E et C/U de la TP a été entrepris sur une cohorte de patients (N=124) acceptés sur la liste d'attente de Québec Transplant entre 1997 et 2001. La survie a été estimée en terme de nombre moyen d'années. La qualité de vie appliquée à la survie et l'utilité ont été mesurées avec le SF-36 et la loterie (*standard gamble*), respectivement. L'utilité a été inclue dans la mesure des QALY (*quality adjusted life years*). L'impact économique de la TP a été calculé à partir des coûts directs médicaux pour 3 périodes: la période d'attente, la procédure de TP et la période de suivie post-TP. Dans le calcul des ratios de C/E et C/U, les coûts associés à la procédure ainsi qu'au suivi médical étaient comparés à ceux associés à la période d'attente qui ont servi pour estimer les coûts du suivi médical normal (sans TP). Des analyses de sensibilité ont été réalisées en simulant différentes expériences de survie lors de la période d'attente (1 à 6 années) et de post-TP (1 à 8 années). Ceci a permis d'évaluer l'influence de l'efficacité clinique en terme de survie sur les ratios. Les coûts ont été calculés à partir des données nationales et provinciales. Les coûts futurs ont été actualisés avec un taux de 5%.

Résultats: Les données proviennent d'une période d'observation de 1,090.0 mois-personnes, contribués par les non-transplantés (N=124), et 1,421.5 mois-personnes, contribués par les receveurs (N=91). Le nombre moyen d'années et de QALY gagnés par la TP étaient 0.57 (95% CI: 0.36-0.78) et 0.62 (95% CI: 0.36-0.78), respectivement. La qualité de vie était meilleure chez les receveurs que chez les candidats. Les scores d'utilité étaient également plus élevés chez les receveurs que chez les candidats: 0.76 (95% CI: 0.69, 0.83) versus 0.17 (95% CI: 0.12, 0.22). Le coût moyen par patient durant la période d'attente était de $15,015 ou $1,708 (95% CI: $1,327 - $2,090) par mois. Le programme de TP a induit un coût d'évaluation et de suivi de $9,622 par patient. Le coût moyen d'une TP était de $49,314 (95% CI: $39,216 - $69,465). Le coût moyen de suivi post-TP par patient par mois dans la 1ère, 2ième, 3ième et 4ième année étaient $2,804 ($1,840 - $3,792), $1,643 ($1,090 - $2,291), $1,749 ($804 - $2,690) et $971 ($768 - $1,175), respectivement. Les ratios de C/E et C/U associés au programme de TP étaient de $302,160 par année et $245,149 par QALY gagnées, respectivement. Ces estimés reflètent les caractéristiques du programme Québécois en terme de critères d'admission, de nombre d'organes ainsi que l'expérience de l'équipe de transplantation. Les ratios de C/E et C/U extrapolés étaient de $62,074 par année et $72,278 par QALY gagnées, respectivement. Des analyses de sensibilité ont produit des ratios de C/E et C/U qui ont variés. **Conclusion**: La TP est une procédure coûteuse qui améliore en moyenne la qualité de vie et l'utilité. Elle augmente la survie pour quelques patients mais pour un temps prolongé. Le ratio de C/U est plus favorable que le ratio C/E, car la TP augmente la qualité de survie. Une période de suivi prolongé cependant améliore le ratio de C/E.

Statement of Originality

This thesis was undertaken to determine the cost-effectiveness and cost-utility of lung transplantation in a Canadian transplant program. This research constitutes original scholarship in the pharmaco-epidemiology and pharmaco-economics of respiratory diseases.

This work advances the literature since it undertakes a costing model and outcomes study of lung transplants in Quebec, Canada and this for different disease groups. This economic evaluation will prove useful in future evaluations of new interventions in the respiratory and transplant fields.

This project does not contain previously published material, except where reference is made in the context of this thesis.

I personally carried out the literature review, data collection, and patient interviews, analyses and write up of the thesis with the highly appreciated guidance and contribution of the committee members recognized in the acknowledgements.

Disclaimer

This study is based in part on de-identified data provided by the University Health Network (UHN). The interpretation and conclusions contained herein do not necessarily represent those of the UHN or the Ontario Department of Health.

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List of Abbreviations

α: alpha

APR-DRG: all patient refined diagnosis related-group (APR-DRG).

BAL: bronchoalveloar lavage

BOS: bronchiolitis obliterans syndrome

c.à.d.: c'est à dire

CCOHTA: Canadian Coordinating Office for Health Technology Assessment

CF: cystic fibrosis

CHUM: Centre Hospitalier de l'Univeristé de Montréal

CIHI: Canadian Institute for Health Information

COPD: chronic obstructive pulmonary disease

CMV: cytomegalovirus

CT: computed tomography

DRG: diagnosis related-group

ER: emergency room

FEV_1: forced expiratory volume in one second

Hg: mercury

HIV: human immunodeficiency virus

HRQOL: health related quality of life

HSV: herpes simplex virus

ICD-9: International Classification of Disease version 9 (ICD-9)

ICU: intensive care unit

i.e.: id est

IPF: idiopathic pulmonary fibrosis

ISHLT: International Society of Heart and Lung Transplantation

kPa: kilopascal

LAM: lymphangiomyomatosis

LY: life year

MIBI : miraluma

MIS: Management Information Systems

mm: millimeters

MSSS: Ministère de la Santé et Services Sociaux

N: sample size

NHP: Nottingham health profile

NIRRU: Niveau D'Intensité Relatif des Ressources Utilisées

OB: obliterative bronchiolitis

OCCP: Ontario Case Cost Project

p: probability

$PaCO_2$: partial pressure of carbon dioxide

PaO_2: partial pressure of oxygen

PH: pulmonary hypertension

p-m: person-month

PPH: primary pulmonary hypertension

PVD: pulmonary vascular disease

QALY: quality adjusted life year

QOL: quality of life

QWB: quality of well-being

RAMQ: Régie de l'Assurance Maladie du Québec

RESD: restrictive disease

SaO_2: oxygen saturation

S.D. : standard deviation

SG: standard gamble

SIP: sickness impact profile

TBB: transbronchial biopsy

TTO: time trade-off

UHN: University Health Network

U.S.: United States

VAS: visual analogue scale

%: percent

>: greater than

<: less than

≥: greater or equal than

≤: less or equal than

1. Introduction

In recent years, there have been a large number of published economic evaluations of different health care services. This has been spurred by the increased number of new diagnostic and therapeutic technologies, their associated costs, and the limited resources to pay for them (Laupacis et al., 1992). The health care system being continuously threatened with financial cutbacks has given rise to the importance of studying concomitantly the results of clinical and economical evaluations of health care systems. Such studies provide information as to whether the implementation and utilization of a procedure would be wise, given the health care resources available. Since the widespread use of lung transplants, in 1991, many have attempted to study its clinical and economic impact within their respective countries (Ramsey et al., 1995a; Maurer et al., 1996; Gartner et al., 1997; van Enckevort et al., 1997; 1998; Al et al., 1998; Anyanwu et al., 2002).

In North America lung diseases are associated with a high morbidity and mortality rate (CDC, 1996, 2002; Statistics Canada, 2002). The health care related costs of end-stage lung disease have been estimated in the billions (Bresnitz, 1997). Patients with advanced lung disease experience a loss of respiratory function. Their health state is exacerbated by acute respiratory symptoms, which increase in severity and frequency to the point where the individuals are no longer responsive to standard medical therapy (Smith, 1997). For these patients, two treatments remain. The first is palliative care, which tries to diminish symptoms and the outcome is always death. The other consists of respiratory aids such as home oxygen therapy (O'Donohue,

1997) and long-term ventilator support (Gracey, 1997). These management forms of care prolong life but are associated with a decreased quality of life (Gartner et al., 1997) and a high cost. In the United States, the cost for home oxygen therapy, in 1993, for chronic obstructive pulmonary disease (COPD) and chronic hypoxemia, was 1.4 billion dollars (O'Donohue, 1995). The cost for home care ventilator support, for chronic lung disease, was reported to be on average $7,642 or $8,596 per patient, per month, depending upon whether care was given by a licensed nurse or a registered nurse, respectively (Sevick et al., 1996).

In the past decade, lung transplantation has emerged as a therapeutic option for many end-stage pulmonary diseased patients. This procedure offers these individuals a chance at an increased survival (Hosenpud et al., 1998, Charman et al., 2002) and an improved quality of life (Gross et al., 1995; TenVergert et al., 1998). It is a very costly intervention, which is followed by an expensive prophylactic protocol in the post-transplant phase for the possible risk of rejection of the allograft and infection. A cost-effectiveness study, conducted by Ramsey et al. (1995a), estimated the mean charge per recipient for lung transplantation surgery and postoperative care to be $164,989. Important costs are also incurred after the procedure. Ramsey et al. (1995a) reported that two thirds of the overall costs of lung transplantation were associated with the post-transplant phase. They estimated that the average monthly charge for lung transplant recipients was $11,197 in the first year, and $4,525 per month after that. The average monthly cost for waiting list patients was $3,395. Although not peer-reviewed, a study conducted in Canada, estimated the average cost

of the initial hospitalization for patients receiving lung transplants in 1992 and 1993 to be $114,953 (Canadian dollars) and $153,885 for a 5-year post-transplant follow-up (Maurer, 1996, abstract). The study also reported a pre-operative cost of $14,225.

Given the reported costs of lung transplants and costs pertaining to traditional therapy for lung diseases, one may question the cost-effectiveness of transplantation over standard therapy. Increased survival after transplantation and improvement in quality of life is not always the case for all recipients and it is yet unclear whether transplantation increases survival for some pulmonary conditions. As there is a continuous scientific effort in the medical field for new and improved options for the management of respiratory diseases, as well as for clinical events associated with the procedure, the benefits of lung transplantation should continue to be addressed.

This project was conducted in order to assess from a health care perspective the cost-effectiveness and cost-utility of lung transplantation in Canada. The potential gain in survival, health related quality of life, utility as well as the economic impact of lung transplantation was also studied.

2. Literature review

2.1 Definition and epidemiology of diseases appropriate for lung transplantation

Advances in immunosuppression, surgical techniques and in the experience of perioperative care, have rendered lung transplantation a widespread therapeutic option for many end-stage pulmonary diseases. End-stage lung disease may be defined as a chronic, nonmalignant lung disease that permanently impairs activities of daily living (Bresnitz, 1997). The type of diseases to which lung transplantation may be proposed fall into four categories: pulmonary vascular disease (PVD), restrictive lung disease, obstructive airway disease (OAD) and suppurative disease (Smith, 1997).

2.1.1 Pulmonary vascular diseases

The pulmonary vascular diseases (PVD) include primary pulmonary hypertension (PPH), pulmonary hypertension secondary to systemic disease or primary cardiac abnormalities such as Eisenmenger's syndrome.

PPH is characterized by a mean pulmonary artery pressure greater than 25mm Hg at rest, or greater than 30 mm Hg during exercise, normal pulmonary artery wedge pressure, and absence of secondary causes (Rubin, 1993). In this disorder, the lung arteriopathy reduces the pulmonary vascular distensibility; reduces the total cross-sectional area; and vasoconstricts the pulmonary resistance vessels which subsequently results in an elevated pulmonary arterial pressure and pulmonary vascular resistance. In response to the elevated pressure, the right ventricle

hypertrophies but subsequently fails (Manaker et al., 1997). Six percent of cases have a family history of this disorder (Langleben, 1994). The mode of transmission is not yet clear. Cases with a family history of the disease demonstrate autosomal dominance, incomplete penetrance and seem to feature genetic anticipation, which translates as an increased severity and earlier onset in successive generations (Rubin, 1993). Symptoms related to PPH include dyspnea, fatigue, chest-pain, syncope or near-syncope, leg edema and palpitations (Rich, et al., 1987; Sandoval et al., 1994). Women are 2 to 3 times more likely than men to have PPH and the average age of diagnosis ranges from 23 to 39 years (Brenot, 1994; Sandoval et al., 1994).

PPH is a rare disease but precise estimates of incidence and prevalence are difficult to obtain because no population-based registry is available (Bresnitz, 1997). D'Alonzo and his colleagues observed a case-fatality ratio of 55% and that death usually occurs within 10 years of the diagnosis (1991). The median survival was 2.8 years from the time of diagnosis or 4.4 years from the time of development of initial symptoms (D'Alonzo et al., 1991). A more recent population based study on the mortality from PPH in the US from 1979-1996 reports that, women are 2.5 times and blacks are 3.5 times more likely to die from PPH than men and whites, respectively (Lilienfeld et al., 2000). The average annual age-adjusted mortality rate reported, in this study, was 2 per 1 million and 5 per 1 million in men and women, respectively. An increased rate was also found in men after the age of 35, and in women after the age of 45 (Lilienfeld et al., 2000). It has also been noted, that in the absence of transplantation, PPH has a 3-year survivorship (Lilienfeld et al., 2000).

The secondary causes of PH include disorders of the heart and lung, such as Eisenmenger's syndrome and chronic pulmonary embolism, respectively. An increased pulmonary vascular resistance characterizes Eisenmenger's syndrome and a systemic-to-pulmonary circulation with a right to left shunting of the blood (Vongpatanasin et al., 1998). The pathophysiology of the disease, summarized by Vongpatanasin and his colleagues is as follows: in individuals with intracardiac shunting, blood initially shunts from the systemic to pulmonary circulation because the resistance in the latter is lower. Therefore, there is a left-to-right shunting which results in an increased pulmonary blood flow. If this defect is large and persists, over months to years, irreversible injury will occur to the pulmonary vasculature. Such injury includes arteriolar medial hypertrophy, intimal proliferation and fibrosis, and capillary and arteriolar occlusion. The result will be obliteration of the arterioles and capillaries of the lungs and an increased pulmonary vascular resistance. Once the vascular resistance and arterial pressure of the lungs approach the systemic vascular resistance and its arterial pressure, the shunt will reverse. The resultant right-to-left shunting of the blood will lead to hypoxia and erythrocytosis.

Patients with Eisenmenger's syndrome will eventually present one or more of the following clinical symptoms: a) dyspnea on exertion, fatigue, or syncope which is due to a low systemic output, b) headaches, dizziness, or visual disturbances as a result of erythrocytosis and hyperviscosity, or c) symptoms of congestive heart failure. Other complications include arrhythmias, which can lead to sudden death,

hemoptysis, cerebrovascular accidents caused by hyperviscosity, cholelithiasis, hypertrophic osteoarthropathy, and decreased renal function (Vongpatanasin et al., 1998).

It is estimated that, 8% of individuals with congenital heart disease and 11% of patients with left-to-right shunting will develop Eisenmenger's syndrome (Eisenmenger, 1897; Young et al., 1971). Most patients live for 20 to 30 years of age. The survival rates at 10, 15 and 25 years of age have been estimated to be 80%, 77% and 42%, respectively (Kidd et al., 1993; Saha et al., 1994). A more recent study, reported a median survival of 53 years (Cantor et al., 1999). Furthermore, the same study noted a large variation with respect to life expectancy and, risk factors for mortality included a younger age at diagnosis and increased severity with respect to functional class, right ventricular hypertrophy and the presence of supraventricular arrhythmias.

2.1.2 Restrictive lung diseases

The restrictive lung diseases (RESD) include idiopathic pulmonary fibrosis and fibrosis secondary to connective tissue diseases, sarcoidosis, pneumoconioses and eosinophylic granulomatosis, (Smith, 1997). Idiopathic pulmonary fibrosis (IPF) is the second most frequently diagnosed interstitial lung disease (Bresnitz, 1997). The symptoms include an insidious dyspnea upon exertion and a nonproductive cough (Manaker et al., 1997). Upon examination, fine bibasilar inspiratory rales and clubbing is also common later in the disease (Manaker et al., 1997). The pathology

of IPF has been described, in its early stage, as the inflammation of the mononuclear cells in the alveolar interstitium and that filling of the alveolar airspaces predominate (Gaensler, et al., 1966). The more advanced disease is characterized by the deposition of collagen and fibrosis, which perturb the normal lung architecture (Cherniak et al., 1995). The natural progression of the disease is that of respiratory disability and eventually death, 39% of these patients die from respiratory failure (Panos et al., 1990). Its prevalence is around 3 to 5 cases per 100,000 (Crystal et al., 1984), and presents itself in one's 50's or 60's and is predominantly found in men. Coultas (1993) suggested, after the review of lung specimens at autopsy, that the disease occurs up to 10 times more in the general population and goes undiagnosed. Its incidence has been reported to be around 15 per 100,000 per year (Coultas et al., 1994). In case series reports, the median survival has been noted to be 3 to 5 years (Crystal et al., 1984; Panos et al., 1990), and the mean survival for patients with IPF is suggested to be 28.2 months after diagnosis (Schwartz et al., 1994). A registry based study in the state of New Mexico, reported a median survival of 4.2 years (Mapel et al., 1998). Age-adjusted death rates associated with pulmonary fibrosis in the US, in 1991, have been reported as follows: 50.9 per 1 million in men and 27.2 per 1 million in women (Mannino et al., 1996). In both cases, the rates were higher in older age groups.

Sarcoidosis has been defined as "a multisystem disorder of unknown causes" (Yamamoto et al., 1992). It presents itself with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions (Hosoda et al., 1997). The liver,

spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones and other organs may also be involved (Hosoda et al., 1997). It is diagnosed when clinical and radiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas (Hosoda et al., 1997). It has been suggested that up to 40% of patients are asymptomatic and are often diagnosed after an initial finding of an abnormal chest radiograph (Manaker et al., 1997). 35% of patients present systemic symptoms of fever, anorexia, weight loss, fatigue and myalgias (Manaker et al., 1997). Patients with sarcoidosis usually don't have any long-term sequelae and spontaneous remissions are common (Manaker et al., 1997). The National Center for Health Statistics does not publish morbidity data separately on sarcoidosis and therefore information on incidence is somewhat limited. It has been estimated that sarcoidosis affects primarily young and middle aged adults and is found to be 10 times more frequent in African Americans than in Whites. Bresnitz et al. (1983), using information on military populations, reported an incidence rate of 81.8 per 100,000 in African Americans versus 7.6 per 100,000 in Whites. A more recent study, using US data from a population-based survey, reported that in 1991, the age-adjusted mortality rate attributable to sarcoidosis was 1.6 per 1 million and 2.5 per 1 million in men and woman, respectively. Both black men and women had higher mortality rates, and these rates were highest in the 45 to 54 year age group for both sexes (Gideon et al., 1996). Overall, between 1979 and 1991, 5791 people have died from sarcoidosis in the US (Gideon et al., 1996).

In the International Classification of Disease system codes, pneumoconioses includes asbestosis, coal workers' pneumoconiosis, silicosis, byssinosis, and an "other" category (i.e. hard-metal diseases) (Bresnitz, 1997). Exposure to asbestos has been associated with mechanical injury to the lung and to the potential development of cancer (Gardner, 1941). Furthermore, a dose-response effect has been associated with asbestos and death from asbestosis (Merewether et al., 1930). Today, with the much decreased threshold limit value of asbestos at 0.2 fibers per cubic centimeter, greater worker awareness and the reduced use of asbestos, no significant asbestosis from exposure that first occurred during the last 30 years has been observed (Gaensler et al., 1990). Silicosis refers to the occupational disease caused by the inhalation of crystalline silica. It has been hypothesized that the pathogenesis of silicosis is initiated by the generation of oxidants induced by the inhalation of silica (Ghio et al., 1990). The cascade of events that follow the generation of oxidants lead to modifications of macrophage function, activate humoral and immune systems, and lead to the interaction of cells such as the T and B cells. This leads to collagen deposition and pulmonary parenchymal damage, which is known as silicosis (Davis, 1986). Once the process of this disease has begun it progresses even though the exposure to silica has stopped. This has been suggested to be due to the retention of silica (in the form of quartz) in the lungs and in the lymph nodes or possibly due to the process of inflammation and repair of the lungs (Hughes et al., 1973). Symptoms of silicosis include dyspnea, which may develop suddenly, fatigue, weight loss, fever and pleuritic pain (Buechner et al., 1969, Suratt et al., 1977; Banks et al., 1981). Estimates of the prevalence of silicosis are unknown because there is no registry of

cases in the US Coal workers' pneumoconiosis (CWP) is a lung condition which results from the inhalation, deposits of coal mine dust, and the tissue's reaction to its presence (Lapp et al., 1992). Simple pneumoconiosis has no clinical symptoms, nor physical signs (Leathart, 1972). Chronic cough and sputum is more common in dust-exposed workers than in non dust-exposed workers. These clinical signs are related to "industrial bronchitis" which is caused by inhalation of larger dust particles and which chronically affect the mucociliary escalator (Kibelstis et al., 1973; Morgan, 1978). In 1992 the age-adjusted death rate attributable to pneumoconioses and related diseases was 9 per 1 million and 98% of deaths occurred in males (NIOSH, 1996).

Eosinophilic granulomatosis is a rare interstitial lung disease, which is characterized by an accumulation of atypical hystiocytes in nodular granulomatous lesions (Manaker et al., 1997). Two thirds of patients usually present nonproductive cough and dyspnea, which are usually present for several months before diagnosis and about one third complain of fever, fatigue and weight loss (Manaker et al., 1997). In 20 % patients, often recurrent, spontaneous pneumothorax occurs and is due to the rupture of the subpleural blebs (Manaker et al., 1997). The prognosis is favorable; Friedman et al. (1981) in a follow-up study reported a mortality of 2%.

2.1.3 Obstructive airways diseases

The obstructive airways diseases (OAD) include emphysema, chronic bronchitis and α_1-antitrypsin deficiency. COPD, which includes emphysema and chronic bronchitis, is by far the most frequent chronic pulmonary disease in adults. It is primarily characterized by a progressive and irreversible expiratory airflow obstruction.

In the US, in 1993, chronic obstructive lung and related diseases was the fifth leading cause of mortality reaching an age-adjusted death rate of 21.4 per 100,000 (CDC, 1996). The Canadian statistics reported that, in 1997, COPD and allied conditions were the fourth leading cause of mortality with an age-adjusted death rate of 29 per 100,000 (Statistics Canada, 2001). The latest data, in the US, have shown that, in 1993, COPD and emphysema resulted in 1,975,000 days of in-hospital care (Graves, 1995). The average length of stay was 7.2 days. Similarly, in Canada, the average length of stay for diseases of the respiratory system was 7.2 days in 1996-1997, Quebec averaging 9.2 days (Statistics Canada, 2001).

Emphysema is defined as "an increase beyond the normal in the size of airspaces distal to the terminal bronchiole from destruction of the walls of the distal airspaces (World Health Organization, 1961). Emphysema can cause disabling symptoms of dyspnea, functional limitations and may lead to early death (Burrows et al., 1987). In 1995, the American Thoracic Society reported that 1.7 million Americans were affected with emphysema. Chronic bronchitis is defined as the "chronic or recurrent

excessive mucous secretion in the bronchiole tree that is diagnosed clinically by the presence of cough with expectoration not attributable to other lung diseases" (Medical Research Council, 1965). In 1994, COPD was the cause of 96,500 deaths and the age-adjusted mortality rate was 36.9 per 100,000 (Singh et al., 1995). COPD progresses slowly and is asymptomatic for many years until the sixth or seventh decade of life (Manaker et al., 1997). The most important cause of COPD is cigarette smoking, it accounts for 90% of cases. The prevalence, in 1993, of COPD was reported as 61.9 per 1000 age-adjusted population (Benson et al., 1994). Based on a US population of 250 million, this translates to 16 million individuals with COPD. The morbidity associated with this disease is high. In 1993, 273,000 Americans were hospitalized either for emphysema or chronic bronchitis (Graves, 1995). The average in-hospital stay of individuals with COPD was 50% longer than that of the general population and had two times the restricted activity days and twice the bed disability days per year (Feinleib et al., 1989). The cost associated with COPD, assuming only 20% of those afflicted with the disease had end-stage lung disease, in 1994 dollars would be $1.4 to $3.8 billion dollars (Bresnitz, 1997). The mortality and morbidity of COPD is expected to continue. Smoking rates among adolescent females has continued to rise in the US since 1977 (CDC, 1993). The same trend is also seen in Canada. In 1997, Canadian female adolescents, aged 12-19 years, consisted of 16.6% of Canadian smokers as compared to 14.9% of males of the same age group (Statistics Canada, 2001). Quebec had the highest percentage of smokers in this age group, 20.8% and 22.5% for females and males, respectively.

α_1-antitrypsin deficiency is an autosomal hereditary disorder that may cause panacinar emphysema in affected individuals (American Thoracic Society, 1995). This disorder is associated with low or absent levels of the enzyme, which prevents the digestion of lung parenchyma by plasma proteases. This deficiency accounts for 2% to 3% of emphysema cases (Crystal, 1990). A severe form of this disorder usually translates into a greater chance of mortality at a younger age than other COPD forms (Larsson, 1978). Furthermore, smokers are more likely to develop this clinical disorder than nonsmokers. In the US, 1% to 2% of the white population is a carrier for the deficiency Z allele associated with this disorder (American Thoracic Society, 1989). It is estimated that the phenotype occurs in 100,000 individuals (ATS, 1989). Therapeutic costs associated with this deficiency have been estimated to range from $375 million to $1.85 billion (Snider, 1989).

2.1.4 Cystic fibrosis and other bronchiectatic diseases

Cystic fibrosis (CF) is a type of suppurative disease. It is an inherited autosomal recessive disorder of exocrine glands (Davis et al., 1996) caused by a mutation on chromosome 7 (Tsui, 1995). CF is diagnosed when there is an abnormal elevation of sweat chloride, obstructive lung disease and pancreatic insufficiency (Davis, 1996). This disease has been associated with symptoms which include chronic cough producing thick mucus; excessive appetite combined with weight loss; skin which tastes very salty; and, repeated or prolonged bouts of pneumonia (Canadian Cystic Fibrosis Foundation, 2000). It is estimated that 1000 new cases are diagnosed each year in the US, with the highest incidence being in whites (1 case per 3300 live

births) (CF Foundation, 1996). The prevalence of CF has been increasing in the USA and is attributable to a better management of the disease including physiotherapy, antibiotics and nutritional supplementation (Fiel et al., 1994; Fitzsimmons, 1993). CF patients are on average diagnosed at 3 years old and their life expectancy today is around 40 years (CF Foundation, 1996). The median survival age in 1995 was 30 years. The case fatality rate of CF patients was 2.1 per 100 in 1994 (CFF, 1996). It has been estimated, that in 1995, the total annual health-care cost for CF, in the US was approximately $900 million. The total cost for severe patients only was estimated to be $326 million (Fitzsimmons, 1996). In Canada, one in every 25 people is a carrier of the gene and one in every 2500 children born has the disease (Canadian Cystic Fibrosis Foundation, 2000). There are presently 3,300 cases that are treated in CF clinics in Canada and over 41% of CF patients are over 18 years of age (Canadian Cystic Fibrosis Foundation, 2001).

Bronchiectasis is not a disease in itself, but represents the end outcome of many pathologic processes. Bronchiectasis is defined as an irreversible and abnormal damage to the bronchi and, dilatation of the affected airways (Hansell, 1998). The pathogenesis of bronchiectasis, whether it is congenital or acquired, has been much debated. The hypothesis now accepted by many includes both these facets (Cole, 1984). The hypothesis proposed states that colonizing pathogens damage the bronchial epithelium and impair the mucociliairy clearance mechanism, thus leading to an environment, which enables the growth of pathogens in the stagnant mucus. The immune response to the infection is ineffective and only seems to increase the

damage to the process of mucociliary clearance. The inflammatory response to this infection is to activate the production of neutrophils, which release proteolytic enzymes, to the affected area, thus further damaging the epithelial bronchial cells. It is from this host immune response damage and microbial invasion that the vicious circle arises.

Symptoms of bronchiectasis usually develop early in age. Clinical symptoms include recurrent respiratory infections, chronic cough and large production of purulent sputum, hemoptysis, respiratory insufficiency and corpulmonale, anemia, chronic sinusitis and finger clubbing (Hansell, 1998). Recurrent respiratory infections are one of the primary complications of bronchiectasis and the most common cause of morbidity. The most common pulmonary causes of death are due to complications such as respiratory insufficiency and cor pulmonale. The prevalence of hemoptysis is highest in cystic fibrosis patients ranging form 10 to 62% and treatment includes bronchial artery embolization or surgery (Marwah et al., 1995).

2.1.5 Summary of end-stage lung diseases indicated for lung transplantation

A summary of the different types of end–stage lung diseases with their respective mortality rates are presented in table 1 according to their respective disease category.

Table 1. End-stage lung diseases indicated for transplantation

Category of disease	Type of disease	Rates
Pulmonary vascular diseases	PPH	Age-adjusted mortality (1979-1991): Males: 2 per 1 million Females: 5 per 1 million
	Eisenmenger's syndrome	Survival rate: 80% at 10, 77% at 15 and 42% at 25 years old
Restrictive lung diseases	IPF	Incidence: 15 per 100, 000 / year Age adjusted mortality (1991) Males: 50.9 per 1 million Females: 27.2 per 1 million
	Sarcoidosis	Age-adjusted mortality (1991): Males: 1.6 per 1 million Females: 2.5 per 1 million
	Pneumoconioses and related diseases	Age-adjusted mortality* (1992): Males: 9 per 1 million *(98% of deaths occurred in males)
Obstructive airway diseases	COPD: Emphysema α_1 – antitrypsin deficiency	Age-adjusted mortality (1994): 36 per 100,000
Suppurative diseases	Cystic Fibrosis Bronchiectasis	Median survival (1995): 30 years Case-fatality rate (1994): 2.1 / 100 cases

Although the above mentioned lung diseases are different with respect to their cause and prognosis, their common pathway is end-stage lung disease where the severity of the disease increases and becomes chronic. Aside from palliative treatments and respiratory aids, lung transplantation is the only option offering end-stage lung diseased patients a possibility of a longer survival and an increased quality of life.

2.2 Forms of care for the management of end stage lung disease

2.2.1 Treatment of dyspnea

Dyspnea is the most common and disabling symptom in advanced lung disease and is defined as an unpleasant awareness of breathing (Burki, 1987; Shwartzstein et al., 1990). With the progression of the disease, dyspnea will occur with minimal exercise and ultimately at rest. The cellular and biochemical mechanisms leading to dyspnea are not well understood and specific receptors associated with the sensation of dyspnea have yet to be identified (Hansen-Flaschen, 1997).

The treatment of dyspnea is difficult. In conscious subjects, no medical intervention seems to successfully eliminate dyspnea (Davis, 1994). However, it has been suggested that several palliative forms of care and non-pharmacological treatments may be effective in providing some relief to the breathlessness (Hansen-Flaschen, 1997). Some have suggested managing dyspnea with relaxation therapy (Renfroe, 1988) or desensitization with guided mastery (Carrieri-Kohlman et al., 1993) in order to increase tolerance to the symptoms. Filshie et al.. (1996) suggested that acupuncture may relieve dyspnea, although its effects may be short-term.

Many studies have focused on the effectiveness of respiratory aids in the treatment of dyspnea. In studying noninvasive positive-pressure ventilation via facemask, Meduri et al. (1996) reported a short-term relief of dyspnea in hypercapnic and hypoxemic patients. Similarly, Diaz et al. (1999) suggested that noninvasive mechanical ventilation in patients with advanced COPD improved many clinical and

physiologic parameters, including dyspnea and exercise capacity. Another group reported that helium:oxygen noninvasive pressure support reduced dyspnea and PaCO2 levels, as compared to air:oxygen, in patients with decompensated COPD and may reduce the need for endotracheal intubation (Jolliet et al., 1999).

2.2.2 Home oxygen therapy

Long-term oxygen therapy has been shown to be effective in the treatment of patients with end-stage chronic obstructive pulmonary disease and hypoxemia. In 1980, the Nocturnal Oxygen Therapy Trial Group and in 1981, the Report of the Medical Research Council Working Party both reported that continuous oxygen therapy was associated with increased survival as compared to nocturnal oxygen or oxygen for shorter periods of time during the day. Furthermore, many studies have suggested that long-term oxygen therapy also improves quality of life and more specifically increases exercise tolerance and improves neuropsychiatric functions (Cotes et al., 1956; Petty et al., 1968; Neff et al., 1970; Woodcock et al., 1981; Heaton et al., 1983). The use of long-term oxygen therapy has also been associated with many physiologic improvements such as reduction in pulmonary artery pressure, control of the progression of pulmonary hypertension and the reduction of hematocrit levels when erythrocythemia is present (Levine et al., 1967; Abraham et al., 1968; Petty et al., 1968; Nocturnal oxygen therapy trial group 1980; Weitzenblum et al., 1985).

2.2.2.1 Indications for home oxygen therapy

The indications for continuous oxygen therapy as presented in the Nocturnal Oxygen Therapy Trial, 1980, include: Arterial partial pressure of oxygen (PaO_2) equal to or less than 55 mm Hg or arterial oxygen saturation (SaO_2) equal to or less than 88%, PaO_2 of 56 to 59 mm Hg or SaO_2 89% with the following conditions:

A. Electrocardiographic evidence of cor pulmonale, or

B. Edema due to congestive heart failure, or

C. Erythrocytosis with hematocrit greater than 56%.

2.2.2.2 Home oxygen delivery systems

Oxygen delivery equipments are of three types: stationary, portable and ambulatory (O'Donohue, 1997). The first are designed for stationary use and include oxygen concentrators, liquid oxygen reservoirs or large cylinders. These systems are indicated for patients who do not move beyond the limits of the system or who use oxygen during sleep. The portable system usually weighs 10 lb or more and consists of a steel cylinder attached to wheels. It is indicated for patients who occasionally move beyond the limits of a stationary system for fewer than 2 hours per day and for a minimum of 2 hours per week. The ambulatory systems weigh less than 10 lb when they are filled with oxygen and are carried by the patient. These systems include liquid refillable units and aluminum or fiber-wrapped lightweight cylinders. Ambulatory equipment are usually indicated to patients who regularly pass the limits of the stationary oxygen system and who do so for more than 2 hours per day and for a minimum of 6 hours per week.

2.2.3 Long-term ventilator support

COPD and other chronic lung diseases are the second most frequent causes of ventilator dependence (Scheinhorn et al., 1994). Such use is required when the individual is incapable of maintaining adequate alveolar ventilation without aid in order to survive or to maintain an acceptable quality of life level. Depending upon the severity of the alveolar state, patients require either continuous or partial ventilation. With partial ventilation, patients are given mechanical ventilation during the night, which enables them to function without assistance during the day (Gracey, 1997).

The decision to provide mechanical ventilation, or to continue terminal and palliative care, is not always easy. The outcomes and the effectiveness of the intervention are not always predictable. Dales et al. (1999) report that one of the problems associated with mechanical ventilation is that many of the patients cannot be weaned from the ventilator and those who do, often go back to the same level of respiratory disability. The authors suggest that COPD decision aids such as, audiocassettes and a booklet on intubation and mechanical ventilation and its outcomes, can provide patients enough information so as to make a decision with satisfaction and confidence. The authors further note a strong association between females and the decline to intubation. Gender, therefore, may be important to take into account when such therapeutic options are considered.

Forms of ventilator support include the noninvasive type where assisted ventilation is carried out without an endotracheal tube. Noninvasive positive pressure ventilation can be carried out using a pressure-controlled ventilator, a volume-controlled ventilator, a bilevel positive airway pressure ventilator, or a continuous positive airway pressure device (Rabatin et al., 1999). This form of ventilation has been seen to improve gas exchange and functional status in patients with chronic respiratory failure (Criner et al., 1999). It has also been suggested that noninvasive mechanical ventilation delivered through a face or nasal mask during an acute respiratory failure, in patients with chronic obstructive lung disease, may be as effective as intubating and therefore may reduce complications, reduce the duration of hospitalization and improve survival, as compared with more invasive techniques (Schneider, 1997; Laube et al., 1999). The acute effects of noninvasive positive pressure ventilation seem to be quite positive. This technique however is associated with a few problems, which may affect patient compliance. Criner et al. (1999) reported that 36% of complaints dealt with the mask and similarly 36% dealt with the ventilator source. The specific complaints included mask leaks (43%), skin irritation (22%), rhinitis (13%), aerophagia (13%) and discomfort from mask headgear (7%).

2.2.4 Pre-transplant cardiopulmonary rehabilitation

End–stage lung diseased patients have a decreased exercise tolerance, strength and thoracic mobility (Ries, 1990). Patients, who become potential lung transplant recipients, are encouraged, to stay active in order to better cope with the physical demands and complications associated with the post-transplant period.

The physical evaluation process, during the pre-transplant period, is carried out in order to better understand the patient's physical limitations and to prescribe an appropriate exercise regimen and whether there should be a change in the patient's oxygen therapy use. The physical therapy process may consist of aiding patients with endurance exercises, teaching them proper breathing techniques and exercises, relaxation methods as well as exercises in flexibility and mobilization (Downs, 1996).

During the waiting list period, the candidate is informed of the importance of breathing control, coughing maneuvers, airway clearance and chest wall mobility exercises in order to help with a better management of the post-operative period (Downs, 1996). Many patients enlist in cardiopulmonary rehabilitation programs, which usually include training to improve ventilation and mucociliary clearance, and aerobic exercises with stretching and aiming to strengthen (Connors et al., 1993). The need for any supplemental oxygen therapy is also evaluated here.

2.3 Lung transplantation

The first lung transplant conducted was in 1963 in a 58 year old man and was a single lung transplant (Blumenstock et coll., 1993). The poor prognosis was due to rejection of the donor lung, infection, and the incomplete healing of the anastomotic site (Reemtsa et al., 1993; Paradis et al., 1995). The first successful single L-Tx was carried out in 1983 by the Toronto Lung Transplant Group (1986) and the first double L-Tx in 1985 (Patterson et al., 1988). Since then, the registry of the International Society for Heart and Lung Transplantation (ISHLT) (2002) reports that in between 1985 and 2001 there have been 2862 heart-lung transplants, 8043 single lung transplants and 6543 bilateral/double lung transplants. In Canada, lung transplantation has been on the rise. The Canadian Institute of Health Information (CIHI) (2003) reported 298 single, 593 double and 58 heart-lung transplants carried out from 1993 through 2002.

Although there has been an increase in the number of lung transplants performed in Canada in the past decade, the donation rate has failed to meet the demand. As of the end of 2002 there were 50 and 88 patients waiting for a single and double lung transplant, respectively (CIHI, 2003). The Canadian Organ Replacement Register reported that the cadaveric organ donor rate, in 2002, was 13.0 per million (CIHI, 2003). Of these organ donors, less than 20% will be suitable for transplantation (Sundaresan et al., 1993).

2.3.1 Selection for lung transplantation

Marshall and colleagues (1990) explain that transplantation should be considered when a patient's health has deteriorated despite medical therapy, is believed to have a life expectancy of less than 1 to 2 years and should be New York Heart Association (NYHA) class 3 or 4. That is, patient has marked limitation in physical activity and, patient is not able to carry on any physical activity without symptoms, respectively (NYHA Classification, Appendix IV, 2001). Furthermore, patients should be under 65 years old, psychologically stable and free from any important co-morbid conditions that might affect their chance of survival in the post-transplant phase. In order for a patient to be listed in a transplant program, the transplant team has to evaluate whether the patient's disease is severe enough to warrant a transplant and whether the patient is strong enough to survive the wait for when an organ does become available. This timing of referral has been also referred to as the "transplant window" (Marshall et al., 1990).

In order to aid in the identification of the so-called transplant window, guidelines for the selection of potential candidates have been put in place. The criteria follow the international guidelines for the selection of lung transplant candidates as published by Maurer and colleagues (1998). The guidelines for establishing eligibility are disease specific and are presented in detail in Appendix A (section A1.2).

2.3.2 Common indications for each type of transplant procedure

The two most important clinical indications for single lung transplantation are emphysema and idiopathic pulmonary fibrosis; for bilateral/double lung transplantation, important clinical indications include cystic fibrosis and emphysema; and for heart-lung transplantation, pulmonary hypertension and congenital heart disease are the most indicated (table 2).

Table 2. Indications for transplantation.

	Type of Transplantation		
	Single Lung (1995-2001)	Bilateral/Double Lung (1995-2001)	Heart–Lung (1982-2001)
Congenital	-	-	35%
Emphysema	54.4%	22.5%	4%
Cystic Fibrosis	1.1%	33.0%	17%
Primary Pulmonary Hypertension	1.3%	8.3%	26%
Idiopathic Pulmonary Fibrosis	23.8%	9.1%	3%
Alpha-1-antitrypsin	8.7%	9.9%	3%
Other	9.1%	15.3%	8%
Re-transplantation	1.6%	1.9%	-
Acquired heart disease	-	-	4%
Total	100%	100%	100%

Adapted from the registry of the ISHLT, 2002.

2.4 Follow-up care in lung transplantation

Improvements in patient selection, organ preservation, operative techniques, and postoperative care in lung transplantation have led to improved outcomes. However, many life-threatening complications still remain. Important limiting factors of success include infection, chronic rejection characterized as obliterative bronchiolitis and the risk of lymphoproliferative disorders.

Once lungs are harvested they remain susceptible to many pathogens increasing the risk of infection. Furthermore, immunosuppressive treatment, for the control of rejection, is maintained throughout the patient's life rendering the individual susceptible to many types of infections and the development of certain types of lymphomas. Transplant patients undergo a strict drug regimen and are routinely followed for the early detection of rejection and infections.

2.4.1 Post-operative care in the post-transplant phase

Morbidity and mortality in the first few weeks following transplantation are usually associated to airway complication such as stenosis of the anastomotic site, to the reimplantation response and to primary graft failure (DeMeo et al., 2001).

During the immediate period, following transfer to the intensive care unit (ICU), the gas exchanges and chest radiographs of the recipient are continuously monitored. In 20% of cases, early graft dysfunction or the reimplantation response, associated with the perioperative period may arise due to reperfusion injury, which leads to endothelial dysfunction (Haydock et al., 1992; Sleiman et al., 1995; Chaparro et al., 1995). Fifteen percent of cases present symptoms that are similar to an adult respiratory distress syndrome (DeMeo et al., 2001). In such cases, selective lung ventilation may be required. The use of nitric oxide or extracorporeal membrane oxygenation may also be considered (Glassman et al., 1995; Date et al., 1996; Christie et al., 1998).

In single lung transplant recipients with emphysema, a complication may arise which involves the overinflation of the native lung and results in a mediastinal shift and compression of the donor lung. Treatment of this condition includes the early use of a double-lumen endotracheal tube with sequential lung ventilation (Gavazzeni et al., 1993). Some centers practice volume reduction of the native lung (Corris, 1997).

In the early postoperative period, patients may be transferred out of the ICU. Chest radiographs are monitored for ill-defined perihilar infiltrates and septal lines which may suggest acute rejection of the grafted lung (Corris, 1997). Lung function formal testing such as spirometry, vital capacity, forced expiratory volume in one second (FEV_1) total lung capacity and diffusing capacity are performed as soon as possible after surgery. It has been suggested that a 5% to 10% reduction in the FEV_1 or vital capacity is a sensitive and specific marker of donor lung dysfunction (Otulana et al., 1989; 1990; Hoeper et al., 1992; DeMeo et al., 2001). Furthermore, formal lung function testing during the 3 months after surgery has aided in the early diagnosis of lung infection or rejection. When a patient's condition worsens, a new infiltrate on the chest radiograph appears, or a drop in lung function is detected a bronchoscopy is carried out.

Primary graft failure occurring in the early post-operative period is an important and severe form of early graft dysfunction due to an ischemia-reperfusion injury

(Unruh, 1995). Such graft failure presents itself with a progressive pulmonary edema, not of cardiac origin, pulmonary hypertension, and low oxygenation and decreased lung compliance. Christie and his colleagues (1998) noted an incidence of 15%, and that patients were ventilator dependent beyond the fifth day of transplantation (Christie et al., 1998). The authors also found that patients with such a complication had a significantly higher length of stay in the hospital and reported a one-year actuarial survival of 40% as compared to 69% for patients without primary graft failure.

Other complications include vascular anastomotic stricture or thrombosis at the site where the donor's bronchus is intussuscepted into that of the recipients. Anastomotic stenosis is now the most common large airway complication that may lead to early graft failure (DeMeo et al., 2001). This stricture can be identified by a hypoperfusion of the graft during perfusion lung scans (Corris, 1997) or visualized directly with bronchoscopy. Decrements in spirometric values may also be an indication. Patients, in such cases, may present with dyspnea and chest tightness and focal wheezing (Kshettry et al., 1997). A stent placement or a balloon dilatation is used for the management of a stenosis at the anastomotic site (Susanto et al., 1998).

Aside from the management of these complications, Corris (1997) mentions the importance of extubating the lung recipient for physiotherapy and rehabilitation as quickly as possible. These types of therapies will reduce the pooling of secretions in the lower respiratory tract and thereby reducing the risk of pneumonia.

2.4.2 Post-transplant physical rehabilitation

Physical rehabilitation should be commenced as soon as possible following transplantation. Many problems during the initial post-operative phase may impede in the patient's recovery namely, disruption of the lung function (Egan, et al., 1989), decreased physical mobility and static positioning due to surgery and pain (Butler, 1995 and Biggar et al., 1993). It has been well noted that bed rest is associated with a decrease in ventilation, a decrease in oxygen uptake and other cardiopulmonary effects (Dean, 1985; Chase et al., 1966; Saltin et al., 1968). Mobilization and body positioning by the physiotherapist is therefore very important in order to increase the ventilation-perfusion as well as to facilitate and increase the drainage of lung secretions as well as liquids from chest tubes (Zadai, 1981; Lannefors et al., 1992; Zausmer, 1968). Patients are also helped in airway clearance due to the decrease in mucociliary clearance, in order to decrease the possibility of an infection. Different coughing maneuvers, for secretion removal, such as the Huff coughing, are adapted, which are less painful and take less energy (Downs, et al., 1996). Therapy in this early post-operative period is continued in order to improve general mobility and patient's ambulatory status.

Following discharge, patients continue their pulmonary rehabilitation, as outpatients, in order to increase their physical function, strength and endurance, which is handicapped due to musculoskeletal limitations. This helps in keeping a follow-up on the patient's status and whether a reevaluation should be carried out and exercise regimen altered (Downs, 1996).

2.4.3 Infection prophylaxis

Lung transplant units now routinely use prophylactic intravenous antibiotics against likely pathogens (Williams et al., 1997). Specific prophylactic treatments are also added for complications that may arise from a specific lung disease, e.g. the use of inhaled aminoglycosides in CF recipients (Madden, 1995). Furthermore, ganciclovir, an antiviral agent, is generally taken in order to avoid infection with cytomegalovirus (CMV) from serologic mismatching (Williams et al., 1997).

The risk of infection associated with the actual lung transplantation is important. Donor lungs remain ischemic for several hours before they are reperfused with the recipient's blood supply (Chaparro et al., 1997). It has been noted that the period of ischemia along with the interrupted lymphatic drainage, provides favorable conditions for the growth of potential pathogens (Aeba et al., 1993). Furthermore, the loss of neurological innervations and the impairment of mucociliary function lead to abnormalities in the clearance of secretions (Mancini et al., 1986; Dolonish et al., 1987).

Infection prophylaxis is therefore very important. The techniques of gentle suction or lavage of donor lungs are carried out in order to obtain, from lung secretions, specimens for Gram stain and culture (Low et al., 1993). In order to identify the presence of colonizing bacteria or fungi, the culture of bronchial tissue trimmed from the donor lung may also be carried out (Kramer et al., 1993). These techniques are used in order to aid in the prophylactic treatment. Furthermore,

routine immediate prophylaxis is carried out, until donor data are available (Corris, 1997).

The immediate prophylaxis of infections depends on the underlying disease of the patient. In some centers, the use of flucloxacillin and metonidazole is standard in patients with non-suppurative lung disease, because of the high potential of occult aspiration in the donor lung (Corris, 1997). In this case, flucloxacillin is given for 48 hours and metonidazole is given for 7 days until the inspection of the anastomotic site (Corris, 1997). Recipients with bronchiectasis or CF infected with pseudomonades are given antipseudomonal treatments (Corris, 1997). Patients with infected airways by *Aspergillus* are given antifungal treatment, such as nebulized amphotericin twice a day, in order to reduce the incidence of dissemination of the fungal infection (Corris, 1997). Fluconazole prophylaxis is used in cases where the donor lung exhibits infection with *Candida* (Corris, 1997). In cases that necessitate the prolongation of mechanical ventilation beyond the two days, the use of nebulized antibiotics (e.g.. colistimethate sodium or tobramycin) is helpful in preventing the colonization of the lungs with gram-negative bacteria (Ramsey et al., 1993).

In lung transplantation the most common viral pathogen is the CMV. The most important effect of CMV is pneumonitis. The patients who are the most at risk are those who are antibody-negative for CMV and receive an organ from an antibody-positive donor (Wreghitt et al., 1988). The incidence of CMV disease in this group has been reported to range from 15% to 30% (Corris, 1997). Other causes include the

reactivation of the virus due to the immunosuppressive therapy (Smyth et al., 1991). Some reported prophylactic regimens include the use of high-titer anti-CMV immunoglobulin given weekly for 6 to 8 weeks post-transplantation until the patient's serum converts (Gould et al., 1993). Other regimens include the use of ganciclovir for 14 days to 6 weeks or more. Studies have reported that this type of prophylaxis may in effect retard the onset and decrease the severity of the infection; without this effort, the incidence of pneumonitis related to CMV ranges between 17% and 27% (Duncan et al., 1991; Gould et al., 1993). Since ganciclovir is viristatic in nature it may fail to prevent CMV disease (Bailey et al., 1992) and is sometimes used in combination with hyperimmune globulin. Resistance to ganciclovir, after prolonged exposure, has been noted in many patients (Kruger et al., 1999). These patients have an increased viremia, an earlier onset of chronic rejection in the form of obliterative bronchiolitis (OB) and a shorter survival.

During the first three months after transplantation infection prophylaxis against bacteria, fungi, viruses and protozoa continues. Bronchoalveolar lavages should always be examined in order to exclude the diagnosis of *Aspergillus* or *Pneumocystis carinii*. As for infection prophylaxis in the late period, beyond the 3-month period, some centers withdraw *Pneumocystis* prophylaxis after 1 year and others have reported to continue the treatment indefinitely. Corris (1997) reports that as in the latter regimen there has not been any case of *Pneumocystis* in his center in the past 200 consecutive lung transplantations.

2.4.4 Acute lung rejection

Acute lung rejection usually occurs in the first 3 to 6 months and most patients have at least one episode (DeMeo et al., 2001). Transbronchial biopsy remains the gold standard for diagnosing acute lung rejection (Guilinger et al., 1995; Tikkanen et al., 2001). Treatment consists of a high dose of corticosteroids, usually methylprednisolone for 3 days (DeMeo et al., 2001). When patients do not respond even after a second dose of steroids, cytolytic therapy, as in total lymphoid irradiation, may be considered (Valentine et al., 1996).

Studies have shown that infection and rejection are sometimes concurrent (Higenbottam et al., 1987; Tazelaar et al., 1991) and since they are both common, bronchoalveolar lavage should also be performed at the same time as the transbronchial biopsy (Higenbottam et al., 1988; Starnes et al., 1989).

2.4.5 Chronic rejection

During the late postoperative period, beyond the three-month point, monitoring for chronic rejection is very important. Chronic lung rejection usually begins between 6 months to one year and is characterized by obliterative bronchiolitis (OB). It is an inflammatory disorder of the small airways (bronchioles), which leads to severe airflow obstruction (Burke et al., 1986) and vascular sclerosis affecting the pulmonary arteries and veins. Although it has been seen to occur within 2 months of transplantation, most cases appear between 6 and 18 months after surgery (Kramer, 1994). The early development of bronchiolitis obliterans syndrome (BOS) associated

with a rapid decline in FEV_1 suggests a poor long-term prognosis (Glanville et al., 1987; Corris, 1997). It has been suggested that the best prevention of this syndrome would be if acute rejection were controlled in the first six months after transplantation (Corris, 1997). The identification of OB at an early stage confers that the diagnosis would be made at the inflammatory phase, as opposed to the fibrotic phase, and increased immunosuppressive treatment could arrest the loss of pulmonary function (Yousem et al., 1996).

The prevalence of OB has, in earlier studies, been reported to range from 34% to over 50% (Bando et al., 1995; Sundaresan et al., 1995; Reichenspurner et al., 1996). Some studies have found it to be present in up to 40% of patients 2 years after transplant (Egan et al., 1995; Radley-Smith et al., 1995) and in between 60-70% of patients who survive past 5 years (Heng et al., 1998). The most recent data published by the ISHLT, compiled between 1982 and 2001, shows a prevalence of 30% during the second and third year following lung transplantation and, 33% during the fourth and fifth year in those who survive (ISHLT, 2002).

To date, chronic rejection is the most important cause for a re-transplantation (Fournier et al., 1993; Novick et al., 1993; Shennib et al., 1993) and is an important cause of mortality in the late post-operative phase (Paradis et al., 1993). It is managed by increasing the immunosuppression of the patient with such treatment as corticosteroid therapy and inhaled cyclosporine, tacrolimus and mycophenolate mofetil. Refractory rejection may be managed using extracorporeal photophoresis

when patients with OB are unresponsive to standard and increased immunosupression. (Salerno et al., 1999; O'Hagan et al., 1999).

2.4.6 Malignancy in transplant recipients

The use of immunosuppressive drug therapy, in order to reduce the chances of a rejection, in transplant patients may increase their risk of developing certain types of neoplasms. These include, non-Hodgkin's lymphoma, squamous cell cancers of the lip and skin, Kaposi's sarcoma (Kantor et al., 2000), carcinoma of the perineum and vulva, and tumors in the kidneys and in the hepatobiliary tract (Penn, 1993). The associated morbidity and mortality to these disorders are significant. In lung transplant recipients the incidence of post-transplant lymphoproliferative disorder has been reported to range from 6.4% to 20% (Armitage et al., 1991; Walker et al., 1995; Aris et al., 1996; Montone et al., 1996). Others have reported a lower incidence of 1.8% (Levine et al., 1999). Recent published data (2002) from the ISHLT report malignancy and lymphoma prevalence rates of 5.1% at one-year follow-up and 9.6% during the fourth and fifth year post-transplantation.

2.5 Post lung transplant morbidity

2.5.1 Other drug related post-transplant morbidity

Many of the drugs prescribed to lung transplant recipients are associated with a number of important co-morbid conditions. At 1 and 5 years post-transplantation, 49.5% and 87.1% of recipients will develop hypertension, 23.9% and 38.8% will

develop renal function impairment, 14.8% and 17.7% will develop hyperlipidemia and 17.5% and 25.9% will develop diabetes, respectively (ISHLT, 2002).

2.5.2 Patterns of hospitalization in the post-transplant phase

The percentage of lung recipients requiring hospitalization after transplantation seems to diminish year by year just as the number of hospitalizations due to the concomitant presence of rejection and infection (ISHLT, 2002). Estimated hospitalization patterns and their reason are presented in table 3.

Table 3. Post-transplant prevalence of hospitalizations

Hospitalization due to:	1 year post-Tx prevalence	2 and 3 year post-Tx prevalence	4 and 5 year post-Tx prevalence
Rejection and Infection	15.1%	7.3%	4.5%
Infection alone	23.4%	17.9%	15.6%
Rejection alone	7.1%	5.7%	4.2%
Other	9.7%	8.4%	9.0%
No hospitalization	44.7%	60.7%	67.7%

Adapted from the registry of the ISHLT, 2002.

2.6 Survival following lung transplantation

The ISHLT (2002) presents overall recipient survival rates for all diseases on 14,246 lung transplants carried out between 1990 and 2000. The patient half-life (time where 50% of patients survive) reported for all transplants was 4.1 years. The conditional half-life reported for all transplant recipients surviving the first year was 6.5 years. Survival by type of lung transplant received is presented in table 4.

Table 4. Lung recipient survival statistics

	Bilateral/Double lung transplantation N=6,448	Single lung transplantation N=7,798	All lung transplants N=14,246
6 months	79.5%	79.3%	79.4%
1 year	74.1%	72.5%	73.2%
3 years	59.4%	55.5%	57.2%
5 years	49.5%	42.2%	45.3%
10years	25.9%	18.9%	22.9%

Adapted from the registry of the ISHLT (2002).

The United Network for Organ Sharing (UNOS, 2003) reports US actuarial survival statistics for lung transplants carried out between 1996 and 2001. For single lung transplants, the reported 1 and 3-year survival was 75.9% (n=1038) and 55.8% (n=885), respectively. For double lung transplants, the reported 1 and 3-year survival was 77.8% (n=873) and 59.9% (n=826), respectively.

The CIHI has published Canadian actuarial survival rates, computed from 1991 to 1998 data (2000). The survival rates for single lung recipients (n=262) at 1, 2, 3 and 4 years post-transplant were 71%, 63%, 57% and 53%, respectively. For double lung transplants (n=376), the survival at 1, 2, 3 and 4 years post-transplant was 73%, 67%, 62% and 56%, respectively.

The survival data show a higher survival rate with double lung than single lung transplants. Data gathered by the ISHLT (2002), on adult lung transplants, also show better survival statistics in transplants carried out between 1998 and 2001 versus those carried out between 1993 and 1997 (p=0.003). The registry also reported

survival statistics for different lung diseased recipients between 1990 and 2001. The 1 and 3 year survival was: 79.5% and 61.5% for emphysema (n=4,643); 74.7% and 59.8% for alpha$_1$-antitrypsin (n=1,288); 77.9% and 61.5% for cystic fibrosis (n=1,809); 66.4% and 50.2% for idiopathic pulmonary fibrosis (n=1,981); 64.7% and 55.1% for primary pulmonary hypertension (n=714) and; 68.1% and 53.1% for sarcoidosis (n=303), respectively.

Hosenpud et al. (1998), in the US, attempted to determine specific mortality risks after lung transplantation relative to the waiting list for different end-stage pulmonary diseases. The data observed show that patients with emphysema fare better on the waiting list than the CF and IPF group ($p. < 0.0001$). CF patients however, had a better survival on the waiting list than the IPF group ($p. <0.03$). After transplantation, a marginal survival difference was observed between the emphysema and IPF patients ($p = 0.06$). In this study, the CF group (n=318 recipients; n=252 candidates) seemed to benefit the most from this procedure. The 1, 6 and 12- month relative risks for CF patients were 0.87, 0.61 and 0.61, respectively. For the IPF group (n=230 recipients; n=208 candidates) the 1, 6 and 12-month reported relative risks were 2.09, 0.71 and 0.67, respectively. The risk of mortality after transplantation for the emphysema group (n=843 recipients; n=308 candidates) never went below the risk of remaining on the waiting list. The 1, 6 and 12-month reported relative risks were 2.76, 1.12 and 1.10, respectively.

A more recent study conducted by Charman et al. (2002) in the UK presented similar results for most disease groups except for the obstructive lung disease group where a survival benefit from transplantation was observed. The reported 1, 6 and 12-month risks after transplantation relative to that of continued waiting were: 2.77, 0.55 and 0.32 for obstructive lung diseases (n=163); 2.42, 0.21 and 0.15 for cystic fibrosis (n=174); 0.62, 0.58 and 0.58 for bronchiectasis (n=51); 2.23, 0.65 and 0.46 for pulmonary fibrosis (100) and; 1.18, 0.37 and 0.34 for pulmonary hypertension (n=68), respectively.

2.7 Retransplantation

One of the most important long-term complications arising in the post-transplant phase is chronic rejection in the form of OB. When medical therapy is not able to reverse the progressing airflow obstruction of the attained lung, lung retransplantation is the only management form of therapy for the chronic rejection of the allograft. Pulmonary retransplantation has been attributed mainly to obliterative bronchiolitis (63%), acute graft failure (23%), airway healing complications (6%) and severe acute rejection (4%) (London Health Sciences Center data report, 2000).

Today, the Pulmonary Retransplant Registry, which was established in late 1991, holds complete data on 250 patients from 48 centres in North America, Europe, and Australia. With such information, the registry has been able to identify predictors of survival and graft function after pulmonary retransplantation.

Novick et al. (1998) observed, from retransplantations occurring between 1985 and 1996 (n=230), the following survival rates: 47% ± 3%, 40% ± 3%, and 33% ± 4% at 1, 2 and 3 years, respectively. The reported significant factors in increased effectiveness of retransplantation were: ambulatory status, not ventilator supported preoperatively, a higher retransplant experience in performing center and an interval of at least 2 years in between both transplants. For patients, retransplanted after 1991, that had not been ventilated and were ambulatory had a 1-year survival rate of 64% ± 5%. Patients who were non-ambulating and ventilated had a 1-year survival of 33% ± 4%.

2.8 Post-transplant causes of mortality

A summary of the causes of death in lung recipients is presented in table 5, as were reported from the ISHLT on data observed between 1982 and 2001 (2002). The primary causes of mortality in the first year following lung transplantation are graft failure and infection. Beyond the one-year mark, OB, infection and graft failure are significant causes of mortality.

Table 5. Post-lung transplant causes of death.

	0-30 days post-Tx (n=962)	31 days –1 year post-Tx (n=1,230)	>1-3 years post-Tx (n=953)	>3-5 years post-Tx (n=479)
Cardiac allograft dysfunction	1.2%	0.8%	1.2%	1.5%
Cardiac	9.3%	3.5%	2.1%	3.1%
Cytomegalovirus	0.5%	4.0%	1.7%	0.6%
OB	0.7%	5.9%	30.0%	33.0%
Lymphoma	0.1%	3.2%	2.4%	1.7%
Malignancy (other)	-	1.9%	4.1%	7.9%
Infection (Not CMV)	24.6%	38.3%	24.9%	18.8%
Acute Rejection	5.9%	4.4%	2.1%	0.8%
Graft failure	31.1%	17.0%	16.0%	17.8%
Technical	8.8%	3.0%	0.9%	0.2%

Adapted from the registry of the ISHLT (2002).

One-year mortality risk factors observed in 5,242 lung transplants carried out between 1996 and 2001 were: congenital heart disease, ventilator dependence, total assistance for activities of daily living, patient was in ICU or hospital, the diagnosis of primary pulmonary hypertension, double lung transplants for IPF patients, donor CMV+ / recipient CMV-, donor cause of death, year of transplant (1996), donor cigarette history, donor/recipient mismatch, donor and recipient age, body mass index and bilirubin levels (ISHLT, 2002). Protective factors at one-year post-transplant were: the diagnosis of COPD and study center volume with respect to number of transplants carried out (>30 transplants/year) (ISHLT, 2002).

2.9 Post-transplant health-related quality of life

The definition of quality of life as stated by the World Health Organization (1947) is: "... not only the absence of infirmity and disease but also a state of physical, mental, and social well-being." Health related quality of life (HRQOL) could therefore be thought of as a trilogy of domains. Simmons et al. (1987), in their study of kidney transplant recipients, defined these health domains as a) physical well-being, which includes symptoms and ability to perform daily activities; b) emotional well-being, which includes mental health, anxiety, self-image, self-esteem and happiness; and c) social well-being, which includes interpersonal relationships and the adjustment of oneself at work, school and at the home. The Medical Outcome Study (MOS) group proposed eight domains of health concepts to be used when assessing HRQOL in clinical and research practices (Ware et al., 1992). The domains included are: physical functioning, role functioning-role physical, bodily pain, general health, vitality, social functioning, emotional functioning-emotional role and mental health. The numerous HRQOL instruments, which are based upon these domains, are: the SF-36 questionnaire, the Nottingham Health Profile (NHP), and the Sickness Impact Profile (SIP).

Health related quality of life is an important well-being issue in patients with terminal lung disease. Patients in this late stage of the disease experience a significant morbidity which results from symptoms of dyspnea, recurrent infections, limitation of activities, side effects of medication and admissions to hospitals (Fishman et al., 1971; Dudley et al., 1980). In addition to these burdens, lung

transplant candidates may also be affected from psychological, psychiatric and social factors (Craven et al., 1990). These may include: anxiety, depression, the fear of dying, coping with a disabling or life-threatening disease, financial concerns and the issue of relocation (Limbos et al., 1997, 2000; TenVergert et al., 1998).

Studies assessing quality of life in post-transplant patients are not frequent. Reasons for this might include the fact that lung transplantation is one of the youngest solid organ transplant procedures, very few centers consistently transplant more than 30 patients a year, and major changes in surgical techniques and indications for lung transplantation have occurred (Gross et al., 1997). Although many have reported that lung and heart-lung transplantation does increase HRQOL (Craven et al., 1990; Busschbach et al., 1994; Gross et al., 1995; Cohen et al., 1998; Caine et al., 1996; Limbos et al., 1997; 2000), there still remain some aspects that may continue to impair a recipient's possibility of recuperating to an acceptable overall level. HRQOL not only includes health related factors, but also includes satisfaction with life, happiness, employment, body satisfaction and sexual functioning (Limbos et al., 1997). It is important to note that, in the post-transplant phase, these factors may fully or partially improve, and may not improve at all.

The postoperative period is associated with a strict drug regimen and rigid follow-up care. Immunosuppression therapy for maintenance of patients against rejection predisposes lung recipients to an increased risk of infection as well as other life threatening complications (ISHLT, 2002). Drug physical side effects include

hypertrichosis and gingival hypertrophy with cyclosporine A; and Cushingoid features with the use of corticosteroids (Gross et al., 1997). Many have mentioned the worrying high incidence of noncompliance among younger CF recipients and the need to examine quality of life (QOL) and this issue in this group (Gross et al., 1997).

Chronic rejection in the form of OB may lead to functional and physical limitations. OB is associated with a decline in pulmonary function and may decrease QOL (TenVergert et al., 1998). One study reported that although HRQOL does improve after transplantation, OB significantly reduces energy and physical mobility when assessed cross-sectionally and patients report more depressive symptoms and anxiety when questioned longitudinally (van den Berg et al., 2000).

To accurately assess the effectiveness of lung transplants, the quality of life should also be assessed, throughout the follow-up period, in order to obtain the overall effect of the procedure on the individual. Ramsey et al. (1995b) report quality of life data obtained cross-sectionally with the SIP. The study population consisted of 21 patients on the waiting list and 23 lung transplant recipients. Results from the study show improvements in mean SIP scores after 4 months of transplantation however no significant difference was observed. Furthermore, comparisons carried out within specific end stage lung diseases seemed to show an improvement in HRQOL after the 4-month post-transplant period. More specifically, patients with CF and COPD seemed to benefit the most with respect to their quality of life. The authors attribute the statistical non-significance of the comparisons to the small sample size.

A study carried out by TenVergert et al. (1998) reports an improvement in physical and psychological functioning, from the NHP, in 24 lung recipients followed longitudinally from the waiting list up to 19 months post-transplant. The median age of the population studied was 40-49 years old, 63% were men and the most frequent diagnosis was emphysema (54%) followed by cystic fibrosis (30%). The results of this study suggest a significant improvement in physical and psychological functioning at the 4 month post-transplant period and that a positive trend in health related quality of life is sustained in the long run (at 19 months post-transplant).

A more recent pilot study (Lanuza et al., 2000) undertaken on a small number of patients (n=10), followed from the waiting list until the third month after surgery, reported similar results. The authors noted significant improvements in the reporting of physical functioning and ambulation, and satisfaction with their quality of life, current health status and physical strength. No significant improvements were noted in the psychological symptoms of patients. Limbos and colleagues (2000) also reported that transplanted recipients (n=73) averaged better scores than candidates (n=36) in general, physical and psychological health. The authors did however report important areas of impairment such as in psychological functioning. Emotional health and role limitations associated to emotional health, as captured by the RAND-36, did not differ between the two groups.

A few studies have also suggested gender differences with respect to HRQOL. Domains dealing with sexual issues, body image and satisfaction, and the changing of roles may be more affected in women than in men (Craven et al., 1990). Limbos and colleagues (1997) attempted to study, in women lung recipients (n=34) and candidates (n=7), changes in quality of life, sexual satisfaction and body satisfaction. The authors noted that the physical and general health, controlling for age and depression, in transplanted women did improve, but no significant difference was observed with respect to emotional well-being and health, role limitations, and social functioning as compared to candidates. With respect to body satisfaction, transplant lung recipients reported better satisfaction with their bodies as compared to candidates. Conversely, although not significant, candidates reported better sexual satisfaction than recipients.

The ISHLT (2002) also reports estimates on functional status for lung recipients in the post transplant phase. Their most recent report, based on US data collected from April 1994 to December 2001, shows that at 1 year (n=4,039), 84.3% of recipients have no limitations in functional activity and that only 2% require total assistance. At 5 years (n=1,372), 86.5% have no limitations and 1.7% of recipients require total assistance.

Despite these improvements in HRQOL, many studies have shown that lung transplant recipients experience difficulties in returning to work (Craven et al., 1990; Busschbach et al., 1994; Gross et al., 1995; TenVergert et al., 1998). TenVergert and

his colleagues (1998), reported that 19 months after transplantation, 33% of patients were working part time and that none of the patients had returned to work full time. Another study, carried out by Paris et al. (1998), noted that only 37% (22/60) of those able to return to work did so after transplantation. The study group consisted of transplant patients in the US (n=49) and in Canada (n=50). The return-to-work numbers were identical in both countries, 11 and 11 people, respectively. The mean age and time since transplantation, was similar in both countries. As for education, there was a higher percentage of US citizens in the 12-16 years (76% vs. 46%) and a higher percentage of Canadians in the less than 12-year education group (32% vs. 6%). Pre-transplant employment status was 50% employed, 44% disabled and 6% retired. The recipients most affected were those who were younger and had no job experience and, older patients who had been out of work for a long time. The authors note that increased effort should be made in patients whose opinion of being able to work differs from the one given by the health care professional.

These studies elucidate the need to further explore health related, social and emotional issues in post-transplanted patients. More specifically, to address potential gender differences, age differences that may be associated to the underlying type of disease (e.g. CF group), as well as many socio-demographic factors that were not taken into account in some of the studies mentioned. Also, some clinical indices such as spirometry measures (FEV_1), as well as the presence of infections might have been interesting to take into account as predictive factors. Finally, with the increased life expectancy seen in recipients, it is important to assess quality of life systematically

throughout the follow-up period, as opposed to cross-sectionally, in order to obtain the most precise utility estimate for this costly procedure.

2.10 Preferences for a health state

The following section on preference for a health state is summarized as described in Drummond et al., (1997) (p. 146 – 150). Drummond and colleagues state that "preference is an umbrella term under which utilities and values may be categorized. These different types of preferences differ on the basis upon which they are measured. This includes (i) the way the question is framed: whether the outcome is certain or uncertain and (ii) the way the subject is asked to respond: whether the subject is asked to perform a scaling task or to make a choice. The outcome (s) described should be a path from now till death consisting of one or more health states for a specified period of time. A question framed under certainty asks the subject to compare 2 or more outcomes and choose between them or to scale them. The subject is asked to assume that the outcome would occur for certain. A question framed under uncertainty asks the subject to compare 2 alternatives where at least 1 of the alternatives contains uncertainty that is it contains a probability. The difference between these 2 forms of questioning is that the certainty method does not capture the subjects risk attitude while the uncertainty method does."

The preference measurement instruments fall into 4 categories based on the response method (scaling versus choice) and framing of the question (certainty or uncertainty). The scaling method, which is easier to administer and takes less

respondent time, includes questions under certainty and the tools here include the rating scale, category scaling, visual analogue scale (VAS) and the ratio scale (Drummond et al., 1997). The choice methods under certainty include instruments such as the time trade-off (TTO), paired comparison, equivalence and person trade-off (PTO). All these instruments elicit values. The choice method under uncertainty includes the standard gamble (SG), which elicits a utility (Drummond et al., 1997).

Nord (1992) summarizes the distinction between the 5 most used instruments as follows: the standard gamble, time trade-off and person trade-off may be called equivalence techniques or trade-off techniques which face the subjects with a choice between pairs of conditions. Nord (1992) states that the question is basically: "how much are you willing to sacrifice of certainty (SG), life span (TTO) and the health of others (PTO), respectively, in order to improve your own quality of life (SG and TTO) or that of an imaginary patient (PTO). With the rating scale and ratio scale (magnitude estimation), subjects are asked to apply numerical scales directly to conditions".

Of these two response methods Nord (1992) states that few people use numerical scales when expressing quality of life, in everyday situations and Drummond et al. (1997) state that choosing is a natural human task. All other factors equal, choice-based methods over scaling methods should be preferred (Drummond et al., 1997).

As for whether utilities or values should be elicited, Drummond et al., (1997) refer to the: "Von Neumann-Morgenstern (1944) utility theory which indicates that utilities are appropriate for problems that involve uncertainty or certainty or both; values are only appropriate for problems that involve certainty". Furthermore, utilities capture the individual's risk attitude, which is essential for problems that contain uncertainty (Drummond et al., 1997). Most researchers argue because future health outcomes are clearly uncertain preferences should be measured under uncertainty (utilities) (Mehrez and Gafni 1991; Gold et al., 1996; Drummond et al., 1997).

2.10.1 Measures of utility

A quality of life index can also be a utility measure which is a probability reflecting both health and patient preferences for treatment and outcome (Guyatt, 1993). A person's HRQOL can be pictured as a continuum where its limit at the top is perfect health and lower limit a bad health state, usually death (Torrance, 1986). This outcome deals with the value a patient places on a specific health state and its perceived general, mental and physical health. The utility score represents this preference or desire for a health state that is measured on a scale of 0.0 to 1.0.

In the standard gamble patients are asked to imagine a situation in which they must choose between two health states. To remain in their current impaired health state or, to go through a procedure, which would restore their health perfectly. This procedure carries a specified risk of death. The probability of death is varied until the patient reaches the point of indecision, that is finding either approach equally

appealing, and the outcome is a utility score which ranges from 0 for death to 1 for perfect health (Torrance, 1976).

The other two utility measurement instruments, mentioned above, are the time trade-off and the visual analogue scale. The TTO is a technique developed by Torrance and his colleagues (1972) as an alternative to the standard gamble, which seems to be easier to administer. In this technique, patients are asked how many years of life they are willing to give up in order to be in good health. Basically, the TTO method compares the following: living in their current diseased health state for the rest of their lives or, having a specified shorter life span but in a healthy state. The amount of years they are willing to give up is varied until they are indifferent between both choices.

In turn, the VAS can be used as developed by the EuroQol group. It is a line, which is calibrated, like a thermometer, from 0 to 100. Zero, at the bottom of the line depicts the worse imaginable health state and 100, at the top, the best health state imaginable. The respondent is asked to place a mark on the line which best depicts his or her current health state.

Indirect measures of utility can be obtained from the Health Utility Index (MARKs), Quality of Well Being (QWB) system and the EuroQol (EQ-5D), which are hybrid instruments. These instruments are multi-attribute health status classification systems, which are pre-scored values in terms of a preference measure

(Drummond et al., 1997). The utilities obtained from these instruments reflect the value that the general population assigns to different health states.

2.10.2 Review of studies on the utility of lung transplants

One of the first studies attempting to obtain utility values in lung transplant recipients is a pilot study carried out by Busschbach and his colleagues (1994). The authors report an improvement in the utility of cystic fibrosis patients after transplantation as compared to the waiting list. The results should be accepted with caution due to the small number of patients interviewed, 3 transplant recipients and 3 candidates, as well as to the potential for recall bias on some questions eliciting quality of life before the transplant procedure.

Another study, using the QWB scale to derive utilities after transplantation, observed a mean score of 0.54 ± 0.198 and a median of 0.599 (Gartner et al., 1997). Limitations of the study include a small sample size (n=19 recipients) and a point estimate of utility at 1 year after transplantation. Furthermore, the small study sample was recruited at one study center and 80% were females.

Another study conducted by Ramsey and colleagues (1995b) report utility values on a cohort of patients obtained with the standard gamble. Data was obtained from 21 candidates and 23 lung recipients. Results from the study show that utility scores within the 4 months following surgery (0.73±0.24) did not improve significantly when compared to those measured during the waiting list period (0.65±0.26).

Significant improvements were observed only after the four-month period (0.89± 0.15) as opposed to the waiting list.

Al and colleagues (1998) followed a cohort of patients in the Dutch lung transplantation program (n=120). These authors reported mean quality of life utility scores, obtained from the EuroQol, for waiting list and transplant patients as well as patients that were in the screening program. The authors attempted to observe the utility of the lung transplant program from the screening period up until over 2 years post-transplant. The utility of being at the screening period was reported to be 0.52 ± 0.2 (n=169). The utility for patients waiting up to 6, 6-9, 9-12, 12-15 and over 15 months was 0.55 ± 0.16, 0.50 ± 0.18, 0.45 ± 0.2, 0.40 ± 0.15 and 0.40 ± 12, respectively. As can be seen, there seems to be a decrease in the utility as patients wait longer. As compared to waiting list scores, recipients reported higher utility scores within the first 3 months (0.83 ± 0.16) of transplantation, and these scores kept improving well up to the 2-year mark (0.91 ± 0.1).

A more recent multicenter cross-sectional study (Anyanwu et al., 2001) reports health utilities obtained on 87 waiting list and 255 lung and heart lung transplant patients. Utility scores were obtained by two methods, using the visual analogue scale and the EuroQol. Health utility scores obtained from transplant patients were divided into 4 time periods: 0-6, 7-18, 19-36 and >36 months and separated with respect to the type of transplantation received (single, bilateral or heart-lung). As compared to waiting list patients, transplant recipients had significantly better utility

scores. When comparing the 4 different post-transplant time periods, no significant difference or trend was observed. However, there seemed to be a consistent improvement, after 6 months, in scores for bilateral and heart-lung transplantation as compared to single transplantation.

2.11 Economic evaluation

With the continuous threatened changes in the health care system and the pressure to contain cost, economic evaluations have been on the rise. These evaluations inform and provide guidance to third party payers (government, insurance companies) and health care providers (clinic, hospital, clinicians) in making decisions about the adoption and utilization of competing health care procedures, treatments or programs. Such studies may also support the continuance of existing and already implemented health care services. It has been suggested that economic evaluations should always be of a comparative form and the results should always be expressed as an increment. That is, a treatment under study should always be compared to the alternative forms of treatment and to the absence of treatment (when applicable). The costs and consequences should always be presented as incremented ratios and not as totals or averages (Drummond et al., 1997). Finally, economic evaluations coupled to clinical results will eventually classify therapies, on the basis of their incremental net benefits, as to whether they are more or less cost-effective than the alternative medical practices (Laupacis et al., 1992).

2.11.1 Types of economic evaluations

There are four types of economic evaluations. One type consists of a cost-minimization analysis. In this case, the clinical results of two or more practices are almost identical, and this analysis allows the comparison of their costs; the decision will then be based on the costs (Johannessson et al., 1991). A second type of evaluation consists of undergoing a cost-effectiveness analysis. In this case, the incremental costs from the alternatives are compared to the incremental common clinical result. The clinical consequences are measured in natural or physical units, such as, number of years gained or the reduction of blood pressure (Winston, 1991). A third type consists of a cost-utility analysis. This type of analysis is a form of a cost-effectiveness study where the clinical results are measured as a utility, such as quality adjusted life years (QALY). The QALY combines the quantitative (mortality) and qualitative (quality of life) changes in one measure. That is, it may represent the quantity and quality of a person's life (Patrick et al., 1993). The utility is a preference of one health state over another, and when introduced into the analysis, should correspond to the global preferences of the patients or general population (Culyer, 1989, 1990). This type of analysis, as compared to the cost-effectiveness one, has the advantage in that it uses QALY's gained, a generic measure of outcome, which takes into consideration both the morbidity and mortality associated with a program (Torrance, 1986; Drummond et al.,1997). The fourth type of economic evaluation consists of a cost-benefit analysis in which the incremented consequences are expressed in dollars (Johansson, 1995; Johannesson, 1996). This type of method may evaluate society's willingness to pay for this benefit (Viscusi, 1996).

2.11.2 Review of end-stage lung disease economic burden

Patients with end stage lung disease experience important morbidities such as dyspnea and limitation to their daily activities. Hospitalizations are common (Bresnitz, 1997) and the prolongation of life is aided with respiratory aids such as home oxygen therapy (O'Donohue, 1995) and ventilator support (Sevick et al., 1996; 1997). The economic burden of lung disease on the health care system is obvious. The cost of COPD and allied conditions can reach up to $20 billion in the US. If one uses the data observed in the US to extrapolate this cost in Canada it would reach $1.25 billion (average pharmacotherapy at $500 per year and assuming 10% of the population (n=30 million) had end stage lung disease). In specific indications such as cystic fibrosis, infections are very prevalent and patients require frequent medical attention. Expensive pharmaceuticals such as antibiotics and enzyme therapy are common in this population (Lieu et al., 1999). It is easy to see how the medical related costs associated to these conditions run into the billions per year (O'Donohue, 1995; Bresnitz, 1997; Sevick et al., 1996; 1997; Lieu et al., 1999). Medical care for cystic fibrosis patients in the US, in 1996, has been estimated to reach $314 million (Lieu et al., 1999). The annual cost per patient averaged $13,300 and ranged from $6,200 to $43,300 per patient. Patients over the age of 18 had an average cost of $15,000 per year. The authors break down the cost drivers as follows: 47% of total costs are attributed to hospitalizations, 18% to DNase (Pulmozyme), 12% to outpatient clinic visits, 10% to outpatient antibiotics and 13% to other medication.

Lung transplantation can be a beneficial alternative medical option for treating these patients. It is however associated with an intense medical regimen of follow-up care and drug therapy. Complications associated with this procedure are life threatening and include infections, acute and chronic rejection as well as other conditions associated to the medications taken (ISHLT, 2002). Furthermore, failure of the graft in terms of obliterative bronchiolitis necessitates a retransplantation. Hospitalizations and expensive anti rejection and infection prophylactic drugs are important costs associated with this procedure.

2.11.3 Review of lung transplant economic evaluations

The high cost associated with lung transplantation has elicited an interest in its economic evaluation. Further ascertainment of cost associated to the preoperative, postoperative and follow-up care of lung transplantation is needed in order to compare its costs and effects to the ones incurred from standard end-stage lung disease therapy practiced today.

A Canadian study conducted by Maurer (1996, abstract) reported a lung transplant cost-effectiveness ratio of $62,860 (CDN) per life year gained. This study was based on 32 transplant patients (1992 to 1993) and 5 year projected estimates. The reported post-transplant follow-up costs in the 1st, 2nd, 3rd, 4th and 5th year were $43,695, $30,700, $30,780, $23,200 and $25,400, respectively. The breakdown of these costs is not available.

Ramsey and colleagues (1995a) carried out one of the first peer-reviewed economic evaluations on lung transplants, a cost-effectiveness study. The costs and outcomes of lung recipients (n=28) were compared to those incurred by patients while on the lung transplant waiting list (n=24) in a US University Medical Center. The perspective taken was of third-party payers and all direct medical costs incurred from the procedure were of interest. The costs included for transplantation were: the transplant procedure itself (lung acquisition, hospitalization, physician fees) and monthly post-transplant costs (subsequent hospitalizations, physician fees, outpatient visits, and pharmacy charges). Physician fees and charges for hospitalizations and clinic visits were obtained from the hospital billing service. Outpatient medication charges were obtained from the pharmacy and included the average wholesale price plus dispensing fees. Home health-care service fees were also assessed. The costs included for waiting list patients were the same with the exception of those associated with the transplant procedure. Lifetime expected costs for transplant recipients were calculated as the sum of the cost categories formerly mentioned and the lifetime follow-up costs which were computed by projecting the average monthly cost over the calculated life expectancy. Lifetime expected costs for waiting list patients were calculated by projecting average monthly costs over their estimated life expectancy. Survival data for both patient groups are obtained from previous published data from the St-Louis International Lung Transplant Registry (1993). The authors use these existing data to estimate the life expectancy of the study subjects and to incorporate survival statistics that may predict survival beyond the 3 years.

Ramsey et al. (1995a) reported that the mean charge for transplantation and postoperative care was $164,989 and, the median charge was $152,071. Almost 66% of this cost was attributed to hospital and pharmacy charges, 18.2% to physician fees and 15.9% to the acquisition of the organ. The average hospital stay for the transplant procedure was 23.4 ± 11.6 days. Patients on average stayed 14.6 ± 9.2 days in the ICU. Cost estimates in the post transplant phase were reported to be $16,628 in the first 6 months after transplantation and subsequently dropped to $5,440 in the following 6 months. After the first year, average monthly charges were estimated to be $4,525. These expenses were primarily due to repeat hospitalization and outpatient pharmacy costs. Cost estimates for the waiting list period were reported to be on average $3,395 per month. This average monthly charge was primarily made up of hospitalization charges and physician bills. The authors note that, on average, waiting list patients had higher in hospital patient days per year than recipients, 16.8 versus 10.6 days, respectively. Finally, the authors estimate the lifetime average cost for lung transplant recipients to be $424,853. Conversely, the average lifetime cost estimated for waiting list patients was $157,310. Future costs were discounted at a rate of 5%. The incremental cost per QALY gained, or attributed to the transplantation, was estimated to be $176,817.

Limitations of this study, as reported by van Enckevort and colleagues (1997), include the small sample size, the cross-sectional design and the lack of including screening and indirect costs, which may have underestimated the incremental cost. A selection bias may also have occurred if patient characteristics were different for the

two groups, transplant recipients and candidates, studied. Furthermore, although Ramsey et al. converted charges to costs, one has to keep in mind the implication that charges don't mean costs (Finkler, 1982). In the US, many government programs (Medicaid) pay less than the average cost of health care services. At this point, self paying patients and private insurance companies make up for this difference by not only paying for the costs of the service but also the money lost from the discounts given to the above mentioned organizations. These payers pay the charges that take into account the costs and any losses that may have occurred.

Another pilot study, conducted by Gartner and colleagues (1997), investigated the cost-utility of lung transplantation with the QWB scale. These authors attempted a threshold analysis to estimate the survival gains that must be achieved for lung transplantation to be considered a beneficial use of society's resources. In this study only direct costs of the transplantation itself were estimated that is, for medical care received during the operative admission. Costs taken into account were: all costs associated with diagnostic, laboratory and surgical procedures; room and board (including nursing care resources), equipment, and related ancillary support services (e.g. ventilator equipment and respiratory care); supplies; and pharmaceuticals. These costs were estimated from hospital charges, adjusted by cost/charge ratios. Physician costs included, were those associated with the transplant surgery. These fees were obtained from the Medicare Physician Fee Schedule. Under this system, the fee that is reimbursed to a physician is the product of a procedure-specific relative value unit (RVU), and a conversion factor, which is a nationally uniform dollar

amount for the procedure, in this case surgery. The authors reported that the average cost of the transplant procedure and hospitalization it entailed was $153,921 ± $133,981. The costs ranged from $63,405 to $598,482. The authors conclude that the life years gained from transplantation must be at least 2.7 years for surgery to be worth its median cost of $94,324 with a utility of 0.59. Apart from the small sample size and overrepresentation of females, which puts into question the generalizability of the results, one of the major limitations of the study was that it did not involve the comparison of any alternatives and did not carry out an incremental cost-utility analysis. Secondly, the costs associated to treating end-stage lung disease patients by transplantation are not isolated to the surgery itself. Trying to estimate the economic impact this procedure has on society, direct non-medical costs such as out-of–pocket costs for the patients and indirect costs (time seeking care) should have been included in the analysis. Finally, no matter the perspective taken, costs on donor acquisition and preparation as well as, costs associated with the evaluation of these patients as to their eligibility should have been included in the analysis. The costs presented seem to be an underestimation even when the authors intended to deal with the lung transplantation process as a one time surgical procedure.

In the Netherlands, a group of authors (van Enckevort et al., 1997) attempted to conduct a technology assessment of the Dutch Lung Transplantation program experience from 1990-1995. During this period, 425 patients were referred to the program of which, 303 and 179 were accepted for the outpatient and inpatient screening, respectively. Following the screening, 120 patients were accepted and put

on the lung transplant waiting list. There were 57 lung transplants that were carried out and subsequently, 55 and 54 patients entered the inpatient and outpatient follow-up period. The study attempted to provide information on the lifetime incremental costs associated to this lung transplant program as compared to the absence of the program. Costs in the latter case were based on costs incurred in the pre-transplant period. For the analysis, the authors took a societal viewpoint. The costs included in the study were attributed to different time periods: outpatient screening, inpatient screening, pre-transplantation, waiting list period, transplantation, inpatient follow-up and outpatient follow-up care in post-transplant phase. Given the societal perspective, the type of costs included were: direct medical costs, direct non-medical costs and indirect non-medical costs. Costs were ascertained from the financial administration of the University Hospital and from external sources of information.

From a subsequent technology assessment (van Enckevort et al., 1998), the total program costs per transplant recipient was estimated to average US $394,330 of which 92% consisted of direct medical costs. 65% of these medical costs were incurred during the outpatient follow-up period. The average hospital stay after transplantation was reported to be 60 days, 11 of which were spent in the ICU. The cost attributed to the waiting list period, conventional treatment of disease, was estimated to average US $470 per patient per week up to 6-months before death. Average weekly costs increased to about US $670 within this 6-month time period. The incremental cost-effectiveness ratio was reported to be US $72,000 per life-year gained and US $90,000 when costs were discounted at 5%. The incremental cost-

utility ratio was reported to be US $61,000 per QALY gained and US $71,000 when discounted at 5%.

In this study, all relevant costs were taken into consideration. Also, transplant recipients acted as their own control dealing with the possibility of any selection bias. The authors suggest the use of their model in assessing incremental costs to be relevant to other health care and transplant programs that do not have an appropriate control group.

A scenario analysis carried out (Al et al., 1998) suggested that decreasing the influx of patients to the program, in hospital screening and or increasing the number of available donors per year may decrease the costs per life and per QALY gained. This is attributed to the fact that an important part of the cost is incurred during the screening of the patients and that many patients die during the waiting list period, which don't benefit from a survival nor quality of life increase. There are less patients surviving to reach transplantation in order to see the benefits to reduce the cost-effectiveness ratio from such gains.

A more recent study conducted by Anyanwu and colleagues in the UK (2002) attempted to report cost-utility estimates for single and double lung transplants carried out between 1995 and 1999. The costs included in this study were direct medical costs and included: pre-transplant costs, donor screening and acquisition, transplant procedure and post-transplant follow-up costs. For a pre-transplant mean

survival of 2.7 years, the authors reported a mean cost for conventional care of US $24,600 and a mean cost of US $4,772 for assessment as to eligibility in the program. The transplantation costs were estimated at US $48,031 and $47,703 for single and double lung transplants. The projected mean cost for a 15-year post-transplant survival was US $99,236 and $103,454 for single and double lung transplants. Finally, the discounted cost-effectiveness and cost-utility estimates reported for single lung transplantation were US $50,825 per life year and $48,241 per quality adjusted life year gained, respectively. The estimates for double lung transplants were US $45,393 per life year and $32,803 per quality adjusted life year gained, respectively.

2.12 Conclusion

Many have attempted to study the quantitative and qualitative benefits that may be gained from lung transplantation. That is, survival and health related quality of life, respectively. Although the improvements seen in some HRQOL aspects, which is conferred by lung transplantation, is not debated, few have used this qualitative index as an outcome measure. Those who have attempted to do so have encountered, as seen, some limitations with respect to their design. Most importantly, many failed to adjust for many important variables that needed to be accounted for when explaining quality of life that may also be important predictive factors for survival. These factors include age, sex, underlying type of end stage lung disease, type of lung transplantation such as single, double (en bloc) or bilateral, and the presence of chronic rejection as characterized by obliterative bronchiolitis. Also, other clinical factors such as FEV_1 scores and the presence of infection or acute rejection at time of

interview should be noted. A few authors did attempt to study survival and quality of life as a function of pre-transplant diagnosis (Ramsey et al., 1995b), but the power of their study was low and was not able to detect any significant difference with a high degree of confidence.

Subsequent studies should therefore try to remedy some of these limitations. An attempt to take these variables into consideration and adjust for them should be the aim of a new study. Furthermore, a longitudinal approach to the study design is recommended when studying the effect of lung transplantation on survival, health related quality of life and on the utility of the health state. A before and after measures approach in the analysis deals with the comparability of two different groups and therefore this method takes into account any inter-group variability. In the study of lung transplantation, a valid comparison group, serving as a proxy for no transplantation, is the experience of patients on the waiting list (van Enckevort et al., 1997).

Carrying out such an outcomes study of health related quality of life in a new patient population, specifically eastern Canadian transplant recipients, is important. The demographics of Canadians as opposed to other populations are different. Differences include language as well as, different values and life styles. Such a study will elucidate potential predictors and specific patient characteristics that may aid in identifying factors that may impede in reaching an acceptable overall HRQOL during the post-transplant phase.

Although the continued maintenance and presence of lung transplantation, in Canada, is not questioned, the different opportunity costs associated with the program are of interest. No peer-reviewed study has been carried out, in Canada, to determine the cost-effectiveness or cost-utility of lung transplants. Furthermore, these ratios might prove to be different from the ones assessed in other countries. As mentioned, this specific population is different and obviously has access to a different health care system as opposed to the US, the UK and the Netherlands. In Canada, all citizens are insured for health services. Canada has largely controlled the costs of health care by funding and giving a global budget formula, which is used to fund hospitals (Battista et al., 1994). In the US, not all patients are covered universally. Patients are covered under different systems: public, as in Medicaid, Medicare; and from private insurance companies. The different sources of cost estimates, depending on the coverage of the patient, are different between countries and therefore, the economic impact of lung transplantation may differ between different societies and health care programs.

Finally, the economic part of this study will be useful in presenting an evaluation model for Canadian transplant and lung disease related studies. The description of health care utilization as well as the costing approach will provide an informative reference for future studies.

3. Objectives and hypotheses

The primary objective of this study is to determine from a health care system perspective the cost-effectiveness and cost-utility of lung transplantation. Also, to determine the clinical effectiveness of lung transplantation with respect to survival by disease group; the health related quality of life and; utility.

The study hypothesis is that:

- The cost-utility analysis will show a higher contrast then the cost-effectiveness analysis because lung transplantation increases survival and improves HRQOL.

That is:

a. Lung transplantation will be more effective than standard therapy for end-stage lung disease. It will lead to a longer survival rate as compared to those who are eligible for transplant, but have not yet undergone the procedure.
b. Lung transplantation will also improve HRQOL and utility.
c. The direct costs associated with lung transplantation and follow-up care will be higher, in transplant recipients, than the direct costs associated with standard treatment for end-stage pulmonary disease patients.

4.0 Methods

4.1 General description of study design

A historical and concurrent cohort study was undertaken in order to study the clinical effectiveness, HRQOL and economic impact of lung transplants. The economic evaluation of lung transplantation was carried out using an incremental cost-effectiveness and cost utility analysis. Clinical and cost data were ascertained in part retrospectively and prospectively. Data pertaining to HRQOL were captured cross-sectionally as well as longitudinally.

The clinical and economic effect of lung transplantation was ascertained by comparing events observed after transplantation with events prior to this time point. This defines three natural time periods of study: pre-transplantation, transplantation and post-transplantation. The treatment comparator thus becomes events observed in the pre-transplant phase where eligible patients await lung transplantation. The reference cost is the cost spent for normal care of patients on the waiting list.

4.2 Definition of the population

The study population consists of patients, aged 18 years and over, with end-stage pulmonary disease that have been enlisted on the Quebec transplant waiting list as candidates for lung transplantation.

To enter the study, cohort members had to be listed, for the first time, as active potential recipients for a lung transplant as of January 1st, 1997. Before 1997, lung

transplants were carried out at the Montreal General Hospital and it was not possible to validly define the cohort and ascertain complete clinical information prior to this date. On January 1st, 1997 the lung transplant program in Montreal was moved to the Hôpital Notre-Dame. Since then, there was a standardization of the lung transplant program's eligibility criteria for admission, clinical follow-up and uniformity of the transplant team (see Appendix A, section A1 for full description).

The closing date for entry into the cohort was May 31st, 2001 and the cohort was subsequently followed for an additional time period until October 28th, 2001. This cohort consisted of an open population where members were gained as they were enlisted on the Quebec lung transplant list. If candidates, members on the waiting list, were removed from the list, they were censored from the study at the date of inactivation. If reactivation occurred, member re-entered the study and time experience was accrued from that time point. A member was followed until the study end date or until death; once transplanted, a cohort member only left the population if death occurred.

In order to carry through the cost-effectiveness analysis, cost estimates and data on clinical effectiveness were collected retrospectively (all information from January 1st, 1997 to October 18th, 2000) and prospectively (from October 19th, 2000 to October 28th, 2001) throughout the study period by reviewing medical charts and interviewing patients. The time line is presented in figure 1.

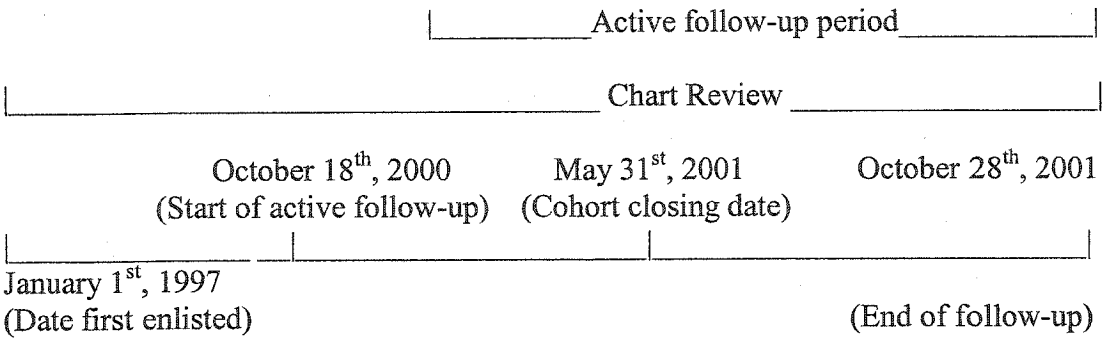

Figure 1. Time line for survival analysis

Health related quality of life and utility, a preference measure concerning health state, were assessed cross-sectionally and longitudinally. The cross-sectional design ascertained the outcomes in candidates and lung recipients at one point in time during an interview session. Transplant recipients were eligible to participate in the assessment of HRQOL if their transplantation had occurred between, January 1st, 1992 (instead of January 1st 1997) and October 28th, 2001. This permitted the estimation of HRQOL and utility for a longer post-transplant period of time exceeding the study period. The longitudinal data were ascertained from candidates who became lung recipients during the active follow-up period. This permitted the collection of pre and post-transplant HRQOL and utility data. Assessment of these measures commenced on October 18th, 2000 and proceeded until the end of follow-up.

4.3 Identification of cohort

The cohort was identified at the Hôpital Notre-Dame which houses the lung transplant program since 1997. The list of patients referred, candidates and lung

recipients was obtained from the lung transplant program. Information on this list for candidates and recipients included: the patient's name and surname, medical file number at the study center, the type of end-stage lung disease for which the transplant was indicated, the date of birth, date of acceptance and enlistment on the Quebec transplant waiting list, the date of transplantation (if any), the type of transplantation (single, double or heart-lung) if any, the date of death if the patient was deceased, the patient's phone number and address. A patient flow chart of the lung transplant program during the study period is presented in figure 2.

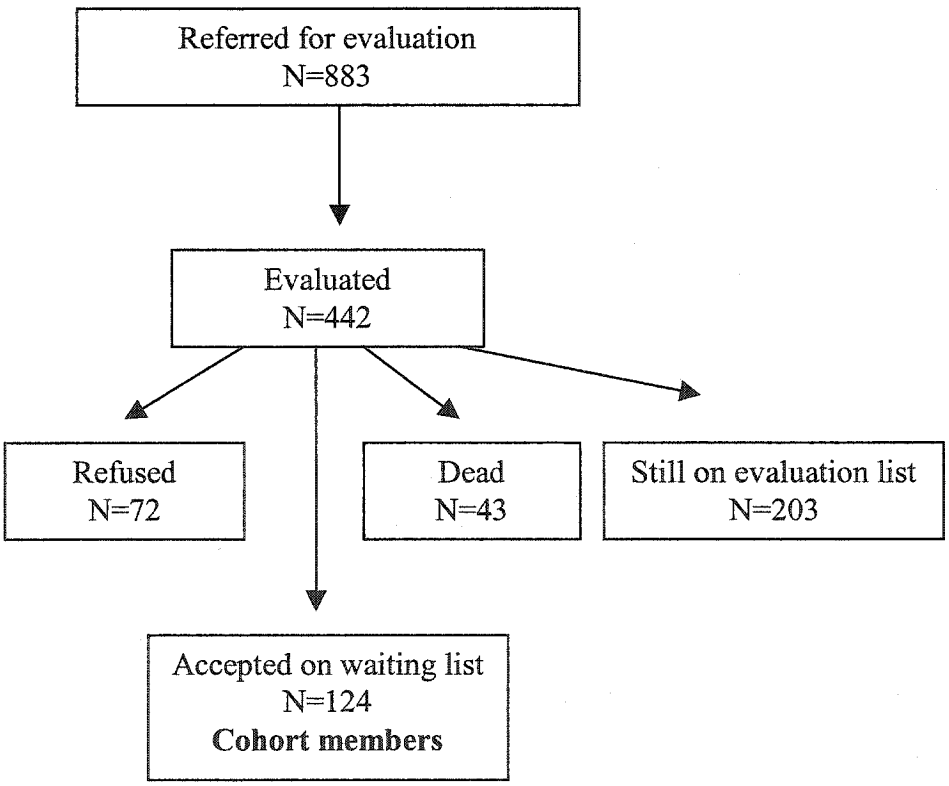

Figure2. Patient flow chart of the Montreal lung transplant program

4.4 Recruitment and follow-up of study patients

4.4.1 Recruitment

Patients in this study were approached and recruited at the lung transplant clinic during their follow-up visits. The protocol of follow-up care at the study center is described in more detail in Appendix A, section A2. Once the patient agreed to learn more about the study, the interviewer explained the goals of the study as described in the informed consent form in the language of their choice (Appendix H, section H1, English version presented). Those who wished to participate and signed the consent form were then entered into the study. Those who declined to participate were not contacted further. Their age, sex, transplant status and lung disease were recorded.

Patients who were not met during these follow-up visits (because they had moved to another province, or had been transplanted for over a year and follow-up visits at the study center were not frequent) were contacted via mail by the lung transplant program. The mailed package they received included: a personally addressed cover letter introducing the study, the informed consent form, a health related quality of life questionnaire (version 2 of the SF-36), and a pre-addressed and stamped return envelope. Recipients were also informed that a follow-up telephone call would be made in order to obtain some additional information relating to their health state and health care utilization. Patients who returned a signed consent form and filled out the questionnaire were included in the study.

4.4.2 Patient follow-up

Patients that were on the waiting list and those who had already been transplanted at time of initial contact were interviewed once during the study period. Waiting list candidates were also followed to determine whether they would become lung transplant recipients during the active follow-up period. Newly transplanted patients were interviewed within a minimum of one month following their release from the hospital and then interviewed approximately every 3 months during one of their follow-up visits.

The interview consisted of questions concerning health care utilization patterns, employment status, medical insurance, financial assistance and any patient borne costs (for questionnaire see Appendix H, section H2). Following this questionnaire, patients were then given the SF-36, a health related quality of life measure, which they filled out on their own. Utility was also measured during the same sitting.

For participants contacted by mail, a telephone call was placed and the same questions were elicited. The utility score was then obtained by telephone.

4.5 Clinical outcomes

The main outcome of interest in this study is the clinical effectiveness of lung transplantation in terms of its potential survival gain and associated health related quality of life and utility.

4.5.1 Main clinical outcome: death

4.5.1.1 Assessment of death

Assessment of death was obtained from the patient's medical file and through contact with the lung transplant follow-up program. The study center (Hôpital Notre-Dame), being affiliated to the Centre Hospitalier de l'Université de Montréal (CHUM), made it possible to review medical files at other hospitals also affiliated to the university. These hospitals were St-Luc and Hôtel-Dieu de Montréal, which houses the adult cystic fibrosis clinic in Montreal. When a patient died outside the CHUM, the date of death and a summary report was obtained, from the health care facility, as to the deceased patient's in-hospital stay.

4.5.1.2 Number of survival years

Survival was measured in mean life years. Survival after transplantation was compared to the survival observed without transplantation, which was estimated from observations during the waiting list. This approach however underestimates the survival experience without transplantation due to the fact that patients are censored from the waiting list because of the transplant procedure. This bias was dealt with by presenting sensitivity analyses that simulated different person-time experiences, than the one observed, for the non-transplant phase (for more details, see section 4.9.3.3).

4.5.2 Secondary clinical outcomes

Hospitalizations were assessed for patients on the waiting list and for lung transplant recipients. Hospitalizations related to respiratory exacerbations and

infections add to the burden of disease during the non-transplant phase, as do those associated to rejection and infection during the post-transplant period.

4.5.2.1 Definition of a hospitalization

A hospitalization was defined as having been admitted as an inpatient at a health care facility, irrespective of the length of stay. All hospitalizations were defined and categorized according to the information provided on the hospital summary sheet. All information and diagnoses were taken into account. The primary diagnosis as noted was kept and further validated with the treatment provided and types of special exams as described on the sheet. Hospitalizations due to an infection and or rejection were defined as: the presence of microorganisms in microbiologic data and from pathology evidence from biopsy. Appendix A describes the protocol for identifying the presence of an infection and rejection (section A2.3). When no descriptive information was available on the summary sheet, the ICD-9 codes available were reviewed for their description and discussed with the head of the lung transplant clinic (Dr Charles Poirier) for validation.

In the pre-transplant phase, hospitalizations were grouped into three categories: (i) infection and or respiratory exacerbation, (ii) hospitalization due to preventive treatments (antibiotic, antiparasitic and antiviral, therapy), (iii) all other hospitalizations.

In the post-transplant phase, hospitalizations were grouped into 6 categories: (i) infection (bacterial, parasitic, fungal, CMV, Zona-viral, or other); (ii) acute rejection (noting proportion also having an infection concomitantly); (iii) obliterative bronchiolitis (noting proportion also having an infection concomitantly); (iv) complications due to treatment; (v) 1-day surgery (bronchoscopy and/or stent placement, other endoscopic procedures); (vi) all other.

The fourth category, complication due to treatment, includes all hospitalizations that had as a diagnosis an effect that was secondary either to a procedure or to a medication.

4.5.2.2 Identifying a hospitalization

A hospitalization was noted on every occasion that there was mention of one, irrespective of the presence of a hospital summary sheet in the patient's medical file. When a hospitalization did not occur at the study center, the patient's medical file at the other affiliated hospitals were reviewed. For hospitalizations occurring outside the CHUM, the cause and the length of stay was retained.

4.5.3 Health Related Quality of Life (HRQOL) outcome measures

4.5.3.1 Definition of HRQOL

HRQOL evaluates quality of life, as defined by the WHO (p. 43), within the health and patient care context.

4.5.3.2 HRQOL assessment

The HRQOL outcome was assessed using the short form version (SF-36) of the Medical Outcomes Study survey (Ware et al., 1993). The SF-36 is a validated 36-item questionnaire assessing eight HRQOL domains: (i) physical functioning, (ii) role physical (role limitations due to physical health problems), (iii) bodily pain, (iv) general health, (v) vitality, (vi) social functioning, (vii) role emotional (role limitations due to emotional problems), and (viii) mental health (psychological well-being and distress).

The SF-36 has been shown to have a good reproducibility. Internal consistency was reported with a Cronbach's alpha of 0.80 to 0.90 in all the health concepts with the exception of the social functioning dimension, which was attributed an alpha of 0.67 (McHorney et al., 1994). Construct validity, assessed by McHorney and colleagues (1993) supported earlier findings, which suggested that the SF-36 could discriminate between different severity health states (Brazier et al., 1992; Jenkinson et al., 1994).

4.5.3.3 Transformation of SF-36 scores

Each health concept has a score, which was transformed to range from 0 to 100, where a higher score is indicative of a better quality of life.

Raw scores obtained with the SF-36 version 2, were transformed to a 0-100 scale following the SF-36 Health Survey manual and interpretation guidelines.

$$\text{Transformed Scale} = \frac{[(\text{Actual raw score} - \text{lowest possible raw score})]}{[\text{Highest} - \text{lowest possible raw score}]}$$

No other manipulation of the data was needed. There was no missing data on any of the questionnaires.

4.5.4 Utility

Utility represents the preference or desire for a health state. It is measured on a scale of 0.0 (indifferent between life and death) to 1.0 (perfect health), that is, the more preferable a health state is, the higher the utility score.

4.5.4.1 Assessment of utility

In the following section the methods as to utility assessment will be described as suggested by Stalmeier and colleagues (2001) (Additional interview methods are presented in section 4.4).

Utility was assessed using the standard gamble, a preference measurement instrument. Intra-rater reliability has been estimated at 0.77 and test-retest reliability at 1 week or less has been estimated at 0.80 (Froberg et al., 1989). Patients are asked to imagine a situation in which they must choose between two health states. To

remain in their current impaired health state or, to go through a procedure, which would restore them to perfect health. This procedure carries a specified risk of death. The probability of death is varied until the patient reaches the point of indecision, that is finding either approach equally appealing, and that value is turned into a utility score which ranges from 0 to1.

During the interview, the standard gamble was supplemented with the use of a probability wheel. The wheel was an adjustable disk with two sectors, each of two different colors, which could be adjusted for the size of the two to be readily changed (Torrance 1976a; Furlong et al., 1990). The subject was asked to consider two choices, and to tell the interviewer which one they would prefer: choice 1, choice 2 or that both choices seemed equally appealing and that they were indifferent between the two (they could not chose choice 1 over 2 or vice versa). The interviewer proceeded as follows in a narrative format:

"Choice 1 is that you would remain in your current overall health state for the rest of your life.

In Choice 2 we will suppose that there is a pill that would restore you to perfect health (as perfect for someone of your age), however, this intervention also has an immediate risk of death. In choice 2, as depicted on the probability wheel you will get either 2A or 2B.

Let's suppose that the chance of having perfect health after this intervention is 50% and that the risk of death is also 50 %. Which do you prefer choice 1, to remain in

your current health state for the rest of your life, choice 2 to undergo the intervention OR do both choices seem equally appealing or the same to you (You can't decide.)."

The utility value retained followed the example as depicted by Drummond and colleagues (p.199). Depending on the subject's answer the probability in choice 2 was varied. If subject accepted a 50% risk of death then the probability wheel increased to a 60% chance of death. If patient accepted this risk of death then the wheel showed an increased chance of death, in increments of 10%, until the subject switched his choice on two adjacent questions or was indifferent at that point. For instance if patient accepted a 60% chance of death but not a 70% chance of death (i.e. chose to remain in current health state) the utility was taken to be halfway i.e. 1 - 0.65 = 0.35. If patient did not accept a 50% chance of death (i.e. preferred to stay in ones current health state) then the probability wheel showed a 40% chance of death and so forth in decrements of 10% until the subject switched his choice on two adjacent questions or was indifferent at that point. If patient did not accept a 20% but accepted a 10% chance of death then the indifference point was then taken to be halfway i.e. 1 - 0.15 = 0.85. If the participant expressed indifference at a question, then it was at that point that utility was taken. For instance, if patient was indifferent when presented with a 40% chance of death, the utility was taken to be 1 - 0.40 = 0.60.

4.5.4.2 Patient preferences

In this study utility for the pre and post-transplant health state were elicited from patients as opposed to the general public. On ongoing debate exists among experts regarding whose utilities should be measured. Many have argued that disutility of a health state should be measured from patients with the illness (Nord, 1992; Nord et al., 1999; Ubel et al., 2000). Ubel and colleagues (2000) state: "the general public does not necessarily know what it is like to experience the specific illnesses being evaluated in C/E analyses, whereas patients actually experience the illnesses in question. By measuring patients' assessments of their own health related utility, we are sure to capture the values of people who know what the illnesses encompass". Second, when utilities are elicited from the general public the health states under study have to be described. The description of the health state will always be incomplete and therefore may bias the results (Llewellyn-Thomas et al., 1984; Ubel et al., 2000). Third, the public may be biased against people with disabilities or illnesses or who are older and this may be reflected in their estimates of utility (Hadorn, 1992; Busschbach et al., 1993; Rodriguez et al., 2000). Neuberger and colleagues (1998) in assessing priorities for allocation of donor liver grafts showed that the views of the public are at variance with those of clinicians. Ratcliffe (2000), in her study of public preferences for the allocation of donor liver grafts for transplantation, showed that respondents would sacrifice some gain in efficiency of the transplantation program for an increase in equity or fairness in the allocation process. Respondents usually give preference to programs that support the fair innings approach (Williams, 1997).

Given these issues and the fact that lung transplantation involves numerous health stages as well as a rigid medical follow-up care that is difficult to describe to the general public we elicited utilities from patients in our study.

In order to account for any potential differences in utility estimation of the pre and post transplant health state and the QALY gained we varied the pre-transplant utility in our sensitivity analyses. We chose a waiting time utility of 0.30 as published by Anyanwu and colleagues (20001).

4.5.5 Effectiveness

4.5.5.1 Quality adjusted life years

One of the advantages in obtaining the health utility of a health state is that it can be used to compute quality adjusted life years (QALYs). A QALY takes into account both the quality (reduced morbidity) and quantity (reduced mortality) that may or may not be gained from an intervention and combines these two into one health outcome measure (Drummond et al., 1997). The QALY is calculated by multiplying the years of life of a patient by the utility obtained for that health state. For instance, if a patient with emphysema lives for 2 years after being transplanted and the health utility obtained is 0.6 for that period, then the QALY for lung transplantation in this particular case is 2 x 0.6 = 1.2 QALYs. As seen, a QALY summarizes into one measure the quantitative and qualitative effects of an intervention. This can be of particular interest when comparing different interventions that have different effects on survival and quality of life.

4.5.5.2 Calculating quality adjusted life years

The utility associated with the waiting list experience was taken to be constant throughout this period. The waiting period is rather short (9 months on average) and regression analyses showed no significant effect of time on the magnitude or direction of this outcome.

The average utility assigned to the post-transplant period is presented in 1-year increments. The analysis on utility was carried out with the full quality of life cohort i.e. deceased patients were also included and contributed a utility of 0. Subgroup analyses were also carried out for the OAD, CF and Bronchiectasis disease groups. There was not enough information to accurately estimate utility in the pulmonary vascular and restrictive disease groups. A sensitivity analysis was carried out in order to determine the influence of varying utility during the waiting list on the potential QALYs gained.

QALYs were calculated for the waiting list period and the post-transplant phase as described in Drummond, p.178. For instance, the QALY for a follow-up of 12 months, assuming that the baseline utility is 0.6 and becomes 0.7 in the first 6 months and, 0.8 in the following 6 months, totals:

QALY = [1/2 (0.6+0.7)*6months + 1/2 (0.7+0.8)*6months]/12 months = 0.7 QALY

4.6 Economic outcomes

In the following sections we describe costs (4.6.1), the different types of health resource use studied in each period of time (section 4.6.2) and how the resources were valued (4.6.3).

4.6.1 Description of costs

Costs have been categorized (Luce and Elixhauser, 1990) and are summarized as follows:

(i) *Direct medical costs*: These costs are associated with all treatments and health care utilization pertaining to the disease

(ii) *Direct non-medical costs*: These costs pertain to financial resources that are incurred by the patients. These include transportation and sleeping accommodations while seeking medical care, any housing modifications to accommodate the patient's health status, and any paid help required due to physical limitations imposed by the disease.

(iii) *Indirect costs*: These costs are related to the time spent by the patient while seeking medical care, time spent by family members attending to the patient. Also, the change in employment productivity may also be included in this category.

4.6.2 Description and measurement of health resource use

Health care resources used were accounted for and measured from information obtained in each patient's medical file and through patient interview. Information

captured included all diagnostic testing, procedures undertaken on patient and medical care received (for a sample of some report forms used in data collection see Appendix H, section H3).

A detailed description, measurement, source of data and unit value for each of the economic resources, included in this study, is presented in Appendix B and follows the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) guidelines for costing (1996).

We separated the costs generated during three specific time periods: waiting list period, transplant procedure and costs following the procedure.

4.6.2.1 Resource use during waiting list period

Direct medical costs observed and accounted for in the waiting list were associated to the following health care resources and those used (see Appendix B sections for detailed list and description of calculation methods):

- during a hospitalization (section B3.1, B3.2, B3.3)
- during a one-day surgery or endoscopy (sections B2.1, B2.2 & B2.3)
- during an emergency room visit (section B2.4)
- during an ambulatory care visit (section B2.5)
- during an outpatient follow-up visit (sections B2.6 & B2.7)
- during a home care visit by a nurse or inhalation therapist (section B4)
- for outpatient medications (section B5.2)

- for home oxygen therapy (section B7)
- physician fees (section B6)

Direct non-medical and indirect costs were also valued, however, they were presented separately.

Direct non-medical costs accounted for included use of:

- transportation to and from medical care (section B8.1)
- ambulance (section B8.1)
- sleeping accommodations (B8.2)

Indirect costs accounted for:

- time spent by patients and family members seeking medical services (section B9)

4.6.2.1.1 Resource use during waiting list induced by transplant program

During the waiting list period there were costs induced by the transplant program. These costs included the resources used during the evaluation process of eligible patients and the operating costs of the lung transplant program. Although these costs were incurred before transplantation they were included in the costs belonging to transplantation.

4.6.2.2 Resource use during transplantation

Direct medical costs observed and accounted for transplantation were associated to the following health care resources and those used (see Appendix B sections for detailed description of calculation methods):

- Quebec transplant program: donor organ acquisition and harvesting (section B1)
- during the hospitalization for the transplant procedure (section B3.4, B3.5)
- physician fees (section B6)

No indirect costs were attributed to this section. Family members and friends were able to come and visit during the off working hours (section B9).

4.6.2.3 Resource use during post-transplant period

Direct medical costs observed and accounted for in the post-transplant phase were contributed by the following health care resources and those used (see Appendix B sections for detailed list and description of calculation methods):

- during a hospitalization for a rejection and infection (section B3.4)
- during a hospitalization for other reasons (section B3.2 & B3.3)
- during a one-day surgery or endoscopy (sections B2.1, B2.2 & B2.3)
- during an emergency room visit (section B2.4)
- during an ambulatory care visit (section B2.5)
- during an outpatient follow-up visit (sections B2.6 & B2.7)
- during a home care visit by a nurse or inhalation therapist (section B4)

- for outpatient medications (section B5.1)
- physician fees (section B6)

The direct non-medical and indirect costs were of the same nature as mentioned previously during the waiting list period (section 4.6.2.1).

4.6.3 Valuation of health resource use

The resource valuation was based on national and provincial cost data and is presented for each health care resource use in Appendix B. Costing was based on information from the Ontario Case Cost Project (OCCP) and the Ministère de la Santé et Services Sociaux in Québec (MSSS). Physician fees for consults and diagnostic acts as well as medication costs were obtained form the Régie de l'Assurance Maladie du Québec (RAMQ).

4.6.3.1 Valuation of hospitalizations and resource use based on the OCCP

The OCCP's goal is to apportion total hospital costs to each patient visit based on the health care resources utilized during the visit. This case costing method follows the Canadian Institute for Health Information's (CIHI) Management Information Systems (MIS) Guidelines. These guidelines provide the steps to standardize the collection and reporting of data, which allows for the comparison of costs across hospitals. These guidelines provide an improved method for measuring resources and activities by integrating financial, statistical and clinical databases. The Institute of

Health Economics (IHE, 1997/1998) proposes the use of this information, when carrying out a cost-list, due to the high quality of the data.

Given this information, we decided to use cost data from the University Health Network (UHN), which is part of the OCCP and holds the Toronto lung transplant program. The cost estimate attributed to the transplant hospitalization, hospitalizations due to post-transplant infection and rejection as well as, diagnostic and laboratory resources used, were obtained from the UHN.

4.6.3.2 Identification and valuation of lung transplant related hospitalizations in the UHN

The UHN contained information on all lung transplant patients whose procedure was carried out between 1997 and 2001. Patients who were less than 18 years of age and patients whose diagnosis of end-stage lung disease was not clear were removed from the analyses. A total of 135 lung transplant recipients were studied. The database contained all resources utilized and diagnostic procedures carried out during the hospitalizations for the transplant procedure, as well as post-transplant hospitalizations, and a breakdown of costs for each resource utilized. The reason for admission was captured by clinical data describing up to 10 clinical diagnoses, coded in ascending order for the primary, secondary, tertiary (etc...) diagnosis.

The diagnoses were coded according to the International Classification of Disease version 9 (ICD-9) coding scheme, which permitted to identify hospitalizations due to infections (any type: bacterial, viral, CMV, etc...), and rejections. Hospitalizations

due to a rejection were identified according to the following ICD-9 codes: 996.84 defined as complications of transplanted lung; E878.0 defined as surgical operation and other surgical procedures as the cause of abnormal reaction of patient, or of later complication, without mention of misadventure during operation and this as first or second in the sequence of diagnoses. Bronchiolitis obliterans was identified with codes 996.84 as first, E878.0 as second or third diagnosis and 491.8 as second or third diagnosis and 516.8 if bronchiolitis obliterans organizing pneumonia was present. The treatment of rejection, during the hospitalization, was also validated with the presence of medications specific to this treatment, such as solumedrol or solu-cortef.

The valuation of lung transplant related hospitalizations were based on cost data provided by the UHN for each resource utilized during the hospitalization (for more details as to the type of resources valorized see Appendix B, section B3.4)

4.6.3.3 Valorisation of hospitalizations with the "Niveau D'Intensité Relatif des Ressources Utilisées" (NIRRU)

The Quebec ministry of health and social services has developed a database, which provides information on the amount of health resource utilized during an inpatient stay for a specific all patient refined diagnosis related-group (APR-DRG). The health resources utilized, during the hospitalization, are summarized in an index whose value is based on the primary and secondary diagnoses, disease severity and co-morbidity, whether there is a death during the hospitalization and a prolonged length of stay. This index of resource use is called the Niveau D'Intensité Relatif des

Ressources Utilisées (NIRRU). In 2000-2001, the value of 1 NIRRU unit was $3,448.52.

4.6.3.3.1 Valuation of lung transplantation based on NIRRU

The average cost of a lung transplant based on the NIRRU index attributed for procedures carried out during the 2000-2001 period was also estimated for the validation of cost estimates (for more details see Appendix B, section B3.5).

4.6.3.3.2 Valuation of hospitalizations based on NIRRU

When we could not obtain complete information on costs associated with specific resource use, we decided to use data from the MSSS. Cost related to pre-transplant hospitalizations and those described as other in the post-transplant phase (section 4.5.2.1) were based on the NIRRU (2001). One-day surgery related costs were based on data from the annual financial AS471 report of the CHUM (MSSS, 2001).

4.6.4 Converting Ontario costs to Quebec costs

A correction factor was taken into account in order to estimate the cost of resources in Quebec from costs obtained in Ontario. The correction factor was obtained from data published by Statistics Canada, for both provinces, on the total operating expenses per total patient day in teaching hospitals. The correction rate was calculated by taking the ratio of the average Quebec to the average Ontario total operating cost. The rate obtained was 58.2% (Appendix C).

4.6.5 Differential time for costing in past years

When costs were reported in years prior to 2001, changes in the consumer price index were used to adjust for the different year sources of data. Statistics Canada reports specific indexes for health care. The components included in this group were health care goods, medicines and pharmaceutical products, medicines prescribed, non-prescribed medicines, health care services, eye care and dental care. Table 6 depicts the average annual consumer price index for health care in Canada, and the percent variation with respect to each year.

Table 6. Percent variation in consumer price index for health care

Year	Consumer Price Index	Percent variation between years
1997	107.4	...
1998	109.8	2.2
1999	112.3	2.3
2000	114.8	2.2
2001	117.9	2.7

Statistics Canada, 2002

4.6.6 Presentation of costs

Resources utilized for each category were identified and costs were presented as an average cost per patient alive at the beginning of each period studied (table 10, section 5.1). Patients contributed information to each period as long as they were present at the beginning of the period. Once they died, they no longer contributed information to the following time periods. The identification of resources followed the CCOHTA (1996) suggested format.

4.7 Other study variables

4.7.1 Predictors of mortality

Other variables studied, as potential risk factors for mortality, were: age enlisted on the waiting list (years); sex (female / male), type of end-stage lung disease: OAD, CF and Bronchiectasis, restrictive disease and PVD, type of transplant enlisted for (double / single). Additional variables studied, in lung recipients alone, included: age at transplantation (years), time accrued on the Quebec transplant waiting list (months), hospital length of stay for transplantation (days), donor sex (female / male), donor age (years), donor and recipient CMV (positive / negative), ischemic time of organ (minutes), presence of rejection during the hospitalization for the transplant (yes / no), number of rejections during the post-transplant period and number of hospitalizations due to infection and or rejection, diagnosis of OB (yes/no) (Appendix A, sections, A2.3.1 & A2.3.2).

4.7.2 Predictors of HRQOL and utility

The SF-36 assesses the physical role, emotional role, bodily pain, social functioning, vitality and mental health domains with respect to the last four weeks at time of completion of the questionnaire. It was therefore important to include any clinical events that occurred during those 4 weeks, since they may impact these outcomes. Variables studied, besides status (recipient / candidate) at interview, were: age at interview (years); sex (female / male); time since transplantation (months); type of transplant received (single, double or heart-lung); disease diagnosis: OAD, CF & bronchiectasis, restrictive and PVD; FEV_1 (forced expiratory volume in one

second) % predicted, at time of interview; hospitalized in the past month (yes / no); inpatient LOS (days); presence of infection in the past month (yes / no).

For predicting utility, an additional variable, the reported health transition question, on the SF-36, was studied. This variable measured to what extent the patient evaluated, in general, his or her present health state as opposed to one year ago. This variable was represented in an ordinal fashion and scores ranged from 1 (much worse) to 5 (much better). This factor was studied in order to take into consideration the perception of one's baseline health status and whether this influenced a patient's response.

4.7.3 Predictors of cost of transplantation

In this study, potential predictors of the cost of transplantation studied included age at transplantation (years), sex (female / male), type of disease (OAD, CF & bronchiectasis, restrictive and PVD), length of stay (days) and whether hospitalization ended with a death (yes / no).

4.8 Source of information for different time periods and resources

The main sources of information used in this study are the following:

Table 7. Summary sources of information

Measures	Waiting list	Transplant	Post-transplant
All clinical data	Patient medical file	Patient medical file	Patient medical file
Donor information	-	Quebec Transplant	-
Health care resource use	Patient medical file	Patient medical file	Patient medical file
Medication	Patient medical file Drug Database	Patient medical file Drug Database	Patient medical file Drug Database
Health related quality of life	Interview	-	Interview
Utility	Interview	-	Interview
Home oxygen therapy Medical devices	Patient medical file & Interview	-	Patient medical file & Interview
Non-medical costs	Patient medical file & Interview	-	Patient medical file & Interview
Indirect cost	Patient medical file & Interview	-	Patient medical file & Interview

4.9 Statistical analysis

4.9.1 Descriptive analysis

Descriptive statistics were presented for cohort characteristics in the pre and post-transplant phase. Clinical events, such as the number of deaths and hospitalizations namely due to infection, rejection and other reasons, were described for the pre-transplant period as well as for the post-transplant period in 6 month increments (0-6, >6-12, >12-18, >18-24, >24-30, >30-36, >36-42 and >42 months). Survival was described for the waiting list as well as for the first month, second to third month, and beyond the third month post-transplant period. Descriptive statistics were also presented for cost during the waiting list, transplant, and post-transplant period. Post-

transplant average costs were described and presented for the 6-month post-transplant interval periods.

HRQOL and utility were described for candidates and recipients respectively. In addition, recipient scores were described with respect to time since transplantation (year one, two, three, four and, five and beyond). Post-transplant scores obtained from patients initially interviewed as candidates, who subsequently became recipients, were presented for two time periods, within 4 months and beyond the post four-month period.

Comparison of means and categorical data was carried using a t-test and X^2, respectively. All estimates were presented with their 95% confidence interval (CI). A statistical significance of p less than 0.05 was chosen.

4.9.2 Statistical modeling

4.9.2.1 Survival analysis

The effect of transplantation on survival was studied using a Cox regression model with transplantation as a time-dependent covariate. The hazard associated with transplantation is compared to the one observed during the waiting list period. That is, transplantation (exposure) is compared to the time experience without transplantation, which corresponds to the waiting list time (unexposed).

More specifically, hazard ratios, for the full cohort, were studied for 4 time periods: (i) the waiting list, (ii) the first 30 days following transplantation, (iii) > 30 to 91 days and, (iv) > 91 days post-transplantation. These post-transplant time periods were defined and studied in order to take into consideration the high post-operative clinical risk associated with any surgery. We assumed that there was an immediate 30-day high risk of death followed by a decline. The second period was studied to coincide with the early post-operative risk of death and the third (>91 days) with the late post-operative clinical period, where it was assumed that the risk was constant. Such an analysis accounted for the time at risk contributed by the individual while they were under observation and did not assume that the effect of transplantation on survival, as described by the hazard ratio, was constant over the time periods.

In all these analyses, the person-time for the reference period started to be accrued at entry unto the waiting list. Patient follow-up was carried out until the end of the study or until death. For those who had died during the study period, the date as noted on the death certificate was retained as the end date. For those who had survived until the end of the study, October 28th, 2001 was retained as the end date.

Risk factor assessment was also carried out. Apart from studying the crude hazard rates associated with transplantation, age accepted into the waiting list, sex (female/male), type of lung disease (OAD, CF& bronchiectasis, restrictive, PVD) and type of transplant enlisted for, were studied and included in the model. Interaction terms studied were: (i) age put on waiting list and sex, (ii) sex and type of transplant

enlisted for, (iii) sex and type of lung disease and, (iv) sex and post-transplant time period.

4.9.2.1.1 Determining potential risk factors for mortality in transplant recipients

Potential important predictors of mortality in recipients were analyzed using a Cox regression model. Potential significant interaction terms studied were: (i) ischemia time and recipients age at transplantation, (ii) ischemia time and donor age, (iii) donor age and recipients age at transplantation, (iv) donor age and donor sex, (v) recipient age and sex, (vi) recipient sex and waiting list time, (vii) recipient sex and type of transplant, (viii) recipient sex and donor's sex, (ix) recipient CMV status and donor's CMV status, (x) OB and sex, (xi) OB and recipient age, (xii) rejection during hospitalization and recipient age, (xiii) rejection during hospitalization and sex.

An additional analysis was carried out studying the effect of developing bronchiolitis obliterans syndrome on survival. This variable was studied as a time-dependant covariate, for three specific time periods: first, second and third year post-transplantation. Crude mortality rate ratios were presented.

4.9.2.1.2 Survival analysis restricted to specific disease groups

Additional survival analyses, restricted to disease group, were carried out. The first restricted survival model was for the obstructive airways disease group. The second restricted survival model was carried out for the cystic fibrosis and bronchiectasis disease group. These two disease categories were combined because

of the similar disease process. The third survival model was for the restrictive lung disease group, which included the pulmonary fibrosis and sarcoidosis patients. Due to the small sample size, no analysis was presented for the pulmonary vascular disease group (n = 4). The variables adjusted for and included in the models were: age accepted into the waiting list, sex, type of transplant enlisted for and the number of hospitalizations patient had during the waiting list period.

4.9.2.2 Modeling HRQOL and utility

4.9.2.2.1 Cross-sectional analysis of the eight health domains of the SF-36

The cross-sectional analysis consisted of comparing transplant recipients versus candidates at one point in time. Each of the eight health domains, general health, physical functioning, physical role, bodily pain, vitality, social functioning, emotional role and, mental health were analyzed, using a multiple linear regression model, in order to ascertain whether transplant status, as well as potential predictive factors could explain them.

The variables assessed and included in the original model were: status, age at interview, sex, time since transplantation, FEV_1 (% predicted), type of transplant received, type of lung disease, whether hospitalized in the past month, number of days in hospital, and the presence of an infection and rejection in the past month. Final predictive regression models, for each of the 8 health domains, were chosen using a backward elimination approach with a 0.10 level of significance to stay.

Testing the residuals of each of the eight outcomes suggested no major violations of the normality assumption

4.9.2.2.2 Longitudinal analysis of the change in HRQOL

In the longitudinal section of the analysis, the main interest was whether a difference, in the eight health related quality of life outcomes, would be observed after transplantation as opposed to the waiting list period and, whether this was maintained in the follow-up period. The three time periods studied were: waiting list, within 4 months of transplantation and beyond 4 months. The GENMOD procedure in SAS was used in this analysis and compared change in scores observed in the first and second period post-transplant with respect to the waiting list period. The interpretation of results was based on GEE parameter estimates. Secondary analyses were also carried out taking into consideration potential important predictors of HRQOL and utility with respect to the 2 different time periods. Within the 4 months post-transplantation, a multiple linear regression was carried out taking into account the potential effect of the baseline score reported by patients during the waiting list, age at interview, sex, FEV_1 (% predicted) at interview, time spent on waiting list, inpatient LOS (days) and whether a patient had an infection (yes/no) within a month of interview. Final predictive models, for each of the 8 health domains and utility, were chosen using a stepwise regression approach with a significance level of entry of 0.05 and a significance level to stay in the model of 0.10. Due to the small number of observations in the second time period, beyond the 4-month period, a simple linear

regression was carried out to determine potential predictors and correlates of HRQOL.

4.9.2.2.3 Analysis of utility

Utility as assessed by the standard gamble was also analyzed similarly as described in the previous section, cross-sectionally and longitudinally. The only exception being in the cross-sectional analysis, the reported health transition question, on the SF-36, was also included in the analysis.

In order to deal with death, an additional model was studied which included the 8 deceased patients (N=113). The utility assigned to them at the date of death was 0. Utility in this case was studied as a function of status, age at interview or death, sex, disease diagnosis, type of transplant enlisted for and time since transplantation. There were no major violations of the normality assumption after testing the residuals of utility with each independent variable. Final model was selected with the backward selection process using a 0.10 significance level to stay.

Potential predictors of utility in transplant recipients alone were also studied. The variables analyzed were age at interview, sex, type of transplant received, time since transplantation (months), time spent on waiting list (months), FEV_1 (% predicted) at interview, whether patient was hospitalized, had an infection or rejection in the past month, and more specifically ever had a rejection (Yes/No) and the score as reported for the health transition state. An additional analysis restricted to candidates waiting

on the list was also carried out. Potential predictors studied, of candidate reported utility, were age at interview, sex, type of disease, time spent on waiting list at interview (months), FEV_1 (% predicted) at interview, oxygen needed during the day (liters per minute), whether patient was hospitalized and had an infection within a month of interview.

A longitudinal analysis of the change in utility was also carried in the 13 newly transplanted patients. Again, 12 of the 13 contributed preference measures in the first 4 months post-transplantation and 8 beyond the 4-month period. One of these patients had died approximately one month post-transplantation. The utility assigned at time of death was 0. Missing values in the first four months was due to one prolonged patient hospitalization and, in the second period, one death (as mentioned), and four had not yet reached 4 months of transplantation. Final predictive models, for each of the periods studied, were chosen using a stepwise regression approach with a significance level of entry of 0.05 and a significance level to stay in the model of 0.10. Same predictive factors were included as in the HRQOL longitudinal study, mentioned above, however utility baseline scores were included here.

4.9.2.3 Analysis of the cost of transplantation

A multiple linear regression was carried out in order to determine the important cost drivers of the hospitalization due to the transplant procedure. Variables studied, included age at transplantation, sex, type of disease, length of stay and whether hospitalization ended with a death. An interaction term was also studied which

included length of stay and death. Costs were transformed in their natural logarithm when analyzed.

4.9.3 Economic evaluation

4.9.3.1 Study perspective

This economic study was carried out from a health care perspective. The costs considered under this perspective include direct medical costs. The patient perspective was also studied, however, the direct non-medical and indirect costs were presented separately.

4.9.3.2 Economic analysis

In the incremental cost-effectiveness and cost-utility study, we compared the costs related to screening, the transplant program, transplantation and post-operative associated events to those incurred once patients were accepted on the waiting list (a proxy for non-transplantation or usual care). These outcomes were ascertained for the full cohort and for specific disease groups (cystic fibrosis and bronchiectasis) where the clinical effectiveness was positive (i.e. rate ratios showed a protective effect).

4.9.3.2.1 Cost-effectiveness analysis

An incremental cost-effectiveness analysis produces an index that takes into account two elements: the cost of the intervention and comparator and the number of life years gained (LYG) from the intervention under study.

The incremental cost-effectiveness ratio of lung transplantation was computed as follows:

[Average cost (transplant group) – Average cost (waiting list group)]

÷

[Average LY (transplant group) – Average LY (waiting list group)]

The incremental ratio represents the difference between the costs associated with the lung transplant program and treatment of lung recipients and the costs of treatment associated with patients while waiting for a transplant, divided by the difference between the survival experience after and the one observed before transplantation.

4.9.3.2.2 Cost-utility analysis

An incremental cost-utility analysis produces an index that takes into account 3 elements: the cost of the intervention and comparator, the number of life years gained from the procedure, and the changes in quality of life. A ratio is obtained which combines the transplantation effects on survival and QOL in a single outcome called QALY (Quality Adjusted Life Years).

The incremental cost-utility ratio of lung transplantation was computed as follows:

[Average cost (transplant group) – Average cost (waiting list group)]

÷

[Average QALY (transplant group) – Average QALY (waiting list group)]

The incremental ratio represents the difference between the costs associated with the lung transplant program and treatment of lung recipients and the costs of treatment associated with patients while waiting for a transplant, divided by the difference between the QALY associated with lung transplantation and that while waiting.

4.9.3.3 Methodological issues regarding survival time estimates

The cohort studied reflects the dynamics of the Quebec lung transplant program with respect to: (i) health policies in patient selection and acceptance into the program, (ii) organ availability and donor selection criteria and, (iii) experience and success of the lung transplant team with the lung transplant procedure.

The survival time during the waiting list is artificial because it is influenced by the selection process and is also associated with censoring due to transplantation. Transplantation in turn depends on the number of available donors and the number of patients on the waiting list. The survival time in the post-transplant phase, although less biased, represents the lung transplant team experience in Montreal with the population treated in Quebec. These parameters may change in time with consequences on survival and clinical decision-making. Moreover, conducting the same study later would increase the post-transplant person-time by allowing survivors to provide more person-month of follow-up.

A sensitivity analysis was carried out to determine the degree of influence of varying survival during the waiting list and the post-transplant phase on the mean life years and QALYs gained. Eight additional survival times were studied therefore for the non-transplant experience: 12, 18, 24, 30, 36, 42, 48 and 60 months. An additional sensitivity analysis was carried out in order to study the effect of varying the success of the transplant team. The additional survival times studied for the post-transplant phase, assuming an increased success rate, was 2.75, 4 and 8 years.

4.9.3.4 Modeling cost-effectiveness and cost-utility beyond the study period

Buxton et al. (1997) have addressed the issue of modeling events and scenarios after the end of a study. Due to the short post-transplant follow-up in this study, we extrapolated the cost-effectiveness and cost-utility associated with lung transplantation based on the conditional half-life survival (6.5 years), for recipients surviving the first year, reported by the ISHLT (2002). Recipients that were alive at the end of the study were therefore attributed a 7.5 year survival.

Waiting list survival was modeled on estimates observed in the first year of our study cohort. A constant death rate was kept in the analysis. Candidates that were still alive on the waiting list at the end of the study were attributed the half-life survival observed for the full cohort (2.5 years).

Additional analyses were carried out to determine the degree of influence of varying survival during the waiting list and the post-transplant phase on the

incremental cost-effectiveness as well as cost-utility estimates associated with lung transplantation. Assuming a 10-year follow-up, non-transplant and post-transplant survival experiences studied were 1, 2, 3 and 5 years and 2, 4, 6 and 8 years, respectively.

Costs occurring beyond the study period during the non-transplant phase were based on monthly estimates observed for the full cohort. Cost-estimates during this period do not vary significantly from one month to the other. If a patient's health state worsens (increase in health care resource use) or improves (decrease in health care resource use) significantly they are removed from the cohort of eligible patients active on the waiting list. Attributing, therefore, a constant monthly cost throughout the non-transplant period is reasonable. Costs occurring beyond the fourth year of post-transplant follow-up were based on estimates observed in the third year of transplantation. This 3rd year estimate was used in order to take into account potential health care resource utilization patterns associated with an increasing incidence of infections and chronic rejections which plagues the success of long-term post-transplant survival.

4.9.3.5 Issue relating to overhead costs

In our study, overhead costs were included in the valuation of resource use. Although in the short-term overhead costs do not vary significantly, in the long run costs are variable. Programs servicing a larger population or programs added to hospitals may induce larger overhead costs (Drummond et al., 1997, pp.62-66). In

order to deal with this issue, 21.2% of costs, which represents the overhead to the total operating cost of the CHUM, were removed and, C/E and C/U ratios were also presented with overhead costs being omitted.

4.10 Discounting

The effects and costs were discounted at a rate of 5%. This discount rate was chosen because it represents the most conventional rate used and accepted (Weinstein & Stason 1977; Krahn et al., 1993; Drummond, 1997). Discounting was carried out while assuming that all costs were incurred at the end of each year with the exception of the costs incurred during the waiting list. It was assumed that these costs represented immediate costs incurred once patient entered the program. As part of a sensitivity analysis we also varied the discount rate to 3% as recommended by the Panel on Cost-effectiveness in Health and Medicine (Weinstein et al., 1996).

4.11 Issue of missing information

4.11.1 Losses of follow-up due to death

During the active study period, 8 patients died before they were contacted for participation in the study. These losses to follow-up due to death created missing information in the study of HRQOL and utility outcome measures. Various approaches were studied in order to deal with the potential selection bias that could influence the results. At the time of death, three of these patients were candidates and the remaining were recipients.

For the study of utility, as mentioned, these patients were included in the analysis and a score of 0 was retained. The missing information for the HRQOL outcome measures was more difficult to deal with. The question was what score should be attributed to each of the eight health domains for death without invalidating their psychometric properties. The dilemma consisted in whether to attribute a score of 0 or 100 to each of these outcome scales. For example, when one dies should a score of 0 or 100 be attributed to their score of bodily pain i.e. are they in a lot of pain or no pain when they die. Another example, for role emotional, does being dead decrease or increase limitations due to one's psychological state. Finally, after reviewing the literature, it was concluded that the transformations proposed by some authors (Diehr et al., 2001) on a group of veterans, were not based on a cohort similar to our study population. Furthermore, given the importance to study quality of life in patients who survive, the deceased patients were removed from the HRQOL outcomes analyses.

4.11.2 Other missing information

Due to the rigid follow-up of patients on the list (Appendix A, section A2.1), information as to hospitalizations and clinical events in candidates is probably very accurate. In three instances, there was mention of a hospitalization without a clear note of the length of stay. In these cases, all due to a respiratory exacerbation, a length of stay of 6 days was attributed to each in-patient stay.

4.12 Statistical package

The data was analyzed using the SAS statistical software version 8.0 (SAS Institute, Inc, Cary, NC, 1999-2001).

4.13 Ethical considerations

A copy of the protocol was submitted to the Ethics Committee of the Notre Dame Hospital and the study was approved (Appendix H, section H4). The recruitment of patients and chart review began as of the date of acceptance. Throughout the study, no data was identified to a specific patient and all information was kept in confidence.

5.0 Results

5.1 Cohort characteristics

Overall, 124 patients entered the Quebec transplant waiting list during the period between January 1st, 1997 and May 31st, 2001. Of those, 91 patients became lung transplant recipients and 33 remained on the waiting list (i.e. candidates) either because they had not yet found a donor by the end of the study (most recent candidates) or because they died while waiting. During the study period, 40 deaths were observed (32.3%). Twenty-four occurred among the 91 recipients (19.4%), and 16 among those on the waiting list (12.9%).

Characteristics of patients included in the survival analysis are presented in table 8. As seen, the bronchiectasis disease group spent, on average, the longest time in the study, that is, from waiting list until death or censoring due to the end of the study. The longest waiting list experience was observed in the pulmonary vascular disease (PVD) followed by the bronchiectasis group. Also, patients projected for a double lung spent a longer time on the waiting list as opposed to those being listed for a single lung transplant. Characteristically, cystic fibrosis patients were, on average, the youngest group and females also tended to be younger than males.

Table 8. Cohort characteristics

Total cohort (N = 124)	
Variables	**Mean ± S.D. (median)**
Age at entry into program (years)	46.46 ± 13.11 (50.70)
Time spent on waiting list (months)	8.79 ± 5.79 (7.87)
Total follow-up time in study (months)	20.25 ± 14.09 (17.48)
Number (Percentage)	
Gender	**Mean Age ± S.D.** [a]
Male: N = 55 (44.4%)	49.09 ± 10.91
Female: N = 69 (55.6%),	44.36 ± 14.37
Diagnosis group	**Mean Age ± S.D.**
Obstructive Airways Disease: N = 56 (45.2%)	53.63 ± 6.67
Cystic Fibrosis: N = 29 (23.4%)	27.26 ± 6.46
Bronchiectasis: N = 7 (5.7%)	47.47 ± 4.70
Restrictive diseases: N = 28 (22.6%)	51.54 ± 10.31
Pulmonary vascular diseases: N =4 (3%)	47.84 ± 8.60
	Mean ± S.D. (median)
Time spent on waiting list by disease group	(months)
Obstructive Airways Disease	9.13 ± 5.80 (8.72)
Cystic Fibrosis	9.15 ± 6.79 (7.16)
Bronchiectasis	10.08 ± 4.98 (8.11)
Restrictive diseases	6.33 ± 3.42 (7.39)
Pulmonary vascular diseases	16.27 ± 5.78 (14.55)
Time spent on waiting list by type of transplant enlisted for	**Mean ± S.D. (median)** [a]
Single lung: N = 68 (54.8%)	7.81 ± 4.01 (7.52)
Double lung: N = 56 (45.2%)	9.99 ± 7.26 (7.93)
	Mean ± S.D. (median)
Total follow-up time in study, by disease group	(months)
Obstructive Airways Disease	23.36 ± 14.19 (19.40)
Cystic Fibrosis	18.36 ± 12.46 (14.92)
Bronchiectasis	30.01 ± 13.41 (30.46)
Restrictive diseases	12.66 ± 12.37 (8.76)
Pulmonary vascular diseases	26.55 ± 15.27 (23.31)

[a] χ^2, t-test: significant difference, $p<0.05$

Recipient characteristics are presented in table 9. In our cohort, more than half of recipients had an obstructive airways disease (OAD) and were enlisted for a single lung transplant.

Table 9. Demographic characteristics of recipients

	Recipients (n=91)
Variables	**Mean ± S.D. (median)**
Age at entry into lung transplant program (years)	46.81 ± 13.44 (51.16)
Age at transplantation (years)	47.55 ± 13.37 (51.73)
Average follow-up in post-transplant period (months)	15.62 ± 12.65 (13.27)
	Number (Percentage)
Gender:	
Male	40 (44.0%)
Female	51 (56%)
Diagnosis group:	
Obstructive Airways Disease	49 (53.8%)
Cystic Fibrosis	19 (20.9%)
Bronchiectatic	6 (6.6%)
Restrictive diseases	14 (15.4%)
Pulmonary vascular diseases	3 (3.3%)
Type of transplant enlisted for	
Single lung	56 (61.5%)
Double lung	35 (38.5%)

A complete follow-up account of cohort members within each diagnosis group is presented in the following table (Table 10). The total person-months contributed by cohort members during the study period was 2511.5 person-months with the obstructive airways disease group contributing the highest person-months followed by the cystic fibrosis and bronchiectasis group and the restrictive and pulmonary vascular disease groups.

Table 10. Flow chart describing cohort progression throughout study period

	TOTAL COHORT	OAD	Cystic fibrosis & Bronchiectasis	Restrictive disease	PVD
Total N	124	56	36	28	4
Total person-months	2511.5	1308.2	742.5	354.6	106.2
Died while waiting on list	16	2	7	7	0
Censored	17	5	4	7	1
Person-months contributed to waiting list	1090.0	511.5	336.0	177.4	65.1
Transplant recipients	91	49	25	14	3
Person-months contributed by recipients	1421.5	796.7	406.5	177.2	41.10
Died in Post-Tx. period	24	12	2	9	1
0-6 months Total	91	49	25	14	3
Died	14	6	2	5	1
Censored	10	4	4	2	0
Person-months	459.2				
>6-12 months Total	67	39	19	7	2
Died	3	3	0	0	0
Censored	15	11	3	1	0
Person-months	348.3				
>12-18 months Total	49	25	16	6	2
Died	4	2	0	2	0
Censored	14	6	7	0	1
Person-months	238.0				
>18-24 months Total	31	17	9	4	1
Died	0	0	0	0	0
Censored	10	6	2	1	1
Person-months	148.8				
>24-30 months Total	21	11	7	3	-
Died	1	0	0	1	
Censored	5	2	3	0	
Person-months	102.2				
>30-36 months Total	15	9	4	2	
Died	2	1	0	1	
Censored	5	2	3	0	
Person-months	66.7				
>36-42 months Total	8	6	1	1	
Died	0	0	0	0	
Censored	3	2	1	0	
Person-months	41.4				
>42-<51 months Total	5	4	-	1	
Died	0	0		0	
Censored	5	4		1	
Person-months	16.9				

N = number of subjects observed at beginning of each follow-up period

5.2 Survival distribution of cohort members

Figure 3 describes the survival curve observed during the waiting time period (N=124). The overall survival probability at 6 months and 1 year was 93.6 % and 79.7% respectively. The total person-months contributed to the study while waiting for transplantation was 1090.0 person-months. One has to keep in mind however that, due to censoring, this is an underestimation of the true non-transplant person-months experience. During this period, patients were censored either because (i) they became lung recipients, (ii) died while waiting or (iii) the study period ended.

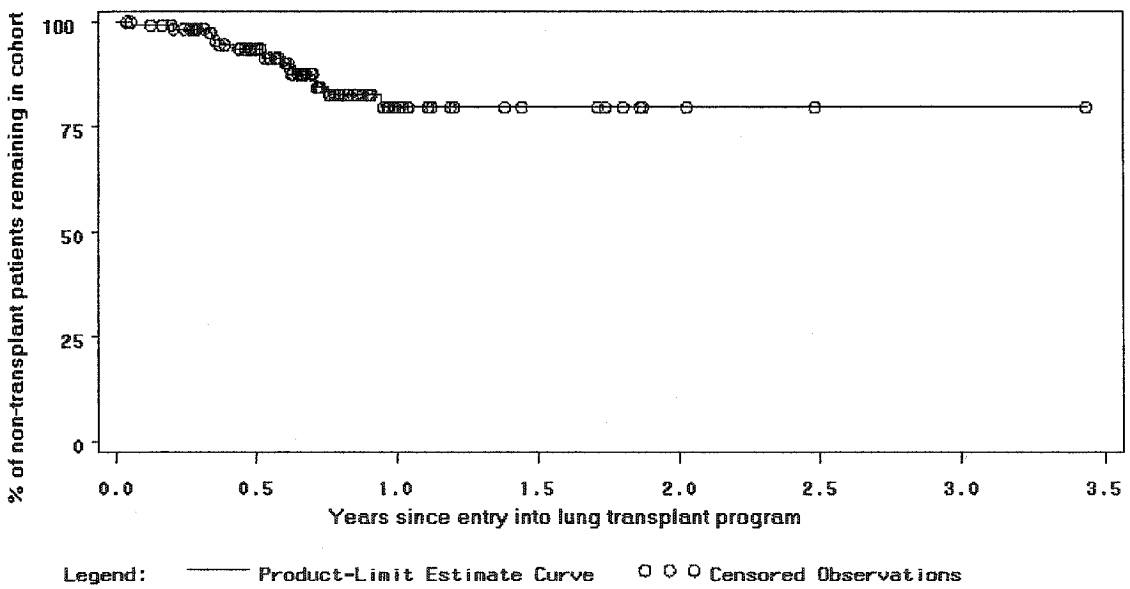

Figure 3. Survival distribution of cohort while waiting for transplantation.

Figure 4 describes the survival curve observed in the transplant patient population (N=91). The overall survival probability at 1, 2 and 3-years post-transplant was 79.6%, 72.6% and 55.7%, respectively. During the study period, the lung transplant patients contributed a total of 1421.5 person-months of follow-up.

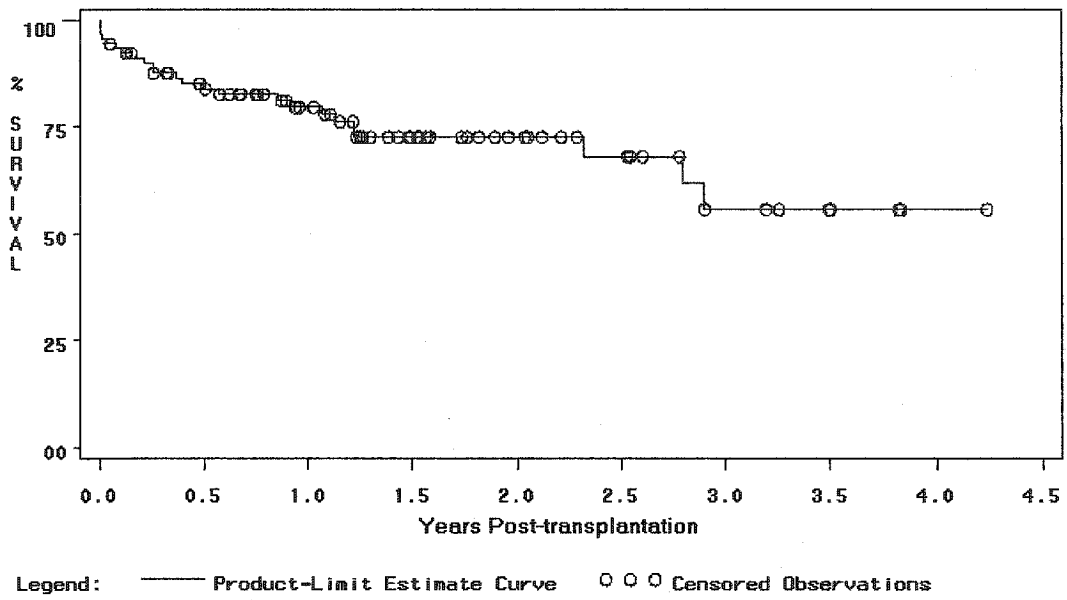

Figure 4. Post-transplant survival distribution for lung transplant recipients

Survival curves by type of transplant procedure are presented in figure 5. The survival probability observed for single lung transplants carried out on 56 patients, for years 1, 2 and 3 post-transplantation were 76%, 62% and 46%. The one-year survival probability estimated for the 35 double lung transplant recipients was 81%.

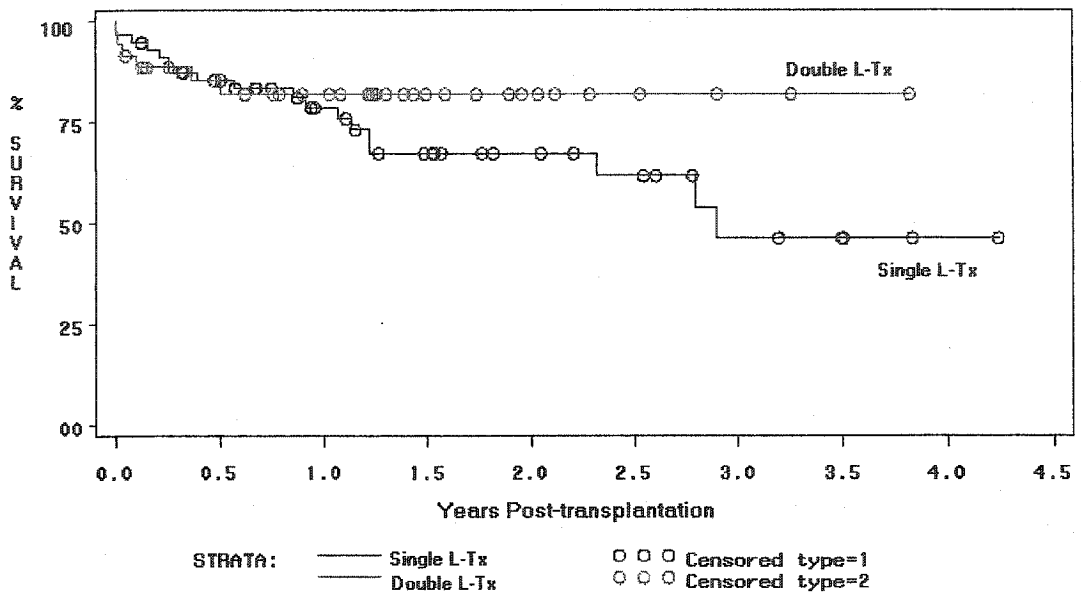

Figure 5. Post-transplant survival distribution by type of lung transplant

5.2.1 Survival associated with lung transplantation versus no transplantation

5.2.1.1 Mortality rate ratios of lung transplantation relative to the waiting time

The mortality rate observed during the waiting list period was 16 deaths per 1,090.0 person-months or 1 death per 68.1 person-months. The mortality rate observed during the post-transplant phase was 24 deaths per 1,421.5 person-months or 1 death per 59.2 person-months.

We studied the effect of transplantation on survival within discrete time periods (table 11). Results obtained by Cox regression show that, in the first 30 days post-transplant, recipients have a mortality rate that is 4.77 times that of the one observed

during the waiting list period. Further study of additional post-transplant time periods does not show any protective effect associated with transplantation.

Table 11. Crude mortality rate ratios associated with the post-transplant period as compared to the waiting list

	Death Rate Ratio	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	4.77	1.77, 12.68	0.002
>30 – 91 days post-Tx	2.20	0.75 6.49	0.15
91 days and beyond	1.19	0.40, 3.58	0.75
Log likelihood = 342.014			

Sub-group analyses, with respect to different disease diagnoses, showed varying rate ratios with time since transplantation (figure 6). A detailed analysis is presented in the following sections.

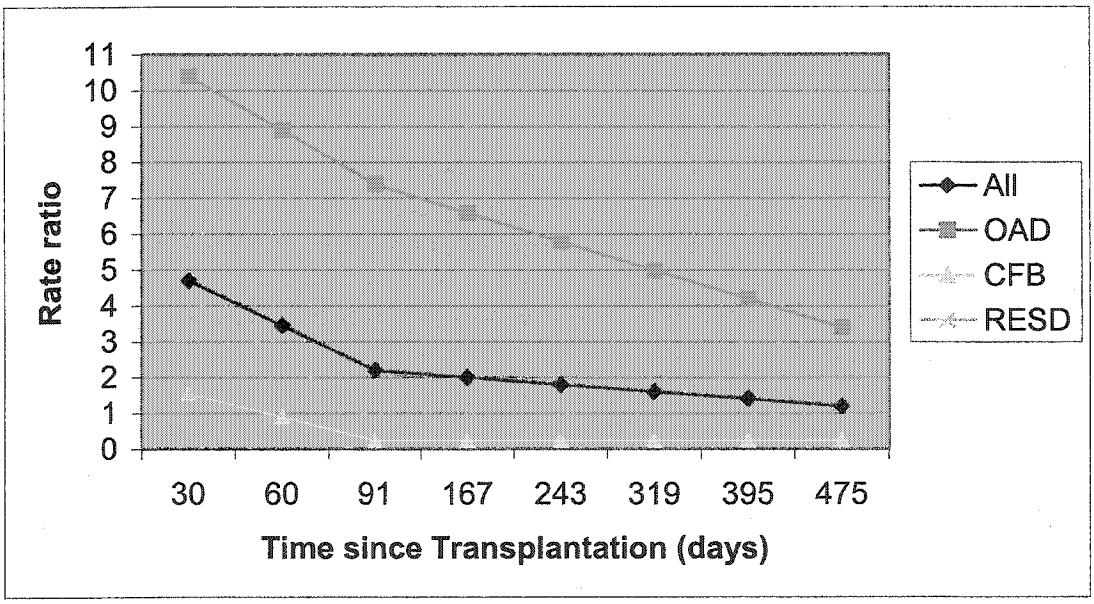

Figure 6. Mortality rate of transplantation relative to the rate while waiting

5.2.1.2 Life years gained in full cohort

Independently of the study of rate ratios associated with the procedure, we also calculated mean life years gained from transplantation by comparing the waiting time (the proxy for the non-transplant experience) and post-transplant experience of the cohort. Despite the high mortality rate ratio observed (table 11), a mean life year benefit, conferred by lung transplantation, was observed. The estimates were based on the 1,090 person-months experienced on the waiting list among the 124 patients (for an average of 8.8 months per patient) and, the 1,421.5 person-months experienced in the post-transplant phase among the 91 recipients (for an average of 15.6 months per recipient). The incremental mean life years (LY) gained per patient, for the full cohort, was 0.57 (95% CI: 0.36, 0.78) (see Appendix F, table F1).

Because the waiting list served as a proxy for non-transplantation, we carried out an extensive sensitivity analysis by varying the person-month experience in the pre-transplant phase and its effect on the mean life years gained estimate (see section 5.5.2 for the various scenarios studied).

5.2.1.3 Adjusted mortality rate ratios associated with transplantation

Adjusted mortality rate ratios for potential important confounders and explanatory variables are presented in table 12. After adjusting for all other variables in the model, females are on average 2.03 times more likely to die than males, at any given point in time and irrespective of the disease diagnosis. Although not significant, patients listed for a double lung are two times less likely to die than those enlisted for

a single lung transplant. Age accepted into the program does not have an effect on survival. None of the interaction terms studied were significant.

Table 12. Adjusted mortality rate ratios for total cohort population

Variables	Death Rate Ratio*	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	3.98	1.45, 10.88	0.007
>30 – 91 days post-Tx	2.05	0.67, 6.29	0.21
Beyond 91 days post-Tx	0.85	0.25, 2.82	0.79
Age put on waiting list	1.00	0.97, 1.03	1.00
Sex (female versus male)	2.03	1.04, 3.99	0.04
Type of transplant enlisted for (double versus single)	0.47	0.16, 1.37	0.17
Reference: Restrictive disease	1.00	-	-
PVD	0.26	0.03, 2.38	0.24
Obstructive Airways Disease	0.16	0.07, 0.36	0.0001
CF & Bronchiectasis	0.39	0.13, 1.20	0.10

* Mortality rate ratios presented for specific post-transplant time periods versus the waiting list are adjusted for all other variables in the model: age, sex, type of transplant enlisted for and disease. Log likelihood =319.580.

5.2.2 Sub-group survival analysis study by type of end-stage lung disease

Survival rates were also studied for each type of disease diagnosis: pulmonary vascular disease, obstructive airways disease, cystic fibrosis and bronchiectasis, and for the restrictive disease group. Crude and adjusted survival estimates are presented.

5.2.2.1 Sub-group survival analysis for patients with pulmonary vascular disease

The pulmonary vascular disease cohort consisted of 4 patients one of which, died beyond the 30-day mark. No additional data on mortality rate ratios are presented due to the limited information available. With respect to mean life years gained, no benefit was observed in this group (-0.21 LYs (95% CI: -1.58, 1.16)) (table F5).

5.2.2.2 Obstructive airways disease group: survival analysis

The crude mortality rate ratios (table 13) do not show any survival benefit associated with transplantation in the OAD. The death rate in the first 30 days post-transplant is 10 times that of the one observed during the waiting list. The magnitude and direction of the mortality rate ratios continue well beyond the 30-day mark. Inversely, lung transplantation conferred the highest benefit in mean life years to the OAD group with 0.59 LYs (95% CI: 0.27, 0.92) gained (table F2).

Table 13. Crude mortality rate ratios for the OAD group

	Death Rate Ratio*	**95% CI**	**P value**
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	10.23	1.24, 84.67	0.03
>30 – 91 days post-Tx	7.39	1.08, 50.67	0.04
Beyond 91 days post-Tx	3.40	0.35, 32.98	0.29

*Mortality rate ratios, obtained by a Cox non-proportional regression, are presented for each specific post-transplant time period with the waiting list serving as the reference group. Log likelihood = 95.317

A multivariate Cox regression model adjusting the mortality rate ratios for important predictive factors, in OAD patients, is presented in table 14. The adjusted death rates associated with transplantation never fall below the one observed during the waiting list. Although not significant, females are more likely to die on average than males and, the number of hospitalizations experienced during the waiting list has a negative effect on survival.

Table 14. Adjusted mortality rate ratios for the OAD group

	Death Rate Ratio*	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	10.15	1.14, 90.24	0.04
>30 – 91 days post-Tx	8.85	1.21, 64.92	0.03
Beyond 91 days post-Tx	4.98	0.45, 55.72	0.19
Age put on waiting list	1.01	0.92, 1.10	0.87
Sex (female versus male)	3.79	0.79, 18.08	0.10
Type of transplant enlisted for (double versus single)	1.06	0.10, 11.48	0.96
Hospitalizations, number (During waiting list)	1.74	0.87, 3.48	0.12

* Mortality rate ratios presented for specific post-transplant time periods versus the waiting list are adjusted for all other variables in the model: age, sex, type of transplant enlisted for and number of hospitalizations. Log likelihood = 87.190

5.2.2.3 Cystic fibrosis and bronchiectasis disease group: survival analysis

Due to the small number of patients and events, in the CF and bronchiectasis patient group, post-transplant mortality rate ratios are presented for two periods (table 15). The crude death rate observed in the first 30 days post-transplantation is 1.4 times that of the one observed during the waiting list. Once having survived the first 30 days however, CF and bronchiectasis recipients are on average 3.6 times less likely to die than during the waiting list. In mean life years gained, transplantation conferred a survival benefit of 0.58 LYs (95% CI: 0.21, 0.95) (table F3).

Table 15. Crude mortality rate ratios for the CF and bronchiectasis group

	Death Rate Ratio*	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	1.43	0.16, 12.76	0.75
Beyond the 30 days post-Tx	0.28	0.03, 2.49	0.25

*Mortality rate ratios, obtained by a Cox non-proportional regression, are presented for each specific post-transplant time period with the waiting list serving as the reference group. Log Likelihood = 59.381

The results obtained after multivariate adjustment (table 16), show that transplantation confers on average a protective effect against mortality. Furthermore, hospitalizations during the waiting list benefit survival on average.

Table 16. Adjusted mortality rate ratios for the CF and bronchiectasis group

	Death Rate Ratio*	**95% CI**	**P value**
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	0.84	0.08, 8.46	0.88
Beyond 30 days post-Tx	0.16	0.02, 1.61	0.12
Age put on waiting list	0.94	0.87, 1.03	0.20
Sex (female versus male)	1.35	0.22, 8.26	0.74
Hospitalizations, number (During waiting list)	0.67	0.40, 1.12	0.12

Mortality rate ratios presented for specific post-transplant time periods versus the waiting list are adjusted for all other variables in the model: age, sex and number of hospitalizations. Log likelihood = 54.303

An additional analysis restricted to CF patients showed no significant difference with respect to the crude mortality rate ratios observed in table 15. Cystic fibrosis patients were, on average, 1.55 times (0.17, 14.32) more likely to die in the first 30 days post-transplant and, 4.2 times (death rate ratio = 0.238; 95% CI: 0.03, 2.11) less likely to die beyond this period, as compared to the waiting list. Adjusted mortality rate ratios were similar with the ones observed in table 16. Females had a higher death rate and every hospitalization before transplant conferred a survival benefit.

5.2.2.4 Restrictive disease group: survival analysis

In recipients with a restrictive disease, the results show (table 17) that the mortality rate is on average higher in first 30 days of transplantation than the one observed during the waiting list. The effect of transplantation tends towards a

survival gain beyond the 30 days but does not reach statistical significance. In mean life years, this group had an average gain of 0.53 LYs (95% CI: 0.04, 1.01) (table F4).

Table 17. Crude mortality rate ratios for the restrictive disease group

	Death Rate Ratio*	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	4.26	1.01, 18.03	0.05
Beyond 30 days post-Tx	0.79	0.08, 7.41	0.84

*Mortality rate ratios, obtained by a Cox non-proportional regression, are presented for each specific post-transplant time period with the waiting list serving as the reference group. Log likelihood =77.644

Adjusted mortality rate ratios for patients with a restrictive disease are presented in table 18. The adjusted death rates did not change significantly from the crude estimates. The results show that females are on average less likely to die than males. Furthermore, patients who are enlisted for a double lung are less likely to die, on average, than patients enlisted for a single lung. Also, each additional hospitalization experienced during the waiting list translates into a decrease in survival.

Table 18. Adjusted mortality rate ratios for the restrictive disease group

Post-transplantation	Death Rate Ratio*	95% CI	P value
Reference: waiting list period	1.00	-	-
First 30 days post-Tx	6.77	1.09, 41.99	0.04
Beyond 30 days post-Tx	0.77	0.06, 10.58	0.85
Age put on waiting list	1.01	0.96, 1.06	0.73
Sex (female versus male)	0.32	0.07, 1.44	0.14
Type of transplant enlisted for (double versus single)	0.12	0.02, 0.76	<0.025
Hospitalizations, number (During waiting list period)	3.22	1.38, 7.52	0.007

* Mortality rate ratios presented for specific post-transplant time periods versus the waiting list are adjusted for all other variables in the model: age, sex type of transplant enlisted for and number of hospitalizations. Log likelihood = 62.402

5.2.3 Determining important predictive factors of mortality in lung recipients

An additional study was carried out to determine potential risk factors in lung transplant recipients alone (N=91). A multivariate analysis adjusting for potential predictors of survival in recipients is presented in table 19. None of the interaction terms studied were significant.

Table 19. Adjusted mortality rate ratios for transplant recipients

	Death rate ratio*	**95% CI**	**P value**
Reference: First 30 days post-Tx	1.00	-	-
>30 – 91 days post-Tx	0.63	0.14, 2.81	0.54
91 days and beyond	0.10	0.01, 0.75	0.03
Age at transplantation (years)	0.97	0.91, 1.03	0.35
Sex (female versus male)	2.39	0.56, 10.26	0.24
Reference: Restrictive disease group	1.00	-	-
PVD	6.28	0.22, 178.02	0.28
OAD	0.49	0.10, 2.45	0.38
CF & Bronchiectatic diseases	0.06	0.01, 0.62	0.02
Time spent on waiting list (months)	0.76	0.62, 0.94	0.01
Type of transplant received (Double versus Single)	0.70	0.12, 4.11	0.69
Donor Age	1.02	0.93, 1.07	0.43
Donor Sex	1.99	0.44, 9.10	0.37
CMV status of receptor (+ versus -)	1.24	0.40, 3.80	0.71
CMV status of donor (+ versus -)	0.61	0.17, 2.18	0.44
Ischemic time of donor organ	1.01	1.00, 1.02	0.10
Rejection of organ during the hospitalization for transplant	0.57	0.11, 3.00	0.51
Hospital length of stay for transplantation (days)	1.01	0.10, 1.03	0.42
Number of acute rejections	1.11	0.76, 1.64	0.58
Number of hospitalizations due to infection during post-transplant	1.23	0.56, 2.67	0.61
Diagnosis of obliterative bronchiolitis	0.68	0.12, 3.84	0.66

*Mortality rate ratios presented for specific post-transplant time periods and potential predictors are adjusted for all other variables in the model using a Cox regression model. Log likelihood = 133.31. None of the interaction terms studied were significant.

The effect of OB on survival was also studied as a time dependent variable where, once a patient develops OB the patient is positive for this health state for the rest of the follow-up period. The results of this analysis suggest that once having developed OB in the second year post-transplant, the risk of death during this period is, on average, 9.4 (95% CI: 1.32, 66.67) times that of any other period. Furthermore, having OB in the third year and beyond is associated with a risk of death, which is on average 14.95 (95% CI: 1.32, 168.41) times that of patients never having developed obliterative bronchiolitis.

5.3 Health related quality of life and utility

As stated in the methods section (p.70), for the description of HRQOL and utility we decided to include lung recipients who had been transplanted as far back as January 1st, 1992. In this analysis 105 patients completed the interview (n=34 candidates and n=71 transplant recipients). At interview, candidates had been on the waiting list for an average of 6.0 ± 5.9 months. The recipients interviewed had been transplanted for an average 33.4 ± 29.5 months. More details and demographic characteristics of these patients are presented in Appendix D (section D1.1).

5.3.1 HRQOL mean scores: cross-sectional comparison of patients on the waiting list and transplanted recipients

All HRQOL domain scores are, on average, higher in post-transplant survivors than in candidates on the waiting list (table 20).

Table 20. Mean scores of the eight health domains as measured in the SF-36

Transformed scores (0-100)	**Candidates (n=34) Mean ± S.D.**	**Recipients (n=71) Mean ± S.D.**	**t- value**	**P value**
Physical Functioning	27.9±23.5	70.1±27.9	-7.61	0.0001
Role Physical	21.5±23.7	69.2±26.1	-9.02	0.0001
Bodily Pain	54.5±29.8	71.3±27.6	-2.83	0.006
General Health	24.0±18.2	70.3±19.5	-11.63	0.0001
Vitality	45.4±13.4	68.0±17.6	-6.64	0.0001
Social Functioning	46.3±28.0	78.0±25.2	-5.81	0.0001
Role Emotional	57.4±39.2	84.0±21.1	-3.72	0.0006
Mental Health	67.6±18.9	77.0±16.1	-2.64	0.0001

This improvement however is not maintained, for all studied domains, throughout the post transplant period (table 21). The results show that physical functioning, role physical, social functioning, vitality and general health reported from recipients are significantly better than those reported by candidates no matter the post-transplant period.

Table 21. Mean HRQOL scores by pre and post-transplant period

	Pre-Tx	First year §	Second year	Third year	Fourth year	Fifth year and beyond
Respondents	N=34	N=23	N=13	N=7	N=10	N=18
Health domains (0-100)	**Mean ± S.D.**					
Physical Functioning	27.9±23.5	76.3±25.4	77.3±26.4	72.9±22.1	82.0±18.9	49.2±29.6
Role Physical	21.5±23.7	75.8±20.8	77.4±25.5	52.7±26.2	83.1±24.7	53.5±25.0
Bodily Pain	54.5±29.8	76.0±23.5	70.8±33.7 NS	74.4±18.0 NS	79.5±27.1	59.8±30.0 NS
General Health	24.0±18.2	75.6±17.9	75.2±17.8	69.6±15.3	74.1±14.1	57.9±22.6
Vitality	45.4±13.4	71.5±19.6	68.8±17.5	65.2±16.5	75.0±16.4	60.4±14.7
Social Functioning	46.3±28.0	80.4±25.2	80.8±25.8	83.9±20.0	87.5±17.7	65.3±27.6
Role Emotional	57.4±39.2	84.4±20.3	87.2±19.1	81.0±20.8 NS	85.8±26.7	81.5±22.1
Mental Health	67.6±18.9	79.8±16.3	75.4±17.1 NS	70.0±19.8 NS	80.5±16.2 NS	75.6±13.9 NS

§All variables are significantly different as opposed to waiting list period, t-test <0.05
NS Effects are not significantly different from waiting list

5.3.2 Predicting HRQOL through multivariate analysis

In the multivariate analysis, recipients scored better on average in all HRQOL domains. Increased time since transplantation however negatively affected all health domains with the exception of role emotional and mental health. For an in-depth interpretation of the results observed for predicting HRQOL see Appendix D (section D2).

For physical functioning, age and being hospitalized within 1 month of interview negatively affected the scores. For role physical, CF and bronchiectasis patients scored higher than all other disease groups. Age and the number of days spent as an inpatient within 1 month of interview however were negatively associated with role physical.

For bodily pain, the CF and bronchiectasis group reported less pain than all other disease groups. Patients with a double lung transplant and those having been hospitalized (≤ 1 month of interview) however reported, on average, higher bodily pain than single lung recipients and those not having been hospitalized, respectively.

For both general health and vitality, CF and bronchiectasis patients scored higher, on average, than all other patients. Double lung recipients and those having been hospitalized within 1 month of interview however reported lower general health and vitality.

Patients with CF and bronchiectasis as well as pulmonary vascular diseases scored higher, on average, in social functioning, than other diseases. Double lung recipients however reported lower social functioning scores than single lung recipients. In-patient length of stay (≤ 1 month of interview) was also negatively associated with social functioning.

Regarding the role emotional domain, CF and bronchiectasis patients scored higher on average than all other groups. For mental health, females and patients with an obstructive airways disease scored lower than males and all other diseases, respectively.

5.3.3 HRQOL in the longitudinal cohort (before and after transplantation)

The characteristics of patients included in the longitudinal analysis of HRQOL are presented in detail in Appendix D (section D1.2).

Simple cross-sectional comparison of means showed no significant difference between the two post-transplant periods and the waiting list for most of the HRQOL outcomes except for the general health domain (table 22). There was however, on average, an improvement observed in physical functioning and role physical. The results also show a downward trend in bodily pain (i.e. patients are reporting more pain). With respect to lung function there was a significant difference in FEV_1 (% predicted) scores obtained before and after transplantation. FEV_1 (% predicted) scores were in the order of 27.9 ± 13.2 before transplantation and, 61.9 ± 19.6 and 65.1 ± 16.3, < 4 and ≥ 4 months post-transplantation, respectively. This translates into a 34% (95% CI: 20.1%, 48.0%) and 37.2% (95% CI: 23.7%, 50.8%) improvement in FEV_1 (% predicted), respectively.

Table 22. Comparison of HRQOL means obtained longitudinally (before and after transplantation)

		Post-transplantation[a]	
HRQOL outcomes	Waiting list (N=13)	Period 1(<4 months) (N = 11)	Period 2 (≥4months) (N=8)
	Mean ± S.D.	**Mean ± S.D.** **Mean difference* (95% CI)**	
Physical Functioning	28.9 ± 24.7	39.6 ± 29.2 10.7 (-12.1, 33.5)	40.0 ± 35.9 11.2 (-16.4, 38.7)
Role Physical	27.4 ± 32.1	40.3 ± 31.7 12.9 (-14.2, 40.1)	28.9 ± 29.5 1.5 (-27.8, 30.8)
Bodily pain	56.9 ± 36.9	45.6 ± 22.3 -11.2 (-37.7, 15.2)	35.5 ± 25.4 -21.3 (-52.5, 9.8)
General Health	26.6 ± 21.2	69.3 ± 22.8 § 42.7 (24.0, 61.3)	49.6 ± 26.5§ 23 (1.1, 44.9)
Vitality	50.0 ± 14.4	51.7 ± 22.9 1.70 (-14.2, 17.6)	40.6 ±18.6 -9.4 (-24.5, 5.8)
Role Emotional	52.6 ± 37.9	62.1 ± 31.9 9.6 (-20.5, 39.6)	53.1 ± 37.5 0.6 (-35.0, 36.1)
Social Functioning	44.2 ± 31.7	48.9 ± 29.3 4.6 (-21.4, 30.7)	43.9 ± 29.9 -0.5 (-29.7, 28.7)
Mental Health	68.1 ± 17.3	70.5 ± 16.5 2.4 (-12.0, 16.8)	66.9 ± 18.3 -1.2 (-17.8, 15.4)

§t-test significant difference, $p<0.05$, with respect to pre-transplantation
[a]t-test, no significant difference between periods 2 and 1.
* Mean difference between post-transplant time period and waiting list

5.3.3.1 Predicting HRQOL in the longitudinal cohort as a function of time

The longitudinal results are based on studying the effect of time since transplantation, < 4 months and ≥ 4 months, for each of the health domains. Multivariate adjusted models are also presented where relevant. For an in-depth interpretation of the longitudinal study of HRQOL see Appendix D (section D3).

General health significantly improved within and beyond the 4 months after transplantation as compared to the waiting list. A negative predictor of general health

was age. For physical functioning there was an improvement on average, although not significant, after transplantation. A significant positive predictor of physical functioning post-transplant was the baseline scores reported during the waiting list. Negative predictors included age at interview and the presence of an infection. For role physical, although non-significant, an improvement was also observed post versus pre-transplantation. Age was negatively associated and baseline scores during the waiting list were positively associated with role physical. Bodily pain did not improve on average after transplantation (patients reported more pain). Significant negative predictors were age and length of stay as an inpatient within a month of interview. A positive predictor was bodily pain reported during waiting list. Vitality did not seem to improve after transplantation and a negative predictor was age. For social functioning there was an improvement only after the 4 months of transplantation and positive predictors included social functioning scores before transplantation as well as the time spent on the waiting list. For role emotional there was an improvement on average, although non-significant, after as compared to before transplantation. Significant negative predictors included age and the number of days one had spent in hospital within a month of interview. Mental health scores seemed to improve within the 4 months of transplantation and then declined on average, both not significant. Significant negative predictors included age at interview and positive predictors included mental health scores reported before transplantation and the time spent on the waiting list.

5.3.4 Utility

Utility was measured in candidates (n=34) and recipients (n=71) at the same time as HRQOL. Results show that recipients reported, on average, significantly higher utility scores (0.82 ± 0.23) than candidates (0.18 ± 0.16). Additional computations were carried out by attributing a utility score of 0 to patients that had died during the active recruiting period of the study. Pre-transplant mean utility, with the 3 additional deceased patients (N=37) was 0.17 ± 0.17. The post-transplant mean utility scores, including the 5 deceased patients, for the first (N=24), second (N=13), third (N=9), fourth (N=10) and, ≥ fifth year (N=20) were 0.80 ± 0.29, 0.87 ± 0.24, 0.64 ± 0.40, 0.94 ± 0.07 and 0.62 ± 0.30, respectively.

A correlation analysis between the utilities obtained from the standard gamble and the 8 health domains assessed with the SF-36 showed a significant correlation between all variables. The correlation coefficients between utility and the health domains are as follows with: physical functioning the $\rho = 0.67$ ($\alpha < 0.001$); role physical the $\rho = 0.68$ ($\alpha < 0.001$); bodily pain the $\rho = 0.40$ ($\alpha < 0.001$); general health the $\rho = 0.72$ ($\alpha < 0.001$); vitality the $\rho = 0.67$ ($\alpha < 0.001$); social functioning the $\rho = 0.53$ ($\alpha < 0.001$); mental health the $\rho = 0.32$ ($\alpha < 0.001$); role emotional the $\rho = 0.44$ ($\alpha < 0.001$).

5.3.4.1 Predictors of utility

Multivariate analysis of utility and potential predictors, ascertained cross-sectionally in patients alive (N=105), showed that recipients report utility scores that

are on average six times higher than candidates. After including the deceased patients (n=8), the results did not change significantly (table 23). In this analysis (N=113), recipients reported adjusted utility scores (0.78), which were, on average, 4.4 times higher than those reported by candidates (0.18).

Table 23. Effect estimate of lung transplantation, on utility, adjusted for important predictors in interviewed and deceased patients (N=113)

	ß*	95% CI	P value
Intercept	0.178	-0.154, 0.509	0.30
Status (recipient versus candidate)	0.605	0.463, 0.747	0.0001
Age at interview (years)	-0.001	-0.007, 0.004	0.66
Sex (female versus male)	-0.016	-0.116, 0.085	0.76
Time since transplantation (months)	-0.002	-0.004, -0.0001	0.04
Reference: Restrictive disease			
PVD	0.060	-0.168, 0.288	0.61
Obstructive Airways Disease	0.094	-0.044, 0.232	0.19
CF & Bronchiectasis	0.043	-0.157, 0.243	0.68
Type of transplant enlisted for			
Ref: Single lung			
Double/Bilateral lung	0.124	-0.060, 0.308	0.19
Heart-lung	0.257	-0.181, 0.696	0.25

*Coefficients, obtained by MLR, are adjusted for every other variable in the model. The model explains 51.9% of the variability observed. F-value = 16.53, p. < 0.0001

5.3.4.2 Determining predictors of utility before transplantation

Predictors of utility, ascertained cross-sectionally during the waiting list, are presented in table 24. The presence of neither an infection nor being hospitalized affected utility. The model studied did not significantly explain the variability observed in utility.

Table 24. Multivariate model of potential important predictors of candidate reported utility (N=34)

	ß*	95% CI	P value
Intercept	0.376	-0.118, 0.869	0.15
Age at interview (years)	-0.002	-0.010, 0.007	0.72
Sex (female versus male)	-0.022	-0.166, 0.121	0.76
Reference: Restrictive disease			
PVD	-0.088	-0.335, 0.159	0.49
CF & Bronchiectasis	-0.121	-0.369, 0.126	0.35
Obstructive Airways Disease	0.101	-0.138, 0.340	0.42
Time spent on waiting list	-0.003	-0.015, 0.009	0.65
Oxygen needed (liters / minute^2)	0.008	-0.036, 0.052	0.73
FEV_1 (% predicted)	-0.0003	-0.005, 0.005	0.90
Hospitalization (yes/no) within a month of interview	0.044	-0.243, 0.331	0.77
Presence of an infection (yes/no) within a month of interview	0.091	-0.066, 0.249	0.27
Reported health transition	-0.039	-0.104, 0.026	0.25

*Coefficients, obtained by MLR, are adjusted for every other variable in the model. The model explains 29.6% of the variability observed. F-value = 0.84, p. = 0.60

5.3.4.3 Determining predictors of utility after transplantation

Potential important predictors of utility, ascertained cross-sectionally in interviewed recipients, are presented in table 25. Apart from time since transplantation, none of the variables studied significantly explain the variability observed in recipient reported utility.

Table 25. Multivariate model of potential important predictors of recipient reported utility (N=71)

	ß*	95% CI	P value
Intercept	0.752	0.293, 1.211	0.002
Age at interview (years)	0.003	-0.004, 0.009	0.40
Sex (female versus male)	-0.037	-0.146, 0.072	0.51
Time spent on waiting list (months)	0.006	-0.002, 0.014	0.13
Time since transplantation (months)	-0.004	-0.007, <-0.001	0.02
Reference: Restrictive disease			
PVD	0.094	-0.216, 0.404	0.56
Obstructive Airways Disease	-0.119	-0.303, 0.066	0.21
CF & Bronchiectasis	0.120	-0.117, 0.358	0.32
Type of transplant enlisted for			
Ref: Single lung			
Double/Bilateral lung	-0.028	-0.268, 0.212	0.82
Heart-lung	0.158	-0.301, 0.618	0.50
FEV_1 (% predicted)	<-0.001	-0.004, 0.003	0.68
Hospitalization (yes/no) within a month of interview	-0.064	-0.224, 0.096	0.44
Presence of an infection (yes/no) within a month of interview	-0.030	-0.155, 0.095	0.64
Presence of a rejection (yes/no) within a month of interview	0.070	-0.261, 0.401	0.68
Ever having been diagnosed with a rejection (yes/no)	0.109	-0.015, 0.234	0.09
Reported health transition	0.034	-0.051, 0.119	0.44

*Coefficients, obtained by MLR, are adjusted for every other variable in the model. The model explains 32.2% of the variability observed. F-value = 1.74, p. < 0.07

After proceeding with model selection techniques, a more comprehensive model in explaining utility is presented in table 26, where age, a natural predictor of utility, and FEV_1 (% predicted) were forced in. The results show that for every year transplanted, there is an average decrease in the adjusted utility by about 0.04 units. Furthermore, patients in the OAD group tend to report lower adjusted utility scores by an average of 0.16 units than other lung diseases. Interestingly, ever having a rejection versus never experiencing one is associated with a higher utility by an average of 0.13 units, when adjusting for all other variables.

Table 26. Reduced multivariate model in predicting recipient reported utility (N=71)

Variable	ß*	95% CI	F value	P value
Intercept	0.837	0.502, 1.172	24.49	<0.0001
Age at interview	0.001	-0.003, 0.006	0.31	0.58
FEV_1 (% predicted)	-0.001	-0.003, 0.003	0.03	0.86
Time spent on waiting list (months)	0.006	-0.001, 0.013	2.66	0.11
Time since transplantation (months)	-0.003	-0.005, -0.001	9.44	0.003
Obstructive airways disease group	-0.161	-0.294, -0.028	5.77	<0.02
Ever having been diagnosed with a rejection (yes/no)	0.126	0.010, 0.243	4.60	<0.04

*Coefficients, obtained by MLR, are adjusted for every other variable in the model. This reduced model was obtained by backward elimination with an alpha level of 0.10 to stay in the model. Age at interview and FEV_1 were forced in. The model explains 26.4% of the variability observed. F-value =3.83, p. = 0.003

5.3.5 Longitudinal study of utility (before and after transplantation)

Of the 34 candidates interviewed, 15 became lung transplant recipients during the study period. Utility mean scores of candidates who became lung recipients (n=15) and those who remained on the list (n=19) were 0.20 ± 0.17 and 0.17 ± 0.17, respectively. There was no difference between the reporting of utility between these two groups.

The crude estimates suggest, as compared to the waiting list, an increase in utility by an average of 0.35 units (95% C.I: 0.15, 0.56) within the first 4 months and 0.33 units (95% C.I: 0.15, 0.53) beyond the 4 months of transplantation. There was no difference in the utilities observed within these two time periods. Multivariate analysis showed that for every day spent as an inpatient, there is a decrease in the reported utility, which averages -0.008 units (95% C.I: -0.012, -0.004), when

adjusting for time since transplantation. Furthermore, for every month gone by, within the first four months of transplantation, there is a decrease in utility, which averages -0.12 units (95% C.I: -0.236, -0.01). Once reaching the post 4-month period however, there is an increase in utility by an average of 0.12 (95% C.I: 0.027, 0.215) units for every month gone by, up to the 9-month period studied.

5.4 Economic impact of lung transplantation

5.4.1 Health care burden associated with the pre-transplant phase

In this section, the economic burden of the pre-transplant phase will be ascertained. Outpatient and inpatient resources will be covered as well as medications and home oxygen therapy. Patient-borne costs will also be presented.

5.4.1.1 Types of hospitalizations in the pre-transplant phase

The total number of hospitalizations observed in the waiting list cohort (N= 124), as noted in the medical file, is 116 (an average of 10 hospitalizations per 100 person-months). Half of the candidates however did not have any hospitalization recorded in their medical file. The main cause of a hospitalization is infection with an incidence rate of 7 per 100 person-months. The incidence rate of a hospitalization due to an infection and exacerbation by type of disease diagnosis is presented in table 27. Cystic fibrosis patients are also admitted for preventive care towards infections at a rate of 14 hospitalizations per 100 person-months.

Table 27. Incidence rate of hospitalizations during the waiting list by group of end-stage lung disease

	PVD N=4	OAD N=56	CF N=29	BRONCH N=7	RESTR N=28	TOTAL N=124
Due to:	Number of hospitalizations					
Infection & Exacerbation	-	33	19	5	15	72
Infection prophylaxis	-	-	37	-	-	37
Other	-	1	3	-	3	7
Total person-months	65.1	511.5	265.5	70.5	177.4	1090.0
Rate of infection (per person-month)	-	0.06	0.07	0.07	0.08	0.07
# of patients with at least one noted hospitalization	0	22 (39%)	24 (83%)	4 (57%)	12 (43%)	62 (50%)

5.4.1.1.1 Economic burden of hospitalizations in the pre-transplant phase

The average cost of a hospitalization due to an infection or exacerbation (n=72) and for infection prophylaxis (n=37), based on the NIRRU scores for the CMG group encompassing respiratory insufficiency (as described in Appendix B, section B3.1), was $9,652 and $10,998, respectively. For all other causes of hospitalisation (n=7), the average cost reached $5,739. The total cost of all hospitalizations, was estimated to be $1,142,101 (based on NIRRU). The total physician fees, consults, and diagnostic acts, associated with these hospitalizations reached $85,828. The average hospitalization cost (including physician fees) per patient while on the waiting list, after taking all cohort members into account (n=124), was $9,210 ± $13,429. This translates into an average cost per patient per month of follow-up of $1,047 (95% CI: $778, $1,315). The sensitivity analysis carried out did not show a significant difference between the average costs obtained (Appendix E, table E1). The least

conservative estimate obtained was $8,575 ± $12,023 and the most conservative estimate was $9,731 ± $13,774.

5.4.1.2 Pre-transplant emergency room visits

During the waiting list period, 8 patients visited the emergency room. The total cost associated with these visits was estimated to reach $2,526 and the physician fees reached $1,062. The average cost of these visits, after taking all cohort members into consideration, was $29 ± $117 (Appendix E, table E2).

5.4.1.3 Pre-transplant one-day surgery

During the study period, 9 patients received a bronchoscopy. The total cost associated to this procedure was estimated to be $5,288 (Appendix E, table E3). The physician fees reached $1,043. The average cost per patient attributed to the cohort was $43 ± $154. In addition, four patients required resources from digestive endoscopy. Total costs reached $909 and the average cost per patient in total cohort reached $7 ± $40.

5.4.1.4 Pre-transplant ambulatory care visit

Four patients visited the ambulatory care unit. Two patients visited the unit on 9 occasions each, for intravenous therapy. The remaining two visited the unit one day for installation and follow-up of catheter line. The total cost attributed to resources used in this department was $970 and the average cost per patient was $8 ± $66 (see Appendix B, section B2.5, for more details).

5.4.1.5 Pre-transplant outpatient follow-up visits

5.4.1.5.1 Screening for eligible candidates: evaluation

During the study follow-up, 883 patients were referred to the lung transplant program, of whom 50% (N=442) were evaluated (figure 2, methods section 4.3). From this group, 16% (N=72) were excluded, 10% (N=42) died and 46% (N=203) were kept on the evaluation list. Finally, 28% (N=124) of patients accepted on the Quebec transplant list, which made up our study cohort. As part of the eligibility process each patient underwent many tests as described in Appendix A (section A1.1). The cost of an evaluation for each patient was estimated at $2,484 (same for all patients due to the similar tests undertaken). The total cost attributed to the 441 patients, not considered eligible for evaluation after a consultation with a physician, was $32,017. The total cost for those evaluated (N=442) reached $1,097,928 (for all diagnostic tests and physician fees). Broken down, the total cost of the evaluation process for the 124 candidates in our cohort was estimated to be $308,013. The cost for those patients who were refused or who died before they could be placed on the list was $285,660. The total cost for the remaining 203 patients still on hold (evaluation list) was estimated at $504,252, assuming they had finished their evaluation process.

In summary, the lung transplant program induced an evaluation cost, for each candidate (N=124), of $2,484. An additional cost was induced by the evaluation of patients who died and were refused (i.e. not put on the waiting list) which increased

the average to $2,562 per cohort member. The additional average cost per patient in cohort induced by those still on the evaluation list was estimated to reach $4,067.

5.4.1.5.2 Outpatient follow-up visits during the waiting list

A total of 632 follow-up visits were documented for cohort members while on the waiting list. The average number of outpatient clinic visits per patient during this period was 5.1 ± 5.9. The total cost of all outpatient visits reached $60,700 (including physician fees and diagnostic resources) (Appendix E, table E4). The average cost per patient attributed to resources utilized was estimated at $349 ± $371 (Appendix E, table E5). The average physician fee cost attributed to each patient was estimated to be $140 ± $147.

Patients, during the waiting time period, visited a physiotherapist 3 times a week for 6 weeks. Patients were seen for approximately 2 hours each visit for respiratory education and rehabilitative physiotherapy. The cost for a physiotherapy related outpatient visit was $44.64. The total cost for the full cohort was $24,910 and the average cost per patient $201 (for more details see Appendix B, section 2.7).

5.4.1.6 Home care during the waiting period

Of the 124 cohort members waiting for a transplant, 35 patients received home care rendered by nurses and inhalotherapists. There was a total of 661 visits noted in the patient medical files of which, 335 were due to nursing and 326 due to respiratory care. The average number of visits during the waiting time from these professionals,

among these 35 subjects, was 11.2 ± 15.7 and 11.7 ± 15.8, respectively. The cost of these services totaled $19,971 and the mean cost per subject was $571 ± $873 (for more details see Appendix B, section B4). The average cost per patient during the waiting list, taking into consideration the full cohort (n=124), was estimated to be $161 ± $527.

5.4.1.7 Outpatient medications during the waiting period

The estimated cost of outpatient medications during the waiting time, for the average 9-month stay, was $1,455 ± $1,599 on average per patient (see Appendix B, section B5.2).

5.4.1.8 Home Oxygen therapy during the waiting period

Home oxygen therapy use was extrapolated from data obtained from 31 candidates interviewed while they were on the waiting list (see Appendix B, section B7 for more details). The cost of home oxygen therapy among users (26 out of the 31 patients) was estimated to average $978 ± $534 which included the refill portable cylinders for the total waiting period. Each patient used, on average, 3 cylinders per month to go out of the house. The average cost of the medical devices (oxygen concentrators, nebulizers and compressors) per user was estimated to be $3,091± $1,798.

The total average extrapolated cost, of home oxygen therapy and medical devices, for the full cohort (n=124) while waiting was $3,412 ± $2,604. An outline on the

costs associated with home oxygen therapy and inhalation devices is presented in Appendix B (section B7, table B5).

5.4.1.9 Pre-transplant patient borne costs

5.4.1.9.1 Pre-transplant: direct non-medical costs

The direct non-medical costs pertain to transportation while seeking care. The average distance traveled by patients in the cohort (n=124) during the waiting list was 247 km ± 390 km. The cost attributed to transportation during the waiting period was valued at $204 ± $297 per patient (Appendix B, section B8.1).

During the waiting period, 14 patients were transported by ambulance to the hospital. Two of these patients had 2 rides, which brings the total to 16 ambulance rides. The total cost of ambulance use was $2,295 and the average per user was $164 ± $60. The use of an ambulance attributed to the full cohort (n=124) during the waiting list was valued at an average cost of $19 ± $56 per patient (Appendix B, section B8.1).

Seventeen patients needed accommodation services to receive medical care: a total of 26 nights were recorded. The total cost reached $3,026 with an average cost of $24 ± $76 per patient in cohort (n=124) (Appendix B, section B8.2).

5.4.1.9.2 Pre-transplant indirect costs

Time spent by patient, and family members or friends, while seeking medical care was also valued. The average time spent by the candidates (n=124) seeking medical attention was estimated to be 54.6 hours ± 33.4 hours. The cost computed to represent time lost during waiting list totaled an average of $867 ± $530 per patient in cohort. The average time spent by family members and friends accompanying patients, while on the waiting list, was reported to be 23.9 hours ± 26.3 hours. This time lost, by family members and friends, was valued at an average of $399 ± $423 per patient during the waiting list (for calculation see Appendix B, section B9).

5.4.2 Cost of lung transplantation

5.4.2.1 Costs associated with lung harvesting

The resources and costs associated with the identification, surgical retrieval of the donor lungs and transportation are presented in detail in Appendix B (section B1). The average cost of organ acquisition, and maintenance, attributed to each lung transplant patient was estimated at $5,325 ranging from $2,300 to $18,403 (table B1).

5.4.2.2 Physician fees attributed to the hospitalization for transplantation

The total cost computed for physician fees was based on consults and diagnostic procedures carried out on all transplant patients (n=91). A detailed description of the different consults and diagnostic testing carried out is presented in Appendix E (table E9). The computed total physician fees were $832,493. The average cost per patient attributed to physician fees during this hospitalization for the transplant procedure

totaled $9,148 ± $2,401. The discounted cost (discount rate of 5%) was $8,713 ± $2,287.

The average cost of physician fees, per disease diagnosis, per patient is as follows: pulmonary vascular disease (n=3): $10,032 ± $1,629; obstructive airways disease (n=49): $8,853 ± $1,9641; cystic fibrosis (n=19): $8,451 ± $480; restrictive disease (n=14): $10,777 ± $4,507; bronchiectasis (n=6): $9,524 ± $1,460.

5.4.2.3 Valuation of the inpatient stay for transplantation

The average cost of a hospitalization for a transplant procedure, after correcting data obtained from the UHN for Quebec, was estimated at $37,040 ± $33,201 (see methods section 4.6.3.1 and 4.6.4 and, Appendix B, section B3.4). The cost per day was also computed and averaged $1,386 ± $1,310 per inpatient day. The discounted cost (5%) for transplantation was on average, $35,276 ± $31,620. The discounted cost per day was $1,320 ± $1,248. The average cost of a hospitalization for transplantation for different types of disease diagnoses is presented in table 28. The lowest cost was observed in patients with cystic fibrosis and the highest cost in patients with a pulmonary vascular disease.

Table 28. Cost of the inpatient stay for lung transplantation by disease group

	Average cost ± S.D. (Full hospitalization)	**Average per day cost ± S.D.**
Obstructive airways disease	$35,416 ± $35,095	$1,293 ± $1,088
Cystic fibrosis	$27,215 ± $18,017	$1,127 ± $398
Bronchiectasis disease group	$46,914 ± $37, 335	$1,243 ± $169
Restrictive disease group	$39,768 ± $27,149	$1,603 ± $1,724
Pulmonary vascular disease group	$51,458 ± $53,931	$1,772 ± $2,122

The use of the UHN data, part of the OCCP, is explained in section 4.6.3.1. The data obtained from the UHN included a case costing system on resources utilized during hospitalizations and clinical data for a larger population of lung recipients. Estimating the cost of transplantation in Quebec from this Ontario cohort data set was also carried out due to the similarities between the transplant recipient populations. A validation of the comparability of these two cohorts (Quebec, Ontario) with respect to patient characteristics and medical practices is presented in Appendix E (section E3, tables E6 and E7). Cost estimate of a lung transplantation using the Quebec NIRRU index score is also presented in section 5.4.2.5.

5.4.2.4 Predictive cost drivers of the transplant procedure

Important cost drivers of the hospitalization for the transplant procedure are presented in table 29. Results show, after adjusting for all other variables in the model, that females hospitalized incur costs that are on average 14% greater than those for males. Furthermore, the interaction term between length of stay and death may be interpreted as follows: in patients that survive, each additional hospitalization day is associated, on average, with a 2% increase in cost. In patients who died during

this hospitalization, for every day survived there was an average decrease in the cost of transplantation by 8% when keeping all other variables constant (for more information on calculation examples please see Appendix E section E4: table E8, equation E1). In summary, length of stay and sex are significant predictors of the hospitalization cost for transplantation.

Table 29. Multivariate model in predicting hospitalization costs of lung transplantation

Variable	**ß***	**95% CI**	**P value**
Intercept	16,432.23	9,136.21-29,554.76	0.0001
Age at transplantation	1.003	0.997, 1.009	0.36
Sex (Female versus Male)	1.145	1.008, 1.300	0.04
Type of transplantation (Double versus Single)	1.078	0.882, 1.300	0.46
Disease Type Reference OAD			
PVD	1.080	0.868, 1.343	0.49
CF	1.138	0.919, 1.409	0.24
RESD	1.142	0.975, 1.339	0.10
BRONCH	1.220	0.910, 1.634	0.19
Length of Stay (LOS)	1.020	1.017, 1.022	0.0001
Death (D) in hospital (Yes versus No)	0.893	0.717, 1.112	0.31
Interaction term (LOS*D)	1.009	1.003, 1.162	0.003

*Beta estimates presented have been transformed from their natural logarithm by taking (ln^{-1}). Estimates are adjusted for all other variables in the model. The model presented explains 76.0% of the variability observed in the cost of a hospitalization due to transplantation. F value = 39.28, p. < 0.0001

5.4.2.5 Cost estimate of transplantation in Quebec using the NIRRU score

A sensitivity analysis as to the estimate of the average cost of transplantation in Quebec was also carried out by using information based on the NIRRU scoring of lung transplantations during the 2000-2001 fiscal years. The average cost estimated,

based on the average relative intensity of resources used (NIRRU = 10.1615) for all lung transplant hospitalizations, was $35,042. The average cost of lung transplants carried out at the UHN during the same fiscal year was estimated at $67,454. The NIRRU cost computed for transplants in Quebec was on average 52% ($35,042 / $67,454) of those carried out in Ontario.

When restricting the analysis to typical cases, that is, excluding deaths and atypical cases, the average estimated cost based on the NIRRU was $33,053. The average cost of transplantation for typical cases (2000-20001) from the UHN, excluding all deaths and highest LOS, was computed to be $54,241. The average NIRRU based cost, calculated for typical cases transplanted in Quebec, was 60.9% of the cost estimated for Ontario cases.

Statistics Canada reported that, on average, hospital costs in Quebec are 58.2% of those reported in Ontario (section 4.6.4 and Appendix C). This correcting factor estimate falls closely between the Quebec / Ontario cost estimates calculated (52.0% and 60.9%). This added to the confidence of using the correcting factor.

5.4.3 Cost associated with the post transplant phase

5.4.3.1 Description of type of hospitalizations in the post transplant phase

The clinical events requiring a hospitalization are summarized in table 30. In the first year post-transplant, the most prevalent primary cause of a hospitalization is the presence of an infection. The event of an acute rejection made up almost 9% of hospitalizations. Hospitalizations due to complications encompass adverse events

due to medication or treatment (i.e. pneumothorax due to bronchoscopy). Hospitalizations described as "other" include various reasons such as psychosis, hernia, cholecystectomy, ethmoidectomy, etc.... By the third year, obliterative bronchiolitis makes up almost 42% of hospitalizations followed by infection as a cause.

Table 30. Prevalence of hospitalizations in post-transplant period

	Post-transplantation		
Hospitalization due to:	**1st year (N=91)**	**2nd year (N=49)**	**> 3rd year (N=21)**
Total number	135	29	12
Infection	25.93%	31.03%	16.67%
Acute rejection	8.89%	6.90%	-
Obliterative Bronchiolitis	0.74%	3.45%	41.67%
Complications due to treatment	7.40%	6.90%	-
One-day surgery (Stent placement / dilation)	18.52%	3.45%	-
Other	38.52%	48.27%	41.67%

The results also show that in some cases, a rejection and infection occurred concomitantly (table 31). Infection was a risk throughout the whole follow-up period. In the first 6 months, almost 5% of recipients were at risk of being hospitalized for an infection and the risk fell to 3.5% in the second part of the first year and slightly decreased thereafter. Acute rejections were observed in the first 18 months post-transplant, but mostly in the first 6 months. By the beginning of the third year OB became an important cause for hospitalizations.

Table 31. Description of the type of hospitalizations by post-transplant period

Hospitalization due to:	**0-6 months**	**>6-12 months**	**>12-18 months**	**>18-24 months**	**>24-30 months**	**>30-36 months**	**>36 months**
Infection:	23	12	7	2	1	-	1
CMV	(4)	-					
Other viral	(1)	(3)					
Infection with rejection	(1)	-	(1) OB				
Acute rejection	8	4	2	-	-	-	-
With infection	(2)	(1)	(1)				
OB	-	1	1	-	5	-	-
Complications due to treatment	8	2	1	1	-	-	-
1-day surgery (Stent, dilation)	16	9	1	-	-	-	-
Other	36	15	8	6	1	3	1
Person months contributed to each interval	459.21 person-months	348.30 person-months	237.96 person-months	148.85 person-months	102.21 person-months	70.73 person-months	48.25 person-months
Total N contributing to interval	N=91	N=67	N=49	N=31	N=21	N=15	N=8

5.4.3.2 Economic burden of a hospitalization due to a post-transplant infection

During the post-transplant follow-up period 35 out of 91 (38.5%) patients were hospitalized for an infection. In the fist year, 35 hospitalizations (average length of stay 16.8 ± 24.3 days) occurred among 29 recipients. In the second year, 9 hospitalizations occurred (average length of stay 20.8 ± 19.2 days) among 8 recipients. In the third year, 2 hospitalizations occurred between 2 recipients (average length of stay of 3.5 ± 0.7 days).

The estimated average per day cost of a hospitalization due to an infection in transplant recipients, based on data from the UHN cohort data set and correcting it for Quebec, was $658 ± $302 (for more information see methods section 4.6.3.1.1 and

appendix B, sections 3.4). Based on this per day estimate, the discounted average costs (5% rate), including physician fees, per patient alive in cohort per year post-transplant was $4,411 ± $12,406, $2,472 ± $7,590, $90 ± $413 and $287 ± $812, for year 1, 2, 3 and 4, respectively. For additional information on these costs and per hospital based estimates, see Appendix E, section E5.1.

5.4.3.3 Economic burden of a hospitalization due to a rejection

During the study period, 13 out of 91 (14.3%) patients were hospitalized for a rejection episode. In the first year 13 hospitalizations were due to a rejection (average length of stay of 16.9 ± 14.5 days) among 9 recipients. In the second year there were 3 hospitalizations (average length of stay 37.0 ± 23.6 days) among 2 patients and in the third year, 5 hospitalizations (average length of stay 50.2 ± 65.4 days) due to chronic rejection were observed in 2 patients. The estimated average per day cost of a hospitalization due to a rejection in transplant recipients, based on data from the UHN cohort data set and correcting it for Quebec, was $787 ± $446 (for more information see methods section 4.6.3.1 and appendix B, section 3.4).

After taking all cohort members alive in each year into account, average per patient costs including physician fees, discounted at 5% were as follows: $1,952 ± $7,727, $1,743 ± $9,052 and $8,507 ± $37,282 for year 1, 2 and 3, respectively. The results show that OB became an important economic burden in later years. For additional information on these costs and per hospital based estimates, see Appendix E section E5.2.

5.4.3.4 "Other" post-transplant hospitalizations

During the study period we observed 70 hospitalizations for different reasons: 51 hospitalizations (experienced by 40 recipients) in the first year post-transplant, 14 (experienced by 12 recipients) in the second year and 5 (among them 3 recipients) beyond this post-transplant mark. Causes for hospitalization included: pneumothorax, hemothorax, cardiovascular problems (i.e. tachycardia,), thrombosis, embolisms, colitis, ethmoidectomies, cholecystectomies, gastric and digestive problems, pain, neoplasms, depression, cataracts and hip replacement.

Due to the variability of hospitalizations and the fact that they were patient specific we did not have cost estimates from Ontario for each of these hospitalizations. We estimated the costs of these hospitalizations based on NIRRU scores obtained from the MSSS in Quebec (section 4.6.3.2)

After taking all cohort members alive in each year into account, average costs, based on NIRRU scores, including physician fees attributed to each post-transplant time period, discounted at 5% were: $4,169 ± $7,955 and $2,716 ± $5,854 for the first 2 six months; $1,233 ± $3,474 and $1,424 ± $3,691 for the second year semesters, $340 ± $1,557 and $2,052 ± $5,450 for the third year semesters and $1,625 ± $4,593 for year four, respectively. For more information on NIRRU scoring see Appendix B, sections B3.2 and B3.3 and for a breakdown of these costs, see Appendix E, section E5.3.

5.4.3.5 Post-transplant one-day surgery

One-day surgery includes interventions usually requiring operating room time where the patient is discharged that same day after a brief observation period, lasting on average a couple of hours. In this patient population the most frequent one-day surgeries included bronchial dilations, bronchoscopies and gastro-intestinal endoscopic procedures (see Appendix E, section E5.4).

5.4.3.5.1 Bronchial dilation

Sixteen bronchial dilations were carried out in the first 6 months, 9 in the second half and one in the 12 to 18 months post-transplantation. The average estimated hospital cost of a bronchial dilation and physician fees were $458 and $355 respectively. The average costs, discounted at 5%, after taking all cohort members into consideration, contributed by bronchial dilations to each post-transplant period were: $136 ± $679, $104 ± $445 and $15 ± $105, respectively (for total costs see Appendix E, table E16).

5.4.3.5.2 Bronchoscopy

In the first, second, third and fourth year post-transplantation, 199, 36, 15 and 3 bronchoscopies were carried out, respectively. The estimated cost of a bronchoscopy, bronchial biopsy and related diagnostic resources was $460. Total physician fees reached $313. The average cost discounted at 5% per patient alive in the cohort, due to this procedure were: $1,101 ± $955 and $546 ± $638 for the first 2 six months; $392 ± $494 and $146 ± $378 for the second year semesters, $321 ± $534 and $134 ±

$374 for the third year semesters and $196 ± $400 for year four, respectively (for a breakdown of the resources valorized during a bronchoscopy and total costs see Appendix E, tables E17 & E18).

5.4.3.5.3 Other post-transplant one-day surgery

In the first, second and third year post-transplantation, 3 coloscopies and 6 oeso-gastro-duodenoscopies (OGD), 1 colposcopy and 1 OGD, and 2 OGDs were carried out, respectively. The discounted average costs attributed, to each patient, per period were: $19 ± $72 and $15 ± $93 for the first two 6-month periods, $13 ± $61 for the second year and, $12 ± $54 and $16 ± $64 for the third year semesters. For a detailed account of resource valuation see Appendix E (table E19).

5.4.3.6 Post-transplant emergency room visits

During the follow-up period, there were 23 visits to the emergency room during the first year, 7 in the second and 2 in the third. The average costs for these visits per patient alive, discounted at 5% for the first, second and third year semesters were: $97 ± $245 and $22 ± $87, $64 ± $176, $16 ± $71 and $16 ± $64, respectively. For a breakdown of the costs included in these estimates see Appendix E section E5.5 (table E20).

5.4.3.7 Post-transplant ambulatory care visit

Overall, there were 264 visits reported, among 16 patients, to the ambulatory care unit for the treatment of a rejection and for CMV prophylaxis. The average costs

associated to ambulatory care visits, discounted at 5%, per patient alive in cohort in the first year were $189 ± $2,141 and $37 ± $77, and $19 ± $62 and $16 ± $79 in the second year semesters, respectively. The average costs, discounted at 5%, associated to pharmacy use incurred during these visits were: $2,907 ± $3,500 and $140 ± $790 for the first year and, $13 ± $38 and $8 ± $43 for the second year semesters, respectively (for more details and the breakdown of costs see Appendix E section 5.6, tables E21, E22 & E23).

5.4.3.8 Post-transplant outpatient visits

5.4.3.8.1 Operating costs associated to lung transplant program

At the study center, there are 2 receptionists working at the lung transplant clinic. The assistant of the lung transplant coordinator was a medical secretary, who is in charge of all administrative functions related to the lung transplant program and to collect all medical information from each patient referred to the lung transplant program. There were also personnel from the paramedical services (nutritionist, social services), which visit candidates at the clinic regularly. As described in Appendix B (section B2.6.1), the total costs attributed to the transplant programs (operating and paramedical) for one-year in operation was estimated to be $305,188. This cost included salaries for receptionists, medical secretaries and paramedical services, and costs for supplies (paper, pens, etc...). The average cost of these services attributed to each patient in the lung transplant program was $509 per year. The post-transplant discounted cost (5%), per transplant recipient, for year 1, 2, 3 and 4 was $485, $462, $440 and $419, respectively.

5.4.3.8.2 Medical post-transplant follow-up visits

The average number of times a recipient visited an outpatient clinic for medical follow-up in the 1st, 2nd, 3rd and >3rd year post-transplant was 28, 17, 11 and 8 visits, respectively. The costs associated with outpatient follow-up visits were high during the initial year post-transplant and decreased as time went by, as do the number of visits per patient. The average costs per patient related to outpatient visits, discounted at 5% were: $1,534 ± $830, $1,097 ± $550, $803 ± $471, $593 ± $416, $512 ± $383, $384 ± $292, $578 ± $323 in the first, second and third semesters and, the fourth post-transplant year, respectively. For a breakdown of costs per period see Appendix E, tables E24 and E25.

5.4.3.8.3 Physiotherapy, outpatient post-transplant rehabilitative visits

Rehabilitative physiotherapy and physio-respiratory education are part of the follow-up outpatient lung transplant program. The frequency is for 2 hours 3 times a week for an average of 8 weeks. The costs associated to these resources utilized were $274 per patient. Total cost, for full cohort, was $24,919. The 5% discount cost for per patient was $261 (for more details as to the calculation of this estimate see Appendix B, section B2.7).

5.4.3.9 Post-transplant outpatient medications

The costs associated to medications contributed a significant amount to the economic burden of lung transplantation in the long-term (table 25). The most-

expensive drugs were the ones used in the maintenance of a potential rejection of the donor organ (Neoral, tacrolimus, prednisone, imuran, MMF). These drugs are used for the patient's life span. The anti-infectious drugs utilized were the highest in the first 2 years post-transplant and were less utilized after the 30-month post-transplant period. Types of drugs categorized as "other" are all medications taken by patients that do not fall in the two previous categories. The average cost per patient in the cohort, discounted at 5%, attributed to outpatient medications as shown in table 32 were: $11,680 in the first year, $10,288 in the second year, $8,164 in the third year and $4,275 in the first half of the fourth year post-transplant respectively. For undiscounted costs and average costs incurred by users of different types of medications see Appendix E, section 5.8 tables E26 to E29.

Table 32. Summary of discounted costs (5%) associated with outpatient medications

Per patient in cohort	**Anti-Rejection Mean ± S.D.**	**Anti-infection Mean ± S.D.**	**Other Mean ± S.D.**
0-6 months (n=91)	$2,945 ± $2,311	$2,191 ± $2,828	$924 ± $1,015
>6-12 months (n=67)	$3,108 ± $2,203	$1,419 ± $2,315	$1,093 ± $1,047
>12-18 months (n=49)	$3,032 ± $1,870	$1,183 ± $2,822	$930 ± $905
>18-24 months (n=31)	$3,267 ± $2,574	$983 ± $2,131	$893 ± $732
>24-30 months (n=21)	$2,789 ± $2,091	$794 ± $1,463	$762 ± $561
30-36 months (n=15)	$2,696 ± $2,027	$377 ± $963	$745 ± $794
36-42 months (n=8)	$3,195 ± $1,784	$229 ± $565	$851 ± $439

5.4.3.10 Post-transplant home nursing care

During the post-transplant period, fifteen recipients received home nursing care by nurses (n=56 visits: 4.3 ± 2.9) and inhalotherapists (n=27: 3.6 ± 2.0) in the first 6 months of transplantation. The number of such visits totaled 83 and the average cost per visit reached $168 ± $94. The total average cost per patient was of little economic impact and reached $28 ± $73 (discounted = $27) (for a description see Appendix B, section B4).

5.4.3.11 Post-transplant patient borne costs

5.4.3.11.1 Post-transplant direct non-medical costs: Transportation

The costs associated to transportation, discounted at 5%, from one's residence in order to receive medical care, are presented in table 33. Results show that the average discounted costs attributed to transportation in the first, second, third and fourth year post-transplant were $800, $838, $503 and $311, respectively (see Appendix E, table E30 for a breakdown of non-discounted costs). The costs seem to decrease after the second year, which concord with the observed decrease in frequency of medical care sought (for more details as to method of calculation see Appendix B, section 8.1).

Table 33. Summary of distance traveled and costs associated to receive medical care

	Mean ± S.D. Km	**Discounted cost (5%)**
0-6 months (n=91)	1,007 km ± 2,062 km	$441 ± $904
>6-12 months (n=67)	818 km ± 1,758 km	$359 ± $770
>12-18 months (n=49)	973 km ± 2,206 km	$553 ± $694
>18-24 months (n=31)	984 km ± 2,990 km	$285 ± $409
>24-30 months (n=21)	510 km ± 844 km	$284 ± $441
>30-36 months (n=15)	395 km ± 689 km	$219 ± $231
>36 months (n=8)	586 km ± 726 km	$311 ± $233

In the first 6 months post-transplantation, 17 recipients were transported by ambulance to the hospital for medical care. Three of these patients had 2 rides each and one had 4 ambulance rides. The average number of rides per user observed was 2.5 ± 5.3 and the cost incurred $414 ± $890. In the second half of the first year there was a total of 9 ambulance rides among 7 recipients. The average number of rides per user was 1.29 ± 0.49 and the incurred cost $389 ± $190. In the first six months of the second year, there was a total of 6 ambulance rides among 5 recipients and the average cost incurred per user was $150 ± $56. In the second half of the second year there were 3 ambulance rides noted among 3 recipients and the average cost incurred per user was $156 ± $13. At the beginning of the third year there was 1 ambulance ride noted and the associated cost incurred by the user was $167. The average costs per patient alive in the cohort attributed to ambulance use, discounted at a rate of 5% were $40 ± $100, $39 ± $128, $45 ± $155, $14 ± $43 and $7 ± $31, in the first, second and third year post-transplant semesters, respectively (see appendix E, table E31, for totals and undiscounted average costs).

5.4.3.11.2 Accommodations needed for post-transplant medical care

In the fist year post transplant 14 patients needed one hotel night each of accommodation. In the second, third and fourth year, 11, 7 and 2 nights of accommodation were needed. The average costs per patient alive in cohort, discounted at a rate of 5%, attributed to sleeping accommodations were $10 ± $31 and $10 ± $31, $13 ± $35 and $17 ± $40, $19 ± $41 and $20 ± $41, and $24 ± $44, in the first, second, third and fourth year post-transplant semesters, respectively. For totals and undiscounted costs see Appendix E, table E32 in; for more details as to method of calculation see Appendix B, section 8.2.

5.4.3.11.3 Post-transplant indirect costs

The time spent by the recipient and family members or friends accompanying the patient while he or she was seeking medical care was also valued. The average time spent by patients seeking medical care, in each post-transplant time period, and the economic impact associated with this time lost is presented in table 27. The average time spent by patient seeking medical care in the first, second, third and fourth years were 137, 69, 51 and 33 hours per year, respectively. The discounted average costs per patient in the cohort associated with time lost while seeking medical attention were $2,070, $1,005, $710 and $442 in the first, second, third and fourth year post-transplantation, respectively (table 34). For total and undiscounted costs and for more detail see Appendix E table E33 and for method of calculation see Appendix B, section B9.

Table 34. Economic impact of time spent by patient while seeking medical care

Post-transplantation	**Hours spent Mean* ± S.D.**	**Discounted cost (5%)**
0-6 months (n=91)	82 hours ± 52 hours	$1,235 ±$787
>6-12 months (n=67)	55 hours ± 36 hours	$835 ± $540
>12-18 months (n=49)	42 hours ± 28 hours	$610 ± $410
>18-24 months (n=31)	27 hours ± 21 hours	$395 ± $298
>24-30 months (n=21)	29 hours ± 25 hours	$407 ± $353
>30-36 months (n=15)	22 hours ± 15 hours	$303 ± $213
>36 months (n=8)	33 hours ± 18 hours	$442 ± $238

*Mean is per recipient alive at beginning of each period studied

The costs associated with the time spent by family members or friends accompanying the patient during a follow-up visit are the same and might even reach double of what is seen for recipients due to the additional time these members and friends may need to reach the patient's home. In estimating this cost, we assumed that all patients were accompanied for 25% of visits, which is a conservative estimate given the increased independence of patients after transplantation. Estimates of the cost for time lost by family members and friends are presented in table 35 with a sensitivity analysis varying the time needed for the visit (from the same time to twice the time noted for recipients). For a detailed account of resource valuation see Appendix B (section B9).

Table 35. Costs associated with time lost by friends and family members accompanying recipients to medical care visits.

	Sensitivity analysis		
Post-transplantation	Assuming friends and family need same time	Assuming friends and family need time and a half for each visit	Assuming friends and family need double the time for each visit
Year 1 (0-12 months)	$518	$776	$1,552
Year 2 (>12-24 months)	$251	$377	$754
Year 3 (>24-36 months)	$178	$266	$532
Year 4 (>36-+months)	$111	$166	$332

5.5 Economic Evaluation: Cost-effectiveness and cost-utility analysis

5.5.1 Quality adjusted life years

In order to assess the potential quality adjusted life years associated with transplantation, average utility scores were calculated for the full cohort and separately for the obstructive airways disease group and cystic fibrosis and bronchiectasis disease groups. For the restrictive and pulmonary vascular disease groups, due to the small number of patients interviewed, quality adjusted life years were calculated using utility scores obtained from the full cohort. The average utility scores during the waiting list and per post-transplant year are presented in table 36. A utility score of 0 (for death) was assigned to each of the eight deceased patients. The date of this utility score was taken to be the date of their death.

Table 36. Utility estimates by period of time, before and after transplantation

	Full cohort	OAD group	CF & Bronchiectasis group
Time periods	Mean ± S.D.		
Waiting list	0.17 ± 0.17 (n=37)	0.23 ± 0.19 (n=16)	0.11 ± 0.12 (n=8)
1st year	0.80 ± 0.29 (n=24)	0.77 ± 0.27 (n=9)	0.83 ± 0.26 (n=10)
2nd year	0.87 ± 0.24 (n=13)	0.73 ± 0.36 (n=4)	0.93 ± 0.17 (n=8)
3rd year	0.64 ± 0.40 (n=9)	0.78 ± 0.22 (n=5)	0.95 ± 0 (n=2)
4th year	0.94 ± 0.07 (n=10)	0.90 ± 0.10 (n=3)	0.98 ± 0.03 (n=3)
5th year and beyond	0.62 ± 0.30 (n=20)	0.52 ± 0.28 (n=9)	0.72 ± 0.38 (n=7)

The incremental average QALY gained per patient, for the full cohort, was 0.62 (95% CI: 0.50, 0.73) (see Appendix F, table F1). The mean QALY gained was higher than the LY (0.57 (95% CI: 0.36, 0.78)) gained because of the increased quality of life conferred by transplantation.

The highest QALY benefit observed from transplantation was in the CF and bronchiectasis group with an average of 0.81 (95% CI: 0.58, 1.04) QALYs gained per patient (table F3). This was followed by the OAD group with an average QALY gained of 0.51 (95% CI: 0.35, 0.68) per patient (table F2). Similarly, the average QALY gained in the RESD group was 0.51 (95% CI: 0.23, 0.79) per patient (table F4). No significant difference was observed in the PVD group, (0.44, 95% CI: -0.28, 1.16) (table F5).

5.5.2 Sensitivity analysis

5.5.2.1 Different scenarios of waiting list and post-transplant survival

The mean LY and QALY estimates presented throughout the study are the ones that reflected the dynamics of the lung transplant program during the observational period (i.e. patients present on waiting list, organ availability and success rate of transplant team). Varying these factors would yield different results with respect to the person-time experiences of patients in the lung transplant program as non-transplant and transplant patients.

Different person-month scenario experiences were considered in order to deal with the censorship due to transplantation, which decreases artificially the survival estimate of patients without transplantation in our study. An additional person-month scenario was studied to consider an increased success rate of the transplant team. The influence on varying the person-month experiences on the incremental LYs and QALYs conferred by lung transplantation is presented in table 37. Due to the increased quality of life reported in the post-transplant phase, as opposed to the waiting list, the QALY estimates were less susceptible to become negative (not beneficial) with survival variations.

Table 37a. Effect of varying the mean survival experience during waiting list and post-transplant period on the potential LYs and QALYs gained

Non-Tx Survival*	Transplant survival*	Non-Tx QALY	Transplant QALY	LY gained	QALY gained
1.50 years (2232 p-m)	1.30 years (1422 p-m)	0.26	0.74	-0.20	0.48
2.00 years (2976 p-m)	1.30 years (1422 p-m)	0.34	0.74	-0.70	0.40
3.00 years (4464 p-m)	1.30 years (1422 p-m)	0.51	0.74	-1.70	0.23
4.00 years (5952 p-m)	1.30 years (1422 p-m)	0.68	0.74	-2.70	0.06
6.00 years (8928 p-m)	1.30 years (1422 p-m)	1.02	0.74	-4.70	-0.28
0.73 years (1090 p-m)	**2.75 years (3000 p-m)**	0.12	1.64	2.02	1.52
0.73 years (1090 p-m)	**4.00 years (4368 p-m)**	0.12	2.43	3.27	2.31
0.73 years (1090 p-m)	**8 years (8736 p-m)**	0.12	4.79	7.27	4.67

* Bold cells indicate where survival was varied. P-m: person-months

5.5.2.2 Reported utility on QALY estimates

Increasing the utility associated with the non-transplant phase decreased the QALY gained due to lung transplantation. Given a non-transplant utility of 0.30, lung transplantation ceases to provide a QALY benefit when patients have a 2.5-year survival during the waiting list ((0.30*2.5) = 0.75 QALYs while waiting versus 0.74 QALYs after transplantation).

Table 37b. Effect of varying utility during the waiting time on the QALYs gained

Non-Tx Survival*	Transplant survival*	Non-Tx QALY Varying utility from 0.17 to 0.30	Transplant QALY	QALY gained
1.50 years (2232 p-m)	1.30 years (1422 p-m)	0.45	0.74	0.29
2.00 years (2976 p-m)	1.30 years (1422 p-m)	0.60	0.74	0.14
3.00 years (4464 p-m)	1.30 years (1422 p-m)	0.90	0.74	-0.16
4.00 years (5952 p-m)	1.30 years (1422 p-m)	1.20	0.74	-0.46
6.00 years (8928 p-m)	1.30 years (1422 p-m)	1.80	0.74	-1.06
0.73 years (1090 p-m)	**2.75 years (3000 p-m)**	0.22	1.64	1.42
0.73 years (1090 p-m)	**4.00 years (4368 p-m)**	0.22	2.43	2.21
0.73 years (1090 p-m)	**8 years (8736 p-m)**	0.22	4.79	4.57

* Bold cells indicate where survival was varied. P-m: person-months

5.5.3 Summary of costs

A summary of the direct medical costs incurred and captured throughout the study follow-up period is presented in table 38a, 38b, and 38c. The costs presented are the sum of all average costs, observed in the previous section (5.4) in disaggregated form, per patient in cohort. The average cost per patient incurred during the 8.8 ± 5.8 months of waiting time reached $15,015 or $1,708 per month (table 38a).

Table 38a. Summary of mean costs incurred per patient during waiting time

	PRE-TRANSPLANT PERIOD (N=124)
	Mean direct medical cost per patient (Discounted at a rate of 5%)
Hospitalizations (including physician fees)	$9,210 (95% CI: $6,846 - $11,574)
Outpatient clinic visits	$349 (95% CI: $284 - $414)
Physician fees (outpatient diagnostic acts)	$140 (95% CI: $114 - $166)
Physiotherapy visits	$201 (95% CI: $201 - $201)
Emergency room visits	$29 (95% CI: $8 - $50)
One-day surgery	$50 (95% CI: $16 - $84)
Ambulatory care unit visits	$8 (95% CI: $0 - $20)
Home care visits	$161 (95% CI: $68 - $254)
Outpatient medications	$1,455 (95% CI: $1,174 - $1,736)
Oxygen therapy and medical devices	$3,412 (95% CI: $2,954 - $3,870)
Total	**$15,015 (95% CI: $11,665 - $18,369)**
Cost per person-month	**$1,708 (95% CI: $1,327 - $2,090)**

The fixed costs induced by the lung transplant program, in the pre-transplant phase reached $2,993 per patient. The average cost of lung transplantation in this study totaled $49,314 (table 38b). The direct mean medical costs incurred after transplantation are presented in table 38c for each follow-up year.

Table 38b. Summary of mean costs incurred per patient for transplantation

	Fixed mean costs per patient: Related to the lung transplant program incurred before transplantation (Discounted at a rate of 5%)
Evaluation process for those not on list	**$6,629**
Evaluation process for candidates (N=124)	**$2,484**
Lung transplant program operating costs	**$509**
	TRANSPLANTATION (N=91) Mean direct medical cost per patient (Discounted at a rate of 5%)
Organ acquisition and harvesting	$5,325 (sensitivity range $2,300 - $18,403)
Transplant procedure and inpatient follow-up care	$35,276 (95% CI: $28,670 - $41,872)
Physician fees	$8,713 (95% CI: $8,236 - $9,190)
Total	**$49,314 (95% CI: $39,216, $69,465)**

Table 38c. Summary of mean costs incurred per patient during post-transplant period

	POST-TRANSLPLANT PERIOD		
	Mean direct medical cost (95% CI) per patient per year (Discounted at a rate of 5%)		
	OUTPATIENT	**INPATIENT**	**MEDICATIONS**
Year 1 (n=91) (0-12 months)	$8,717 ($6,678 - $11,048)	$13,248 ($6,167 - $20,339)	$11,680 ($9,235 - $14,125)
Year 2 (n=49) (>12-24 months)	$2,560 ($2,069 - $3,059)	$6,872 ($2,051 - $11,838)	$10,288 ($7,986 - $12,590)
Year 3 (n=21) (>24-36 months)	$1,835 ($1,469 - $2,201)	$10,989 ($1,664 - $20,314)	$8,164 ($6,515 - $9,811)
Year 4 (n=8) (>36-+months)	$1,193 ($1,042 - $1,344)	$1,912 ($784 - $3,040)	$8,550 ($7,387 - $9,713)
	Total Post-transplant cost	**Cost per patient per month**	
Year 1	$33,645 ($22,081 - $45,501)	$2,804 ($1,840 - $3,792)	
Year 2	$19,720 ($12,106 - $27,488)	$1,643 ($1,009 - $2,291)	
Year 3	$20,988 ($9,648 - $32,326)	$1,749 ($804 - $2,690)	
Year 4	$11,655 ($9,213 - $14,097)	$971 ($768 - $1,175)	
TOTAL	**$86,008 ($53,048 - $119,412)**		

The total mean direct medical costs incurred per patient in the cystic fibrosis and bronchiectasis disease group during the 9.3 ± 6.4 months of waiting list follow-up was $27,347 (95% CI: $21,337 - $33,408); which translates to an average cost per month of $2,941 (95% CI: $2,294 - $3,592). The average cost of lung transplantation in this patient group was estimated at $45,977 (95% CI: $38,068 - $63,937). Finally, the average cost associated with the post-transplant follow-up of these patients was $69,254 (95% CI: $31,919 - $115,338) (see Appendix G, table G1a, b and c for a breakdown of the costs).

The direct non-medical and indirect costs incurred throughout the study are presented in table 39.

Table 39. Summary of direct non-medical and indirect costs

	Direct non- medical costs Mean (95% CI)		**Indirect costs Mean (95% CI)**	
	Total	Cost per person-month	Total	Cost per person-month
Pre-transplant	$247 ($171 - $323)	$28 ($20 - $37)	$1,266 ($1,098 - $1,434)	$144 ($125 - $163)
Year 1	$899 ($489 - $1,309)	$102 ($73 - $138)	$2,846 ($2,311 - $3,899)	$323 ($263 - $443)
Year 2	$927 ($640 - $1,214)	$105 ($73 - $138)	$1,382 ($1,109 - $1,907)	$157 ($126 - $217)
Year 3	$549 ($385 - $713)	$62 ($44 - $81)	$976 ($769 - $1,360)	$111 ($87 - $155)
Year 4	$335 ($277 - $393)	$38 ($32 - $45)	$608 ($503 - $824)	$69 ($57, $94)

5.5.4 Cost-effectiveness and cost-utility ratios observed during the study period

In the present cohort the average cost of lung transplantation observed during our follow-up period, from a health care perspective, reached on average $302,160 per one life year saved and $245,149 per quality adjusted life year saved (see table 40 for calculation components of these estimates).

Table 40. Incremental cost-effectiveness and cost-utility ratio

Total cohort	Cost/Effectiveness ratio of total costs*	Cost/Utility ratio of total costs*
Incremental cost	$144,944 - $15,015 = $129,929	$144,944 - $15,015 = $129,929
Incremental effectiveness	1.15 LY - 0.72 LY = 0.43 LY	0.65 QALY - 0.12 QALY = 0.53 QALY
	$129,929 / 0.43 LY = $302,160 per life year gained	$129,929 / 0.53 QALY = $245,149 per QALY gained

*Total includes medical direct costs per patient on average per period studied: waiting list and total post-transplant period (discounted at 5%).

When excluding the additional $6,629 induced by patients not accepted on the list, during the evaluation process, the C/E and C/U estimates reached $286,74 ($123,300 / 0.43) per LY and $232,642 ($123,300 / 0.53) per QALY gained, respectively. The discounted costs per LY and QALY gained, when overhead costs were excluded, decreased to $238,102 and $193,177, respectively (for more details see methods section 4.9.3.5).

Including non-medical and indirect costs to total medical costs yielded C/E and C/U estimates (discounted at 5%) ranging $318,461 per LY and $258,374 per QALY gained, respectively.

Varying the discount rate to 3% yielded a C/E and C/U of $295,214 per LY and $229,056 per QALY gained, respectively.

In the cystic fibrosis and bronchiectasis disease group the incremental cost per life year and quality adjusted life year gained, when taking the health care viewpoint, were $221,605 and $137,332 and (for calculation components see Appendix G, tables G2 & G3). When excluding the additional estimated $6,629 induced by patients not accepted on the list, during the evaluation process, the C/E and C/U estimates reached $206,539 per life year ($90,877 / 0.44) LY and $127,996 per QALY ($90,877 / 0.71) QALY gained, respectively.

5.5.4.1 Modeling the cost-effectiveness and cost-utility of lung transplantation beyond the study period

The extrapolated mean life expectancy of end-stage lung disease patients awaiting transplantation and recipients was 2.2 ± 0.7 and 5.7 ± 3.03, respectively. The discounted (5% and 3%) C/E and C/U ratios based on extrapolations beyond the study follow-up period (discussed in section 4.9.3.4) are presented in table 41.

Table 41. Extrapolated incremental cost-effectiveness and cost-utility ratios

	Discounted (5%)	Discounted (3%)
Incremental cost-effectiveness	($207,600 - $49,311) / (4.69 LY – 2.14 LY)	($215,239 - $50,055) / (5.06 LY – 2.17 LY)
Ratio*	$62,074 per life year gained	$57,157 per life year gained
Incremental cost-utility	($207,600 - $49,311) / (2.55 QALY – 0.36 QALY)	($215,239 - $50,055) / (2.75 QALY – 0.37 QALY)
Ratio*	$72,278 per QALY gained	$69,405 per QALY gained

*Ratios are not exact due to rounding.

Including extrapolated direct non-medical and indirect costs yielded projected C/E and C/U (discounted at 5%) estimated reaching $65,020 per LY and $75,708 per QALY gained, respectively.

Varying the waiting list utility from 0.17 to 0.30 yielded a C/U projected estimate (discounted at 5%) of $82,874 per QALY gained.

5.5.4.2 Effect of varying the non-transplant and transplant survival experience on the cost-effectiveness and cost-utility ratios

Different case survival scenarios and their effect on the cost-effectiveness and cost-utility ratio (table 42) were studied. The incremental cost estimates were based on the cost per month observed for each period (i.e. pre-transplant, transplant and post-transplant) (table 38a, b and c) (for more information see section 4.9.3.3 and 4.9.3.4). The incremental QALYs observed were for each corresponding year and the utilities used in the calculation of the QALYs are presented in table 36 (for calculation methods see section 4.5.5.2).

As seen, the effect of prolonging the survival associated with non-transplantation was associated with a lung transplant procedure that was costlier and less effective (table 42). Inversely, prolonging non-transplant survival, on the cost-utility estimate, decreased the incremental cost for every QALY gained (table 42). This is due to the fact that the QALY associated to each additional year while waiting does not

counterbalance the cost associated for the waiting time and thus decreases the incremental cost of lung transplantation.

Furthermore, the results show that prolonging post-transplant survival decreased the cost per life year and QALY gained (table 42). That is, transplantation became more favorable. The increment in cost incurred per year was not very high due to the fact that an important percentage of costs (fixed and transplant procedure costs) were incurred early on (tables 38b and 38c).

Table 42. The effect of varying survival and utility on the C/E and C/U ratio

Assuming a 10-year follow-up & a survival benefit of (years)	C/E	C/U	$C/U_{(WL=0.30)}$
1 year with no Tx and 2 years with L-Tx:	$237,199	$213,117	$242,907
1 year with no Tx and 4 years with L-Tx:	$82,954	$99,957	$106,058
1 year with no Tx and 6 years with L-Tx:	$52,178	$65,670	$68,249
1 year with no Tx and 8 years with L-Tx:	$39,041	$48,897	$50,313
2 years with no Tx and 2 years with L-Tx:	No gain	$229,802	$320,330
2 years with no Tx and 4 years with L-Tx:	$116,544	$98,367	$111,905
2 years with no Tx and 6 years with L-Tx:	$61,113	$62,958	$68,242
2 years with no Tx and 8 years with L-Tx:	$42,694	$46,294	$49,089
3 years with no Tx and 2 years with L-Tx:	No gain	$252,444	$504,581
3 years with no Tx and 4 years with L-Tx:	$217,394	$96,606	$119,448
3 years with no Tx and 6 years with L-Tx:	$76,028	$60,115	$68,234
3 years with no Tx and 8 years with L-Tx:	$47,822	$43,633	$47,758
5 years with no Tx and 2 years with L-Tx:	No gain	$335,149	No gain
5 years with no Tx and 4 years with L-Tx:	No gain	$92,461	$143,710
5 years with no Tx and 6 years with L-Tx:	$195,560	$54,006	$68,215
5 years with no Tx and 8 years with L-Tx:	$68,392	$38,143	$44,722

All costs based on direct medical costs, except where noted.

Costs and clinical effects were discounted at a rate of 5%

6.0 Discussion

Apart from the cost-effectiveness and cost-utility results, our study presents results related to survival, HRQOL, utility and costs related to end-stage lung disease and transplantation. Each result is discussed with its limitations and interpretations. Some limitations however are discussed separately because they may affect all the results.

6.1 General study limitations

6.1.1 Patients on waiting list as proxy for non-transplant experience

A proper alternative to which lung transplantation can be compared has raised some concerns. Comparing the costs and effects of lung transplants to those associated with standard therapy implies a selection bias as end stage lung diseased patients accepted to be put on the waiting list differ from those who were not accepted. To resolve such issues a peer-reviewed model has been proposed by a group, from the Office for Medical Technology Assessment, in the Netherlands. Van Enckevort and colleagues (1997), proposed to estimate the alternative, no transplantation, on what was observed during the waiting list period. All patients, transplanted or not, passed the same screening process and therefore are similar (i.e. good internal validity). This strategy however has several limitations because most of the patients on the waiting list become transplanted. Therefore the group on the waiting list does not provide an accurate picture of the survival experience of true controls that do not undergo lung transplantation. The pre-transplant follow-up is therefore shorter than what would be expected without transplantation. The waiting

list control group provides a very biased (i.e. poor external validity) representation of the true pre-transplant experience. Moreover, several factors related to the selection process of the local transplant clinic's policies might affect the generalizability of the results. In the following section we are going to describe these biases and discuss their possible effect on the interpretation of the results.

6.1.1.1 Issues of Internal validity: Transplant censorship bias

A type of bias is introduced when the waiting list period for some patients is cut short due to the fact that they became lung recipients. This censorship bias due to transplantation will affect: (i) the rate ratios when comparing survival after transplantation relative to the one without, (ii) the life years (LY) and quality adjusted life years (QALY) when comparing the benefits of transplantation and (iii) the number of events experienced and health care resources utilized.

When studying the rate ratios, we assumed a constant death rate during the pre-transplant period. Therefore the rate ratio is not affected by censorship. Because the pre-transplant survival time is short (<2.5 years on average) and the death rate is high the increase will therefore always be minimal. However if the death rate increases with time (because disease becomes more severe), the rate ratio would be more favorable for lung transplantation. Therefore, the results we present are likely to be valid and if biased, in a conservative direction.

Although the choice of waiting list candidates as a proxy for non-transplanted patients has a good internal validity (the same population is studied before and after transplantation) it produces a very biased estimate of the control experience. This censorship bias overestimates the mean LYs and QALYs gained with transplantation by underestimating the actual survival associated with the pre-transplant phase. In order to account for this bias we developed different scenarios, which are presented and described in detail in section 5.5.2.1 (table 37a). Extrapolations of survival estimates beyond the study period were carried out for both the pre-transplant and post-transplant period (section 5.5.4.1). The sensitivity analyses carried out throughout the study presented a wide range of person-time experiences with transplantation (1 to 8 years) and without transplantation (1 to 6 years).

Censorship due to transplantation also underestimates the number of events experienced and health care resources utilized before transplantation. This overestimates the incremental difference in costs. Because the number of events is time dependent with direct effects on cost, we calculated the overall cost for the time period observed in the study. We then computed a cost-per month of follow-up. This monthly cost was then attributed to every extra month added to the follow-up through the different scenarios of survival time. One assumption is that the number of events does not change with time during the pre-transplant phase. It is a reasonable assumption (section 4.9.3.4).

6.1.1.2 Issue of external validity: selection bias related to waiting list selection

Although international guidelines have been well established, one has to keep in mind the potential of a bias due to the type of patients accepted into the program. The selection of eligible patients into the program and medical care rendered are implicitly based on each study center's policies and experience with the program, respectively. This type of bias is difficult to measure and influences the generalizability of the results across countries and/or different centers practicing lung transplantation. The type of patients accepted into the program influences, not only the survival but also, the health related quality of life and utility before and after transplantation. The stage at which patients are captured in the program, with respect to their disease state, may underestimate or overestimate the incremental difference in QALYs gained due to transplantation. When healthier patients are admitted in the waiting list the QALY gained that is captured is reduced and inversely, when sicker patients are admitted the QALY gained due to transplantation is overestimated. The utility associated with the pre-transplant phase was also subject to sensitivity analysis in order to observe variations in the QALY (section 5.5.2.2, table 37b).

6.1.2 Post-transplant experience: Issue of external validity

Apart from the patient and transplantation related risk factors that are studied, and discussed later on in this chapter, post-transplant survival is influenced by the type of patients that are accepted for lung transplantation among the pre-determined pool of candidates, donor selection criteria, the surgeon's technical experience with the procedure and the medical follow-up care rendered by the lung transplant team.

What we have in summary is the Montreal lung transplant experience. To deal with this problem and give a broader perspective with different success rates we computed the cost-effectiveness analysis with different post-transplant survival scenarios (section 5.5.4.2, table 42). Cost estimates for the post-transplant phase when survival time was changed is described in section 4.9.3.4

As a lung transplant team's experience with the procedure and follow-up of lung recipients increases so does the survival success in the post-transplant phase. Although, this renders lung transplantation more costly, because of the increased follow-up, it becomes more effective due to the increased life year gained.

An additional influential factor, with the present-day limitations in organ availability, is the acceptance of marginal donors. Quebec Transplant (2003) defines a donor as marginal if at least one of following criteria apply: older donors (> 55 years), a higher smoking exposure (> 20 pack years), lower blood gas levels (PO_2 < 350 mg), the presence of purulent secretions and chest radiographic infiltrates. Although we did not study the effect of donor characteristics on mortality, some authors have reported findings that suggest an association may exist. Using similar criteria for assessing marginal donors and their influence on post-operative function, Pierre and colleagues (2002) reported an increased mortality, within 30 days of transplantation, in patients having received than in those not having received marginal donor lungs. Another study, reporting on the association between donor cause of death and post-operative outcomes, found that death from a traumatic brain

injury significantly increased one's chance of early rejection episodes and the development of bronchiolitis obliterans (Ciccone et al., 2002), which is an important limiting factor in the success of long-term lung transplantation (ISHLT, 2002).

In the present study centre context, marginal donors are accepted on a case-by-case basis. It is not common practice; however, when a case is valued severe enough with little life expectancy a marginal donor may be considered. The acceptance of marginal donor organs largely depends on each transplant centre's policy and pool of candidates. Given the published results, a centre's use of marginal donors would negatively influence the clinical effect to cost ratio of lung transplantation. The high cost associated with the transplant procedure, as well as the important fixed costs induced early on in the program, would need to be balanced with a significant clinical benefit.

6.1.3 Misclassification bias

6.1.3.1 Issue of differential follow-up

It is possible that follow-up of patients in the post-transplant phase, as compared to the waiting list, may have been more rigid. Patients on the waiting list were seen at the study center every three months and all new medical information was noted in their charts at that time. After transplantation all patients were followed at the study center. Therefore, it is very possible some clinical event or medical visits may have been missed during the waiting list period, especially in patients who were followed at health care centers not affiliated to the CHUM.

This information bias however is not likely to be important, as it is unlikely to be frequent. As mentioned, candidates on the list contacted the transplant clinic when any new events, such as hospitalizations, occurred. There was also an extensive follow-up during the medical visit at the lung transplant clinic. Both the referring doctor and patient were aware of the importance a new clinical event may have on their waiting list status. All major health events had to be transmitted to the lung transplant surgeon through the coordinating nurse responsible for the management of any new information on patients in the study. Moreover, all candidates living two hours away from the Notre Dame hospital, had to move to Montreal while they were awaiting the transplant and were followed at one of the CHUM affiliated hospitals. Information was ascertained through the medical files.

For all these reasons we do not think this bias had a significant effect on the estimates observed. Finally, if it plays a role, this bias will underestimate the severity and health care resource utilization during the waiting list study period and overestimate the cost-effectiveness ratio of lung transplantation. This would yield a conservative estimate with respect to the cost necessary for one life year gained.

6.1.3.2 Errors in measuring health related quality of life and utility

In the study of health related quality of life, 15 eligible recipients and 1 eligible candidate refused to participate. There were also, 5 deaths among recipients and 3 deaths among candidates during the active recruitment period (October 18th, 2000 to October 28th, 2001). Patients followed at the lung transplant program at the Hôpital Notre-Dame, recipients (n=44) or candidates (n=17), who died prior to the start of the study, could not be interviewed. Both refusal to participate and mortality may introduce a bias because they are likely associated with HRQOL and to transplant status. If the non-participant and deceased candidates (10.5%) tend to score lower than candidates who participate, the observed HRQOL gain, conferred by the transplant procedure, would be underestimated and therefore would be a conservative estimate. Moreover, if non-participating and deceased recipients (22%) score lower than those participating, the benefit conferred in HRQOL from lung transplantation would be overestimated. On the other hand, if the non-participating recipients (16.5%) had better HRQOL, the benefit conferred by the procedure would be once again underestimated. The choice not to attribute any HRQOL scores for these non-participants and deceased patients is explained in section 4.11.1 (methods).

In summary, waiting list scores are very low and therefore people who died are likely to have little influence on these estimates. In the post-transplant period there might be a large difference between survivors (high quality of life) and those who died (low quality of life). This bias would most likely overestimate the effect. However, the cross-sectional manner of measuring HRQOL in this study does not

preclude the fact that there were deaths that occurred in the near future after the interview. Therefore, although HRQOL was elicited in surviving participants, the HRQOL reported reflects the various ranges of health states that may be observed in candidates and recipients.

Utility measures the preference of a health state where the scoring ranges from 0, for death, to 1, for perfect health. In the study of utility, the losses due to death were dealt with by assigning a score of 0 to those who had died before participation in the study could be elicited. This deals with any potential bias that may be introduced by obtaining information solely from survivors. The estimates of utility in candidates and recipients are therefore lower than those had the deceased patients been ignored. This has the effect to decrease overall the incremental QALY gained associated with transplantation and render the cost-utility estimates more conservative. The utility and QALY estimates were therefore valid and if biased were so in a conservative direction.

6.1.3.3 Issues related to the utility measurement tool used

The use of the standard gamble in assessing utilities may have prompted some discussion. As mentioned in section 2.10, the choice of the standard gamble was used based on the fact that utilities versus values (as assessed by ex. the TTO and VAS) should be elicited for health problems that are uncertain and utilities capture the individual's risk attitude, which is essential for problems that contain uncertainty (Mehrez and Gafni 1991; Gold et al., 1996; Drummond et al., 1997).

The standard gamble however is based on the assumption that subjects are "neutral towards probability risks". Duru and colleagues (2002) state if a person has a strong dislike for risk, the SG in this case will overestimate the true utility, while at the same time underestimate it for people who are not risk averse.

In our study, candidates may have been more ready to accept a risk, thus underestimating the utility associated while waiting. Recipients on the other hand may have been more risk averse not wanting to undergo another intervention and this may have overestimated the post-transplant utility. This would have overestimated the QALY gained in our analyses and decreased the C/U estimates. Our results however did show variability in the reported utility as the post-transplant time went by and utility never reached perfect health. Furthermore, our utility scores were highly correlated with the 8 HRQOL domains (section 5.3.4) as assessed with the SF-36, which is an instrument that measures a health context under certainty.

In order to account for a potential bias we presented C/U estimates with a reduced mean QALY gained by increasing the pre transplant utility to 0.30 as opposed to the 0.17 utility observed. This decreased the QALY gained in the denominator yielding more conservative estimates (section 5.5.2.2 and 5.5.4.1).

6.1.4 Interviewer bias

In the present study, it was not possible to be blinded to a patient's transplant status (whether candidate or recipient). The lung transplant clinic on Tuesdays

catered to the follow-up of candidates and the clinic on Wednesdays catered to recipients. To prevent interviewer bias, the procedure in eliciting information was standardized from the use of a questionnaire that was very similar for both candidates and recipients. Furthermore, the assessment of utility was carried out following the same procedure, which was written out, during both interview days, as described by Drummond. The process of interviewing was the same for each patient with the same order: ascertainment of medical and personal information, SF-36 was completed and finally, utility was elicited.

Although an interviewer bias could be introduced, this was contained through the use of standardized questionnaires, case report forms and, the sequence of timing of events during the face-to-face interviews.

6.1.5 Summary

In conclusion, all the problems listed above are real but the use of different scenarios with a wide range of pre and post-transplant survival experiences allows for numerous situations and increases the possibility to generalize the results (see section 6.7).

6.2 Cost-effectiveness and cost-utility of lung transplantation

In this study, the incremental cost per life year and QALY gained for lung transplantation, from the healthcare perspective, was $302,160 (CDN) and $245,149 (CDN), respectively. Although it is difficult to compare costs from one country to

another, due to health care policies, patient populations and donor rates, all studies carrying out an economic evaluation of lung transplants concluded to the high cost relative to the benefits observed (i.e. high cost-effectiveness ratio). The C/E and C/U estimates observed in our study however represent the patient structure of a young program and therefore these estimates are the maximum that one may observe for the Quebec lung transplant program.

In extrapolating beyond our study period, the discounted at 5% and 3% C/E and C/U estimates reached $62,074 per LY and $72,278 per QALY gained and, $57,157 per LY and $69,405 per QALY gained, respectively. Decreasing the QALY gained from transplantation yielded (see section 6.1.3.3) a C/U of $82,874. Including direct non-medical and indirect costs yielded C/E and C/U estimates (discounted at 5%) that reached $65,020 and $75,708 per LY and QALY gained, respectively. The C/E estimate is in the vicinity of the ones reported by Maurer (1996): $62,860 per LY in all patients studied (n=32) and $54,178 per LY for uncomplicated patients. One of the earlier studies, carried out in the US by Ramsey and colleagues (1995), reported a C/U ratio of $176,817. Their pilot study was based on a cross-sectional cohort of few patients (n=24 candidates and n=28 recipients). In the Netherlands, van Enckevort and colleagues (1998) reported a cost per life year and QALY gained of $90,000 and $71,000, respectively in US dollars for a projected 15-year follow-up. This group followed 120 patients on the waiting list, 57 of which became lung recipients. A more recent study carried out in the UK by Anyanwu and colleagues (2002) projected, for a 15 year post-transplant follow-up through modeling, a cost-

effectiveness and cost-utility ratio for single, double and heart-lung transplantation. They reported a discounted cost per life year and cost per QALY gained of $50,825 and $48,241 for single lung, $45,393 and $32,803 for double lung and, $41,720 and $29,285 for heart-lung transplantations.

Unlike our study, and those previously mentioned, which were based on data from a single center, the UK study was based on 677 lung transplants in 7 study centers. The authors discuss the advantage of the study in terms of the numbers but also, the inclusion of a wide range of patient characteristics, patient selection and study center practices. The study confers an increased precision in the estimates and a higher generalizability of the results in terms of type of transplant received, which was never previously presented. Although these are positive issues when interpreting results, the validity of this method may be questioned. It is unclear which diseases and what proportions were present in each type of transplant received. It may not be valid to group different patients with varying disease processes. Furthermore, it is still unclear whether some diseases do benefit and if they should be considered for the procedure.

In our study, the most important benefit observed was in the cystic fibrosis and bronchiectasis disease groups, which are the most important indications for double lung transplants. From a health care perspective, the cost (direct medical) per life year and QALY gained was $221,605 and $137,332, respectively. These estimates are much lower than the ones observed for the total cohort suggesting a better cost

per benefit ratio. Furthermore, throughout our study, the incremental cost-utility ratios were lower than the cost-effectiveness ratios, which suggest an increased overall health preference for the post-transplant phase. Although these estimates are based on our single center experience and low sample size, the uniformity of patient selection within disease groups, as well as the clinical follow-up care, increases the validity of our results.

As mentioned throughout the study, the cost-effectiveness and cost-utility estimates presented were the ones that reflected the characteristics of the Quebec lung transplant program. The estimates were implicitly based on patient selection policies, organ availability and donor selection criteria and, experience and success of the lung transplant team. Variations in these factors yielded different person-time experiences, during the different periods of the program, which influenced the cost and the effectiveness of the intervention. If the policy of acceptance of patients unto the lung transplant waiting list were more open, the person-time experience of not being transplanted would be much greater than the one observed in our study period. On the other hand, if organ donor rates were higher, the availability of acceptable donor organs for transplantation would increase and therefore would subsequently decrease the person-time experience while waiting for a transplant.

A scenario analysis conducted by Al and colleagues (1998) reported that decreasing patient referral and acceptance and/or increasing donor supply would improve the C/E ratio. In our study, we found similar results. Excluding the

additional costs induced by screened patients (for more details see sections 4.3 and 6.6.2.1) not being accepted on the list did result in a decrease in the C/E and C/U estimates by $15,416 and $12,507 on average per patient, respectively. Furthermore, the operative experience and quality of the lung transplant team, with respect to the transplant procedure and medical care rendered may influence the person-time experience in the post-transplant phase. A better success rate would yield higher person-months and vice versa. Increasing the survival by 50% per patient decreased the cost per life year gained by 58% in our study.

The potential to underestimate the mean life years as a non-transplant patient (estimated through the waiting list experience) may have in fact overestimated the benefit associated with this procedure. Patients were censored during the waiting list due to death or due to the fact that they were called for a transplant. The natural observation of the progression of these candidates, with respect to survival, was not possible. In our study, the mean life years contributed by the cohort members as candidates (n=124) and recipients (n=91) were 0.73 and 1.30, respectively. The QALYs observed were 0.12 and 0.74, respectively. The discounted mean life years and QALYs gained, for the full cohort, were 0.43 and 0.53, respectively. The discounted gains observed from our extrapolations beyond the study period were 2.6 LYs and 2.2 QALYs gained (table 36). Survival extrapolations for with and without transplantation were based on data from the ISHLT and from our one-year waiting list survival observations. In the latter, the one-year survival for waiting list patients was 79.7%. Our waiting list survival estimate is much more favorable than the ones

reported by others. Hayden et al. (1993) reported a 6-month survival rate, while waiting for transplantation, of 81% for emphysema, 74% for CF, 60% for PPH and 38% for interstitial lung disease. Given, on average, the higher waiting time survival rate, our results yield a conservative estimate of the benefit conferred from transplantation.

The Dutch study carried out by van Enckevort and colleagues (1998) reported in total, 4.37 life years and 5.20 QALYs gained, from transplantation versus the scenario without the transplant program. Anyanwu and colleagues reported mean life years and QALYs gained in the order of 2 and 2.1 for single lung, and 2.4 and 3.3 for double lung transplants. The differing results are due to the varying follow-up times and survival estimates. Ramsey et al. (1995) reported mean life expectancies for the post-transplant and waiting list groups to be 5.89 and 5.32 years, respectively. In the Dutch study (1998), results were based on the estimated (lifetime) 15-year survival with and without the lung program, which was determined to be 7.4 and 3.0 years, respectively. Similarly, Anyanwu reported a non-transplant survival of 2.7 mean life years and, after a projected 15-year post-transplant follow-up, mean life years of 4.7 and 5, for single and double lung transplants, respectively.

Sensitivity analyses carried out by varying the non-transplant and post-transplant life years yielded varying cost-effectiveness results (section 5.5.4.1, table 42). Increasing the non-transplant experience increased the cost for every life year gained and as predicted, increasing post-transplant experience decreased the cost for every

life year saved. The incremental cost obtained by increasing post-transplant follow-up time, versus non-transplantation, did not substantially increase the additional cost. This is due to the fact that important costs were incurred during the evaluation process and during transplantation, which are not time-dependent.

In terms of the cost-utility estimates (table 42), when the post-transplant QALY is greater than the one observed in the non-transplant phase, increasing the non-transplant survival decreases the incremental cost for every QALY gained for transplantation. This is due to the fact that, because of the low utility associated with end-stage lung disease while waiting for a transplant, increasing the survival of these patients does not warrant the cost it induces. Transplantation therefore, given the better utility associated with it, becomes a better choice for some patients with similar QALY estimates.

6.3 Survival associated with lung transplantation

The survival probability observed after transplantation, between 1997 and 2001, in Montreal is similar to the statistics published by the ISHLT between 1998 and 2001 (2002). The survival rate in Montreal at one, two and three years post-transplantation was 80%, 73% and 56% respectively, compared to 76%, 68% and 58% between 5,595 recipients. The survival probability observed for single lung transplants carried out in our study center (n=56), for years 1, 2 and 3 post-transplantation were 76%, 62% and 46%. The ISHLT (2002) reported similar results for single lung transplants carried out between 1990 and 2000, on 7,798 recipients, with one, two and three year

survival probabilities of 73%, 64% and 55%, respectively. The one-year survival probability for double lung transplant recipients (n=35) in our study was 81%. The ISHLT registry (2002) also reported estimates for double lung transplants carried out during the same period on 6,448 recipients. The estimates reported for 1, 2 and 3 years post-transplantation were 74%, 66% and 59%, respectively.

The risk of death post-transplant is high and, was higher than the mortality rates on the waiting list in the first 30, 30-91 and, 91 days and beyond: rate ratios = 4.77, 2.20 and 1.19, on average, respectively (table 11) (figures and 3 & 4). Although only the first estimate of effect, for the first 30 days, was significant ($p. < 0.002$), the risk of death in the post-transplant phase, on average, never fell below the risk observed during the waiting list (figure 6). In the obstructive airways disease group there was no survival gain on average associated with transplantation (table 13). In the cystic fibrosis, bronchiectasis (table 15) and restrictive disease group (table 17), results suggest a survival gain after the first 30-day high-risk post-transplant period.

Two similar survival studies were carried out. The Hosenpud et al. study (1998) was based on registry data between 1992 and 1994, whereas the Charman et al. study (2002) reported survival data based on their single study center experience between 1984 and 1999. The following table presents a summary of the mortality estimates observed in our study and those reported from the above mentioned authors (table 44).

Table 44. Summary of mortality risks associated with lung transplantation relative to the waiting list by disease group

Hosenpud et al. study 1998	Emphysema (n=1274)	Cystic fibrosis (n=664)	Pulmonary fibrosis (n=481)
1-month	2.76	0.87	2.09
6-month	1.12	0.61	0.71
12-month	1.10	0.61	0.67
Charman et al. study 2002	OLD (n=163)	Cystic fibrosis (n=174)	Pulmonary fibrosis (n=100)
1-month	2.77	2.42	2.23
6-month	0.55	0.21	0.65
12-month	0.32	0.15	0.46
Our study	OAD (n=56)	Cystic fibrosis (n=29)	Restrictive diseases (n=28)
0-30 days	10.23 (1.24, 84.67)	1.55 (0.17, 14.32)	4.26 (1.01, 18.03)
>30-91 days	7.39 (1.08, 50.67)	0.24 (0.03, 2.11)	0.79 (0.08, 7.41)
>91days	3.40 (0.35 – 32.98)	-	-

Hosenpud and colleagues (1998), in the 2 years of follow-up, did not find a survival benefit associated with lung-transplantation in emphysema patients. Although we studied different post-transplant time periods, for a mean post-transplant follow-up time of 16.3 ± 12.7 months, the results obtained were similar. The difference in magnitude of the rate ratios observed is most likely due to the increased precision conferred from the Hosenpud reported estimates.

In the Charman et al. (2002) study however, in the obstructive lung disease group, a survival benefit was reported at 104 days post-transplant. The benefit reported in this study might be due to the fact that there was a total of 21.5% and 22.1% of patients receiving a double lung and a heart-lung transplant, respectively. In our

study, there were no heart-lung transplants included in the survival analysis and there were only 7.1% of patients enlisted for a double lung transplant. Moreover, our results did show a positive association between double lung transplantation and survival (table 19). Ninety-two percent of the transplants indicated for our OAD group however were for a single lung. The ISHLT (2002) reported, for emphysema and COPD, patients that receive a single lung have a worse survival than those receiving a double lung transplant ($p. < 0.0001$) (ISHLT, 2002). Another group of authors (Cassivi et al., 2002) found similar results suggesting single lung transplantation in this disease group is a mortality risk factor. The observed differences, between our study and Charman's, may also in part be explained by the differences in the number of patients included in this disease category. Apart from study center differences as to the type of transplantation offered, their study included 4 patients with asthma and 5 cases of obliterative bronchiolitis, none of which were included in our analyses for this disease group. Furthermore, their analyses were based on their study center experience from 1984 to 1999. During this period, there was the implementation of the international guidelines in selection criteria for lung transplant candidates as well as changes to them (1998). Many contraindications became relative contraindications (i.e. prednisone dependence), which affected this disease group. This in turn suggests that throughout the years, patients in their obstructive lung disease group were not selected following the same eligibility criteria. The type of patients selected, with respect to their disease prognosis, may explain the results. It is not clear what health policy their study center holds with respect to admissions and on donor criteria. For instance, they might be a less

aggressive lung transplant center with respect to accepting marginal donors and this may have an influence on survival in the early (Pierre et al., 2002) and late (Ciccone et al., 2002) post-transplant phase. Moreover, the experience of the lung transplant team in their center, with respect to the surgical procedure and medical follow-up care, is much greater than in ours, which houses the program since 1995. This 9-year difference in transplant experience may have an influence on the success rate of their transplant team and may explain the better results observed in their study.

In our study, mortality rate ratios for the CF (n=29) and bronchiectasis (n=7) patient population were in the order of 1.43 for the first 30 days and fell to 0.28 after this time period. The mean follow-up time was 16.3 ± 11.0 months. Restricting the analysis to CF patients yielded a rate ratio of 1.55 for the first 30 days and 0.24 thereafter. Although not statistically significant in our study, due to the low power, these results are similar to the ones reported by Charman and colleagues (2002) on a group of 174 cystic fibrosis patients (table 44). Hosenpud et al. (1998) also reported a survival benefit associated with lung-transplantation in CF patients, and this right after the 26 days.

Results observed for our restrictive disease group were based on a mean follow-up of 12.7 ± 14.7 months. Although in our study the death rates are higher, the results are in the same direction as those reported by Hosenpud et al., (1998) and Charman et al., (2002) (table 44). The difference with respect to the magnitude of effect observed between our study results and those published, apart from the differing sources of

data as previously mentioned, may be due to the type of patients included. Our restrictive disease group included patients with not only idiopathic pulmonary fibrosis but patients with sarcoidosis and eosinophilic granulomatosis. It is unclear what the composition of the pulmonary fibrosis groups of these two other studies are. Although the same disease process a difference may exist in the survival benefit conferred by transplantation to each of these diseases.

Finally, the study of potential predictors of mortality in our cohort showed that being hospitalized during the pre-transplant period was positively associated with mortality in the restrictive and obstructive airways disease and, negatively in the cystic fibrosis group. A higher number of hospitalizations before transplantation were indicative of a higher severity of disease and episodes of acute exacerbation, which may influence mortality in the post-transplant phase if the patient is not strong enough to undergo the stresses associated with the procedure. Interestingly, we did not observe this trend in all our studied disease groups. In the cystic fibrosis group, the more hospitalizations experienced the better one's survival was on average. In our study population, patients with cystic fibrosis are hospitalized on a regular basis, for intravenous antibiotic treatments, as a preventative measure against infections and not necessarily because they are sick. It has been documented that patients with certain types of infections (i.e. burkholderia cepacia) before transplantation are at a higher risk of death in the early post-transplant period as compared to those not infected (Chaparro et al., 2001). Also, cystic fibrosis patients with no health insurance, and therefore low medical attention, are at a higher risk of dying than

patients with medical insurance and an increased access to health care (Curtis et al., 1997). The protective effect conferred from hospitalizations, although not significant, in cystic fibrosis, may be due in part to the increased medical care received and the maintenance of infections through a pro-active management form of care leading to a better chance of survival in the post-transplant phase.

6.3.1 Mortality in lung transplant recipients alone

In our study population, mortality rates in the post-transplant period decreased as time went by. Once recipients survived the first 3 months of transplantation their risk of death was 10 times less than the risk observed in the first month, after adjusting for important mortality predictors (table 19). Furthermore, post-lung transplant recipients in the CF and bronchiectasis group were 16.7 times more likely to survive than the restrictive disease group, irrespective of the post-transplant time period. Although not significant, patients in the obstructive airways disease group also had, on average, a higher survival rate than the restrictive disease group (survival rate ratio: 2 (95% CI: 0.4 – 10)). A similar study carrying out a Cox regression analysis (Geertsma et al., 1998) also reported that for patients with emphysema the risk of dying in the post-transplant phase is 77% less than other disease groups. Although marginally significant, Hosenpud et al. (1998) also reported that recipients with emphysema had a higher survival rate in the first 30 days post-transplant than patients with interstitial pulmonary fibrosis. Charman et al. (2002), did not detect any significant difference with respect to one-year post-transplant survival. They reported the lowest survival rate for the pulmonary fibrosis group (55%), followed by

the CF and bronchiectasis groups, (71% each) and the obstructive lung disease group (73%). These results concord with the ISHLT registry data (2002), which report that patients with idiopathic pulmonary fibrosis receiving a double lung transplant have a 1.38 risk of death and that COPD patients have a 0.55 chance of dying at one year post-transplant.

In our study population, although with very low numbers, the patients in the pulmonary vascular disease group were 6.3 times more likely to die, on average, in the post-transplant period than recipients in the restrictive disease group. The ISHLT reported (2002) that at one year, primary pulmonary hypertension was associated with a mortality risk of 1.47.

One of the most important limiting long-term factors to the success of lung-transplantation is the development of OB, which is associated with a high mortality in the late post-transplant phase. In our study, patients developing OB in the second year were 9.4 times more likely to die than those free from it. Patients developing OB in the third year were almost 15 times more likely to die than recipients not having developed it at all. These findings are similar to the ones reported by Reichenspurner et al. (1996) where, after the first year post-transplant, patients developing OB have a higher mortality rate than those without it. Registry data, between 1982 and 2001, reported by the ISHLT (2002) show that bronchiolitis is one of the most important causes of death past the first post-transplant year. During the first 2 to 3 years post-transplantation OB accounts for 30% and in the 3 to 5 years

post-transplant accounts for 33% of deaths. This syndrome still remains an important risk factor after the 5-year post-transplant period.

6.4 Health related quality of life associated with lung transplantation

Health related quality of life in our study was assessed, with the SF-36, in terms of its 8 health concepts defined: physical functioning, role physical, bodily pain, vitality, social functioning, role emotional and, general and mental health. The SF-36 was chosen because it is a well-validated and widely used generic scale, which has values for a normal population and allows the comparison of different diseases. More specifically, the SF-36 was used due to its applicability to a wide range of disease-specific states, which was the case in this study where most types of lung diseases were studied. Furthermore, it has also been used in other lung transplant studies. Although the SF-36 includes normal population and disease specific reference data (Ware et al. 1992), it does not include any for transplant patients. Therefore, in our study, HRQOL scores for each domain were transformed to fit a 0 to 100 scale.

A cross-sectional comparison of means, obtained from candidates (n=34) and recipients (n=71), showed significant differences, favoring recipients, for each of the domains (table 20). The percent differences were in the order of 60% and 69% for physical functioning and physical role, 66% and 12% for general and mental health, 33% for vitality, 41% for social functioning and 32 % for emotional role. Cohen and colleagues (1998), who also carried out a cross-sectional analysis, also reported higher HRQOL in recipients than candidates. Another group, Stavem and colleagues

(2000), compared HRQOL in lung transplant candidates and recipients using both a lung-specific (St-George's respiratory questionnaire) and a generic questionnaire (SF-36). The authors reported that both questionnaires gave consistent results and supported the validity of the use of both questionnaires in this patient population. A more recent study, conducted by Napolitano et al. (2002), focusing on HRQOL in lung transplant candidates (n=71), using the SF-36, reported similar results in the magnitude of each of the eight health domains.

After adjusting for important potential predictors, lung-transplantation conferred a HRQOL benefit to each of the eight domains studied (Tables D4 – D11). Our results however showed that time since transplantation negatively influenced on average all the domains with the exception of role emotional and mental health. These findings are similar to those reported elsewhere (O'Brien et al., 1988; Gross et al. 1995).

Furthermore, other factors such as being hospitalized within a month of interview negatively affected most of the domains with the exception of bodily pain and role emotional and mental health. The presence of an infection or rejection within a month of interview however did not significantly affect any of the domains. Our findings are similar to the ones reported by van de Berg et al. (2000), which suggest that these complications do not influence HRQOL or they do but only slightly. Gross et al., (1995) reported lower scores for each of the MOS-20 Health Profiles in patients with obliterative bronchiolitis, although none reached statistical significance. The fact that we observed an effect associated with being hospitalized does not exclude

the possible impact of rejection and infection on the HRQOL domains. Our study results may suggest that the severity of the infection and rejection may come into play. Treating these complications on an outpatient level may not influence significantly HRQOL, or as van de Berg and colleagues (2000) state, that these measures might not be sensitive enough to detect the differences.

In the multivariate models, patients who had received a double lung transplant reported lower physical role scores, more bodily pain, and lower general health, vitality, social functioning, and emotional role scores than single and heart-lung recipients. Patients with cystic fibrosis and bronchiectasis reported better scores, than all other disease groups studied, in role physical, bodily pain, general health, vitality, social functioning and role emotional. These findings are similar to the ones by Smeritschnig and colleagues (2002) who recently reported that among all disease groups studied, the cystic fibrosis recipients had the best improvement in all health domains. The pulmonary vascular disease group also reported better scores in vitality and social functioning.

Patients with a double lung transplant reported lower functioning in at least one domain associated with physical, psychological and social functioning. These limitations might not necessarily be due to the type of transplant received but to patient characteristics. Many studies have reported that recipients are deconditioned at the skeletal level, which has important physical implications (Trulock, et al., 1997; Howard et al., 1994; Orens et al., 1995). Our patients needing a double lung

transplant may be more deconditioned and have a harder time adjusting to the post-transplant period. The survival benefit double lung transplantation confers on average to recipients luckily contrasts these observations.

Lanuza and colleagues (1999) propose that many recipients do not anticipate residual limitations in the post–transplant phase and expectations of post-transplant health during the waiting list may not be realistic. Previous studies have reported lower or no improvement in psychological domains such as role limitations due to emotional health and emotional well being (Cohen et al., 1998; TenVergert, et al., 1998; Limbos et al., 1997; 2000). Poor body image and self-esteem are still issues in the post-transplant phase (Limbos et al., 1997). These types of issues may have explained why females, in our study, reported lower mental health scores than males. Ten Vergert and colleagues (2001) studied health related quality of life before and after transplantation in patients with emphysema versus other indications. They reported that patients with emphysema had persistent problems with sleep and scored consistently lower than all other disease groups in the quality of well-being index, and they also reported higher anxiety levels and depressive symptoms, as assessed by the STAI and self-rating depression scale, respectively. Similarly, patients in our obstructive airways disease group significantly reported lower mental health scores than all other disease diagnoses.

In our longitudinal analyses (section 3, appendix D), the only significant improvement observed was in general health within the 4 months of transplantation,

which was also maintained in the 4 to 9 months follow-up period. General health scores improved in the order of 32% and 46%, respectively. We also observed an upward trend, although not significant, in other domains within the 4 months and beyond the 4 months of transplantation. Physical functioning scores improved by 32% and 46%, respectively. Role physical scores improved by 33% and 21% and; role emotional scores improved by 14.8% and 8.7%, respectively. In social functioning, important improvements were only observed beyond the 4 months in the order of 18.5%. No important clinical change was observed in mental health. In contrast, there was a decrease in bodily pain scores (i.e. more pain reported) by 24% and 32% in the 4 months and beyond 4 months of transplantation, respectively. Vitality decreased by 19% after the 4 months of transplantation. Ten Vergert and colleagues reported significant improvements in mobility and energy (1998), and in emotional states (2001), as assessed by the NHP. Lanuza and colleagues (2000) carried out a prospective study on 10 lung transplant recipients at 1 and 3 months post-transplantation with various measuring instruments. They reported, with the general health/QOL rating scale, improvements in patient satisfaction with quality of life, current health status and physical strength. They did not observe any significant difference with respect to psychological strength.

When comparing our cross-sectional and longitudinal data, we see less improvement in our longitudinal HRQOL results. This may be explained by the fact that in our study there were 2 patients who had important limitations after being

transplanted. One used a wheelchair and the other had a graft lung dysfunction that contributed to the decreased HRQOL scores observed.

Finally, our results question whether there is an important improvement in all health related quality of life domains so soon after transplantation. This result is not surprising if we consider that there are still important limiting factors associated with the post-transplant phase, such as hospitalizations and infections, which do limit the improvement of some HRQOL domains. Furthermore, our results showed a positive association between baseline scores reported during the waiting list and scores reported after transplantation. This suggests that baseline attitudes and the physical, social and psychological health of patients during the waiting list may positively influence some post-transplant HRQOL domains. Cohen and colleagues (1998) did find that pre-transplant anxiety and psychopathology states predict post-transplant psychological and self-reported symptoms.

6.5 Utility associated with lung transplantation

In our study, the utility associated with lung transplantation was higher than the one for the waiting list. The average utility scores observed for candidates (N=37) and recipients (N=76), after assigning a utility score of 0 to the deceased patients, was 0.17 (S.D.: 0.17) and 0.76 (S.D.: 0.30), respectively. Per post-transplant year, the average utility scores (± S.D.) in the 1^{st} (n=24), 2^{nd} (n=13), 3^{rd} (n=9), 4^{th} (n=10) and $>5^{th}$ year (n=20) were: 0.80 ± 0.29, 0.87 ± 0.24, 0.64 ± 0.40, 0.94 ± 0.07, 0.62 ± 0.30, respectively. The group of Ramsey and colleagues (1995b) reported, with the

standard gamble, for the waiting list an average utility score of 0.65 (S.D.: 0.26) (n=24) and a post-transplant utility score of 0.80 (S.D.: 0.24) (n=28). Our results are lower due to the fact that we included 0 scores for the deaths. Although recipient scores are similar, the candidate scores reported by the authors are higher than ours. This may be accentuated by the fact that our interviewed candidates were older (the mean age was 48) than their group's (the mean age was 40). Our multivariate analysis showed on average, although not statistically significant, a negative effect of age on utility in candidates. Gartner et al. (1997) using the quality of well being scale reported, at one year post-transplantation, a mean utility of 0.54 (n=19). These authors included a 0 score for 2 deaths that had risen during their study. The lower utility score reported in this study may be explained by the fact that their utility was ascertained almost solely from females (90%) and single lung transplant patients (n=16), whereas our cohort consisted of 60% females and 53% of single lung recipients. In our study, females and recipients with an obstructive airways disease, for which single lung transplantation is indicated, tended to report on average lower utility scores than males and recipients with other diseases, respectively. The different populations studied explain, in part, the higher utility scores observed in our population.

In increments, the mean post-transplant utility scores observed cross-sectionally, in our study, were 0.78 (n=12), 0.82 (n=12), 0.98 (n=6), 0.78 (n=7), 0.73 (n=5), 0.54 (n=4), 0.97 (n=6) and 0.62 (n=20) for every 6 months, up to >42 months, respectively. Anyanwu and colleagues (2001) carried out a cross-sectional study with

the EuroQol and found similar results. The mean utility value reported for candidates was 0.31 (n=87) and for the first 6 months (n=41), 7-18 months (n=43), 19-36 months (n=61) and >36 months (n=110) post-transplant, the mean utility values were: 0.69, 0.75, 0.67; 0.66, 0.83, 0.85; 0.65, 0.81, 0.86; and, 0.61, 0.82 and 0.87 for single, double and heart-lung transplant recipients, respectively. Calculating the average of all types of transplants yields the following: 0.71, 0.75, 0.75, 0.76 for the first 6 months, 7-18 months, 19-36 months and >36 months respectively. Our results, for the same time periods, are 0.78, 0.87, 0.76 and 0.80, and are similar to the ones reported by Anyanwu and colleagues. There seems to be, however, a difference in the waiting list reported utilities in our study (0.17) and theirs (0.31). This may be due to the fact that their patients were younger (39 versus 48 years of age) and, 39% of candidates were awaiting a heart-lung transplant, whereas in our study only in 8% of such patients was utility elicited. Furthermore, our estimates took into consideration the deaths that took place and the instruments in assessing utility differed (SG versus EQ-5D).

Multivariate analysis in our study showed that recipients had on average higher scores by 0.61 units and that time since transplantation negatively influenced utility. After adjusting for age, sex and time since transplantation, neither the type of disease.

Restricting the analysis to interviewed recipients only, our results showed, after adjusting for age and time spent on waiting list, that time since transplantation, OAD and ever having been diagnosed with a rejection (acute or chronic) significantly

influenced the reported utility. For every year gone by since transplantation, there is an average decrease in utility by a unit difference of 3.6 %. Furthermore, recipients with an underlying OAD tended to report lower utility scores than all other disease groups by an average of 0.16 units. This finding may explain the reported lower utility scores associated with single lung transplants (Anyanwu et al., 2001; Gartner et al., 1997), for which our OAD population was mainly indicated.

Another important factor that we studied was the influence of an infection and acute or chronic rejection (in the form of OB) on utility. The presence of an infection did not influence the reported utility. However, ever having been diagnosed at time of interview with an acute or chronic rejection had a positive effect on utility (after adjusting for age, time spent on waiting list, time since transplantation, underlying disease and FEV_1, which is an important indicator of early signs of OB). Although no group has studied the association of the development of chronic rejection and utility, several authors have reported significant decreases in physical mobility and energy (van den Berg et al., 2000) and in physical functioning (Ten Vergert et al., 1998). These authors did not however observe any difference in the psychological, social functioning and emotional state of patients with and without BOS, as assessed by the NHP. The positive effect, observed in our study, of ever having had a rejection, has to be placed in the context that this result was obtained from patients interviewed, which are survivors. Therefore, their perception of life after having survived life-threatening events such as rejection may be different than those not ever having had a rejection.

In a longitudinal analysis, utility significantly improved in the post-transplant phase, with respect to the waiting list. The average utility reported, from our patients, during the waiting list (n=13), < 4 months (n=12) and, between 4 to 9 months (n=8) post-transplantation were: 0.22 ± 0.17, and 0.57 ± 0.32 and 0.56 ± 0.27, respectively. Al and colleagues (1998) estimating utility with the EuroQol reported longitudinal utility scores for the waiting list and for each 3 months post-transplantation, until year two, that were on average 0.45 (n=27) (for 9 to 12 months of waiting) and, 0.83 (n=30), 0.85 (n=24), 0.84 (n=17), 0.86 (n=15), 0.91 (n=12) and 0.90 (n=11), respectively. These results are much higher than ours. We included a score of 0 for deaths whereas they gave a utility score of 0.30 for the 3 months prior to death. Furthermore, aside from not using the same instrument, we followed fewer patients for a shorter time, which tends to increase the variability in reported utilities. Furthermore, similarly to Al et al. (1998), we did not find a significant improvement within post-transplant periods. This suggests that the early post-operative period is important in determining utility in the future. Our results suggest that a 10-day hospitalization may decrease the utility up to an average of 8%. Any complications that may arise during hospitalization for the transplant or after being discharged may limit utility scores in the future.

6.6 The economic burden associated with lung transplantation

6.6.1 Possible biases in estimating costs

In estimating costs, three biases may occur: methods bias, case or service mix bias and site selection bias. These biases are summarized, in the following sections, as described by Jacobs et al., 1996.

6.6.1.1 Methods bias

Methods bias results from using a costing method that yields costs, which are not representative of the opportunity costs of the services under study. One method might yield costs that differ from long-term variable costs (that is considering them as fixed), or inversely, erroneously consider some fixed costs as being variable. This type of bias is assessed qualitatively due to the arbitrariness of overhead cost allocation (CCOHTA, 1996). In order to deal with this bias, the services rendered and the health care resources utilized, as well as indirect costs, were identified and valued in their natural units: number of visits, physician consultations, hours of time lost, kilometers traveled (etc.). This method takes into consideration marginal costs, which measure the additional cost for each unit of service rendered. A sensitivity analysis was presented with overhead costs being excluded from the C/E and C/U estimates (see methods, section 4.9.3.6).

6.6.1.2 Case or service mix bias

The case or service mix bias appears if the costing method ignores the severity and resource utilization patterns associated with the patient or disease group (CCOHTA,

1996). In this study, the resources utilized during the waiting list period, transplantation and post-transplant period, were systematically captured in detail for each clinical event on a per unit of service rendered basis, for the major part of the economic analysis. Furthermore, resources were valued according to workload units (OCCP, 2001), which provide a more precise estimate of resource intensity within the services rendered. Moreover, the cost of transplantation was estimated through costs, which reflect the resource utilization patterns; co-morbidities, disease severity, and treatment protocols, specific to the lung transplant patient population.

6.6.1.2.1 Transplant related costs induced during pre-transplant phase

In the study of lung transplantation, certain costs incurred during the waiting list period were related to the transplant program and were not associated to resources utilized due to the natural course of the disease. These costs, related to the screening process and operating costs of the lung transplant program, were excluded from this phase and attributed to the total cost associated with the lung transplant program as fixed costs. This dealt with a potential bias that would have decreased the incremental difference in cost associated with lung transplantation making it less costly. Moreover, there were additional costs induced by evaluating patients who died, did not meet the eligibility criteria and for those whose status was put on hold. These costs were also included in the C/E and C/U estimates. However, because the number of patients accepted to be evaluated is program dependent, the C/E and C/U estimates were also presented without these additional costs. This elucidated as to the

potential effect of controlling the amount of patients accepted to be evaluated from referrals on the C/E and C/U of lung transplantation.

6.6.1.2.2 Errors in measuring home oxygen therapy

Information on oxygen therapy use was obtained from patients interviewed while on the lung transplant waiting list in order to obtain, although with lower precision, valid estimates. Patients who had been transplanted many years had difficulty in recalling the exact levels of oxygen use during their time on the waiting list period. Furthermore, this was not always noted in the medical file. However, the estimate of home oxygen use, among candidates during the study period, should not be different from the one had all cohort members (recipients also) provided this information. Home oxygen therapy is dependant on lung function and since all patients accepted unto the waiting list follow the same criteria, with respect to the cut-offs of lung function testing, home oxygen therapy level indications are similar for all. An overestimation of oxygen use may have occurred if there were a higher proportion of recipients with diseases that do not require supplemental oxygen than the one found in candidates. Types of such diseases, for example, are found in the pulmonary vascular disease group. In our study however there were only 4 patients falling in this group and therefore the possible error in measurement is very low.

6.6.1.3 Site selection bias

Site selection bias may be introduced when costs are not derived from locations and settings where the intervention is taking place (CCOHTA, 1996). When cost

data was used from outside Quebec, a conversion factor was used in order to derive inter-provincial hospital cost differences. This factor was based on hospital indicators published by Statistics Canada. The lung transplant programs, in Canada, are situated in university-affiliated hospitals and therefore, the correction factor and cost estimates from outside the province were also obtained from teaching hospitals. Furthermore, we validated the correction factor by estimating transplant costs with the NIRRU (section 5.4.2.5). Furthermore, site selection bias may occur when data are compiled from one site, which may not be representative of the marginal average costs (Canadian costs in this instance) (Jacobs et al., 1996). In our study, the cost of lung transplantation was ascertained for Ontario and Quebec and results were similar (see results section 5.4.2.5, for validation).

6.6.2 Economic burden associated while waiting for a transplant

During the pre-transplant follow-up period, the average direct medical cost per patient incurred during the waiting list was $15,015 for an average cost of $1,708 per month. The evaluation for eligibility reached $9,113 and the lung transplant program operating costs were estimated at $509. While patients were waiting, hospitalizations accounted for 61% of the direct medical costs, home oxygen therapy accounted for 23% and, outpatient medications and medical follow-up care accounted for 10% and 6%, respectively. An earlier study conducted by Ramsey et al. (1995a) found a similar breakdown in the costs incurred during the waiting list. They reported the largest proportion of monthly patient care bills went to hospitalizations and physician fees. In patients with cystic fibrosis and bronchiectasis, the average direct medical

cost per patient during the waiting list period was $27,347 with 72% of costs relating to hospitalizations, 16% for home oxygen therapy and, 7% and 5% for outpatient medications and medical care, respectively. Ramsey and colleagues (1995a) also reported an important burden of hospitalizations in CF patients during the waiting list period. Similarly, Lieu and colleagues (1999) reported as much as 50% of costs in CF patients were due to hospitalizations. These results support the observations of an important burden of disease and economic impact associated with suppurative diseases such as cystic fibrosis.

6.6.3 Economic burden associated with the transplant procedure

Resources and costs associated to the lung transplant procedure accounted for a similar repartition of costs as reported elsewhere. In our study, organ acquisition and harvesting reached $5,325, which accounted for 11% of costs, the transplant procedure and inpatient follow-up care reached $35,276, which accounted for 71% of costs and physician fees reached $8,713, which accounted for 18% of the cost associated with lung transplantation. Ramsey and colleagues (1995a) reported a similar breakdown of charges: organ costs accounting for 16%, hospitalization costs accounting for 66% and, physician fees accounting for 18%, of total charges.

6.6.4 Economic burden associated with the post-transplant follow-up period

The biggest economic burden associated with the post-transplant phase, in our study, was the life-long drug therapy use, which remained stable, on average, per patient per year. The costs associated with medications for years 1 through 4 were

estimated at $11,680, $10,288, $8,164 and $8,550, respectively. Hospitalizations also contributed to the post-transplant economic burden. The magnitude of the cost associated with inpatient care depends on the cohort of patients and their respective complications and co-morbidity that arise throughout the years (tables 30 & 31). Hospitalizations due to infections remained an important risk throughout our study period and the burden of obliterative bronchiolitis, by the third year, contributed to the post-transplant economic burden. Costs related to inpatient care for years 1, 2 and three were $13,248, $6,872 and $10,989, respectively. Apart from drug therapy, the total costs per patient per year appeared to be on a downward trend. In our study, there was a decrease in cost by the 4th year. Cost estimates for years 1 through 4 were $33,645, $19,720, $20,988 and $11,655, respectively. A decrease in the average cost per year, throughout the post-transplant phase, has also been reported elsewhere (van Enckevort et al., 1998; Anyanwu et al., 2002). This may be explained by the fact that, as time goes by, patients that are followed are healthier and require less medical care than patients who died early on in the post-transplant phase. These costs, therefore, relating to future post-transplant periods, are associated with survivor and healthy medical utilization patterns. This trend was also observed in the direct non-medical costs where there was a decrease in costs after the second post-transplant year. This decrease was associated with lower outpatient medical care sought.

6.6.5 Indirect costs

Indirect costs were presented separately in our study because it is still debated whether to include these costs in a patient population such as the one studied.

Indirect costs are based on the premise that patients return to the same productivity level after an illness, which is not necessarily the present case (Rice, 1998). Although most of these patients were disabled before transplantation, not all will have the same degree of productivity after the procedure. Two of our patients returned to work after transplantation; most were on a lifetime disability pension. This may have contributed to the fact that, although some might have been able to work, they did not do so in fear of becoming sick and losing their pension in the process.

Although most patients followed did not return to work it is possible that the younger ones such as those in the cystic fibrosis group may start working in the future. Our study period may not have been long enough to precisely ascertain this effect. Although most CF patients, after interview, wanted to enjoy their life and experience things that their disease had precluded them from doing, the benefit of lung transplantation in terms of productivity, as in returning to work, school or volunteering, may be underestimated here.

6.7 Generalization of results

This study was based on one center and provides data on a relatively limited number of patients. Our results however with regard to HRQOL, utility and survival are quite similar to published data. Regarding the cost-effectiveness and cost-utility analysis, including estimates of the mean LY and QALY gained, as well as costs, is more complex as described in section 6.1.1. Besides the point raised in this section

regarding the choice of waiting list patients as proxy for the control group, which has severe consequences on shortening the non-transplant survival time estimate, other selection factors may make patients on the waiting list different than those observed in other centers. Namely, the patient population pool within which the waiting list candidates are selected and admission policies that may be influenced by the experience of the lung transplant team with the procedure. Different policies regarding selection criteria and type of follow-up care may have an effect on survival, occurrence of events and costs.

However, because patients were selected by international criteria and the sensitivity analyses covered a large range of situations that are likely to include most cases, we may elucidate as to the cost-effectiveness and cost-utility of lung transplantation based on our observations.

Furthermore, cost of procedures may vary from center to center. This is why we used a conversion factor from Statistics Canada when using data obtained from Ontario. We validated the converted Ontario to Quebec costs using the NIRRU. Therefore it is possible to take the number of events observed in one study and allocate them a different cost, using a converting factor relevant to the geographic area one would want to study. The main issue being the validity of the population studied in representing the population followed in another center. As was stated in section 5.4.2.3, the estimates provided by Ontario were based on a lung transplant

population, which was similar to the present one studied in terms of characteristics as well as type of follow-up care received.

6.8 Conclusion and future studies

Keeping in mind that cost-effectiveness is the cost for each additional life year and quality adjusted life year gained, transplantation should be aimed at patients with important pre-transplant medical utilization patterns who have a low HRQOL and utility and, who are able to survive the waiting list period and benefit the most post-transplant survival. Lung transplantation, in this type of patient group will be the most cost-effective: that is, a lower cost for every LY and QALY gained. From our study we conclude that the CF and bronchiectasis group benefited the most from lung transplantation. This disease group had the lowest utility associated with their end-stage lung disease and they profited the most from transplantation in terms of post-transplant survival relative to waiting, mean QALY gained and were marginally surpassed, by the OAD group, in their mean LY gained. In a situation of low organ donor rates, focusing on CF and bronchiectasis patients would optimize the efficiency of the lung transplant program.

As seen, lung transplantation is a very costly intervention that does not necessarily confer a survival benefit for all patient groups. Although no survival benefit was observed for the OAD group in the post-transplant phase relative to waiting, lung transplantation confers a survival benefit to few patients but for a long period of time, as seen in the benefit conferred in mean life years. Our study results suggest potential

gender differences in survival. Are females being accepted at earlier stages of their disease thus decreasing the potential benefit of transplantation as opposed to their male counterparts or are other factors involved. Considering the OAD group is one of the highest indications for lung transplantation today, future studies should aim to clarify patient characteristics, physician referral patterns, donor selection criteria and transplant related factors most influencing survival in this patient group. This would elucidate as to which patient related factors are associated with a long post-transplant survival.

Although important improvements were seen in general health related quality of life and utility measures, there are still important limiting factors associated with the post-lung-transplant phase, which impede in reaching an acceptable overall level. Not all patients reported a utility associated with perfect health. Furthermore, candidates awaiting a lung transplant are faced with many issues and dilemmas concerning the transplant procedure, which are not necessarily captured in the existing tools. For this patient population, larger longitudinal studies are needed with a more sensitive measuring approach towards not only the physical but also the psychological and social health related quality of life functioning. Our results suggest the importance of pre-transplant reported HRQOL on post-transplant scores. Since some authors have reported that a psychosocial intervention during the waiting list improves HRQOL (Napolitano et al., 2002), future studies should not only reproduce these results but also follow candidates after transplantation in order to

elucidate as to the effect a pre-transplant intervention program may have on improving post-transplant HRQOL and utility.

In terms of the cost-effectiveness and cost-utility of lung transplantation, similarly reported by others (van Enckevort et al., 1998; Anyanwu et al., 2002), the results showed that these estimates are sensitive to variations in mean life years and utility estimates during the waiting list. By improving one's preference for the post-transplant health state, the QALYs rendered lung transplantation a favorable program by decreasing the cost for each quality adjusted life year gained. Lung transplantation improved the quality of survival. As for the cost-effectiveness of lung transplantation, the longer the follow-up the better as the non-transplant patients would eventually die. Furthermore, a transplant teams success is very important to the overall picture since an important amount of fixed costs are incurred at time of transplantation and during the evaluation period. A low efficacy rate during the surgical procedure or the immediate post-transplant phase would drive the cost of the lung transplant program very high for very little if any benefit. Although this may be the case for new lung transplant teams and programs, increased experience in surgical techniques and post-transplant medical follow-up care will lead to a decrease in the cost-effectiveness ratio, thus making lung transplantation a more acceptable societal intervention.

The economic part of this study provides information for future health policy decision-making, in Canada. In this study, the lowest C/E and C/U ratio was

observed for the CF and bronchiectasis disease group. This was due to the higher costs incurred during the pre-transplant period (waiting list) and the post-transplant clinical improvement and health state preferences. With increasing experience and success rate of a transplant team, a 50% survival increase on a per patient basis renders lung transplantation a grade C technology (is more effective and costs more than $20,000 but less than $100,000/QALY gained) (Laupacis et al., 1992).

For a society which is deciding to implement lung transplantation, the question to answer "propose lung transplantation or not and to whom", will depend on whether one bases the decision on mean life years or quality adjusted life years. With the limited donor supply one may prefer to base a health care decision in terms of whether there is a survival gain. However, the dilemma persists on how one can quantify the improvement in quality of life even for a trade-off in life years. Although our society may afford the luxury to pay for this expensive intervention, this is not the case for many countries. It is therefore important to try and clarify, in the present day, what patient characteristics and disease groups would most benefit, quantitatively and qualitatively, from this procedure.

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Appendix-A

Clinical protocols of the lung transplant program of the Hôpital Notre Dame

Section A1. Eligibility protocols

A1.1 Admission into the program: evaluation process

Potential lung transplant patients are initially referred to the lung transplant program from their attending physician. A letter is written which includes relevant clinical information as to the patient's present day status and clinical prognosis. The lung transplant program then invites the patient for an initial interview, which normally takes place with the respiratory specialist. During this visit there is a review of the patient's clinical history as well as the determination of the patient's functional status with respect to severity of dyspnea and physical limitations, and whether there is the presence of any obvious contraindications. The lung specialist also explains the risks associated to the procedure, as well as the extensive follow-up care and drug regimen that needs to be maintained. Once both the patient and specialist agree, the evaluation process as to one's eligibility to be put on the Quebec Transplant waiting list begins.

As part of the evaluation process each patient has several consultations with a cardiovascular thoracic surgeon and, may see for evaluation a cardiologist, microbiologist, gastroenterologist, psychiatrist, nephrologist, rhumatologist, oto-rhino-laryngologist and allergist. Several diagnostic and prognostic investigations are also undertaken in order to assess the potential candidacy of the individual. These

tests consist of full lung function tests, diagnostic radiology and, hematology, microbiology, biochemistry and serology testing. More specifically, these tests include: hematology (a complete blood test, vitamin deficiency tests namely for B-12 and for folic acid, clotting time, protein electrophoresis, blood group identification and cross-matching), biochemistry tests (liver, lipid, renal and pancreatic profiles, vitamin D deficiency, hormone level tests), microbiology tests (urine and sputum cultures), serologic tests carried out for the identification of different types of viruses (CMV, toxoplasmosis, herpes, hepatitis, HIV and Epstein Barr virus), full lung function tests, diagnostic testing (chest X-rays, CT-scans of chest, sinuses, a panorex, abdomen and cardiac ultra-sound, mammography for women, bone density, ECG and a coronary angiography) and nuclear medicine tests (namely for lung perfusion and ventilation, and cardiac testing with MIBI persantin).

Once all the diagnostic and prognostic tests had been undertaken, a meeting was scheduled with the transplant team in order to decide whether the patient is eligible. The transplant team consists of the lung specialist, who is also the medical director of the lung transplant program at the study center; the transplant surgeon who is also surgery director of the lung transplant program as well as a member of the thoracic organ committee at Quebec Transplant; the coordinating nurse, a social worker, a dietitian, a physiotherapist and an inhalation therapist.

A1.2 Eligibility for listing on the Quebec lung transplant list

A1.2.1 Inclusion criteria

The decision taken by the transplant team, on eligibility, is based on many factors. These criteria follow the international guidelines for the selection of lung transplant candidates as published by Maurer and colleagues in 1998.

The first criteria for candidacy involved establishing age limits for the different surgical procedures. The age cutoff for a single lung transplant was established at 65. The age limit for a double transplant was 60 years and 55 years for heart-lung transplantation. All patients should be at a stage of their disease that is characterized as New York Heart Association Class III or IV / IV. This namely corresponds, respectively, to: the presence of a marked limitation of physical activity, comfortable at rest, however, less than ordinary activity causes fatigue, or dyspnea; and, patient is not able to carry on any physical activity without symptoms, which are present even at rest. Symptoms are increased with any physical activity.

Disease specific guidelines for establishing eligibility are defined hereafter. Inclusion criteria for patients with chronic obstructive pulmonary disease include an FEV_1, which is less than 25% of the patient's predicted value, and/or significant hypercapnia, which is characterized by a $PaCO_2$ greater or equal to 55mm Hg (7.3 kPa) or the presence of cor pulmonale, resting hypoxia and a rapid decline in lung function or frequent severe exacerbations and a life expectancy limited to 2 years.

Inclusion criteria for patients with cystic fibrosis and other bronchiectatic conditions include an FEV_1 which is less than 30% of the patients predicted value, hypoxemia at rest (PaO_2 < 7.3 kPa), significant hypercapnia ($PaCO_2$ >6.7kPa), loss of weight, and an increased frequency of pneumothorax events and hemoptysis. Eligibility criteria for patients with idiopathic pulmonary fibrosis include hypoxia at rest and /or clinical deterioration with optimal medical therapy, a poor survival prognostic, a progression to right ventricular failure and pulmonary hypertension, an increase in $PaCO_2$, a total lung capacity of less than 60% of the predicted value and the diffusing lung capacity falls below 30% of the predicted value. Inclusion criteria for patients with primary pulmonary hypertension include a lack of response to medical therapy with vasodilators, a mean pulmonary artery pressure greater than 55 mm Hg, a mean right atrial pressure greater than 15 mm Hg, and a cardiac index of less than 2.5 liters. Guidelines for including patients with primary pulmonary hypertension secondary to congenital heart disease include severe and progressive symptoms and with a functional status described as New York Heart Association (NYHA) Class III or IV despite medical therapy.

A1.2.2 Potential exclusion factors

The contraindications to lung transplantation that would exclude a patient, from being a candidate fall into two categories: the absolute and the relative contraindications. The latter, are the ones that could warrant further discussion with the transplant team as to whether a patient could be eligible for transplantation. The

exclusion criteria that have been proposed in the international guidelines (Maurer et al., 1998) are as presented hereafter.

The relative contraindications include:

- A daily required dose of prednisone or prednisolone of more than 20 mg.
- The need for invasive ventilation.
- Colonization with fungi or atypical mycobacterium
- Pleural disease
- Patients with systemic disease such as diabetes mellitus and collagen vascular processes.
- Pan-resistant bacterial colonization of the airways (in cystic fibrosis patients).
- Symptomatic osteoporosis as shown by a bone densitometry.

The absolute contraindications include:

- Severe organ dysfunction (other than the lungs) such as renal dysfunction with a creatinine clearance of < 50mg/ml/min and hepatic dysfunction with portal hypertension or coagulopathy. Patients with left ventricular dysfunction or severe coronary artery disease may be considered for heart-lung transplantation.
- An active cancer or within the last 2 years (exceptions include basal cell and squamous cell carcinoma of the dermis).

- Active infections such as with: the human immuno-deficiency virus; hepatitis B as seen with the antigen positive serology test; hepatitis C with histological proof of liver disease from biopsy.
- Progressive neuromuscular disease.
- An body weight of less than 70% or greater than 130% of ideal body weight.
- Severe psychosocial problems such as important psycho affective disorders.
- Cigarette smoking and substance abuse (drugs and alcohol) in the recent 6 months.

A1.3 Criteria for donor organ allocation

Once a donor has been identified, the lungs are examined as to their quality and whether they are adequate for transplantation. Clinical assessment is carried out by reviewing chest x-rays; the patient's history with respect to the presence of lung disease, infection or chest trauma; donor's arterial blood gases; directly viewing the lungs by bronchoscopy; and, carrying out serology testing for the presence of HIV or hepatitis infections. Once the lungs are considered suitable for transplantation, allocation of organs, at the study center, is carried out the most objectively.

Blood type is used as the first matching criteria. The donor and recipient have to be of identical blood groups. The only instance when this was not the case was when a donor organ of blood type B is allocated to an AB recipient if a B type candidate is not present. This is based on the fact that the blood type AB group is rare. Secondly,

matching is carried out with respect to size, usually based on height. Lastly, the patient waiting the longest is chosen.

Above all this, it is obvious that when one lung is available, only patients who have been registered for a single lung are eligible. When there is a double lung available, those who have been put down as needing two lungs are eligible. However, in extreme cases and on very rare occasions, the double lung might be split and be given to two different candidates. This could be the case if there is a single lung candidate whose health state is very severe and the prognosis is imminent death in the near future. The remaining lung is given to another single lung candidate compatible with the criteria described above.

Section A2. Clinical follow-up protocols

A2.1 Pre-transplant follow-up care

Candidates were followed at the study center once every three months during the waiting list period. These visits were to confirm if the patient was still eligible to be on the waiting list and if any new clinical events had transpired since their last visit. Such events included any hospitalization, the prescription of an antibiotic for an infection or any new medications prescribed. During these visits, patients underwent a spirometry test and were seen by a nurse working for the transplant program. The patients then consulted the surgeon or lung specialist. Information as to any medical change or event that might have occurred in between these visits was noted in the patient's medical file at the study center.

Hospitalized patients contacted the lung transplant clinic as to which hospital and room they were admitted in, as well as to the reason. Dr Pasquale Ferraro, the lung transplant surgeon, was informed of such hospitalizations and visited the patient during their hospitalization, when deemed important. The validation of the presence or absence of any clinical event (during hospitalization) was carried out by getting in touch with the health care facility that had housed the patient during their inpatient stay. Any lab analysis that was deemed of interest was faxed, to the study center, and incorporated into the patient's medical file as well as a complete summary of the patient's stay. The summary included the diagnoses and the type of exams carried out, as well as the treatment during the course of the stay. Referring physicians were also asked to send updates on the candidate's health state or of any new event that had transpired that could be of relevance to the patient's status on the waiting list.

The follow-up of all such information was the responsibility of one nurse. Her job was solely based on managing new clinical information, noting it in the patient's file and updating the lung transplant coordinator, which was also the lung specialist.

Once accepted as a candidate, the patient was enlisted in rehabilitation such as physiotherapy, nutritional and maintenance programs as additional follow-up care. Maintenance programs include home care and support from nurses and or inhalation therapists.

A2.2 Post-transplant follow-up care

All lung transplant recipients were followed at the study center for any subsequent medical problem. All information as to their health status was included in the medical charts. In the first month following discharge, from the transplant hospitalization, recipients visited the clinic once a week. In the second and third month, recipients visited the clinic every 2 weeks. In the following months, follow-up was carried out once a month until patients became stable and twice a year thereafter. This systematic follow-up care was carried out in order to rule out and manage, in a timely fashion, possible complications, infections and rejections. Additional clinic visits were also ordered when there were obvious signs and symptoms of infection or rejection.

A2.3 Clinical protocols for early identification of infection and rejection in the post-transplant phase

Lung function tests were performed regularly, and at every follow-up visit, in order to determine the onset of an infection or rejection. These tests measured the patient's vital capacity, FEV_1, total lung capacity, and diffusing capacity. It has been noted that a 5% to 10% reduction in FEV_1 is a sensitive and specific marker of lung infection or rejection even in the absence of any clinical symptoms or abnormal chest radiographs.

Apart from the scheduled bronchoscopies, including bronchoalveolar lavage and transbronchial biopsy, at 2, 6 and 12 weeks and at 6, 12 and 24 months after

transplantation, a bronchoscopy was also undertaken when clinically indicated such as from chest radiographs and lung function tests.

An additional bronchoscopy was practiced at the end of treating a rejection, a CMV related pneumonia and, when there was an infection with Aspergillosis or when the lung function tests did not seem to improve.

A2.3.1 Identification and treatment of cases with infections

Cases of infection were identified from microbiologic laboratory reports. Specimens for analysis were obtained from bronchoalveolar lavage during biopsy or from bronchial secretions. The tests consisted of a lab culture for the presence of gram positive and negative bacteria, mycobacteria, fungi, parasites and viruses. More specifically, the infectious microorganisms sought are presented in table A1.

Table A1. Summary of important infectious agents tested

Bacteria	*-Legionella* *-Pseudomonas* spp. *-Klebsiella* *-Haemophilus influenzae* *-Burkholderia cepacia* *-Staphylococcus aureus*
Fungi	*-Aspergillus* spp. *-Candida albicans*
Mycobacteria	*-Mycobacterium tuberculosis* -Atypical *mycobacterium*
Parasites	*-Pneumocystis carinii* *-Toxoplasmose gondii*
Viruses	-Cytomegalovirus -Herpes simplex -Paramyxovirus

During the outpatient follow-up phase, the presence of an infection was retained once an antibiotic or antiviral drug was newly prescribed for a determined period of time. The antibiotic in question should not have been used for preventive measures and given regularly as the center's prophylaxis protocol required. Such an antibiotic used at the center, for example, was Septra.

The most frequent antibiotics prescribed included ciprofloxacin, levaquin, ceftin, and vancomycin. The antiviral drugs prescribed included acyclovir, zovirax and cytovene. For the presence of Aspergillosis in patient's BAL, in the period beyond the 6-month post-transplant phase, Sporanox was prescribed for 6 months. Pneumocystis carinii elicited the prescription either of, Trimethoprim, Daspone or Pentamidine. Fungal infections such as Candida were usually treated with Mycostatin.

Prescriptions written out for each patient were also recorded in a database at the study center, allowing the validation of the prescription and hence the presence of infection.

A2.3.2 Identification and management of cases with rejection

Cases of acute rejection were identified on the basis of histopathological features from the transbronchial biopsy. This procedure is the gold standard in diagnosing acute rejection. The protocol for the management of rejection was the combination of

three drugs. This regimen consisted either of prednisone, cyclosporine (neoral) and azathioprine (immuran) or, a combination of prednisone, tacrolimus and mofetil mycophenolate acid (cellcept).

Cases of acute rejection were identified from reviewing the pathology reports in patient's medical file. The diagnosis made by the pathologist was based on the guidelines for the classification of pulmonary allograft rejection established by the International Society of Heart and Lung Transplantation (Yousem et al., 1996). The severity of the rejection was reported according to the grading classification of graft rejection as proposed by the guidelines:

Table A2. Grade classification of rejection

A = Acute Rejection Which may be diagnosed with or without the presence of airway inflammation.	**Grade 0** = No rejection **Grade 1** = Minimal evidence of rejection **Grade 2** = Mild evidence of rejection **Grade 3** = Moderate evidence of rejection **Grade 4** = Severe evidence of rejection
B = Airway Inflammation (Lymphocytic bronchitis/ bronchiolitis).	**B0** = No airway inflammation **B1** = Minimal airway inflammation **B2** = Mild airway inflammation **B3** = Moderate airway inflammation **B4** = Severe airway inflammation
C = Chronic airway rejection (Obliterative bronchiolitis)	**A** = Active **B** = Inactive
D = Chronic vascular rejection	

Adapted from Yousem et al., 1996.

Once an acute rejection was diagnosed, the following treatments were undertaken. For an acute rejection less than Grade 2, treatment consisted of optimizing the levels of prednisone and the anti-rejection drugs already prescribed. Grade 2 and over rejections were treated with 500 to 1000 mg of intra-venous Solumedrol for 3 days and optimizing prednisone levels. Bronchiolitis obliterans syndrome, once diagnosed, was also treated as just described. In addition, the occurrence of OB also warrants a change in the immunosuppressive drug regimen. Cyclosporine may be replaced with Tacrolimus and, Azathioprine with Cellcept (Mofetil Mycophenolate acid).

Solumedrol was given intravenously and required the patient to come to hospital for treatment. All such changes and additions to drug regimen was recorded in medical file.

Appendix B

Economic model of resource valorization

The method and sources used in the valorization of resources are presented in the following sections according to the type of service received:

-Section B1: Quebec Transplant organ related costs

-Section B2: Outpatient resource use

-Section B3: Inpatient resource use

-Section B4: Other health care resources used: Home Care Nursing

-Section B5: Outpatient medications

-Section B6: Physician fees

-Section B7: Home oxygen therapy and therapeutic devices

-Section B8: Direct non-medical costs

-Section B9: Indirect costs

Section B1. Quebec transplant organ related costs

This section estimates the costs associated with the transportation and costs associated to the identification, surgical and retrieval of the organ. The Québec-Transplant budget was, in one part, accorded to the transportation of the organ retrieval team and the organ via ambulance or air. Secondly, to the administrative personnel for the identification and actual retrieval which included resources such as clinical laboratory, diagnostic tests as well as extra personnel needed in the actual retrieval. This portion of the budget was allocated each year to every hospital, which had identified and prepared a donor organ.

The data source used in the estimation of this cost was the Québec-Transplant 2000-2001 Rapport Annuel (1st of April to 31st of March). The financial status for the 2000-2001 year was presented as follows: $1 226 077 for expenses related to the functioning of the program (salaries and other), $1 050 500 for expenses related to the donor organs (transportation and medical evaluation) and $23 015 for building maintenance, payable debts.

The total expenses reported were $2 300 392. The total number of patients having received a transplant in the 2000-2001 year was reported to be 432. The average cost, for the Quebec transplant program, attributed to each transplant patient was estimated to be: $2 300 392 / 432 = $5,324.98.

The assumptions in calculating the average cost associated to lung harvesting was that the retrieval of the different types of organs (heart, liver, kidney and pancreas) was not on average substantially different from the retrieval and maintenance of donor lungs. This amount per patient corresponded to 23% of the total cost. A sensitivity analysis around this percentage is carried out at 10%, 30%, 50% and 80% (table B1).

Table B1. Sensitivity analysis around organ acquisition and organ harvesting cost

Estimated cost per patient	$5,325
Sensitivity analysis	
10% of total budget	$2,300
30% of total budget	$6,901
40% of total budget	$9,202
50% of total budget	$11,502
80% of total budget	$18,403

Section B2. Outpatient resource use

This section deals with clinic visits to the lung transplant clinic for follow-up, visits to the day hospital for intra-venous treatment, one-day surgery and diagnostic procedures such as for a bronchial dilation or bronchoscopy and, ER visits. The costs accounted for, in the valorization of the services used, were hospital overhead costs and costs related to each department (support staff, nursing, supplies). In each sub-section that follows the sources and cost per unit values are presented in order to clarify what was included in the cost for each procedure, service or resource utilized.

B2.1 Overhead cost for the CHUM

In order to estimate the total cost of resources used, overhead costs needed to be estimated and added to specific department related costs. The total operating cost at the CHUM, for the 2001-2002 fiscal year was $496,260,559. The overhead cost reported was as follows: $36,224,292 for maintenance and functioning of the building (maintenance of building and of medical equipment); $24,950,000 for electricity and heating (as well as maintenance of furnaces and boiler rooms); $7,132,913 was for laundry, $14,252,206 went to housekeeping, the cost of the cafeteria was reported to

be $22,681,631, which also includes the salary of the nutritionists. The overhead cost totalled $105,241,042, which made up 21.2% of the total operating cost.

B2.2 One-day surgery

The average cost of a one-day surgery was obtained from the CHUM. The actual expenses reported came to a total of $1,792,955. The salary cost was $1,697,718 and the expenses related to the medical supplies reached $95,237. The number of users, during the 2001-2002 fiscal year, was 17,223.

The average cost per patient was calculated to be $101.07. The overhead cost (21.2%) came up to $21.43 for a total of $122.50.

B2.3 Endoscopy department

Procedures carried out in the endoscopy department include procedures such as bronchoscopies, oeso-gastro-duodenoscopies and colonoscopies. For this patient population the most frequent diagnostic procedure in this section is a bronchoscopy. This procedure is usually carried out in the lung transplant population, in order to determine the presence of an infection from a bronchoalveolar lavage, the presence of rejection from a transbronchial biopsy.

The actual costs for the endoscopy department, at the CHUM, for the 2001-2002 fiscal year was $3,688,849 of which, $1,923,592 was attributed to salaries, $1,735,257 to medical supplies and $30,000 to laundry. In this fiscal year, there were 38,281 procedures carried out.

The average cost of a diagnostic procedure in this department was calculated to be, in 2000-2001 dollars, $93.06 per procedure (2.7% variation rate used to bring costs to 2000 and excluding the $30,000.00 for laundry). Overhead cost attributed to this department was estimated by adding 21.2%.

The total cost attributed to each procedure carried out in this department was $93.06 + $19.73 = $112.79.

Pharmacy costs were patient specific. Medications used were: 1 mg of Ativan (sublingual) ($0.05), 0.4 mg of atropine ($0.46) and 2 mg of Versed ($0.48). The total cost is $0.99. No dispensing fee was added here. These medications are stored in the endoscopy department. Physician fees were procedure specific and dealt with separately.

Once a patient had undergone an endoscopic procedure, they were kept in the one-day surgery department (section 2.2). Therefore, the cost for an endoscopic procedure was: $ 122.50 + $112.79 + $0.99 = $236.28.

B2.3.1 Bronchoalveolar lavage and transbronchial biopsy

When a bronchoscopy was undertaken for the diagnosis of an infection and/or rejection, the following departmental resources may have been used (table B2) and therefore these additional costs were added where relevant.

Table B2. Resource use associated with a bronchoscopy

Resources used	**Total cost**
Microbiology lab testing of the bronchoalveolar lavage (BAL)	
Culture and Stain	$31.84
Fungus detection	$35.25
Mycobacterium detection (Acid fast bacilli test)	$6.82
Parasite detection: *Pneumocystis carinii*	$20.47
Viral detection	$34.11
Total	$128.49
Sputum specimen (culture)	$7.55
Pathology-Surgical report: Bronchial specimens	$106.59
Radiology: Chest X-ray (2visuals)	$24.34
Cytology:	
BAL cell count	$45.67
Special Stains (BAL)	$68.50

Valuation based on UHN data.

The physician fee for a flexible bronchoscopy and transbronchial lung biopsy was $179.60 (Manuel des Médecins, 2001).

B2.3.2 Bronchial dilation

The average cost for a bronchial dilation was based on data obtained by the UHN. The ICD-9 procedure code identifying this event was 33.91 (bronchial dilation). The procedure code was also coupled to the clinical information with an ICD-9 code of 996.84, post-transplant complication and a 591.1 code for disease of bronchus (stenosis). The average cost per patient was calculated to be $787.33. The direct and overhead costs associated to this procedure were $567.71 and $219.62, respectively.

The physician fee for a flexible bronchoscopy and stent placement, for the dilation of the bronchus was $254.60, and to carry out a percutaneous transluminal balloon angioplasty was $100.00 (Manuel des Médecins, 2001).

B2.4 Emergency room visits

A visit to the ER was retained once a patient presented oneself to the ER but was not admitted to the hospital. If patient was hospitalized, following presentation to ER, then the number of days stayed would be included in the length of stay for that specific hospitalization.

A visit to the ER, was valued by data obtained from the CHUM. The total ER expenses in 2001-2002 were $23,261,755, of which, $1,900,037 consisted of salaries and $1,361,718 went to medical supplies and other supplies. There were a total of 115,107 visits.

The average cost for a visit to the ER was based on this information, which yielded an average of $196.20 per visit. The estimated overhead cost was (21.2%), which reached $41.59. The total cost of an ER visit was $237.79.

All other resource use such as laboratory, radiology, and endoscopic procedures were valued as mentioned throughout this section.

For the physician fees, the type of consultation received was also accounted for and based on the physician fee manual.

As for the pharmacy cost, in most occasions, the medications used were the patient's. Since these were dealt with as outpatient medications, they were not considered in this section.

B2.5 Ambulatory care unit

The total 2001-2002 expenses attributed to the day hospital in the CHUM was $2,932,060. The salary cost was $2,722,595, the medical supply cost was $209,465 and other supply costs were $147,000. There were 25,412 patients who visited during this year and the total care days for these patients were 46,831.

The average cost of a care-day in the day hospital was calculated to be $60.79 per day of care, and $112.02 per patient. The overhead cost (21.2%) amounted to $12.89. The total cost per day of care reached $73.68

All medications received will be accounted for. Treatments in this section usually included those for a rejection and CMV prophylaxis namely, methylprednisolone (solumedrol) and, CMV Immunoglobuline and intravenous ganciclovir, respectively.

A dispensing fee of 7.19 was added to the cost for each treatment received during the ambulatory care visit (IHE, 2000). The $7.00 fee in the year 2000 was adjusted for the 2001 year (2.7% rate variation in price index).

B2.6 Outpatient clinic visits

This section included all costs relevant to the follow-up visits at different clinics as well as the lung transplant clinic. In the latter, during each visit, the patient underwent a spirometry test, a chest X-ray, a complete blood count, prothrombin time

and activated partial thromboplastin time, a liver, renal, pancreatic and lipid profile as well as, plasma levels of important anti-rejection drugs (Cyclosporine, Mofetil mycophenolate acid). Summary of resources used, and their associated cost, is presented in table B3.

Table B3. Clinical laboratory and diagnostic resources used during follow-up visits

	Cost
Biochemistry lab tests:	
Liver profile	$8.32
Renal profile	$5.55
Pancreatic profile	$4.16
Lipid profile: HDL/LDL cholesterol Cholesterol Triglycerides	 $6.69 $1.41 $1.10
Hematology:	
CBC (complete blood count):	$3.47
Activated partial thromboplastin time Prothrombin time:	$2.19 $2.19
Radiology:	
Chest X-ray (2visuals)	$24.34
Pharmacology	
Cyclosporin or Tacrolimus Cellcept	$7.64 $3.47 $20.47
Estimated cost	$87.42

In pharmacology, patients usually start with cyclosporin, and those that do not react well are switched to Tacrolimus, and or from Immuran to Cellcept. The average cost calculated for the laboratory analysis and diagnostic testing included cyclosporin and cellcept.

Other resources commonly utilized are presented in table B4 with their associated costs.

Table B4. Summary of common laboratory and diagnostic tests carried out

	Estimated Cost
Antibiotic level – tobramycin /vancomycin/gentamycin	$2.77
CMV Antigenemia	$57.99
Sputum (culture)	$25.01
Culture and stain	$31.84
Vancomycin resistant enterococcus	$30.70
Multi resistant Staph Aureus	$25.01
Clostridium Difficile assay (stool)	$31.84
Urine Culture	$13.64
Urine analysis	$2.77
Blood Culture	$1.14
Blood Gases	$3.81
Thyroid stimulating hormone, T3, T4, Oestradiol, Testosterone, Prolactine	$2.77
Diagnostic Radiology:	
Abdomen, multiple incidences	$46.32
Lumbar spine	$43.28
Sacrum	$43.28
Pelvis (3visuals)	$57.67
Hip	$47.97
Facial bones	$43.75
Hemithorax	$56.96
Sinuses	$43.75
CT-Scan:	
Abdomen with contrast	$81.47
Abdomen without contrast	$64.37
Thorax with contrast	$77.11
Thorax without contrast	$68.53
Pelvis with contrast	$77.21
Pelvis without contrast	$57.10
Head with & without contrast	$89.90
Head without contrast	$38.58
Ultra-Sound:	
Abdomen	$45.07
Cardiac, peripheral venous doppler	$43.92
Pelvis	$45.07
Nuclear Medicine:	
Lung perfusion/ventilation	$165.08
Bone imaging	$169.36
Bone, Total body	$243.38
Esophageal motility	$113.24
Gastric emptying time	$448.99
Myocardial Skeletal imaging	$71.76
Myocardial imaging	$62.47
Magnetic Resonance Imaging: Thorax	$62.99

B2.6.1 Operating costs of the lung transplant program

The study center included a transplant program for many organs in addition to lung transplants. The actual operating cost of the transplant programs was $297,454 in 2001-2002 of which, $292,351 was salary and $5,103 was attributed to supplies. There were approximately 600 patients followed at the transplant outpatient clinics.

The cost associated with paramedical services which included physiotherapy, social work and inhalotherapists were $3,448,201, $4,462,459 and $5,122,100 (salaries, and other equipment), respectively. This totaled $13,032,760 and made up 2.6% of the total operating cost of the CHUM. The paramedical costs attributed to the transplant clinic were $7,734.

The actual operating costs and paramedical services specific to the transplant clinic at the CHUM totaled $305,188. The average cost attributed to each patient followed at the CHUM's transplant programs (n=600) was calculated to be $509 per patient per year. This estimate was attributed to each patient in the lung transplant program. This cost was also added for patients still waiting for a transplant as for the recipients. The cost to patients while waiting was attributed to the transplant program.

B2.7 Rehabilitative physiotherapy and physio-respiratory education

Patients during the waiting list as well as after transplantation visited a physiotherapist. The frequency was 3 times a week for an average of 6 to 8 weeks.

Patients were seen for approximately 2 hours each visit. During the visit, 4 patients were seen at the same time. The cost of each visit was based on the salary scales defined for physiotherapists by the ministry of health. Salaries were based on years of experience. An average of 7 years experience was taken to calculate the per visit rate.

The cost for a visit to the physiotherapist was valued at: $22.32 / hour. The visit was therefore valued at $44.64.

Respiratory education carried out during the waiting list period, for an average of 6 weeks, had a salary cost of $200.88 per patient. This cost was attributed to each candidate on the list (n=124). Physiotherapy aimed at rehabilitation in the post transplant phase, for an average of 8 weeks had a salary cost of $273.84 per patient. This cost was attributed to each transplant recipient (n=91).

Section B3. Inpatient resource use

B3.1 Valorization of hospitalizations due to respiratory insufficiency

The hospitalizations due to respiratory exacerbations and infections, mainly during the waiting list period were valued using the "Niveau d'Intensité Relatif des Ressources Utiliséés" (NIRRU, 2000-2001) method, an index of health resource utilization.

All hospitalizations of a respiratory exacerbation and preventive reasons for infection were characterized as a respiratory insufficiency. The CMG/DRG code

retained, to describe the economic burden of these events, was 4.087. An age restriction was also applied where hospitalizations were presented only for patients aged 18 to 64 years. The 3rd group included ages 65-74. This cut-off was chosen to concord with the eligibility criteria for entering the transplant list. The NIRRU retained was for university affiliated hospital centres, in the province, and for atypical cases with the two highest severity levels, which were coded as having a NIRRU score of 2.6038 and 3.1894, respectively. The index attributed to each hospitalization depended on the average length of stay (LOS). A sensitivity analysis was also carried out, by reestablishing the severity level attributed for the hospital length of stay (for more details and results see Appendix E, table E1). These indexes, of health care resources utilized, were multiplied by $3,448.52, which was the value of 1 NIRRU unit in 2001.

B3.2 Hospitalizations due to all other diagnoses

Valorization of all other hospitalizations was also based on the NIRRU index. The CMG/DRG retained for each hospitalization was based on all of the diagnoses and whether a procedure(s) was carried out. For example, if a cholecystectomy was carried out and this was the main reason for the hospitalization then, the NIRRU was based on that specific DRG and not on the diagnosis establishing patient had an end-stage lung disease. NIRRU scores, for severities 3 and 4, were based on atypical and university affiliated hospital cases. The hospitalization in question was coupled to the NIRRU with the closest LOS.

B3.3 Long-term care costs (rehabilitation centers and convalescence centers)

In Quebec, the cost of long-term care was estimated to range from $124 to $163 per day, all-inclusive (IHE, 2000). The average cost per day, for a stay in a rehabilitation center or convalescence home, was assigned the average of these two estimates, $143.50. Adjusting this cost to 2001 dollars increased the cost to $147.37

B3.4. Valorization of lung transplant related hospitalizations with OCCP

The average cost of a lung transplant was obtained from the Ontario cohort data set. The cost retained was the average cost of the hospitalization for the transplant procedure. The cost of a hospitalization for an infection and rejection was estimated using the average cost per day for such hospitalizations (infection and rejection).

These hospitalizations were based on estimates provided by the UHN, which carries out their costing system according to the OCCP. The resources included in the valorization of these hospitalizations were: operating room time and type of procedure, surgical intensive care unit time, intensive care unit time, nursing care received on specialized and general wards, diagnostic procedures and interventions as well as, laboratory procedures and tests performed during the hospitalization, pharmacy costs (all medication given to patient) as well as paramedical services rendered (i.e. physiotherapy, social services, inhalotherapists and chaplancy).

B3.4.1 Missing pharmacy costs

Pharmacy data, for the hospitalization due to transplantation, was incomplete for patients discharged after February 1st, 2000. For this missing data, a per day average of pharmacy cost was assigned. Eighty-three patients were used in the computation of this average, which yielded, $251.33 per patient day. Costs were adjusted in order to take into account the different timing. The average pharmacy cost for the year 2000 was calculated to be 256.69 (2.2% variation in price index) and $263.79 for the 2001 year (2.7% variation in price index). This average cost per day was then multiplied by the number of days in hospital in order to calculate the total cost of pharmacy for the hospitalization. For hospitalizations due to infections, missing pharmacy costs were also assigned an average. The average was computed from a total of 38 hospitalizations, out of 73, for an infection. The average pharmacy cost was $415.42 per patient day. After adjusting for the differential costing time periods the average cost per patient day was, $424.56 and $436.02 for the years 2000 and 2001. For a rejection, pharmacy cost per patient per day was computed to be $539.56 per patient day. Adjusting this average to the 2000 year yielded $551.43 per patient day (there were no rejections in 2001).

B3.5 Valorization of lung transplantation with the NIRRU

The average cost of lung transplantation based on the NIRRU was also calculated. Data were obtained on procedures carried out during the 2000-2001 period (MSSS, 2001). The index of health care resources used during the hospitalisations for

transplantation was 10.1615, which was multiplied by $3,448.52, which was the value of 1 NIRRU unit in 2001.

Section B4. Other health care resources used: home care nursing

Nursing or inhalation therapy required by the patient at his home was also accounted for. The measurement was the number of visits. These services were well documented in the patient's medical file and included information as to the date, time spent and reason for visit.

The cost for each visit was based on the salary scales defined for inhalotherapists as well as for nurses from their respective federations (APIQ-CHP and FIIQ-CHP, respectively, 2001). For both, salaries were based on years of experience. An average of 6 years experience was taken to calculate the hourly rate.

An average of 1 hour of nursing care was rendered. Furthermore, in order to account for the actual travel time of the health care professional, to and from the patient's house, 30 minutes were added to the total time. One hour and a half was assigned to each visit.

The cost for a visit from an inhalotherapists was valued at $19.76 per hour and therefore, the cost for a visit reached $29.64. The cost for a visit from a nurse was valued at $20.51 per hour and the cost for a visit reached $30.77.

Section B5. Outpatient medications

B5.1 Post-transplant outpatient medication use

The outpatient medications in the post-transplant phase included: (i) immunosupressants drugs such as prednisone, neoral, tacrolimus, immuran, cellcept, (ii) antibiotics and antivirals and (iii) all other. Actual costs were ascertained from the development center at the CHUM. Data obtained consisted of all prescribed medications.

At the study center, a protocol was followed for prophylaxis against infection with cytomegalovirus. Patient/Donor CMV status combinations requiring this prophylaxis regiment were those forming: R+D+, R+D-, R-D+. The prophylaxis regimen consisted of receiving 150mg/kg of CMV Immunoglobulin within 72 hours of transplantation, 100 mg/kg at 2,4,6 and 8 weeks and, 50 mg/kg at 12 and 16 weeks post-transplantation. In addition, an antiviral was also supplemented to this protocol. This regiment consisted of ganciclovir being administered intravenously for the first 35 days post-transplantation, and 1gram orally three times a day for the remaining 2 months (i.e. 35-90 days). The protocol for treating a rejection with grade 2A and above consisted of 500 – 1000 mg of intravenous solumedrol for 3 days. In addition, 3000 mg of oral ganciclovir per day for 6 weeks was also used in treating an acute rejection. Patients received the intra venous treatments during an ambulatory care unit visit. Blood products, such as Cytogam ($650.00 + 5% overhead), reached a cost of $682.50 for 2.5 g (Hema-Quebec sources, 2001).

The cost associated to the outpatient medications were computed using the unit price for each, obtained from the RAMQ list price for medications. A dispensing fee of 7.19 was added to the total cost.

B5.2 Waiting list medication use

During the waiting list period, the costs associated to outpatient medications did not contribute significantly to the direct medical costs. Patients were usually hospitalized when consuming expensive antibiotics due to infections and acute respiratory exacerbations. The economic impact of these outpatient drugs was of little importance as compared to the medication utilization patterns in the post-transplant phase. The cost attributed to the medications consumed during this period was estimated from the drugs consumed in the post-transplant phase that fell in the "all other" group for the 6-months. Such medications were similar to the ones consumed in the pre-transplant period (e.g. inhalotherapy such as drugs falling under the sympathomimetics, corticosteroids, calcium and vitamins as well as the expensive digestive enzymes consumed by CF patients, diuretics, treatments of osteoporosis, cardiovascular and other). This estimation was due to the absence of a detailed account of outpatient medications consumed during the waiting list. The type of medications and the doses were registered at each follow-up visit and this was enough to ascertain the continuance of these "other" drugs during the post-transplant phase. This method dealt with a potential differential misclassification bias, which would have favored the integrity of the post-transplant as compared to the pre-

transplant medications. Final estimation was obtained by extrapolating the cost of the first 6-months post-transplantation to the cost that would be obtained for an average waiting time of 9 months, as observed in this cohort of patients.

Section B6. Physician fees

These fees represent the salary paid to the physician by the Quebec provincial medical insurance plan. These fees are for diagnostics acts and consultations. The dollars paid, for each act, by the Régie d'Assurance Maladie were obtained from the RAMQ website under Manuels: Médecins Spécialistes – Manuel de facturation (2001). All types of physician fees were captured, where applicable.

In the pre-transplant period, patients were either seen by the cardiovascular thoracic surgeon or, the lung transplant coordinator, who was also a respiratory specialist. The physicians examined the patients and assured at each visit whether the patient was still eligible to be kept on the waiting list. The fee attributed to each visit was the initial visit. The reason for this was that patients on the waiting list were seen, at the transplant clinic, every three months. Clinic visits outside of the transplant program were also considered and physician fees were ascertained from their respective specialty.

Once a patient was discharged from the hospital after the transplant procedure, the patient was followed, at the lung transplant clinic, every week in the first month, every two weeks in the second and every month following that until patient was seen

every three months, and 6 months or as needed. During this period the patient saw a respiratory specialist familiar with the post-transplant follow-up care. The fee attributed to the visit was the one of a respiratory specialist.

Section B7. Home oxygen therapy and therapeutic devices

Medical devices used by this end-stage lung diseased population were oxygen concentrators, oxygen cylinders and, compressors and nebulizers (table B5). Oxygen concentrators are medical devices that deliver higher levels of oxygen to the patient. Oxygen cylinders contain compressed oxygen. They are portable and allow patients to regulate the flow rate. Compressors and nebulizers are systems that convert medications to mist for an inhalation treatment. Some of these are also portable.

Table B5. Summary of costs for home oxygen therapy

	Rental	**Buy**
Oxygen concentrator	$125.00/month Includes: emergency power, canules, tubes and filters as well as 3 visits by technician per year for maintenance.	Concentrator: $1,850.00 Emergency power: $245.00 Canules, tubes and filters: $95.00/yr Needing 2 visits from technician for maintenance 60.00$ each/year
Portable oxygen		$75.00 and $15.00 for each refill of cylinders. A flow rate of: 2 liters lasts 4 hours 3 liters lasts 3 hours 4 liters lasts 2 hours
Compressor/ Nebulizer		Electrical: $195.00 and $5 for one aerosol kit (one treatment) Electrical and car chargeable: $295.00, $25.00 aerosol kit for every six months Electrical, car chargeable, and battery: $550.00, and $25.00 aerosol kit for every six months

Source: Medigas, Québec and the Régie Régionale du Québec.

Home oxygen therapy use was obtained from all patients who were interviewed while on the lung transplant waiting list (n=31). This information was obtained only from these patients in order to deal with any potential recall bias on behalf of older transplanted patients versus newly transplanted ones as well as to deal with any potential misclassification bias with respect to the precision and reliability of the oxygen use being recorded in patient's medical file. The average use of home oxygen therapy was then extrapolated to the full cohort (N=124).

The average time spent needing oxygen for an outpatient visit was recorded to be an average 4 to 4.5 hours. Each patient also used on average 3 cylinders per month to go out of the house. In this study, all oxygen concentrators were valued to the cost of a rental.

Section B8. Direct non-medical costs

B8.1 Transportation

The cost of transportation used for seeking medical care was also valued. These are vehicle expenses which, included both operating and ownership costs. The operating costs consisted of gas, oil, tires, repairs and maintenance, license fees and insurance. The ownership costs refer to the depreciation of the vehicle, provincial taxes as well as finance charges. The unit of measurement was the number of kilometers traveled from patient's home to the health care facility where care was sought (outpatient visits, ER, one-day surgery).

Information pertaining to the distance traveled was ascertained by using the patient's postal code (at place of residence) and that of the hospital where care was sought. The distance was quantified as the number of kilometers it would take to travel by car between both points (www.mapquest.com).

Each kilometer was valued at $0.46. This estimate was provided by Canada Customs and Revenue Agency, which was based on expenses claimed for medical purposes.

The use of an ambulance was valorized at $125.00 (per call) and $1.75 was added for each kilometre travelled (Corporation des services d'ambulance du Quebec, 2001) (IHE, 1997-98 report).

B8.2 Accommodations

Some patients living more than 80 km from the hospital center were in need of sleeping accommodations in the city of Montreal. Accommodations were considered for the patient and a family member or friend accompanying the patient for the medical care. Accommodations needed during waiting list period, post-transplant and follow-up visits were considered. The unit of measurement was the number of nights.

The unit value was estimated from rates quoted to McGill University and affiliated hospitals. All hotels were within a 10 km radius of the study center. Rates were

given for every season at each hotel and an average was taken. Each hotel night accommodation was valued at 116.40$.

Patients living at the "Maison des Greffés" in Montreal, had a one night hotel cost tabulated to each outpatient visit. This information was ascertained during the interview process and from the medical file. The postal code (proxy for area of residence) was used to estimate the number of kilometers patient lived from the hospital.

Section B9. Indirect costs

Time spent by the patient or a person accompanying the patient for a medical visit was valued according to the human capital approach. This included time spent during an outpatient follow-up visit, emergency room visit and, for a one-day surgery (bronchoscopy or other). The time needed to reach the health care facility from patient's home and the way back was also included. This time may be considered as work time or leisure time forgone. Wages were used to evaluate the time losses under the assumption that wages reflect productivity.

The unit of measurement was the number of hours. The source of this data came from patient interviews. For a one-day surgery, 8 hours were assigned as time spent and 2 ½ hours for each clinic visit.

The unit value attributed to each hour was $15.88 per hour. This hourly rate was obtained by the Canadian industrial aggregate average employment earnings rate (Statistics Canada, August 2000). This rate took into account all sectors of industry with the exclusion of the agriculture, fishing and trapping, private household and military sectors.

Time spent while being hospitalized as an inpatient for any amount of length of stay, was not included in the analysis. It is not clear what burden the actual hospitalization would have on the patient's daily living.

Appendix C

Ontario to Quebec cost conversion factor

In order to convert Ontario costs to Quebec estimates of costs we used a conversion factor that was obtained from data published from Statistics Canada. The conversion factor used throughout the study, in estimating Quebec costs (where noted) from Ontario estimates, was 58.2% (table C1). That is, every $100.00 in Ontario equaled to $58.20 in Quebec. In order to study potential variations to this estimate, we carried out the same calculations by adding and removing one standard deviation from the proposed means. The conversion factors were 51.0% and 62.9%, respectively.

Table C1. Provincial differences of total operating hospital costs

	Quebec	**Ontario**	**% Difference**
Teaching hosp (N) **Number of beds**	**19** **12076**	**16** **10284**	
Total Operating Expenses per Total patient day (mean +/- s.d.)	638.76±196.17	1098.15±229.94	58.2%
Minimums (mean -1 s.d.)	442.59	868.21	51.0%
Maximums (mean +1 s.d.)	834.93	1328.09	62.9%

Hospital indicators, Statistics Canada 1993-1994.

Appendix D

Appendix to HRQOL and utility results

This section deals with additional analyses that were carried out in the study of HRQOL and utility. The results provided in these sections complement the information presented in chapter 5.

Section D1. Flow chart and characteristics of patients eligible for the study of HRQOL and utility

D1.1 Cross-sectional study of HRQOL and utility

From the 129 eligible patients alive at the start of the recruitment period, a total of 105 participated. At initial interview, 34 were candidates and 71 were transplant recipients (table D1).

Table D1. Patient flow chart describing participation and eligibility for the study of HRQOL and utility

		Post-transplantation				
	Pre-Tx	First year	Second year	Third year	Fourth year	Fifth year and beyond
Eligible	N=38	N=27	N=20	N=7	N=11	N=26
Refusals	N=1	N=3	N=5	N=0	N=1	N=6
Deaths	N=3	N=1	N=0	N=2	N=0	N=2
Respondents	N=34	N=23	N=13	N=7	N=10	N=18

The characteristics of patients included in the study of HRQOL and utility are presented in table D2. Of the potential eligible recipients, 15 refused to participate. People who refused were older at transplantation and had spent less time on the waiting list than participants. As for eligible candidates, only one refused to

participate, a 50 year-old male. The deceased recipients were on average older than their surviving counterparts at entry into the program and had spent less time on the waiting list. The deceased candidates were younger than those alive and had spent a longer time on the waiting list than those interviewed.

Table D2. Characteristics of patients eligible for the study of HRQOL and utility

	Candidates N=34	**Recipients N=71**	**Refusals* N=16**	**Deceased* N=8**
Variables	**Mean ± S.D.**			
Age at entry into program (years)	49.40 ± 11.13	40.58 ± 13.24	50.71 ± 7.69 (Tx) 50 (Candidate)	53.00 ± 12.47 (Tx) 36.81 ± 15.36 (Candidate)
Age at interview (years)	49.91 ± 11.14	44.20 ± 13.49	-	
Time accrued on waiting list (months)	6.00 ± 5.87 at time of interview	10.00 ± 7.00	8.85 ± 3.71 (Tx)	6.37 ± 2.95 (Tx)
Age at transplantation (years)	-	41.42 ± 13.23	51.4 ± 7.7	53.53 ± 12.46
Gender:	**Number (Percentage)**	**Number (Percentage)**		
Female	18 (52.9%)	45 (63.4%)	7/15 females (Tx) 1 male (candidate)	3/5 females (Tx) 1/3 females (candidates)
Male	16 (47.1%)	26 (36.6%)		
Diagnosis:				
OAD	15 (44.1%)	29 (40.8%)	12	2 Tx
Cystic Fibrosis	5 (14.7%)	22 (31.0%)	1	3 Tx
Bronchiectasis	1 (2.9%)	7 (9.9%)	1	-
Restrictive diseases	9 (26.5%)	8 (11.3%)	1 Tx & 1 candidate	3 (candidates)
PVD	3 (8.8%)	2 (2.8%)	-	-
Congenital diseases	1 (2.9%)	3 (4.2%)	-	-

*Tx: refers to transplant recipients and Candidate refers to not-transplanted patients at time of interview, refusal or death.

D1.2 Longitudinal study of HRQOL and utility

Of the 34 candidates interviewed, 15 became lung transplant recipients between October 18th, 2000 and October 28th, 2001. These newly transplanted candidates were on average 54.25 ± 11.34 years old and had spent 9.53 ± 2.46 months on the waiting list, at time of transplantation. This group of patients contributed information as candidates and recipients and therefore made up the longitudinal analysis of HRQOL and utility.

Of these fifteen new transplant recipients, 2 patients had recent transplantations and were still hospitalized therefore could not be interviewed. In the first 4 months post-transplantation (period 1), 11 of the 13 patients completed the health related quality of life questionnaire: one patient died within a month of transplantation and another had a prolonged hospital stay that exceeded the 4 months and could not complete the HRQOL questionnaire. In the beyond 4-month post-transplant period (period 2), 8 of the 13 patients reached this point in time and completed the questionnaire.

The post-transplant time experience in period 1 was on average 2.17 ± 0.95 months and the median 1.86 months. The transplant experience in period 2 was on average 7.54 ± 1.75 months and the median 8.05 months. The range of time since transplantation in period 1 and 2 was: 0.95 to 3.81 months and 4.14 to 9.23 months, respectively.

D1.2.1 Comparison between candidates remaining on the waiting list and those who became newly transplanted during the study

Candidates who received a transplant (n=15) were on average older than those who remained on the waiting list (n=19), 53.6 ± 11.9 versus 47.0 ± 9.8 years of age and, had spent less time on the waiting list, 5.6 ± 2.5 versus 6.4 ± 7.6 months, respectively. The % predicted FEV_1 scores in new recipients were on average lower than candidates still waiting for a transplant, 29.8 ± 16.6 versus 42.1 ± 25.6. Furthermore, 6 out of the 15 of those who became new recipients were females versus 12 out of the 19 who remained on the list.

Further testing of these two groups with respect to the eight health domains showed the following results (table D3). Though not statistically significant, newly transplanted candidates had scored better, on average, in all but social functioning and emotional role.

Table D3. HRQOL mean scores in newly transplanted candidates versus those remaining on the waiting list

Transformed scores (0-100)	**Remained Candidates (N=19) Mean ± S.D.**	**Transplanted Candidates (N=15) Mean ± S.D.**	**Difference (95% CI)***
Physical functioning	24.2±20.8	32.7±26.4	-8.5 (-24.9, 8.0)
Role Physical	16.1±16.0	28.3±30.1	-12.2 (-28.6, 4.1)
Bodily pain	54.4±26.5	54.7±34.6	-0.4 (-21.7, 20.9)
General Health	20.5±15.5	28.4±20.9	-7.9 (-20.6, 4.8)
Vitality	42.8±12.4	48.8±14.2	-6.0 (-15.3, 3.3)
Social functioning	49.3±24.8	42.5±32.0	6.8 (-13.0, 26.7)
Role Emotional	64.0±40.2	48.9±37.6	15.1 (-12.4, 42.6)
Mental Health	66.6±20.6	69.0±17.1	-2.4 (-15.9, 11.1)

*t-test showed no significant difference, at the 0.05 alpha significance level, between these two groups with respect to all eight HRQOL domains.

Section D2. Multivariate analysis of the effect of transplantation on HRQOL

D2.1 Effect of transplantation on physical functioning

HRQOL measured in terms of physical functioning was on average better in transplant recipients as compared to candidates (table D4). Age and time since transplantation, irrespective of all other variables studied, were associated with lower physical functioning scores. Furthermore, the experience of having been hospitalized, while keeping all other variables similar, was also associated with lower physical functioning scores than not being hospitalized.

Table D4. The effect of important predictors and determinants in physical functioning

Variable	ß*	95% CI	F value	P value
Intercept	71.920	52.718, 91.121	53.89	0.0001
Age at interview (years)	-0.864	-0.514, -1.215	23.38	0.0001
Status (Recipient versus Candidate)	50.186	38.826, 61.546	74.98	0.0001
Time since transplantation (months)	-0.354	-0.178, -0.535	14.73	0.0002
Hospitalization (yes/no) within a month of interview	-14.406	-0.483, -28.328	4.11	0.045

*Coefficients are adjusted for every other variable in the model. The model explains 55.9% of the variability observed in physical functioning. F value=31.63, p. < 0.0001

D2.2 Effect of transplantation on role physical

The average score reported by recipients, for role physical, while keeping all other variables constant, was higher than those reported by candidates (table D5) although age and time since transplantation had a negative effect. Patients with cystic fibrosis and bronchiectasis reported, on average, better scores than all other disease groups. Although not statistically significant, double lung transplant recipients scored less, on

average, than single lung and heart-lung recipients. The number of days as an in-patient was also associated, on average, with lower role physical scores.

Table D5. The effect of important predictors and determinants in role physical

Variable	ß*	95% CI	F value	P value
Intercept	42.128	16.935, 67.320	10.74	0.002
Age at interview	-0.463	-0.917, -0.010	4.00	0.05
Status (Recipient versus Candidate)	55.203	42.423, 67.983	71.68	0.0001
Time since transplantation (months)	-0.267	-0.449, -0.086	8.33	0.005
Double lung transplantation	-13.593	-29.565, 2.380	2.68	0.10
CF and bronchiectasis disease group	21.364	6.166, 36.562	7.59	0.007
Inpatient LOS (days) within a month of interview	-1.481	-2.739, -0.222	5.32	0.03

*Coefficients are adjusted for every other variable in the model. The model explains 59.7% of the variability observed in physical role. F value=24.17, p. < 0.0001

D2.3 Effect of transplantation on bodily pain

When all other variables were adjusted for, recipients reported better bodily pain scores than candidates (table D6). Double lung transplant recipients however, reported lower scores as compared to single lung and heart-lung recipients. Time since transplantation was also, on average, negatively associated with bodily pain (i.e. more pain). Cystic fibrosis and bronchiectasis patients reported on average better bodily pain scores, as compared to other disease groups. Finally, being hospitalized within one month of interview negatively influenced the reporting of bodily pain, as compared to not being hospitalized.

Table D6. The effect of important predictors and determinants on bodily pain

Variable	ß*	95% CI	F value	P value
Intercept	50.845	41.942, 59.748	125.29	0.0001
Status (Recipient versus Candidate)	34.483	19.832, 49.135	21.28	0.0001
Time since transplantation (months)	-0.297	-0.504, -0.090	7.87	0.006
Double lung transplantation	-26.991	-44.685, -9.296	8.94	0.0035
CF and bronchiectasis disease group	31.003	15.349, 46.657	15.07	0.0002
Hospitalization (yes/no) within a month of interview	-30.377	-45.914, -14.840	14.69	0.0002

*Coefficients are adjusted for every other variable in the model. The model explains 29.6% of the variability observed in bodily pain. F value=8.31, p. < 0.0001

D2.4 Effect of transplantation on general health

Recipients reported on average higher general health scores than candidates (table D7). Age and time since transplantation however had a negative impact on general health. Double lung recipients reported on average lower scores than other recipients. Cystic fibrosis and bronchiectasis patients reported better scores than all other disease groups. The length of stay as an inpatient was associated, on average, with a decrease in reported general health.

Table D7. The effect of important predictors and determinants on general health

Variable	ß*	95% CI	F value	P value
Intercept	38.107	19.478, 56.737	16.07	0.001
Age at interview	-0.314	-0.650, 0.021	3.37	0.07
Status (Recipient versus Candidate)	57.570	48.119, 67.021	142.55	0.0001
Time since transplantation (months)	-0.260	-0.394, -0.126	14.43	0.0003
Double lung transplantation	-18.440	-30.252, -6.629	9.36	0.003
CF and bronchiectasis disease group	17.378	6.139, 28.617	9.19	0.003
Inpatient LOS (days) within a month of interview	-1.781	-2.712, -0.850	14.06	0.0003

*Coefficients are adjusted for every other variable in the model. The model explains 69.9% of the variability observed in general health. F value=37.92, p. < 0.0001

D2.5 Effect of transplantation on vitality

The average vitality scores obtained in recipients and patients in the PVD, as well as CF and bronchiectasis group, were higher on average than candidates and other disease groups, respectively (table D8). Time since transplantation however was associated with a decrease in vitality. Double lung recipients reported lower vitality scores, than single and heart-lung recipients. Also, hospitalized patients reported lower scores on average than patients who had not been hospitalized, irrespective of all other variables.

Table D8. The effect of important predictors and determinants on vitality

Variable	ß*	95% CI	F value	P value
Intercept	41.009	35.721, 46.296	231.09	0.0001
Status (Recipient versus Candidate)	28.793	20.497, 37.089	46.28	0.0001
Time since transplantation (months)	-0.137	-0.254, -0.019	5.21	0.03
Double lung transplantation	-12.039	-22.191, -1.887	5.40	0.02
Pulmonary vascular disease group	8.475	-1.701, 18.651	2.66	0.10
CF and Bronchiectasis diseases	23.301	14.099, 32.501	24.64	0.0001
Hospitalization (yes/no) within one month of interview	-12.128	-20.914, -3.330	7.30	0.008

*Coefficients are adjusted for every other variable in the model. The model explains 48.2% of the variability observed in vitality. F value=18.45, p. < 0.0001

D2.6 Effect of transplantation on social functioning

Recipients reported higher social functioning scores than candidates (table D9). Time since transplantation however was negatively associated. Patients in the pulmonary vascular disease group and, in the cystic fibrosis and bronchiectasis disease groups reported much better social functioning than patients in the restrictive and OAD groups. Furthermore, study results show a negative association between inpatient length of stay and reported social functioning.

Table D9. The effect of important predictors and determinants on social functioning

Variable	ß*	95% CI	F value	P value
Intercept	38.686	30.282, 47.090	81.40	0.0001
Status (Recipient versus Candidate)	39.430	26.346, 52.513	34.89	0.0001
Time since transplantation (months)	-0.218	-0.208, -0.032	5.30	0.02
Double lung transplantation	-16.974	-33.321, -0.627	4.14	0.05
Pulmonary vascular disease group	21.257	5.116, 37.398	6.66	0.01
CF and Bronchiectasis diseases	35.817	21.064, 50.571	22.64	0.0001
Inpatient LOS (days) within one month of interview	-1.388	-2.650, -0.126	4.65	0.04

*Coefficients are adjusted for every other variable in the model. The model explains 46.5% of the variability observed in social functioning. F value=14.17, p. < 0.0001

D2.7 Effect of transplantation on role emotional

Results show that role emotional was higher in recipients and in patients with cystic fibrosis and bronchiectasis (table D10) as compared to candidates and the other lung disease groups studied. Although not significant, double lung transplant recipients reported on average lower scores than other recipients.

Table D10. The effect of important predictors and determinants on role emotional

Variable	ß*	95% CI	F value	P value
Intercept	52.766	43.161, 62.371	115.94	0.0001
Status (Recipient versus Candidate)	28.568	15.738, 41.397	19.05	0.0001
Double lung transplantation	-17.024	-35.729, 18.534	3.18	0.08
CF and bronchiectasis disease group	25.993	9.270, 42.716	9.28	0.003

*Coefficients are adjusted for every other variable in the model. The model explains 24.0% of the variability observed in emotional role. F value=10.62, p. < 0.0001

D2.8 Effect of transplantation on mental health

Recipients reported higher mental health scores than candidates, irrespective of all other variables studied (table D11). After adjusting for transplant status and disease,

females tended to report lower scores than males. Furthermore, patients in the obstructive airways disease group reported lower scores than other disease groups.

Table D11. The effect of important predictors and determinants on mental health

Variable	ß*	95% CI	F value	P value
Intercept	76.244	69.243, 83.244	455.69	0.0001
Status (Recipient versus candidate)	9.689	2.948, 16.430	8.39	0.005
Sex (Female versus Male)	-6.482	-12.768, -0.197	4.09	0.05
OAD group	-11.708	-17.920, -5.495	13.64	0.0004

*Coefficients are adjusted for every other variable in the model. The model explains 19.5% of the variability observed in mental health. F value=8.16, <0.0001

Section D3. Longitudinal analysis of the eight HRQOL domains

The following sub-sections include results obtained by stepwise regression with a significance level of 0.05 to enter and 0.10 to stay. Full models studied included age at interview, sex, FEV1 (%predicted), presence of infection and hospitalization within a month of interview. Due to the small sample size and the validity of the models questioned, a reduced model was kept.

D3.1 Longitudinal effect of transplantation on physical functioning

The crude results suggest that there is no difference in the reporting of physical functioning before and after transplantation (table D12).

Table D12. Longitudinal analysis of physical functioning

	Estimate*	95% CI	Z	P value
Intercept (before transplantation)	28.85	15.96, 41.73	4.39	0.0001
< 4 months post-transplantation	9.34	-0.16, 18.84	1.93	0.06
≥ 4 months post-transplantation	13.28	-7.31, 33.87	1.26	0.21

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Multivariate analyses carried out suggest that the most important predictor of physical functioning within the four months following transplantation is the patient's score given during the waiting list (table D13). The better a patient scored in the pre-transplant phase the better the patient scored within the 4 months post transplantation. Beyond the four months, the most important predictive factor of physical functioning was the presence of an infection within one month of being interviewed (table D14).

Table D13. Simple regression of physical functioning < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	11.379	-7.738, 30.495	1.81	0.21
Physical functioning baseline score	0.911	0.431, 1.391	18.39	0.002

The model explains 67.1% of the variability observed in physical functioning in the first 4 months post-transplantation. F value=18.39, p. < 0.0001

Table D14. Simple regression of physical functioning ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	266.355	128.57, 404.146	14.36	0.013
Age at interview	-3.465	-5.765, -1.164	8.71	0.03
Presence of an infection (yes/no) within a month of interview	-45.712	-69.660, -21.764	14.00	0.013

The model explains 85.1% of the variability observed in physical functioning, ≥ 4 months post-transplantation. F value=14.33, p. < 0.009.

D3.2 Longitudinal effect of transplantation on role physical

HRQOL in terms of role physical did not seem to improve with transplantation when comparing crude estimates (table D15). Within the four months post-transplantation, the best predictor of role physical was age at time of interview (table

D16). Beyond the four-month period, baseline role physical was a positive post-transplant predictor (table D17).

Table D15. Longitudinal analysis of role physical

	ß*	95% CI	Z	P value
Intercept (before transplantation)	27.40	10.62, 44.18	3.20	0.0014
< 4 months post-transplantation	9.13	-5.20, 23.46	1.25	0.21
≥ 4 months post-transplantation	5.72	-7.42, 18.87	0.85	0.39

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Table D16. Simple regression of role physical < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	149.075	79.935, 218.217	23.79	0.0009
Age at interview	-2.048	-3.322, -0.008	13.24	0.005

The model explains 59.5% of the variability observed in physical role, < 4 months post-transplantation. F value=13.24, p. < 0.005

Table D17. Simple regression of role physical ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	12.700	-9.943, 35.343	1.88	0.22
Physical role baseline score	0.741	0.108, 1.374	8.20	0.03

The model explains 57.8% of the variability observed in physical role, ≥ 4 months post-transplantation. F value=8.20, p. < 0.03

D3.3 Longitudinal effect of transplantation on bodily pain

The results obtained suggest that bodily pain may increase after transplantation as compared to the waiting list period and that there is no improvement, i.e. an alleviation of pain, between the two post-transplant time periods studied, (table D18).

Table D18. Longitudinal analysis of bodily pain

	ß*	95% CI	Z	P value
Intercept (before transplantation)	56.84	37.58, 76.11	5.78	0.0001
< 4 months post-transplantation	-13.61	-27.58, 0.36	-1.91	0.06
≥ 4 months post-transplantation	-18.04	-40.66, 4.58	-1.56	0.12

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

The most important variables in explaining bodily pain in the first 4 months post–transplantation was age and whether recipients had spent time in the hospital within one month of interview (table D19). After adjusting for inpatient length of stay, the older the patient the more bodily pain was reported. Furthermore, for every one day spent in the hospital, there was an average decrease in the reported HRQOL of bodily pain. Beyond the 4-month period, the baseline bodily pain reported was a predictor as well as age (table D20).

Table D19. Modeling of bodily pain < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	103.286	77.748, 128.824	86.98	0.0001
Age at interview	-0.797	-1.285, -0.309	14.19	0.0055
Inpatient LOS (days), within a month of interview	-0.643	-0.869, -0.417	43.02	0.0002

The model explains 90.6% of the variability observed in bodily pain in the first 4 months post-transplantation. F value=38.31, p. <0.0001

Table D20. Simple regression of bodily pain ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	258.662	169.011, 348.313	31.98	0.002
Age at interview	-3.978	-5.472, -2.484	27.25	0.003
Bodily pain baseline score	0.329	0.136, 0.291	11.18	0.02

The model explains 87.2% of the variability observed in bodily pain, ≥ 4 months post-transplantation. F value=17.09 p. < 0.006

D3.4 Longitudinal effect of transplantation on general health

General health improved after transplantation (table D21). Within four months of transplantation new recipients tended to report better general health scores than those reported during the waiting list. Recipients reaching the four months and beyond also reported better scores than those reported during the waiting list.

Table D21. Longitudinal analysis of general health as a function of time

	ß*	95% CI	Z	P value
Intercept (before transplantation)	26.62	15.55, 37.68	4.72	0.0001
< 4 months post-transplantation	40.60	29.97, 51.23	7.49	0.0001
≥ 4 months post-transplantation	23.68	11.21, 36.15	3.72	0.0002

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

The variable that had the most significant impact on general health was age (table D22). Although marginally significant, baseline reported scores seemed to have a positive effect on future reported scores, beyond the four-month period (table F23).

Table D22. Simple regression of general health < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	140.903	85.272, 196.533	32.83	0.0003
Age at interview	-1.349	-2.374, -0.325	8.87	0.02

The model explains 49.6% of the variability observed in general health in the first 4 months post-transplantation. F value=8.87, p. <0.02

Table D23. Simple regression of general health, ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	26.008	-3.627, 55.642	4.61	0.008
GH Baseline score	0.922	-0.008, 1.852	5.88	0.052

The model explains 49.5% of the variability observed in general health, ≥ 4 months post-transplantation. F value=5.88, p. =0.0515

D3.5 Longitudinal effect of transplantation on vitality

The crude estimates suggest that there is no difference in the reporting of vitality in the post-transplant period as opposed to the waiting list period (D24).

Table D24. Longitudinal analysis of vitality

	ß*	95% CI	Z	P value
Intercept (before transplantation)	50.00	42.46, 57.54	13.00	0.0001
< 4 months post-transplantation	0.05	-9.35, 9.44	0.01	0.99
≥ 4 months post-transplantation	-9.38	-20.97, 2.22	-1.58	0.11

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Within the four-months of transplantation vitality was negatively associated with age at time of interview and positively associated with patient baseline scores (table D25). Furthermore, after adjusting for age, every unit score in baseline vitality reported was associated with an increase in post-transplant vitality. Beyond the 4-month period, age was negatively associated with vitality (table D26).

Table D25. Multivariate modeling of vitality < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	80.678	26.454, 134.902	11.77	0.009
Age at interview	-1.286	-1.855, -0.688	24.58	0.001
V Baseline score	0.736	0.170, 1.302	9.00	0.02

The model explains 89.2% of the variability observed in vitality in the first 4 months post-transplantation. F value=33.09, p. = 0.0001

Table D26. Simple regression of vitality ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	242.100	188.295, 295.905	121.23	0.0001
Age at interview	-3.336	-4.224, -2.449	84.54	0.0001

The model explains 93.4% of the variability observed in vitality, ≥ 4 months post-transplantation. F value=84.54, p. < 0.0001

D3.6 Longitudinal effect of transplantation on social functioning

No significant improvement in social functioning was observed (table D27). Within the four-month post-transplant period, social functioning was explained in part by the reported baseline scores (table D28). Beyond this mark, baseline scores still had a positive influence however, the presence of an infection within a month of interview negatively influenced social functioning (table D29).

Table D27. Longitudinal analysis of social functioning

	ß*	95% CI	Z	P value
Intercept (before transplantation)	44.23	27.67, 60.79	5.23	0.0001
< 4 months post-transplantation	-0.45	-7.77, 6.87	-0.12	0.90
≥ 4 months post-transplantation	8.20	-2.35, 18.75	1.52	0.13

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Table D28. Simple regression of social functioning < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	5.530	-12.151, 23.212	0.50	0.50
SF Baseline score	0.867	0.561, 1.172	41.21	0.0001

The model explains 82.1% of the variability observed in social functioning in the first 4 months post-transplantation. F value=41.21, p. = 0.0001

Table D29. Simple regression of social functioning ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	-39.434	-74.467, -4.401	4.87	0.08
SF Baseline score	1.217	0.850, 1.584	42.24	0.002
Time spent on waiting list (months)	5.795	1.943, 9.646	8.69	0.03

The model explains 89.5% of the variability observed in social functioning, ≥ 4 months post-transplantation. F value=21.34, p. <0.004

D3.7 Longitudinal effect of transplantation on role emotional

No difference was observed between pre and post-transplant reported role emotional scores (table D30). In the first 4 months, the number of days spent as an inpatient negatively influenced the scores (D31). Beyond the four-month period, age significantly and inversely explained the variability observed in role emotional (table D32). Furthermore, the effect of the number of days spent in hospital, a month before interview, negatively affected role emotional.

Table D30. Longitudinal analysis of role emotional

	ß*	95% CI	Z	P value
Intercept (before transplantation)	52.56	32.75, 72.38	5.20	0.0001
< 4 months post-transplantation	7.76	-11.03, 26.56	0.81	0.42
≥ 4 months post-transplantation	4.55	-23.42, 32.52	0.32	0.75

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Table D31. Simple regression of role emotional < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	82.662	59.692, 105.631	66.26	0.0001
Inpatient LOS (days) within a month of interview	-0.862	-1.533, -0.191	8.44	0.02

The model explains 48.4% of the variability observed in emotional role in the first 4 months post-transplantation. F value=8.44, p. < 0.02

Table D32. Simple regression of role emotional ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	392.525	299.001, 486.041	67.68	0.0004
Age at interview	-5.517	-7.067, -3.966	48.63	0.0009
Inpatient LOS (days) within a month of interview	-0.330	-0.496, -0.165	15.27	0.011

The model explains 93.7% of the variability observed in emotional role, ≥ 4 months post-transplantation. F value=36.92, p. < 0.001

D3.8 Longitudinal effect of transplantation on mental health

Crude estimates did not show a significant association between transplantation and mental health (table D33). Within 4 months of transplantation, mental health was associated with age and baseline scores (table D34). Past the 4-month period, a positive predictor of mental health was time spent on waiting list (table D35).

Table D33. Longitudinal analysis of mental health as a function of time

	ß*	95% CI	Z	P value
Intercept (before transplantation)	68.08	59.06, 77.09	14.80	0.0001
< 4 months post-transplantation	1.51	-5.42, 8.43	0.43	0.67
≥ 4 months post-transplantation	-1.60	-13.30, 10.10	-0.27	0.79

*Estimate of means were obtained through genmod for generalized linear models with a specified normal distribution and identity link.

Table D34. Multivariate modeling of mental health < 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	67.967	13.927, 122.008	8.41	0.02
Age at interview	-0.650	-1.289, -0.01	5.49	0.05
MH Baseline score	0.532	0.089, 0.974	7.68	0.03

The model explains 72.3% of the variability observed in mental health in the first 4 months post-transplantation. F value=10.45, p. = 0.006

Table D35. Simple regression of mental health ≥ 4 months post-transplantation

	ß*	95% CI	F-value	P value
Intercept	25.252	-12.936, 63.441	1.62	0.16
Time spent on waiting list (months)	5.831	0.721, 10.942	7.79	0.03

The model explains 56.5% of the variability observed in mental health, ≥ 4 months post-transplantation. F value=7.79, p. = 0.03

Appendix E

Appendix to cost estimates

The following sections provide additional information as to the breakdown and calculation methods used in the cost estimates of the different resources used throughout the follow-up period.

Section E1. Sensitivity analysis of the average cost of a hospitalization due to a respiratory insufficiency

The valorization of pre-transplant hospitalizations was based on the NIRRU method (described in section B3.1). The severity index (i.e. NIRRU score) attributed to each hospitalization depended on its average length of stay (LOS). We carried out a sensitivity analysis around the severity index attributed to each hospital, which was based on a cut-off length of stay of 13 days (table E1). The first sensitivity analysis attributed the lowest NIRRU score (2.6038) to 50% of the hospitalizations with the lowest LOS and the highest NIRRU score (3.1894) to the hospitalizations with the highest LOS. The second and third analyses carried out used 20 % of the lowest and 80% of the highest, and 80% of the lowest and 20% of the highest LOS, respectively, in attributing the lowest and highest NIRRU scores. The sensitivity analysis did not show a significant variation in the estimate of an average cost of a respiratory insufficiency or exacerbation in the pre-transplant phase (table E1).

Table E1. Sensitivity analysis around the cost of a pre-transplant hospitalization

	NIRRU scores attributed to % number of hospitalizations:		Cost Mean ± S.D.
	Lower severity NIRRU score: 2.6038	Higher severity NIRRU score: 3.1894	
Observed	44% of hospitalizations had a LOS* of less than 13 days	56% of hospitalizations had a LOS of 13 days and longer	$9,210 ± $13,430
	50% of hospitalizations had a LOS of less than 14 days	50% of hospitalizations had a LOS of 14 days and more	$9,129± $13,322
	20% of hospitalizations had a LOS of less than 5 days	80% of hospitalizations had a LOS of 5 days and more	$9,732 ± $13,774
	80% of hospitalizations had a LOS of less than 25 days	20% of hospitalizations had a LOS of 25 days and more	$8,575 ± $12,024

*LOS: Length of Stay

Section E2. Breakdown of costs during pre-transplant period

This section deals with a breakdown of the costs presented in chapter 5, section 5.4. Each table describes the cost that was accounted for in the total cost and is referenced in the results section. The services and resources utilized are mentioned in the table's title.

Table E2. The average cost of emergency room visits

N = 8 patients	Mean ± S.D.
Physician fees	$144 ± $86
Emergency room costs	$238 ± 0
Resources utilized (Diagnostic & Laboratory)	$78 ± $81
Average per patient in cohort (N = 124)	Mean ± S.D.
Physician fees	$9 ± $39
Emergency room	$15 ± $59
Resources utilized (Diagnostic & laboratory)	$5 ± $27
TOTAL	$29 ± $117

Table E3. Average cost of a bronchoscopy: bronchoalveloar lavage (BAL) & transbronchial biopsy (TBB)

	Cost per procedure	N = 9 bronchoscopies & 1 TBB
Physician fee:		
Flexible bronchoscopy	$105	$941
TB lung biopsy	$75.00	$75
Pathology	$27.00	$27
Endoscopy department & One-day surgery	$236	$2,127
BAL (microbiologic testing)	$129	$2,101
Sputum (microbiologic testing)	$25	
Chest X-ray (2visuals)	$24	
Cytology: BAL cell count	$45	
Sub-total	$223	
Pathology: Bronchial specimens (n=1)	$107	$107
Quebec estimates		$2,118
TOTAL		$5,288

Laboratory and diagnostic test costs were based on UHN data.

Table E4. Average cost of outpatient visits during the waiting list period

Number of visits = 632	Sum	Mean ± S.D.	Median
Physician fees	$17,362	$27 ± 14	$36
Resources utilized (Diagnostic & Laboratory)	$43,330	$69 ± 35	$87

Laboratory and diagnostic test costs were based on UHN data.

Table E5. Average cost per patient of outpatient visits during the waiting list period

N = 124	Mean ± S.D.	Median	Range
Physician fees	$140 ± $147	$107	$0 – $994
Resources utilized (Dx & Laboratory)	$349 ± $371	$262	$0 - $2,174

Section E3. Validation of the use of the Ontario data set

The costs of hospitalizations related to the transplant procedure and due to post-transplant infection and rejection, were estimated from data based on lung recipients followed at the UHN. In the following sub-sections different validations are presented as to the use of this data.

E3.1.1 Comparing Montreal and Toronto cohorts: are the cohorts similar?

In order to assess the similarity of the cohorts a few characteristics were studied: age at transplantation, sex, type of disease diagnosis and transplant received, and patient mortality during the hospitalization for the transplant procedure (table E6). Results show that the cohorts differ with respect to the frequency of disease diagnoses and the type of transplant carried out, double lung transplants are more predominant in the Toronto cohort. These differences, as previously studied, are not likely to influence significantly the cost attributed to a lung transplant.

Table E6. Characteristic differences in transplant cohorts

Variables	**Montreal (N=91)**	**Toronto (N=135)**	**t-value**	**p-value**
Age at transplantation	47.549±13.37	47.32±13.60	-0.13	0.90
			X^2	**p-value**
Sex				
Male	40 (44.0%)	59 (43.7%)	0.0014	0.97
Female	51 (56.0%)	76 (56.3%)		
End-stage lung disease diagnosis				
PVD	2 (2%)	15 (11%)		
OAD	48 (53%)	47 (35%)	13.2605	0.01
CF	20 (22%)	31 (23%)		
RESD	14 (15%)	35 (26%)		
BRONCH	7 (8%)	7 (5%)		
Type of transplantation (double versus single)	35/91 (38.5%)	118/135 (87.4%)	59.55	0.0001
Death during hospitalization	10/91 (11.00%)	20/135 (14.8%)	0.69	0.41

With regard to resource utilization, table E7 shows that medical practices were similar in both centers. The main differences are attributed to relatively rare events

and are patient specific. Furthermore, differences occur in low cost resources and therefore are not likely to influence the cost of transplantation.

Table E7. Resource utilization differences between Montreal and Toronto cohorts

Variables	Montreal Mean ± S.D.	Toronto Mean ± S.D.	Difference (95% CI)	p-value
Length of stay	28.24 ± 25.36	32.77 ± 26.61	-4.53 (-11.51, 2.45)	0.20
Time spent in ICU (hours of care received)	211.38 ±293.86	248.86 ±350.19	-37.48 (-125.44, 50.49)	0.40
Time spent on the ward (hours of care received)	187.14 ± 176.63	154.39 ± 136.01	32.74 (-8.66, 74.14)	0.14
Operating Room time (hours of care rendered in OR)	20.20 ± 5.10	19.46 ± 7.34	0.74 (-1.01, 2.49)	0.37
X-Rays, chest (number)	28.01 ± 18.68	30.42 ± 18.68	-2.41 (-7.41, 2.59)	0.34
X-Rays, abdomen (simple)	0.11 ± 0.41	0.34 ± 0.70	-0.23 (-0.39, 0.07)	0.002
X-Rays, abdomen (complete)	0.52 ± 1.27	0.21± 0.65	0.30 (0.048, 0.56)	0.04
X-Ray (Dorsal)	0.04 ± 0.21	0.04 ± 0.27	-0.0005 (-0.07, 0.07)	0.99
X-Ray (thorax)	0.01 ± 0.10	0.01 ± 0.12	-0.004 (-0.03, 0.03)	0.81
Endoscopy	0.23 ± 0.50	0.04 ± 0.21	0.19 (0.09, 0.28)	0.001
Bronchoscopy	1.58 ± 2.74	1± 0.95	0.58 (0.08, 1.09)	0.06
Transbronchial biopsy, or lung	0.89 ± 1.46	0.73 ± 0.78	0.16 (-0.14, 0.45)	0.35
MRSA	0.4 ± 1.15	1.01 ± 1.71	-0.61 (-1.01, -0.20)	0.002
VRE	1.39 ± 1.57	1.31 ± 2.70	0.08 (-0.54, 0.70)	0.79
Legionella	0.18 ± 0.82	0.53 ± 1.32	-0.36 (-0.66, -0.05)	0.013
Vancomycin (dosage)	0.84 ± 2.48	0.70 ± 2.34	0.14 (-0.50, 0.78)	0.67
Tobramycin (dosage)	0.74 ± 2.18	0.48 ± 1.18	0.26 (-0.18, 0.71)	0.30
Complete Blood Count	33.86 ± 28.50	42.44 ± 33.46	-8.58 (-17.17, 0.005)	0.05
Apt, appt (CS)	53.84 ± 52.20	78.53 ± 65.34	-24.69 (-41.13, -8.25)	0.002
Blood gases	31.28 ± 35.94	67.62 ± 81.05	36.34 (-54.27, -18.42)	0.0001

Section E4. Transplant procedure related costs

This section deals with costs and resources utilized during the transplant and post-transplant phase.

Table E8. Hospitalization for transplant procedure log-cost estimates

Variable	ß*	95% CI	P value
Intercept	9.707	9.120, 10.294	0.0001
Age at transplantation	0.003	-0.003, 0.009	0.36
Sex (Female versus Male)	0.135	0.008, 0.262	0.04
Type of transplantation (Double versus Single)	0.075	-0.125, 0.276	0.46
Disease Type Reference OAD			
PVD	0.077	-0.141, 0.295	0.49
CF	0.129	-0.085, 0.343	0.24
RESD	0.133	-0.025, 0.292	0.10
BRONCH	0.199	-0.094, 0.491	0.19
Length of Stay (LOS)	0.020	0.017, 0.022	0.0001
Death (D) in hospital (Yes versus No)	-0.113	-0.332, 0.106	0.31
Interaction term (LOS*D)	0.009	0.003, 0.015	0.003

*Beta estimates represent changes in the log-cost.

Calculation of the effect of one additional day of length of stay and death on the cost of a hospitalization, while taking the interaction term into account, may be computed as follows:

Equation E1:

$$\log\_cost = 0.020(LOS) + -0.113\ (Death) + 0.009(LOS*Death)$$
$$\log\_cost = 0.020\ (\ 1day) + -0.113\ (1) + 0.009\ (1*1)$$
$$\log\_cost = -0.084$$
$$cost = (\ln^{-1}) - 0.084$$
$$cost = 0.919$$

That is, every one additional day spent in the hospital on the cost of hospitalization, for a patient who eventually dies during the hospital stay, is on average 8% lower than a patient who does not die.

Table E9. Physician fees attributed to consultations and diagnostic testing during the hospitalization for the transplant procedure

N=91 transplant recipients		**COST**
Procedure carried out on donor 2 surgeons = $2500 each	$544.00 Per procedure $5000.00 Per procedure	$5,544.00 per patient TOTAL: $504,504.00
Anesthesiologist: 12.00$/unit base	**Mean ± S.D.** 31.93 units ± 6.79 units (per patient) Sum: 2905.8	**Mean ± S.D.** $383.18 ± $81.51 per patient TOTAL: $34,869.60
Extracorporeal circulation $248.00	10 out of 91 patients	**Mean ± S.D.** $27.25 ± $78.00 per patient TOTAL: $2,480.00
Lung specialist: $75.00 per day during hospitalization	**LOS** **Mean ± S.D.** 28.24 days ± 25.36 days TOTAL: 2570 days	**Mean ± S.D.** $2,118.13 ± $1,901.89 per patient TOTAL: $192,750.00
Pathologist: surgical pathology of organs: $14.00	All 91 procedures	$14.00 per patient TOTAL: $1,274.00
Bronchoscopy: $104.60 per procedure	**Mean ± S.D.** 1.58 ± 2.74 (per patient) TOTAL: 144 procedures	**Mean ± S.D.** $165.52 ± $286.70 per patient TOTAL: $15,062.40
BAL reading: ($12.50)		**Mean ± S.D.** $19.78 ± $34.26 per patient TOTAL: $1,800.00
Transbronchial lung biopsy: $75.00 per procedure	**Mean ± S.D.** 0.89 ± 1.46 per patient TOTAL: 81 procedures	**Mean ± S.D.** $66.76 ± $109.80 per patient TOTAL: $6,075.00
Pathologist: (endoscopic biopsy), $27.00	TOTAL: 81 procedures	**Mean ± S.D.** $24.03 ± $39.42 per patient TOTAL: $2,187.00
Other physician fees: Phlebography: (57.66)	60 out of 91 patients	**Mean ± S.D.** $38.02 ± $27.48 per patient TOTAL: $6,075.00
Chest x-rays 5.25 each	28 per patient on average Total: 2549 chest x-rays	**Mean ± S.D.** $147.05 ± $98.07 per patient TOTAL: $13,382.25
Consults & diagnostic testing		**Mean ± S.D.** $613.66 ± $360.10 per patient TOTAL: $55,842.66
Death report (25.00 each)	10 out of 91 patients	**Mean ± S.D.** $2.75 ± $7.86 per patient TOTAL: $250.00
Autopsy (252.00each)	8 out of the 10 deaths	**Mean ± S.D.** $22.15 ± $71.75 per patient TOTAL: $2,016.00

Section E5. Post-transplant related costs

E5.1 Hospitalization costs due to post-transplant infection

The average cost per day of a hospitalization due to an infection was $658 ± $302. The average cost per transplant patient based on this per day cost, while taking all cohort members alive at each time period, is presented in table E10 (costs include physician fees). The discounted (5%) average costs for year 1, 2, 3 and 4 are: $4,411 ± $12,406, $2,472 ± $7,590, $90 ± $413 and $287 ± $812, respectively.

Table E10.Cost of hospitalizations due to an infection based on per day estimate

Post transplantation	Mean* ± S.D.	Total N alive	Mean** ± S.D.
0-12 months (n=29)	$14,534 ± $19,908	91	$4,632 ± $13,026
>12-24 months (n=8)	$16,692 ± $14,621	49	$2,725 ± $8,369
>24-36 months n=1)	$2,188	21	$104 ± $478
>36 months- + (n=1)	$2,792	8	$349 ± $987

*Mean is per patient hospitalized during period.
** Mean is based on calculations taking all patients alive in the cohort at beginning of period.

The estimated total average cost of a hospitalization due to an infection, in transplant recipients, was $10,334 ± $16,703. Mean costs based on this point estimate are presented in table E11, where physician fees are included in calculations.

Table E11. Cost of hospitalization due to infection based on total average cost

Post transplantation	Mean* ± S.D.	Total N alive	Mean** ± S.D.
0-12 months (n=29)	$13,666 ± $5,401	91	$4,355 ± $7,077
>12-24 months (n=8)	$12,939± $3,997	49	$2,112 ± $5,067
>24-36 months n=1)	$10,549	21	$502 ± $2,302
>36 months- + (n=1)	$10,495	8	$1,312 ± $3,710

*Mean is per patient hospitalized during period.
** Mean is based on calculations taking all patients alive in the cohort at beginning of period.

E5.2 Hospitalization costs due to a rejection

The estimated average cost per day of a hospitalization due to a rejection, based on the Ontario cohort data set, is $787 ± $446. The mean costs per hospitalization including physician fees, based on this day rate, are presented in table E12. The mean costs discounted at a rate of 5%, after taking all cohort members into consideration, are $1,952 ± $7,727, $1,743 ± $9,052 and $8,507 ± $37,282 for year 1, 2 and 3, respectively.

Table E12.Cost of hospitalizations due to a rejection based on per day estimate

Post transplantation	**Mean* ± S.D.**	**Total N alive**	**Mean** ± S.D.**
0-12 months (n=9)	$20,723 ± $17,470	91	$2,049 ± $8,113
>12-24 months (n=2)	$47,091 ± $9,097	49	$1,922 ± $9,505
>24-36 months (n=2)	$103,400 ± $106,312	21	$9,848 ± $39,146
>36 months- +	-	8	-

*Mean is per patient hospitalized during period.
** Mean is based on calculations taking all patients alive in the cohort at beginning of period.

The estimated average cost of a hospitalization was $19,330. Based on this estimate, mean costs attributed to each year are presented in table E13.

Table E13. Cost of hospitalization due to a rejection based on total average cost

Post transplantation	**Mean* ± S.D.**	**Total N alive**	**Mean** ± S.D.**
0-12 months (n=9)	$29,328 ± $14,962	91	$2,901 ± $9,869
>12-24 months (n=2)	$32,036± $13,866	49	$1,308 ± $6,710
>24-36 months (n=2)	$53,006± $18,195	21	$5,048± $16,455
>36 months- +	-	8	-

*Mean is per patient hospitalized during period.
** Mean is based on calculations taking all patients alive in the cohort at beginning of period.

E5.3 Post-transplant hospitalizations related to other causes

The costs associated to hospitalizations due to other causes, based on NIRRU scores, are presented in tables E14 and E15.

Table E14. Average cost of other type of post-transplant hospitalizations

	Per event	Physician fees
Post transplantation	Mean* ± S.D.	Mean* ± S.D.
0-6 months (36 hospitalizations)	$10,147 ± $3,444	$919 ± $1,189
>6-12 months (15 hospitalizations)	$11,579± $5,491	$1,158 ± $1,176
>12-18 months (8 hospitalizations)	$7,531± $3,840	$792 ± $1,000
>18-24 months (6 hospitalizations)	$7,765± $3,093	$347 ± $221
>24 months - (5 hospitalizations)	$11,161± $4,888	$774 ± $555

*Mean is per hospitalization

Table E15. Average cost of other type of post-transplant hospitalizations per patient

Post transplantation	Total N alive	Total cost*	Mean ± S.D. (Per patient in cohort)
0-6 months	91	$398,341	$4,377 ± $8,353
>6-12 months	67	$191,065	$2,852 ± $6,147
>12-18 months	49	$66,587	$1,359 ± $3,830
>18-24 months	31	$48,672	$1,570 ± $4,069
>24-30months	21	$8,257	$393 ± $1,802
>30-36months	15	$35,630	$2,375 ± $6,309
>36 months	8	$15,792	$1,974 ± $5,583

*Total cost includes physician fees

E5.4 Post-transplant one-day surgery related costs

This section deals with costs incurred during a one-day surgery in the post-transplant phase. Undiscounted costs are presented and broken down by post-transplant period of study. A summary of the costs associated with a bronchial dilation (table E16), a bronchoscopy (tables E17 and E18) and other one day surgeries (table E19) are presented hereafter.

Table E16. Average cost of a bronchial dilation

Post transplantation	**Total N alive**	**Total cost***	**Mean ± S.D. (Per patient in cohort)**
0-6 months	91	$13,005	$143 ± $713
>6-12 months	67	$7,315	$109 ± $467
>12-18 months	49	$813	$17 ± $116
>18-24 months	31	-	-
>24 months	21	-	-

*Total cost includes physician fees

Table E17. Valorization of a Bronchoscopy

	<6 months	>6-12 months	>12-18 months	>18-24 months	>24-30 months	>30-36 months	>36 months
Bronchoscopy	**145**	**54**	**29**	**7**	**12**	**3**	**3**
Only BAL	145	54	29	7	12	3	3
With TBB	112	38	23	5	5	3	1
Physician fees	$26,591	$9,524	$5,379	$1,242	$1,765	$620	$416
Department of Endoscopy & One-day surgery	$34,261	$12,759	$6,852	$1,654	$2,835	$709	$709
Microbiology	$22,2586	$8,289	$4,452	$1,075	$1,842	$461	$461
Radiology	$3,529	$1,314	$705	$170	$292	$73	$73
Cytology	$6,622	$2,466	$1,324	$320	$548	$137	$137
Pathology	$11,938	$4,050	$2,452	$533	$533	$320	$107
TOTAL	$105,199	$38,404	$21,165	$4,994	$7,268	$2,319	$1,902

Table E18. Average cost of a bronchoscopy per patient per period

Post transplantation	**Total N alive**	**Total***	**Mean ± S.D. (Per patient in cohort)**
0-6 months	91	$105,199	$1,156 ± $1,003
>6-12 months	67	$38,403	$573 ± $670
>12-18 months	49	$21,165	$432 ± $545
>18-24 months	31	$4,994	$161 ± $417
>24-30months	21	$7,816	$372 ± $618
>30-36months	15	$2,319	$155 ± $433
>36 months	8	$1,902	$238 ± $486

*Total cost includes physician fees

Table E19. Average cost of other one-day surgeries (OGD, coloscopy, colposcopy)

	<6 months	>6-12 months	>12-18 months	>18-24 months	>24-30 months	>30-+ months
Number of one-day surgery	6	3	2	-	1	1
Physician fees Biopsy Pathology	$350.00 $15.00 $27.00	$250.00 $30.00 $54.00	$150.00 $15.00 $27.00	-	$50.00	$50.00
Department of endoscopy and one-day surgery	$1,417.68	$708.84	$472.56	-	$236.28	$236.28
Total	$1,809.68	$1,042.84	$664.56	-	$286.28	$286.28
Total N alive	91	67	49	31	15	8
Average cost per patient	$20 ± $76	$16 ± $98	$14 ± $67	-	$14 ± 62	$19 ± $74

E5.5 Post-transplant ER related costs

This section deals with the costs included when valorizing visits to the emergency room.

Table E20. Valorization of resources utilized during emergency room visits

	0-6 months	>6-12 months	>12-18 months	>18-24 months	>24-30 months	>30-+ months
Visits (N) Patients (N)	19 (15)	4 (4)	7 (6)	0	1	1
Physician fees	$2,467	$434	$943	-	$120	$50
ER & other department	$5,227	$951	$1902	-	$238	$238
Diagnostic & laboratory tests	$1,564	$154	$637	-	$19	0
N alive	91	67	49	31	21	15
Average cost per patient in cohort	$102 ± $257	$23 ± $91	$71 ± $194	-	$18 ± $82	$19 ± $74

E5.6 Post-transplant ambulatory care related costs

This section deals with costs incurred while patients visited the ambulatory care unit. A frequency of the visits (table E21) and breakdown of costs related to the unit (tables E22 and E23) is presented hereafter.

Table E21. Frequency of ambulatory care visits.

Post-transplantation	# of visits (# of patients)	Ambulatory care services (Patient care days)	Total costs incurred
>0-6 months	50 (8 patients)	223 (24 pt care days due to rejection)	$18,034
>6-12 months	15 (6 patients)	32 (18 days)	$2,588
>12-18 months	5 (4 patients)	13 (12 days)	$1,051
>18-24 months	2 (1 patient)	7 (6 days)	$566
>24 months - +	-	-	
		264 patient care day	

# of patients: number of recipients that visited the ambulatory care unit during each period in the post-transplant phase

Table E22. Average cost of ambulatory care visits per post-transplant period

Post-transplantation	*Average cost per patient that visited the ambulatory care unit	**Total N alive**	**Average cost per patient in cohort**
0-6 months	$361 ± $179	91	$198± $2248
>6-12 months	$173 ± $80	67	$39 ± $81
>12-18 months	$210 ± $72	49	$21± $68
>18-24 months	$283 ± $286	31	$18± $87
>24 months	-	21	-

* Average based on number of recipients that visited the ambulatory care unit during each period in the post-transplant phase

Table E23. Pharmacy costs incurred during ambulatory care visits

Post-transplantation	Total Cost	*Average cost per patient per period	**Total N alive**	**Average per patient in cohort**
0-6 months	$277,787	$5,556 ± $3,258	91	$3,052 ± $3,675
>6-12 months	$9,876	$658 ± $1,697	67	$147± $829
>12-18 months	$660	$132 ± $25	49	$14 ± $42
>18-24 months	$265	$132 ± $ 180	31	$9 ± $47
> 24 months	-	-	21	-

* Average based on number of recipients that visited the ambulatory care unit during each period in the post-transplant phase

E5.7 Post-transplant outpatient related costs

This section deals with the utilization patterns of outpatient visits during the post-transplant phase and a breakdown of the costs (tables E24 and E25).

Table E24. Cost summary of post-transplant outpatient visits

0-6 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	1408	15.47 ± 8.70	17
Physician fees	$38,008	$27 ± $18	$36
Resources utilized	$108,603	$77 ± $36	$87
> 6-12 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	823	12.28 ± 6.41	11
Physician fees	$17,798	$22 ± $19	$32
Resources utilized	$59,412	$72 ± $41	$87
>12-18 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	500	10.20 ± 6.22	10
Physician fees	$9,749	$20 ± 19	$16
Resources utilized	$33,633	$67 ± 49	$63
>18-24 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	227	7.32 ± 5.30	6
Physician fees	$4,518	$20 ± $18	$19
Resources utilized	$15,756	$69 ± $59	$63
>24-30 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	134	6.38 ± 5.53	5
Physician fees	$2,836.47	$21 ± $19	$18
Resources utilized	$9,611	$72 ± $63	$63
>30-36 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	76	5.01 ± 4.03	5
Physician fees	$1,471	$19 ± $17	$16
Resources utilized	$5,206	$69 ± $44	$63
> 36 months post-transplantation	**Sum**	**Mean ± S.D.**	**Median**
Number of visits	67	8.38 ± 3.96	7
Physician fees	$1,370	$20± $23	$18
Resources utilized	$4,250	$63 ± $44	$63

*Resources utilized include all diagnostic and laboratory tests carried out on patient

E25. Average cost of post-transplant outpatient clinic visits per patient

	N alive in cohort	Sum	Average total* cost per patient alive
0-6 months	91	$146,611	$1,611 ± $871
>6-12 months	67	$77,210	$1,152 ± $578
>12-18 months	49	$43,382	$885 ± $519
>18-24 months	31	$20,274	$654 ± $459
>24 – 30 months	21	$12,448	$593 ± $443
>30-36 months	15	$6,677	$445 ± $338
>36 months and beyond	8	$5,621	$703 ± $392

*Average total cost includes both physician fees and all resources utilized during outpatient visit.

E5.8 Post-transplant outpatient medication related costs

This section deals with the economic impact of medication use by post-transplant transplant period of study. The medications are summarized on the basis of users and categorized as the anti-rejection (table E26), anti-infectives (table E27) and other types of drug (table E28) groups. A summary of the cost per patient in the cohort is presented in (table E29).

Table E26. Average cost of outpatient anti-rejection drugs per user

Per patient * Per post-transplant period	Mean ± S.D.	Median
0-6 months (n=74)	$3,802 ± $2,127	$3,681
>6-12 months (n=63)	$3,470 ± $2,228	$3,137
>12-18 months (n=47)	$3,485 ± $1,982	$3,617
>18-24 months (n=31)	$3,602 ± $2,838	$3,289
>24-30 months (n=21)	$3,230 ± $2,421	$2,987
>30-36 months (n=14)	$3,344 ± $2,265	$3,330
>36 -42 months (n=8)	$3,884 ± $2,169	$3,766

*Per patient: mean costs of medications taking into account utilization of users

Table E27. Average cost of outpatient anti-infective drugs per user

Per patient * Per post-transplant period	**Mean ± S.D.**	**Median**
0-6 months (n=64)	$3,272 ± $3,060	$2,432
>6-12 months (n=53)	$1,883 ± $2,597	$975
>12-18 months (n=39)	$1,639 ± $3,415	$163
>18-24 months (n=28)	$1,200 ± $2,446	$22
>24-30 months (n=18)	$1,072 ± $1,790	$22
30-36 months (n=12)	$545 ± $1,232	$22
36 -42 months (n=6)	$370 ± $788	$46

*Per patient: mean costs of medications taking into account utilization of users

Table E28. Average cost of other outpatient types of medications per user

Per patient * Per post-transplant period	**Mean ± S.D.**	**Median**
0-6 months (n=66)	$1,337± $1,036	$1,070
>6-12 months (n=56)	$1,374 ± $1,064	$1,144
>12-18 months (n=43)	$1,168 ± $980	$901
>18-24 months (n=31)	$984 ± $807	$772
>24-30 months (n=21)	$882 ± $650	$680
30-36 months (n=14)	$925 ± $921	$614
36-42 months (n=8)	$1,035 ± $534.	$869

*Per patient: mean costs of medications taking into account utilization of users

Table E29. Summary of outpatient medication cost per patient in cohort

Per patient in cohort	**Anti-Rejection Mean ± S.D.**	**Anti-infection Mean ± S.D.**	**Other Mean ± S.D.**
0-6 months (n=91)	$3,092 ± $2,427	$2,301 ± $2,969	$970 ± $1,066
>6-12 months (n=67)	$3,263 ± $2,313	$1,490 ± $2,431	$1,148 ± $1,099
>12-18 months (n=49)	$3,343 ± $2,062	$1,304 ± $3,111	$1,025 ± $998
>18-24 months (n=31)	$3,602 ± $2,838	$1,084 ± $2,349	$984 ± $807
>24-30 months (n=21)	$3,229 ± $2,421	$919 ± $1,694	$882 ± $650
30-36 months (n=15)	$3,121 ± $2,347	$436 ± $1,115	$863 ± $919
36-42 months (n=8)	$3,884 ± $2,169	$278 ± $687	$1,035 ± $534

E5.9 Patient borne costs

This section deals with costs related to transportation (tables E30 and E31) accommodations (table E32) and time spent while seeking medical care (table E33).

Table E30. Transportation related costs while seeking medical care

Post-transplantation	N alive in cohort	Cost associated to total Km traveled	Mean* ± S.D.	Median
0-6 months	91	$42,134	$463 ± $949	$169
>6-12 months	67	$25,256	$377 ± $809	$139
>12-18 months	49	$29,848	$609 ± $765	$271
>18-24 months	31	$9,745	$314 ± $451	$148
>24-30 months	21	$6,897	$328 ± $510	$128
>30-36 months	15	$3,811	$254 ± $267	$190
>36 months	8	$3,024	$378 ± $283	$391

*Mean is per recipient alive at beginning of each period studied

Table E31. Post-transplant ambulance related costs

Post-transplantation	N alive in cohort	Total	Mean* ± S.D.
0-6 months	91	$3,859	$42 ± $105
>6-12 months	67	$2,721.14	$41 ± $134
>12-18 months	49	$2,468	$50 ± $171
>18-24 months	31	$469	$15 ± $47
>24-30 months	21	$167	$8 ± $36
>30-36 months	15	-	-
>36 months	8	-	-

*Mean is per recipient alive at beginning of each period studied

Table E32. Post-transplant costs related to sleeping accommodations

Post-transplantation	N alive in cohort	Total	Mean* ± S.D.
0-6 months	91	$931	$10 ± $33
>6-12 months	67	$698	$10 ± $33
>12-18 months	49	$698	$14 ± $39
>18-24 months	31	$582	$19 ± $44
>24-30 months	21	$466	$22 ± $47
>30-36 months	15	$349	$23 ± $48
>36 months	8	$233	$29 ± $54

*Mean is per recipient alive at beginning of each period studied

Table E33. Post-transplant costs for time spent while seeking medical care

Post-transplantation	N alive in cohort	Total Cost	Cost per patient Mean* ± S.D.	Median
0-6 months	91	$118,024	$1,297 ± $826	$1,293
>6-12 months	67	$58,7134	$876± $567	$773
>12-18 months	49	$33,959	$673 ± $452	$598
>18-24 months	31	$13,503	$436 ± $328	$352
>24-30 months	21	$9,890	$471 ± $409	$4534
>30-36 months	15	$5,256	$350 ± $247	$347
>36 months	8	$4,302	$538 ± $289	$491

*Mean is per recipient alive at beginning of each period studied

Appendix F

Appendix to LY and QALY estimates

This section deals with the mean life years and QALYs gained by transplantation as observed throughout the study period (table F1) and this for specific disease groups (tables F2 to F5). The discounted mean LY and QALY gained during this study are presented in table F6.

Table F1. Summary of mean life-years and QALY per patient in total cohort

Full cohort	**Life-years** **Mean ± S.D.** **(95% C.I.)**	**QALY** **Mean ± S.D.** **(95% C.I.)**
Waiting list period (n=124)	0.73 ± 0.48 (-0.21, 1.68)	0.12 ± 0.08 (-0.04, 0.28)
Post-lung transplantation (n=91)	1.30 ± 1.05 (-0.80, 3.39)	0.74 ± 0.66 (-0.57, 2.05)
	Mean difference* ± S.E.M. **(95% C.I.)**	
Mean life years and quality adjusted life years gained	0.57 ± 0.11 (0.36, 0.78)	0.62 ± 0.06 (0.50, 0.73)

*t-test showed a significant difference in the means, for both life years ($p.< 0.0001$) and quality adjusted life years ($p.< 0.0001$), between waiting list and post-transplant period.

Table F2. Summary of mean life-years and QALY per patient in the OAD group

OAD group	**Life-years** **Mean ± S.D.** **(95% C.I.)**	**QALY** **Mean ± S.D.** **(95% C.I.)**
Waiting list period (n=56)	0.76 ± 0.48 (-0.21, 1.73)	0.18 ± 0.11 (-0.05, 0.40)
Post-lung transplantation (n=49)	1.36 ± 1.10 (-0.85, 3.56)	0.69 ± 0.62 (-0.55, 1.93)
	Mean difference* ± S.E.M. **(95% C.I.)**	
Mean life years and quality adjusted life years gained	0.59 ± 0.16 (0.27, 0.92)	0.51 ± 0.08 (0.35, 0.68)

*t-test showed a significant difference in the means, for both life years ($p.= 0.0008$) and quality adjusted life years ($p.< 0.0001$), between waiting list and post-transplant period.

Table F3. Summary of mean life-years and QALY per patient in the CF and bronchiectasis group

CF & Bronchiectasis disease group	**Life-years Mean ± S.D. (95% C.I.)**	**QALY Mean ± S.D. (95% C.I.)**
Waiting list period (n=36)	0.78 ± 0.54 (-0.31, 1.87)	0.09 ± 0.06 (-0.03, 0.20)
Post-lung transplantation (n=25)	1.36 ± 0.92 (-0.53, 3.24)	0.89 ± 0.70 (-0.54, 2.33)
	Mean difference* ± S.E.M. (95% C.I.)	
Mean life years and quality adjusted life years gained	0.58 ± 0.19 (0.21, 0.95)	0.81 ± 0.12 (0.58, 1.04)

*t-test showed a significant difference in the means, for both life years ($p.< 0.008$) and quality adjusted life years ($p.< 0.0001$), between waiting list and post-transplant period.

Table F4. Summary of mean life-years and QALY per patient in the RESD group

Restrictive disease group	**Life-years Mean ± S.D. (95% C.I.)**	**QALY Mean ± S.D. (95% C.I.)**
Waiting list period (n=28)	0.53 ± 0.29 (-0.06, 1.11)	0.089 ± 0.048 (-0.009, 0.187)
Post-lung transplantation (n=14)	1.06 ± 1.22 (-1.56, 3.67)	0.60 ± 0.74 (-0.10, 2.20)
	Mean difference* ± S.E.M. (95% C.I.)	
Mean life years and quality adjusted life years gained	0.53 ± 0.24 (0.04, 1.01)	0.51 ± 0.14 (0.23, 0.79)

*t-test showed no significant difference in the means in life years between waiting list and post-transplant period ($p.= 0.13$). The difference in quality adjusted life years between waiting list and post-transplantation did reach statistical significance ($p. < 0.03$).

Table F5. Summary of mean life-years and QALY per patient in the PVD group

Pulmonary vascular disease group	**Life-years Mean ± S.D. (95% C.I.)**	**QALY Mean ± S.D. (95% C.I.)**
Waiting list period (n=4)	1.36 ± 0.48 (0.02, 2.69)	0.23 ± 0.08 (0.21, 0.25)
Post-lung transplantation (n=3)	1.14 ± 0.93 (-1.82, 4.11)	0.67 ± 0.57 (-1.15, 2.50)
	Mean difference* ± S.E.M. (95% C.I.)	
Mean life years and quality adjusted life years gained	-0.21 ± 0.53 (-1.58, 1.16)	0.44 ± 0.27 (-0.28, 1.16)

*t-test showed no significant difference in the means, for both life years and quality adjusted life years, between waiting list and post-transplant period.

Table F6. Summary of mean life-years and QALY per patient in total cohort discounted at a rate of 5% per year

Full cohort	**Life-years Mean ± S.D. (95% C.I.)**	**QALY Mean ± S.D. (95% C.I.)**
Waiting list period (n=124)	0.72 ± 0.44 (-0.14, 1.58)	0.12 ± 0.07 (-0.02, 0.27)
Post-lung transplantation (n=91)	1.15 ± 0.87 (-0.58, 2.87)	0.65 ± 0.55 (-0.43, 1.73)
	Mean difference* ± S.E.M. (95% C.I.)	
Mean life years and quality adjusted life years gained	0.43 ± 0.09 (0.25, 0.61)	0.53 ± 0.05 (0.43, 0.63)

*t-test showed a significant difference in the means, for both life years ($p. < 0.0001$) and quality adjusted life years ($p.< 0.0001$), between waiting list and post-transplant period.

Appendix G

Appendix to the cost-effectiveness and cost-utility estimates of lung transplantation in the CF and bronchiectasis disease group

This section deals with the costs incurred by the cystic fibrosis and bronchiectasis diseases groups during the pre-transplant, transplant and post-transplant phases (table G1a, b and c). A summary of the mean LY and QALY gained by transplantation (discounted at 5%) are presented in table G2. An estimate of the cost-effectiveness and cost-utility associated with transplantation in this patient group is presented in table G3.

Table G1a. Mean costs incurred per CF and bronchiectasis patient while waiting

	PRE-TRANSPLANT PERIOD (N=36)
	Mean direct medical cost per patient (Discounted at a rate of 5%)
Hospitalizations	$19,831 (95% CI: $15,550, $24,112)
Outpatient medical care	$1,172 (95% CI: $628, $1,767)
Outpatient medications	$1,986 (95% CI: $1,356, $2,616)
Oxygen therapy and medical devices	$4,358 (95% CI: $3,803, $4,913)
Total	$27,347 (95% CI: $21,337 - $33,408)
Cost per person-month	$2,941 (95% CI: $2,294 - $3,556)

Table G1b. Mean costs incurred per CF and bronchiectasis patient for transplantation

	Fixed mean costs per patient: Related to the lung transplant program incurred before transplantation (Discounted at a rate of 5%)
Evaluation process for those not on list	$6,629
Evaluation process for CF and bronchiectasis patients	$2,484
Lung transplant program operating costs	$509
	TRANSPLANTION (N=25) **Mean direct medical cost per patient** (Discounted at a rate of 5%)
Organ acquisition and harvesting	$5,325 (sensitivity range $2,300 - $18,403)
Transplant procedure and inpatient follow-up care	$31,943 (95% CI: $27,217 - $36,668)
Physician fees	$8,709 (95% CI: $8,551 - $8,866)
Total	$45,977 (95% CI: $38,668, $63,937)

Table G1c. Mean costs incurred per CF and bronchiectasis patient during the post-transplant period

	POST-TRANSLPLANT PERIOD		
	Mean direct medical cost (95% CI) per patient per year (Discounted at a rate of 5%)		
	OUTPATIENT	**INPATIENT**	**MEDICATIONS**
Year 1 (n=25) (0-12 months)	$9,312 ($5,711 - $12,965)	$12,089 ($2,934 - $22,386)	$14,757 ($8,856 - $20,656)
Year 2 (n=16) (>12-24 months)	$2,712 ($1,617 - $3,955)	$1,699 ($0 - $5,477)	$12,234 ($6,130 - $19,038)
Year 3 (n=7) (>24-36 months)	$1,506 ($79 - $2,732)	$1,290 ($0 - $4,338)	$7,824 ($762 - $17,990)
Year 4 (n=1) (>36-+months)	$1,109 (-)	-	$4,722 (-)
	Total Post-transplant cost	**Cost per patient per month**	
Year 1	$36,158 ($17,501 - $56,007)	$3,888 ($1,882 - $6,022)	
Year 2	$16,645 ($7,747 - $28,440)	$1,790 ($833 - $3,058)	
Year 3	$10,620 ($840 - $25,060)	$1,142 ($90 - $2,695)	
Year 4	$5,831 (-)	$627 (-)	
TOTAL	**$69,254 ($31,919 - $115,338)**		

Table G2. Summary of mean life-years and QALY per patient in the CF and bronchiectasis group discounted at a rate of 5% per year

CF & Bronchiectasis disease group	**Life-years Mean ± S.D. (95% C.I.)**	**QALY Mean ± S.D. (95% C.I.)**
Waiting list period (n=36)	0.76 ± 0.49 (-0.25, 1.77)	0.08 ± 0.05 (-0.03, 0.19)
Post-lung transplantation (n=25)	1.20 ± 0.77 (-0.39, 2.79)	0.79 ± 0.59 (-0.43, 2.00)
	Mean difference* ± S.E.M. (95% C.I.)	
Mean life years and quality adjusted life years gained	0.44 ± 0.16 (0.12, 0.77)	0.71 ± 0.10 (0.51, 0.70)

*t-test showed a significant difference in the means, for both life years ($p.<0.02$) and quality adjusted life years ($p.< 0.0001$), between waiting list and post-transplant period.

Table G3. Incremental cost-effectiveness and cost-utility ratio of lung transplantation in CF and bronchiectasis patients

Total cohort	Cost/Effectiveness ratio	Cost/Utility ratio
Incremental cost*	$124,853 - $27,347	$124,853 - $27,347
Incremental effectiveness	1.20 LY - 0.76 LY	0.79 QALY - 0.08 QALY
	$221,605 per life year gained	$137,332 per QALY gained

* Costs included in ratio are direct medical costs per patient per period studied: waiting list and total post-transplant period (discounted at 5%).

Appendix H

Section H1. Informed consent form

Title of the study: An analysis of the effectiveness, consequences and cost of lung transplants.

1. Purpose of the study
The main purpose of this study is to determine the clinical effectiveness of lung transplants and the different treatment modalities for end-stage lung diseases on survival and quality of life. The costs associated with the different treatments will also be assessed.

2. Information requested
For the purpose of this study, information on treatments received and health status will be needed. Medical and pharmacy files, as well as data obtained from the Régie de l'Assurance Maladie du Québec (RAMQ) database, will be reviewed. Participants will also be asked some questions pertaining to their overall health state and quality of life.

3. Other information requested
Upon one of the follow-up visits, the patient will be interviewed for approximately one hour on:

-Use of other health care providers such as physiotherapists or nurses.
-Use of equipment or appliances needed for the maintenance of health.
-Financial resources spent by him/her while seeking medical care (e.g. transportation fees, housekeeping costs, etc.)
-Their overall health status and perceptions of their quality of life.

4. Advantages and risks of the proposed study
This study will provide a better understanding of the economic impact and survival and quality of life associated with the different treatments associated with the different types of end-stage lung disease. This study poses no risk to the participant because only a questionnaire will be submitted to him during one of his visits.

5. Participation in the study
Your participation in this research project is voluntary. If you wish not to participate there will be no prejudice to your medical follow-up or to yourself.

6. Other information
In order to preserve your confidentiality, the information gathered during the study will be recorded without your name. Only during the interview process will your name be recorded by the interviewer. At that point the interviewer will assign an anonymous coding number to your name. This will ensure the confidentiality of your medical files and all information you have given, during the analysis and the dissemination of the

results. Personnel in the study will only have access to the data. Your name will not be recorded in any reports or publications resulting from the study.

Any questions pertaining to this study may be made by contacting Dr Charles Poirier, at the Notre Dame Hospital, at 514-281-6000 ext 5124 or to Mme Carol Lachapelle at 514-281-6000 ext 5387. For any complaints about the study, please contact Mrs Louise Brunelle of the Notre Dame hospital at 514-281-6047.

All patients participating may request to be informed of the results of the study at its conclusion.

Participation into the study is voluntary and once into the study the participant may request to be withdrawn from the study at any point in time with no prejudice to the quality of medical care received.

Patients who decide to participate do not give up any legal rights by signing this consent form.

I, *name of patient* _____ have read and understood the present consent form and hereby voluntarily consent to my participation in the project. I also attest that my participation into the study was explained to me, that all my questions were answered and I was given enough time to make a decision pertaining to my participation into the study. I also give consent to the researchers of this study to access data on medical services that concern me, which may be found in the Régie de l'Assurance Maladie du Québec (RAMQ) and Med Echo (for hospitalization information) databases, and information on medication use from pharmacy databases.

Patient's Signature _____ Date_____

Physician's Signature _____ Date _____

Witness's Signature _____ Date _____

Section H2. Patient questionnaire

The following questionnaire was completed during the interview process with patients. Two questionnaires were given, one for candidates and one for recipients. The questions were similar, the only difference being, for post-transplant resource use, questions were phrased as: *"since having been transplanted"*

Lung Transplantation Study

Patient Questionnaire

1. General Information
2. Information on Health Care Resource Utilisation
3. Information on Medication or Treatment Use
4. Information on Personal Cost Expended due to End Stage Lung Disease
5. Type of Personal Help Received

This questionnaire concerns patients who have been accepted as eligible for a lung transplantation and that are currently candidates.

Thank you for your cooperation

ID 1	Patient # ☐☐☐☐☐☐☐☐
ID 2	Patient initials ☐☐☐
ID 3	Date : ☐☐ ☐☐ ☐☐☐☐ Day Month Year

1. GENERAL INFORMATION

Dem1 Dem2	**Date of birth** ☐☐ ☐☐ ☐☐☐☐ Day Month Year **Sex** Male ☐ Female ☐
Dem3	**Civil status :** Divorced/Separated ☐ Single ☐ Widowed ☐ Married/Partner ☐
Dem4	**Level of education :** Preschool ☐ Technical school ☐ None ☐ Elementary ☐ CEGEP ☐ High-School ☐ University ☐

Dem5	**Are you presently working ?** Yes ☐ No ☐
Dem6	**If Yes,** Specify occupation: _____
Dem7	Are you working : Full time ☐ **Or** part-time ☐
Dem8	**Did you have to modify any aspect of your employment in response to your lung disease ?** Yes ☐ No ☐
Dem9 Dem10 Dem11 Dem12	**If Yes,** 1. Interruption ☐ Since when (months): ☐☐☐ 2. Part-time ☐ Since when (months): ☐☐☐ 3. Change of employment ☐ Since when (months): ☐☐☐ From which occupation _____ to which new one _____
Dem13	**What was the loss in salary that you experienced in relation to these changes in your employment ?** $ _____/year

Dem14	**Do you have any type of health care or drug plan insurance ?** Yes ☐ No ☐
	If yes, from where :
Dem15	government ☐ private insurance company ☐
	other ☐ specify: _____
Dem16	**Up to how much are you covered ?**
	Specify : ☐☐☐ %
Dem17	
	Do you receive any financial assistance ? (from a private company or government)
Dem18	Yes ☐ No ☐
	If Yes,
Dem19	Specify from where: _____
Dem20	What amount (approximately): Less than $10,000 ☐ Between $10,000 et $15,000 ☐ Between $15,000 et $20,000 ☐ Between $20,000 et $30,000 ☐ More than $30,000 ☐
Dem21	What is your home postal code ? ☐☐☐ - ☐☐☐
	Did you have to move (within your city) because of your lung disease ?
Dem22	Yes ☐ No ☐
	Did you have to move to Montreal because of your lung disease ?
Dem23	Yes ☐ No ☐

Dem24	**Do you presently smoke?** Yes ☐ No ☐
	If Yes,
Dem25	For how many years have you been smoking? ☐☐ years
Dem26	How many cigarettes do you smoke on average per day ? Less than 5 cigarettes/day ☐ Between 5 et 10 cigarettes/day ☐ Between 10 et 25 cigarettes/day ☐ More than 25 cigarettes/days ☐
	If No, **Did you ever smoke ?**
Dem27	Yes ☐ No ☐
	If Yes,
Dem28	For how many years ? ☐☐ years
	How many cigarettes do you smoke on average per day ?
Dem29	Less than 5 cigarettes/day ☐ Between 5 et 10 cigarettes/day ☐ Between 10 et 25 cigarettes/day ☐ More than 25 cigarettes/days ☐
	How long has it been since you have stopped smoking ?
Dem30	Less than a year ☐ Between 1 and 5 years ☐ Between 5 et 10 years ☐ More than 10 years ☐

2. INFORMATION ON HEALT CARE RESSOURCE UTILISATION

RSU1	What is the date you were put on the waiting list as a candidate for a lung transplantation? Date ☐☐ ☐☐☐☐ Month Year
	Who has been your attending physician(s) ? Name them: Code
RSU2	_____ ☐☐
RSU3	_____ ☐☐
RSU4	_____ ☐☐
RSU5	_____ ☐☐
RSU6	_____ ☐☐
RSU7	_____ ☐☐
RSU8	_____ ☐☐
RSU9	_____ ☐☐
RSU10	_____ ☐☐

If patient doesn't remember, assign DSR.

In the last year

	What was the frequency of your planned visits with your physician ? Specify, **Type of physician**	**Frequency (Nb of times/month)**	Code
RSU11	_____	RSU12 ☐☐	☐☐
RSU13	_____	RSU14 ☐☐	☐☐
RSU15	_____	RSU16 ☐☐	☐☐
RSU17	_____	RSU18 ☐☐	☐☐
RSU19	_____	RSU20 ☐☐	☐☐
RSU21	_____	RSU22 ☐☐	☐☐
RSU23	_____	RSU24 ☐☐	☐☐

RSU25	How many episodes of acute exacerbations did you present that led you to an unscheduled (unplanned) visit to a physician in a private office ? **Never** **Number of times** ☐ ☐☐ Specify, **Type of physician** **Never** **Number of times** Code RSU26 _____ RSU27 ☐ ☐☐ ☐☐ RSU28 _____ RSU29 ☐ ☐☐ ☐☐ RSU30 _____ RSU31 ☐ ☐☐ ☐☐ RSU32 _____ RSU33 ☐ ☐☐ ☐☐ RSU34 _____ RSU35 ☐ ☐☐ ☐☐ RSU36 _____ RSU37 ☐ ☐☐ ☐☐
RSU38	How many episodes of acute exacerbations did you present and that were treated as an outpatient (CLSC) ? **Never** **Number of times** ☐ ☐☐

RSU39

How many episodes of acute exacerbations did you have led you to visit an emergency Room ?

Never **Number of times**

☐ ☐☐

If Yes,

Name of hospital	Date of arrival dd/mm/yy	Hour of arrival	Date of departure dd/mm/yy	Hour of departure
RSU40	RSU41	RSU42	RSU43	RSU44
RSU45	RSU46	RSU47	RSU48	RSU49
RSU50	RSU51	RSU52	RSU53	RSU54
RSU55	RSU56	RSU57	RSU58	RSU59
RSU60	RSU61	RSU62	RSU63	RSU64
RSU65	RSU66	RSU67	RSU68	RSU69

Note: *If patient doesn't remember or does not know, assign DNR.*

RSU70

Of those emergency room visits, how many times were you transported by ambulance?

Never **Number of times**

☐ ☐☐

RSU71

How many episodes of acute exacerbations did you have that led to a hospitalisation ?

Never **Number of times**

☐ ☐☐

If Yes,

Complete:

Name of hospital	Date mm/yy	Length of stay (days)	Diagnostic	Treated in ICU (days)
RSU72	RSU73	RSU74	RSU75	RSU76
RSU77	RSU78	RSU79	RSU80	RSU81
RSU82	RSU83	RSU84	RSU85	RSU86
RSU87	RSU88	RSU89	RSU90	RSU91
RSU92	RSU93	RSU94	RSU95	RSU96

Note: *If patient doesn't remember or does not know, assign DNR.*

3. INFORMATION ON MEDICATION OR TREATMENT USE

	In the last year, which medications have you been taking on a regular basis ? List them:	Code
RSU97		
RSU98	_____	☐☐
RSU99	_____	☐☐
RSU100	_____	☐☐
RSU101	_____	☐☐
RSU102	_____	☐☐
RSU103	_____	☐☐
RSU104	_____	☐☐
RSU105	_____	☐☐
RSU106	_____	☐☐
RSU107	_____	☐☐
RSU108	_____	☐☐
RSU109	_____	☐☐
RSU110	_____	☐☐
RSU111	_____	☐☐
RSU112	_____	☐☐
RSU113	_____	☐☐
RSU114	_____	☐☐
RSU115	_____	☐☐
RSU116	_____	☐☐
RSU117	_____	☐☐
	_____	☐☐

	In the last year, have you bought any medications that have not been prescribed by a physician to treat your lung disease ? Yes ☐ No ☐ **If yes,** Which ones:
RSU118	_____
RSU119	_____

RSU120	**In the last year**, did you use any homeopathic or natural products in order to alleviate your respiratory symptoms ? Yes ☐ No ☐
RSU121	**If Yes,** How much did you spend ? $_____
RSU122	**During the last year,** were you under home oxygen therapy? Yes ☐ No ☐
RSU123	**If Yes,** How many litters per minute ? ☐☐ / min
RSU124	And, tick which one applies: Day and night ☐ Day only, in permanence ☐ Day, upon effort ☐ Other ☐
RSU125	From where do you obtain this equipment ? Specify: _____

In the last year, did you acquire the services of any of the following health care professionals for problems related to your lung disease ?

	Title of professional		*** Place of visit**		****Number of times**
	Code		Code	Specify	Specify
RSU126	☐	Inhalotherapist	☐	RSU127	RSU128
RSU129	☐	Nurse	☐	RSU130	RSU131
RSU132	☐	Physiotherapist	☐	RSU133	RSU134
RSU135	☐	Psychologist	☐	RSU136	RSU137
RSU138	☐	Social worker	☐	RSU139	RSU140
RSU141	☐	Acupuncturist	☐	RSU142	RSU143
RSU144	☐	Chiropractor	☐	RSU145	RSU146
RSU147	☐	Dietician	☐	RSU148	RSU149
RSU150	☐	Érgotherapist	☐	RSU151	RSU152
RSU153	☐	Other(s) Specify: _____	☐	RSU154	RSU155

*** Place of visit:** 1=outpatient clinic of hospital, 2=private office, 3=CLSC, 4=at home, 5=other (specify), 6=does not know.

****Number of times:** If patient doesn't remember estimate and note corresponding number:

1=at least once
2= between 2 and 5 times
3=between 6 and 10 times
4= between 11 and 20 times
5= more than 20 times
6= does not remember

RSU154	Do you always go to the pharmacy in order to obtain medications that are prescribed by your doctor for your end stage lung disease ? Select all that apply: ☐ I often forget to buy my medications or to renew my prescription. ☐ I sometimes go through a couple of days without any medications before I can go to the pharmacy and renew my prescriptions. ☐ I only buy a couple of the medications that my doctor prescribes me. ☐ I always buy all the medications that my physician prescribes me. ☐ I buy and renew my prescriptions only rarely. ☐ I never buy any of the medications that my doctor prescribes me. ☐ None of these statements apply to me.

4.INFORMATION ON PERSONAL COST EXPENDED DUE TO END STAGE LUNG DISEASE

During the last year, what type of transportation did you use in order to arrive to your medical visits ?

Type of Transport	Number of times	**$/ period of time Specify cost if per week or month**
Private automobile	Cost1	Cost2
Taxi	Cost3	Cost4
Public transport	Cost5	Cost6
Assistance from a friend	Cost7	Cost8

***Note:** If patient doesn't remember or does not know, assign DNR*

Cost9	**In the last year,** have you done any modifications to your housing in order to accommodate your health status due to the lung disease. Yes ☐ No ☐ **If Yes,** Specify and note expenses.

Modifications	**Cost**

Note: *If patient doesn't remember or does not know, assign DNR*

5. TYPE OF PERSONAL HELP RECEIVED

Aid1

In the past year, did you acquire the assistance of somebody in order to help you at home because of your limitations arising from your lung disease

Yes ☐ No ☐

If yes,

Complete:

*Type of aide	Nb of hours /week	Nb of weeks	**Relation	***Paid
Code Specify			Code Specify	Code $
☐ Aid2	Aid3	Aid4	☐ Aid5	☐ Cost10
☐ Aid6	Aid7	Aid8	☐ Aid9	☐ Cost11
☐ Aid10	Aid11	Aid12	☐ Aid13	☐ Cost12
☐ Aid14	Aid15	Aid16	☐ Aid17	☐ Cost13
☐ Aid18	Aid19	Aid20	☐ Aid21	☐ Cost14

***Type of aide:** 1=help with meals, 2=help with bathing, 3=help with the cleaning, 4= help with transportation, 5=other (specify), 6=does not know.
****Relation:** 1=family, 2=friend(s), 3=external services
*****Paid:** 1=yes, by patient, 2=yes, by third party, 3=yes, by patient and third party, 4=no, 5=does not know.
$: Specify cost or DNR= if patient does not know or remember.

Aid 22

In the past year, has a family member or friend missed work to come to your assistance due to any problems related to your lung disease ?

Yes ☐ No ☐

If yes,

specify,

* Relation		Number of days	Profession
Code	Specify		Specify
☐	Aid 23	Aid 24	Aid 25
☐	Aid 26	Aid 27	Aid 28
☐	Aid 29	Aid 30	Aid 31
☐	Aid 32	Aid 33	Aid 34
☐	Aid 35	Aid 36	Aid 37
☐	Aid 38	Aid 39	Aid 40

***Relation:** 1=family, 2=friend, 3= if patient does not remember
Note: *If patient does not remember assign DNR.*

Section H3. Case report forms

In this section, a sample of some case report forms used for capturing resources utilized during a hospitalization, emergency room and outpatient visits, are presented.

HOSPITALIZATION

Patient # ☐☐☐☐☐☐☐☐ Patient initials ☐☐☐

Number of crisis ☐ **Name of hospital :** _____

Time Period:

Waiting list	☐	1-2 year	☐	6 year	☐
Post-transplantation:		2-3 year	☐	7 year	☐
0-3 months	☐	4 years	☐	8 year	☐
3-12 months	☐	5 year	☐		

Date of admission: ☐☐ ☐☐ ☐☐☐☐
Day Month Year

Date of discharge: ☐☐ ☐☐ ☐☐☐☐
Day Month Year

☐☐☐
days of hospitalization

Was patient transported by ambulance ?

Yes ☐ No ☐

Employer : _____

Insurance: _____

Diagnosis at admission : _____

_____

_____

Primary diagnostic : _____

_____

Secondary diagnostic :

_____

_____

Specify whether hospitalization is due to:

- OB ☐
- Acute respiratory infection ☐
- -Rejection ☐
- -Complication (treatment related) ☐
- -Other (Specify): _____

Where there any complications during the hospitalization ?

Yes ☐ No ☐

If yes, describe:

_____
_____
_____
_____
_____
_____

Did patient die during this hospitalization ?

Yes ☐ No ☐

If yes, state date of death:

☐☐ ☐☐ ☐☐☐☐
Day Month Year

Time of death :

☐☐:☐☐
hour minutes

List cause of death as noted on death certificate:

Immediate a) _____
Due to (or as a consequence of)

Sequential b) : _____
Due to (or as a consequence of)

c) : _____
Due to (or as a consequence of)

d) : _____

List all other important morbid conditions :

a) : _____
b) : _____
c) : _____
d) : _____

Surgical intervention (for transplantation)

Was this the patient's first transplantation ?

Yes ☐ No ☐

If No,

Was this a lung retransplantation ? Yes ☐ No ☐

Age of donor : ☐☐

Sex of donor : Female ☐ Male ☐

Type of transplantation : SLTx ☐ DLTx ☐ H-LTx ☐

Recipient Blood type : ☐☐ Rhesus ☐

Ischemic time : _____

Recipient seropositivity for cytomegalovirus : _____

Donor seropositvity for cytomegalovirus : _____

Intra-operative information

Duration of surgery : ☐☐ hours ☐☐ minutes

Duration of anesthesia: ☐☐ hours ☐☐ minutes

Describe: _____

Where there any complications during the surgery ?

Yes ☐ No ☐

If yes, describe:

_____
_____
_____

Intervention:

Describe:

_____
_____
_____

Medications or treatments received by patient during surgery

Name	Dose	Route	Frequency	Qty	$/Unit	Cost

Laboratory and diagnostic testing during hospitalization

	Quantity
Hematology : Specify:	
Microbiology: Specify:	
Biochemistry : Specify:	

Serology :

Cardiology :

Respiratory:

Cytology:

Blood bank

Radiology:
Specify:

Endoscopy:

Other:

Medical consultations during hospitalization

Specify specialty	Date d-m-yr	Code	Fee
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$
	□□-□□-□□□□	□□□□	$

Other professional medical care

Nurses	Hours of surveillance per day	
	Number	**Duration**
Surgical IC:	_____	_____
ICU:	_____	_____
General ward:	_____	_____

Specify specialty	**Date** d-m-yr
Physiotherapist:	
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
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_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
Nutritionist:	
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐
Social Services:	
_____	☐☐-☐☐-☐☐☐☐
_____	☐☐-☐☐-☐☐☐☐

Specify treatments received by patient during hospitalization

Medication or treatment received by patient during hospitalization

Name (Specify)	Dose	Route	Freq	Nb. of days	Qty.	$/Unit	Cost

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

List any new prescribed medication

Name (Specify)	Dose	*Freq.	**Route (code)	Nb. of days	Qty.	$/Unit	Cost

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

Comment: _____

OUTPATIENT VISITS
Patient # ____________ Patient initials ____________ -

Time period:	**Date of visit** Dd/mm/yy	**Diagnosis**	**Patient sent :**
Waiting List ☐ Post-Tx ☐	/ /	- Acute respiratory exacerbation ☐ - Acute respiratory infection ☐ -Rejection ☐ -Complication (treatment related) ☐ -Other (Specify):____________	Home ☐ Hospitalized ☐
Waiting List ☐ Post-Tx ☐	/ /	- Acute respiratory exacerbation ☐ - Acute respiratory infection ☐ -Rejection ☐ -Complication (treatment related) ☐ -Other (Specify):____________	Home ☐ Hospitalized ☐
Waiting List ☐ Post-Tx ☐	/ /	- Acute respiratory exacerbation ☐ - Acute respiratory infection ☐ -Rejection ☐ -Complication (treatment related) ☐ -Other (Specify):____________	Home ☐ Hospitalized ☐
Waiting List ☐ Post-Tx ☐	/ /	- Acute respiratory exacerbation ☐ - Acute respiratory infection ☐ -Rejection ☐ -Complication (treatment related) ☐ -Other (Specify):____________	Home ☐ Hospitalized ☐

Laboratory and diagnostic testing			
Specify from which Department or Laboratory	**Date :** D– mm -yr	**Type of testing / Procedures**	**Number of Units**

Medical Consultations		
Specify Physician Specialty	**Date: Day-month-year**	**Code**
Other health care professionals	**Date: Day-month-year**	**Code**

Medications presently used by patient

Date	Name	Dosage	Frequency	Route	Nb of days	Qty	$/Unit	Cost

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

New medications or treatments prescribed to patient after leaving visit

Date	Name	Dosage	Frequency	Route	Nb of days	Qty	$/Unit	Cost

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

EMERGENCY ROOM VISITS

Patient # ☐☐☐☐☐☐☐☐ Patient initials ☐☐☐

Time period:

Waiting List ☐

Post-transplantation ☐

Date of arrival Dd/mm/yy	Hour of arrival Hour:min	Date of departure Dd/mm/yy	Hour of departure Hour:min

Patient was sent **home** ☐ Patient was **hospitalized** ☐

Diagnosis at admission:

Diagnosis at discharge:

Reason for visit: (Patient's complaint)

Was patient transported by **ambulance** ?

Yes ☐ No ☐

Describe any treatment received during ambulance ride:

Laboratory and diagnostic testing			
Specify from which Department or Laboratory	**Date :** D– mm -yr	**Type of testing / Procedures**	**Number of Units**

Medical Consultations		
Specify Physician Specialty	**Date: Day-month-year**	**Code**
Other health care professionals	**Date: Day-month-year**	**Code**

Medications presently used by patient							
Name	**Dosage**	**Frequency**	**Route**	**Nb of days**	**Qty**	**$/Unit**	**Cost**

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

Medications or treatments received by patient in ER							
Name	**Dosage**	**Frequency**	**Route**	**Nb of days**	**Qty**	**$/Unit**	**Cost**

* Freq. : notez **QD** for every day, **BID** for 2 times a day, **TID** for 3 times a day, and **QID** for 4 times a day.
**Route: 1= inhalation, 2 = intravenous, 3= oral, 4= other (specify)

Section H4. Ethics committee approval

The following pages include the approval of the ethics committee of the CHUM.