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Kidney Transplantation In Elderly Patients With End-Stage Renal Disease

by

Sarbjit Vanita Jassal

A thesis submitted in conformity with the requirements for the degree of Master of Science in Clinical Epidemiology and Health Care Research, Graduate Department of Community Health University of Toronto

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Kidney Transplantation In Elderly Patients With End-Stage Renal Disease

Sarbjit Vanita Jassal
Master of Science 1998
Department of Community, Health, University of Toronto

Abstract

Transplantation compared to dialysis offers superior life-expectancy and quality of life for young patients with renal failure. However the initial risks of mortality and morbidity are high, especially with increasing age. This study uses a decision analysis model to evaluate the costs and benefits of kidney transplantation versus continued dialysis for an older patient with renal failure.

A decision analysis framework was built using SMLTREE software. The base case focused on a 65 year old white, non-diabetic male. Probability, utility and life expectancy data were obtained from the literature and renal registries.

Life-expectancy on dialysis was 2.9 quality-adjusted years at a cost of $338,335. Life expectancy with transplantation was 4.2 quality-adjusted years at a cost of $249,440. The cost-effectiveness analysis showed a dominant situation. Sensitivity analysis revealed that the results were stable across most variables. Transplantation is cost-effective when compared to dialysis for older individuals, suggesting that it should be offered more frequently to well-selected patients.
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Small things, like the turning of a key,
open, as light does a knot of petals,
the mind locked lost in a dead routine.

Michael Smith
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1. Introduction and Research Objectives

The purpose of this chapter is
1. To summarise the findings of this thesis in abstract form
2. To outline the clinical situation of an elderly patient with kidney failure

1.1 Introduction

Renal failure is a common and serious disorder. In Canada, the number of new individuals starting renal replacement therapy was 101 patients per million population (pmp) in 1993 and 104 pmp in 1994\(^1\). The largest contribution to this demand was from patients over the age of 65 years, who currently account for almost half of those starting renal replacement therapy\(^1\). When described as age-specific incidence, the differential rate of growth is even more apparent for example, the population aged 75 years or more had an initiation rate of 81 pmp in 1981 and 289 pmp in 1994\(^1,2\).

Dramatic increases in the number of older patients starting on renal replacement therapy are not limited to Canada\(^2,6\). For example, patients aged 65 years or more represented 46% of new patients starting renal replacement therapy in Italy, 44% in France, 38% in the US and 32% in the UK\(^3\). Incident rates differ across nations for many reasons. Some of these differences result from resource restrictions (e.g. in the UK where dialysis is funded by the government). Others reflect age-related selection bias (e.g. in New Zealand where there is a high overall acceptance rate but a relatively lower population of aged dialysis patients)\(^7\).

Three forms of renal replacement therapy are available - haemodialysis, peritoneal dialysis and transplantation. All three modalities are effective. Haemodialysis is the most commonly used, accounting for at least 55% of all treatments in older patients\(^1\). Haemodialysis, compared to
conservative medical care, offers a proven benefit to survival, and minimal patient demands. In contrast, peritoneal dialysis requires patient or caregiver co-operation, particularly for continuous ambulatory peritoneal dialysis. Peritoneal dialysis has also been shown to prolong survival although it remains debatable whether longevity is equivalent to that seen with haemodialysis.\textsuperscript{1,8-12}

Transplantation is favoured in the younger population but is rarely offered to elderly patients in Canada. In Norway, transplantation is aggressively pursued, particularly in younger age groups.\textsuperscript{3} At the time of registration onto the Norwegian renal registry, for example, the nephrologist and patient are asked if they believe transplantation is the treatment of choice. Those that respond affirmatively are assumed to need a transplant. In younger patients, over 90\% of those registered need a transplant. In those over 75 years of age, this value drops to 46\%. Even more interesting is the striking disparity in the percentage of younger patients and older patients who are judged needy and who eventually receive a graft (81\% vs. 53\%, respectively).\textsuperscript{13}

\section*{1.2 Research Objectives}

Transplantation in the elderly remains controversial because of limited resources; the substantial costs associated with all forms of renal replacement therapy; and the finite amount of available organs and equipment. The aim of this project is to evaluate the benefits and the risks of transplantation in older patients with end stage renal failure. The specific study question is: "What are the risks and benefits associated with kidney transplantation in elderly patients with end-stage renal disease?" The two possible strategies under investigation are either to continue the patient on baseline dialysis treatment or to recommend the patient undergo kidney transplantation.
Continued dialysis is attractive because it is a more stable strategy, would offer a reasonable survival and has few short-term risks. However, continued dialysis is associated with dietary and fluid restrictions, regular attendance at dialysis sessions, and chronic non-specific lethargy. Kidney transplantation would offer a longer life expectancy and a better quality of life. However, transplantation is accompanied by a significant risk of short-term complication and death. The decision analytic model attempts to quantify the implicit trade-offs.
2. Literature review

The purpose of this chapter is
1. To summarise the aetiology, progression and comorbidity associated with renal disease in the elderly
2. To describe the types of dialysis available for older persons with renal failure
3. To review current knowledge about transplantation in the elderly
4. To detail previous studies which compare the outcome from transplantation with that of dialysis
5. To discuss the indirect effects of transplantation on living related donors and on society

2.1 Renal Disease in Elderly Patients

2.1.1 Aetiology

More than a thousand elderly patients are started on to renal replacement therapy each year in Canada at present. Those with acute renal failure typically have a background of chronic renal disease. Factors contributing to such failure include hypotension (from volume depletion, major surgery, sepsis), major angiographic procedures, and the injudicious use of nephrotoxic antibiotics. Chronic renal diseases which progress to renal impairment are also common and include diabetic nephropathy, renovascular disorders, renal failure due to multiple myeloma, and primary glomerular diseases. Finally, age-related changes in renal function predispose the elderly to acute biochemical and electrolyte disorders that necessitate dialysis.

Specific kidney diseases are not unique to elderly patients. Indeed, the spectrum and presenting features of glomerular diseases seen in the older individual remain as diverse as in the younger population. Recent data suggest a similar incidence of primary glomerular disease compared to younger patients (85 pmp per year in the elderly compared with 84 pmp per year in younger
adults). Radiocontrast nephrotoxicity is frequent in older patients due to the likelihood of nephrotoxicity related to subclinical renal disease. Predisposing factors include diabetes, particularly if associated with reduced renal function, severe congestive cardiac failure, dehydration, the volume of contrast administered and the use of high osmolality non ionic contrast media. Hypertension, diabetes, and atherosclerosis are common in the elderly. Renal artery stenosis is a relatively important cause of renal impairment in the elderly patient, where incidence varies from 4% in a general hypertensive population to 37% in patients referred to a tertiary centre.

### 2.1.2 Progression

Nephrosclerosis is the most common cause of end-stage renal disease in the elderly. Most chronic renal diseases progress at a steady rate, causing renal impairment only after a long interval of time. Around 6-10% of all older patients admitted to an acute medical service develop acute renal insufficiency but the majority of patients are left with only mild renal impairment. Mortality is usually related to the patients comorbidities and rarely exceeds 50%. The highest mortality risk is seen in patients with acute renal failure secondary to aortic aneurysm surgery, hepatic failure, shock and renovascular disease. Age itself does not have a significant impact on the prognosis of the patient with acute renal failure once comorbidities are adjusted. Of those patients who do survive to discharge about 3% require chronic dialysis.

### 2.1.3 Comorbidity

Comorbidity increases with advancing age. Although the number of comorbid conditions does not appear to alter the initial choice of dialysis modality it does influence the long term outcome of
the individual\textsuperscript{1,25}. In elderly patients on renal replacement therapy, the chance of death increases by a relative risk of 1.13 (95% CI 1.2-1.48) if one comorbid condition is present and by a relative risk of 1.73 (95% CI 1.59-1.90) if several comorbid conditions are present\textsuperscript{25}. The strongest predictors of survival are high predialysis functional state, good nutritional status and low comorbidity\textsuperscript{24}.

Hypertension, diabetes and cardiac disease are the three most common specific comorbidities. About 28\% of all Canadian dialysis patients are diabetic\textsuperscript{1}. About 66\% of non-diabetic patients have coexistent hypertension and 19\% have had a previous myocardial infarction\textsuperscript{1}. There is also a high prevalence of cerebrovascular disease, carotid atherosclerosis and peripheral vascular disease\textsuperscript{1,26}. Diseases common in the geriatric population, such as osteoarthritis and dementia, are not more prevalent in the older dialysis population\textsuperscript{27}. Renal disease itself does not alter the chances of unrelated disease.

Functional independence is one of the strongest predictors of outcome in the elderly patient starting renal replacement therapy\textsuperscript{24}. In a randomly selected population of haemodialysis patients, 36\% were unable to perform routine chores without assistance\textsuperscript{28}. In the elderly, this figure rises to 68\%\textsuperscript{29}. Regardless of age, diabetic patients are more likely to have decreased functional independence\textsuperscript{28}. Despite improved dialysis techniques and increased survival, renal replacement therapy does not appear to restore patients to their premorbid level of functioning\textsuperscript{28}. As a result, many patients are left dependant on social assistance and chronic care programs created specifically for the dialysis community\textsuperscript{30,31}. 
2.2 Chronic dialysis in the Elderly

2.2.1 Types of Dialysis

Five types of dialysis are commonly available. Namely, in-centre intermittent haemodialysis (IHD), home haemodialysis (HHD), continuous ambulatory peritoneal dialysis (CAPD), intermittent peritoneal dialysis (IPD) and automated peritoneal dialysis (APD). Haemodialysis (IHD and HHD) involves a machine which creates an osmotic gradient across a semi-permeable membrane separating venous blood from dialysate. Nephrotoxins and fluids are thus removed in the dialysate. Treatments are given intermittently, usually thrice weekly for a period of 3-4 hours. In-centre dialysis is costly and labour intensive but suited for older, frail patients. Home dialysis therapies are less expensive and suited for independent patients.

Peritoneal dialysis involves the diffusion of solutes and fluid across the patient’s peritoneal membrane which forms a semi-permeable physiological filter. Dialysate fluid is introduced through an abdominal catheter into the peritoneal space, thereby creating an osmotic gradient across which the nephrotoxins and fluids flow. CAPD involves four or five exchanges per day, performed usually at 4-6 hourly intervals, each day of the week. IPD is usually reserved for inpatient use and done only two or three times a week. APD is performed using a machine which can synchronise dialysate exchanges. Unlike IPD, however, automated peritoneal dialysis is usually performed daily (or nightly), is suitable for home dialysis. Peritoneal dialysis is appropriate for patients who have someone available to assist with dialysis exchanges31.
2.2.2 Comparisons

Many older patients with renal failure are commenced on to IHD because they present late in the course of their disease. Haemodialysis can be initiated via a temporary dialysis catheter relatively easily in the emergency setting. Dialysis treatments can then be performed as frequently as necessary and permanent vascular access can be created at a later date. In contrast, peritoneal dialysis requires the surgical insertion of a transabdominal catheter followed by 4-6 weeks healing for optimal results\(^{35-36}\). Peritoneal dialysis is most suitable for elective dialysis although can be used in emergency settings.

Haemodialysis is more efficient at solute and toxin removal than peritoneal dialysis. However haemodialysis tends to be associated with rapid fluid and electrolyte shifts and can cause cardiac ischaemia and arrhythmias\(^{37,38}\). Peritoneal dialysis, in contrast, offers include better cardiovascular stability, reduced dialysis induced arrhythmias, easier control of hypertension and preservation of residual renal function. Peritoneal dialysis is also preferable if vascular access is problematic. However, the increased intra-abdominal pressures associated with CAPD reduce diaphragmatic movement and may compromise respiratory function. Other disadvantages of peritoneal dialysis include delayed wound healing, abdominal wall hernias, mechanical back pain, recurrent peritonitis and catheter leaks. In addition, protein losses in peritoneal dialysate can exacerbate malnutrition, increase abnormal bone mineralisation and reduce immune function\(^{39-41}\).

The choice of dialysis modality is based on the patient’s clinical history, functional capabilities and the social circumstances. The most common choices are IHD and less commonly CAPD\(^{54,43}\). Most studies show similar survival in both haemodialysis and peritoneal dialysis patients yet some recent data has questioned the effectiveness of CAPD in the long term\(^{44,45}\). However a 0.76 relative
risk of death on peritoneal dialysis compared to haemodialysis (confidence interval 0.69-0.83) was reported from one study in elderly Canadian patients after correction for age and the number of comorbid illnesses. Diabetic patients appear to have better outcome if treated with haemodialysis.

2.2.3 Survival on dialysis

One year survival rates for elderly patients on haemodialysis vary from 65% to 95%. As most national databases define chronic dialysis patients as those who are dialysis dependent for more than 90 days, early deaths are not included. Hence, the true survival rate in older patients is lower than reported given that about 11% of patients aged 65 to 69 die within the first 90 days of treatment. Furthermore, the early mortality rate increases with age (14%, 18%, 19% and 26% for age groups 70-74 years, 75-79 years, 80-84 years and 85+ years, respectively). Significantly worse mortality risk occurs in older patients in the United States relative to Japan or Europe. The reason for this difference is not known.

Peritoneal dialysis offers similar survival probabilities to haemodialysis; however observed survival rates are confounded by modality switching, selection biases and other complexities. For example, patients may switch from CAPD to IHD because of underdialysis, technique failures, fungal peritonitis, or because of failure to thrive. To overcome problems with modality switching, the statistical convention is to attribute death to the treatment used for the previous six month period.
2.2.4 Complications

Hospitalisation is frequent in the dialysis patient. Moreover, the median amount of time spent in hospital is 50% higher in older dialysis patients than younger dialysis patients (15 vs. 10 days per person per year, respectively). The frequency of hospitalisation is also higher in older dialysis patients (1.9 vs. 1.4 admissions per person per year, respectively)\textsuperscript{44,49-52}. Most admissions are related to fluid overload, vascular access problems, or cardiac disease. In peritoneal dialysis, the incidence of peritonitis is similar to that of the centre where the patient is based; however, patients over 80 years of age tend to have a prolonged hospital stay with each episode\textsuperscript{53,54}. There is no difference in hospitalisation rates between haemodialysis and peritoneal dialysis patients.

Intradialytic problems are similar in older and younger patients. The most common problems during haemodialysis are hypotension and hypoxaemia. Both disorders contribute to fatigue, thereby reducing the patient’s confidence and slowing rehabilitation. Hypotension may be minimised by frequent assessment of dialysis target weight, maintaining haemoglobin levels greater than or equal to 100 g/l, avoiding rapid ultrafiltration, monitoring for arrhythmias, minimising antihypertensive medications prior to dialysis and avoiding food during and immediately before dialysis. Hypoxaemia can be prevented by the use of biocompatible membranes and bicarbonate buffered dialysate.

Large amounts of protein may be lost in peritoneal dialysate causing hypoalbuminaemia, malnutrition and hyperlipidaemia. Indeed, malnutrition occurs in up to a fifth of older haemodialysis patients, a third of peritoneal dialysis patients, and may be profound at the time of diagnosis\textsuperscript{39,40,55}. Prevention focuses on routine assessments and diets of more than 35 Kcal/kg/day and 1.0 - 1.2 g/kg/day protein. Vitamin supplementation should be introduced early as dialysis
causes a loss of water soluble vitamins. Additional techniques to improve patients' nutrition include amino acid based peritoneal dialysate; parenteral nutrition containing amino acid, lipid and dextrose solutions given during haemodialysis, anabolic steroids, subcutaneous injection of human recombinant growth hormone, and recombinant human insulin like growth factor-1^{41,56,57}.

Other complications related to dialysis include gastric bleeding, hyperparathyroidism, malnutrition, rapidly progressive cardiac disease, left ventricular hypertrophy and falls^{14,58-60}. Falls occurring post dialysis may result in extensive subdural bleeding because of the heparin used during haemodialysis. Accelerated atherosclerosis is seen in all patients with advanced renal disease, and recent research data implicate advanced glycosylation endproducts and homocysteine in the pathogenesis of the rapidly progressive disease course^{61,62}. Renal bone disease may lead to an increased propensity to vertebral fracture.

2.2.5 Quality of Life on Dialysis

Most elderly patients on renal replacement therapy live at home, although one in four require an attendant^{28,29,64}. About 0.4 - 0.6% of dialysis patients are nursing home residents. Dialysis does not restore patients to their previous level of independence but does tend to prevent further decline^{64}. Numerous quality of life indices have been used to measure the subjective benefits of dialysis^{65-72}. Each study has produced unique results often with significant disparities. Some of the differences seen relate to the tools used and the aspect of life studied whereas others reflect the different populations studied^{67,73}. Most, however, show quality of life being highest for transplant patients, intermediate for home dialysis patients and lowest for in-centre dialysis patients.
Surprisingly, the quality of life of elderly patients on dialysis may be superior to the quality of life of younger patients on dialysis. In a large cross-sectional survey, for example, older patients were found to have relatively worse functional status, higher disease severity scores but paradoxically higher quality of life. The authors hypothesised that older persons may adjust better to chronic illness and appreciate life more than the young. Similar results have been reported elsewhere. Using the time trade off method of utility assessment, older patients scored about 25% better than younger patients on dialysis (0.55 vs. 0.43, respectively).

2.3 Transplantation in the elderly

2.3.1 Patient selection

Canadian reports document a large number of relatively healthy elderly patients on dialysis who have not been offered a renal transplant. In total, over 1700 individuals appeared to be suitable for but have not yet received a transplant. Another report identified 9 ppm per year over 70 years of age who needed transplantation, but observed transplantation rates of only 5 ppm/yr. Several explanations are possible, including inaccuracies in data collection, unique patient preferences and ageism by practitioners.

The criteria for determining suitability for transplantation is that patients be “biologically well maintained elderly patients ... free of recent or metastatic malignancy, active infection, severe extrarenal disease or mental and psychiatric illness”. The suggested pretransplant evaluation in older patients includes cardiac stress testing and echocardiography, with further assessment in those with abnormal findings. Exclusion criteria include advanced peripheral vascular disease,
severe cerebrovascular disease, and severe coronary artery disease not amenable to surgical intervention.

2.3.2 Morbidity and Mortality Outcomes

Patient survival following transplantation is age dependent. The most recent results from the Canadian Organ Replacement Registry (CORR) show a 68% five year survival rate for patients aged 65 years or more compared to an 83% five year patient survival for the 15-44 year old age group. Five year survival rates following transplantation currently range from 54% to 75% in other series (Table 1). Actuarial graft survival rates are lower for older patients than their younger counterparts (62% vs. 68%) however, as many older patients die with a functioning graft, graft survival censored for death actually improves with age. Survival rates regardless of age may be relatively better if the patient is transplanted with a living donor organ than with a cadaveric organ.

The prevention of early death in the older transplantation patient is crucial for long-term survival. Mortality rates are significant immediately after transplantation in all age groups. Extremely high mortality rates have been reported in patients aged 55+, particularly in the diabetic subgroup, and are usually attributable to infections and cardiovascular disease. Recurrent infections may be preventable and contribute to up to 71% of deaths in the elderly transplant recipient. These are related to immune compromise from immunosuppressive medications and are best treated by appropriate use of antibiotics and minimising the necessary use of immunosuppressives. No intervention has been proven to reduce cardiovascular mortality post transplantation but strategies such as lipid lowering medication, blood pressure control, and regular exercise regimes are in use in some centres.
Many other diseases can occur post-transplantation. For example, diabetes secondary to steroid therapy is frequent in older patients where incidence rates range from 3 to 20% depending on the immunosuppressive regimen used\(^{95-108}\). A high prevalence of malignancy is also found in elderly transplant recipients, accounting for up to 16% of deaths\(^{109}\), however the true effect of medication and transplantation is difficult to establish because of the high baseline risk and the heightened diagnostic surveillance.

### 2.3.3 Immunosuppressive use

Acute rejection is less common in elderly patients than younger transplant recipients, possibly because of age-related changes in the immune system\(^{90,110-113}\). During the precyclosporin era, most transplant patients received azathioprine and prednisone to prevent rejection. More recently, studies show a benefit for the older transplant patient who is treated with cyclosporin\(^{114}\). These benefits include a lower incidence of acute rejection (from 48% to 33%), a decreased risk of sepsis, and a lower overall need for prednisone. In another trial, investigators showed that it is possible to change older transplant recipients from a combination of prednisone and cyclosporin to cyclosporin monotherapy without an increase in graft rejection, cyclosporin toxicity or renal dysfunction\(^{115}\). Although some suggest excellent results with cyclosporin monotherapy from the time of transplantation\(^{110}\), a randomised, prospective study from Spain reported otherwise\(^{116}\).

Other immunosuppressants, such as antilymphocyte products, FK506 and mycophenylate mofetil are now widely available\(^{117,118}\). Antilymphocyte products have been associated with increased infection and malignancy and worse survival in some series; however in other series an improved graft survival has prompted some authors to advise a combination of cyclosporin, antilymphocyte
products and prednisone therapy for routine induction\textsuperscript{85,86}. In randomised controlled settings, mycophenylate mofetil reduced the incidence of acute rejection and graft loss without increasing the infective complications\textsuperscript{119}. However it is not widely used at present because of the high acquisition cost.

2.3.4 Quality of life

As with dialysis, many studies examine post-transplant quality of life\textsuperscript{120-137}. All show an improved quality of life with renal transplantation when compared with continued dialysis. Diabetic patients seem to derive particularly large benefits from transplantation in terms of quality of life, although the degree of selection bias introduced by the transplant work-up process is unknown. Two recent studies compare a cohort of dialysis patients wait-listed for transplantation before and after surgery using the time trade off method\textsuperscript{65,75}. Both show a dramatic rise in scores after transplantation (0.41 vs. 0.74, p<0.001)\textsuperscript{75}. In one of the studies patients were also given four hypothetical scenarios: good dialysis, bad dialysis, good transplant and bad transplant \textsuperscript{65}. The mean time trade off scores were 0.54, 0.36, 0.78, 0.46, respectively. The reasons for an improved quality of life with transplantation have not been identified but possibly include higher energy levels, fewer hospital visits, unrestricted life style and improved psychology.

2.4 Transplantation compared to dialysis

2.4.1 Direct Comparisons of Patient Outcomes

The preceding data compare outcomes following transplantation in older and younger patients. Although valuable in understanding the differences expected with age, these data offer only limited insights when counselling an individual patient about the benefits of the various treatment options.
An alternative method is to compare the predicted survival following transplantation with that expected from continued dialysis. With few exceptions\textsuperscript{77,138}, most studies provide little adjustment for comorbid factors, reflect only the pre-cyclosporin era, and are confounded by selection bias. Yet such comparisons provide some insights on transplantation and dialysis for elderly patients.

The first such study that compared transplantation to continued dialysis was published in 1994\textsuperscript{77}. Data were obtained from the Canadian Organ Replacement Register over a 6 year period and included information gathered at the time of initial registration about concomitant illnesses (angina, acute myocardial infarction, cerebrovascular disease, peripheral vascular disease, pulmonary disease and any other serious illness). The time to death was calculated as time from registration rather than the time from transplantation to avoid survival bias. The results showed that the hazard of death was reduced to 0.47 (95% CI 0.33 - 0.67) in those transplanted compared to those remaining on dialysis.

This survival advantage persisted in all subgroup analyses. Indeed, when the subgroup of patients who were diabetic (but had no other comorbid factors) was evaluated, the hazard ratio fell to 0.1 with transplantation compared to dialysis. Nevertheless, the findings of the study are not perfect. As with all registry-based studies, incomplete data collection caused an unspecified number of cases to be censored; comorbidities were scored as present or absent at the time of registration only and hence give no indication of the severity of disease at the time of analysis; and some finer details about the individual’s health were overlooked.

The second study to compare the outcome of transplantation with that on continued dialysis used data from the United States Renal Data Systems (USRDS) and compared patients wait-listed for transplantation who were still on dialysis to those patients who had received a renal transplant and
were no longer receiving dialysis. The underlying assumption was that wait-listed patients should have a similar comorbidity profile as those who have received a transplant. Data from this study showed that the relative risk of death after transplantation for elderly patients was 0.35. The estimated life expectancy was seven years on dialysis and thirteen years with transplantation\textsuperscript{138}.

2.4.2 Indirect Effects on Society

Kidney transplantation for elderly patients remains controversial because of the limited number of cadaveric organs available and the continually growing number of wait-listed patients. Some argue that the use of a cadaveric kidney in a younger patient, rather than an older person, may allow younger individuals to return to work and contribute to society. Before considering the role of kidney transplantation in the elderly, therefore, it is important to consider methods to increase the donor pool. Many leading experts advocate harvesting more organs from older high-risk cadaveric donors, seeking more living donors and xenotransplantation as the methods for increasing the donor pool\textsuperscript{139-146}.

Most studies show that the use of kidneys from older donors is associated with worse renal function and shorter graft survival\textsuperscript{3,141,142,147-153}. Only a few small observational studies show similar graft survival rates and similar rates of primary non function and acute rejection in all donor age groups\textsuperscript{142,151}. Two studies have shown similar graft survival with kidneys from donors aged 55-64 and those aged 65+ years, suggesting that the risk of graft dysfunction does not increase linearly with age\textsuperscript{143,147}. If transplanted into highly sensitised recipients, kidneys from older donors appear to have a higher risk of rejection and greater sensitivity to prolonged ischaemia\textsuperscript{142,153,154}. 
Older recipients tend to have a lower incidence of sensitisation and thus, some authors advocate the use of older kidneys for older patients. In contrast, other authors recommend the avoidance of older kidneys in older (or otherwise high risk) patients. Neither practice has been validated and the utilisation of older kidneys in particular age groups remains controversial. Age matching of the donor kidney to within 5 years of the age of the recipient has not been shown to change outcome. Post-transplantation baseline serum creatinine levels, however, tend to be higher with older donor organs. Most related donors tend to be young adults although similar graft survival has been seen with older living related donors.

The use of organs harvested from a living donor is becoming increasingly common. As expected, patient and graft survival are both higher after transplantation with a living related donor organ than after cadaveric organ transplantation. In many cases, the donor is genetically related to the recipient and the HLA haplotype match is high. However, genetically unrelated donor grafts have also been successful. For cadaveric transplants, the number of haplotype matches closely correlates with a reduced risk of acute rejection and improved graft survival. However, living donor transplantation may be successful regardless of the amount of haplotype matches and recent data show the survival of grafts may be 10-15% better than that of cadaveric grafts.

2.4.3 Indirect Effects on Donors

Experience with living related donation spans more than two decades yet the literature remains divided on the effects of kidney donation. The two main advantages of living donor transplantation are to increase the number of transplants performed each year and to increase the long term benefits to the recipient. However organ retrieval has an immediate mortality risk of 0.03% and a complication rate about 8% for the donor. Complications typically are minor surgical or
post surgical problems such as bleeding or wound infection and can be minimised by careful selection, screening and postoperative care of the donor.\textsuperscript{165-167}

Long-term survival in donors appears to be better than in the general population.\textsuperscript{166-169} In one series 85\% of donors were still alive 20 years after donation whereas the age-matched, survival rate in the general public was 66\%\textsuperscript{168,169}. In the same series, one third of donors developed hypertension.\textsuperscript{169} It is unclear if these subjects were at increased risk of hypertension because of single nephron hyperfiltration or because of normal age related changes. Glomerular filtration rate declines post-donor nephrectomy, especially if the donor is over 55 years of age. In addition, the incidence of proteinuria is much higher after donor nephrectomy than in comparison groups of patients, however, the significance of these changes are not yet clear. Fewer than 0.01\% of patients progress to overt nephrotic syndrome.\textsuperscript{169}

Organ donation has psychological and financial effects on the donor.\textsuperscript{170-172} In a questionnaire survey of 536 living related donors, 70\% felt that they had volunteered to donate their kidney without any solicitation on the part of the recipient or the health care team. About 92\% felt that the experience was rewarding and that they had not suffered any personal harm. Only 0.4\% felt they would not donate their kidney if they had the chance to turn back time. About 20\% felt that they had experienced moderate economic distress as a result of organ donation. The financial implications of organ donation remain unclear as some life insurance policies view organ donation as an indication of good health while others view such individuals as being at increased risk of hypertension, renal disease and chronic disability.\textsuperscript{172}
2.4.4 Cost implications for renal replacement therapy

Reports on the cost effectiveness of transplantation started in the 1970’s. Most authorities claim that transplantation is the least expensive renal replacement therapy in the long-term. However, it is associated with a substantial initial outlay. For example, one report suggests that transplantation yields a net financial loss for the first 4 years following the transplant with the break even point occurring after 4.4 to 5.0 years. The comparison between dialysis and transplantation is further complicated by the specific details of each patient. For example, transplantation costs differ depending on which immunosuppressives are used and on whether the recipient is transplanted with a living donor or cadaveric organ. Similarly, dialysis costs vary with the modality, the setting and cost saving measures (such as dialyser reuse).

Studies looking at the costs of dialysis and transplantation are summarised in Table 2.2 and the three most important are herein described in detail. The first study compared the cost-effectiveness of OKT3 induction therapy with more conventional immunosuppressive therapy and thus addressed the cost of transplantation. Data were collected as part of a five year prospective randomised controlled trial and allowed accurate costing of many aspects of follow up. The exact sources for the costs were not always clear, and reflected data from the Health Care Financing Administration and Medicare, resulting in limited generalizability. Average costs for the first year of transplantation were about $64,000 per patient 1992 US dollars (equal to about $84,000 1997 CDN), and average annual follow up care costs about $6,000 per patient ($8,200 1997 CDN).

The second study came from a single centre in Canada and provided a detailed cost analysis including fully allocated hospital costs. Excluding inpatient care the average annual cost year was $58,000 per patient on IHD and $35,000 per patient for CAPD (updated to 1997 CDN dollars.
using the Canadian Consumer Price Index). Costs were more accurately allocated than in other series as all expenditure associated with running of the medical services, drug costs, costs associated with admissions and outpatient visits were included. However indirect costs such as the effects of lost time at work or expenses incurred by the families of patients were excluded from the analysis.

The third study, also from Canada, calculated costs using diverse data sources including patient chart data, provincial billing systems and patient interview. The costs of hospitalisation were derived from a fully allocated costing model and quoted in 1994 Canadian dollars. Doing so yielded estimates of the annual cost of dialysis to be about $65,500 per patient (1997 CDN dollars). Costs for transplantation were divided into four periods, the pretransplant period, the first 90 days after transplantation, 91 to 365 days after transplantation and the second year of transplantation. Specific costs for acute rejection and complications were not given although the cost of transplantation followed by graft loss was estimated at around $80,000 (1997 CDN dollars). In the first year of transplantation costs were about $68,000 (1997 CDN dollars) and for subsequent years $28,500 (1997 CDN dollars). Living related donation was associated with an additional cost estimated at $800 per retrieval (1997 CDN dollars).
Table 2.1: Patient and Graft Survival Data from Selected Publications

<table>
<thead>
<tr>
<th>Source of data</th>
<th>Year</th>
<th>N</th>
<th>Age</th>
<th>Survival Rates</th>
<th>CyA use</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patient lyr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5yr</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Graft lyr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5yr</td>
<td></td>
</tr>
<tr>
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<td>60+</td>
<td>60</td>
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<tr>
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<td>1981</td>
<td>62</td>
<td>50+</td>
<td>55</td>
<td>40&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
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<td>55+</td>
<td>66</td>
<td>52</td>
</tr>
<tr>
<td>Jordan et al&lt;sup&gt;86&lt;/sup&gt; cadaveric</td>
<td>1985</td>
<td>54</td>
<td>50+</td>
<td>89</td>
<td>72</td>
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<td>198</td>
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<td>91</td>
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<td>45</td>
<td>60+</td>
<td>75</td>
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<td>55-59</td>
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<td>Andreu et al&lt;sup&gt;110&lt;/sup&gt;</td>
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<td>70</td>
<td>&gt;55</td>
<td>97</td>
<td>82-94</td>
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<td>DeLuca et al&lt;sup&gt;184&lt;/sup&gt;</td>
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<td>119</td>
<td>55+</td>
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<td>1995</td>
<td>20</td>
<td>70+</td>
<td>80</td>
<td>74</td>
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CyA  Cyclosporin A used
*  at 18 months
<sup>+</sup> at 3 years
<sup>+</sup> at 4 years
Table 2.2: Summary of selected studies reporting costs of transplantation and dialysis.

<table>
<thead>
<tr>
<th>Publication (currency)</th>
<th>Cost as reported in the study</th>
<th>Costs updated to 1997 CDN dollars</th>
<th>Comments</th>
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<tr>
<td>Shield&lt;sup&gt;79&lt;/sup&gt; (1992 US)</td>
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<td>Per episode acute rejection</td>
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<td>Mean cost of pneumonia</td>
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<td>$30,014</td>
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<td>Annual follow-up</td>
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<td>$8,147</td>
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<td>Madrigal&lt;sup&gt;115&lt;/sup&gt; (1994 US)</td>
<td>Annual cost of CAPD</td>
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<td>Annual cost of IHD</td>
<td>$33,360</td>
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<td>Cost of transplantation (first month post-op)</td>
<td>$14,265</td>
<td>$19,562</td>
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<td>Weydevelt&lt;sup&gt;186&lt;/sup&gt; (1996 US)</td>
<td>Initial cost of transplantation (first 3 weeks)</td>
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<td>Annual cost of transplant follow-up</td>
<td>$8,934</td>
<td>$12,488</td>
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† Table gives the cost as reported in the literature as well as the costs after conversion to 1997 Canadian dollars
<table>
<thead>
<tr>
<th>Study</th>
<th>Category</th>
<th>1995 US</th>
<th>1993 CDN</th>
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<td>Lenisa</td>
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<td></td>
<td>Cost of transplantation (1st year only)</td>
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<td>Annual cost of transplantation follow-up</td>
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<td>Cost of graft failure</td>
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<td>Goeree</td>
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<tr>
<td></td>
<td>(1990 US)</td>
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<td>Cost of death and graft failure</td>
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<td></td>
<td>Laupacias&lt;sup&gt;65&lt;/sup&gt;</td>
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<td>Estimated costs</td>
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<tr>
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<td>(1994 CDN)</td>
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<td>Annual cost of dialysis</td>
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<td>Cost of transplantation (first 3 months)</td>
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<td>Annual cost of transplantation follow-up</td>
<td>$15,376</td>
<td>$15,715</td>
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3. Methods

The purpose of this chapter is to
1. Outline the principles of decision analysis
2. Describe the specific tree structure, including the Markov process and major assumptions
3. Detail the methods used to derive the probability, utility and cost estimates
4. Summarise the values included in the model
5. List the techniques used to validate the results

3.1 Principles of Decision Analysis Modelling

3.1.1 Fundamental Principles

Decision analysis is a scientific method for evaluating the relative worth of one or multiple interventions\textsuperscript{191-194}. In the health care setting, the main strength of the method lies in quantitatively evaluating both life expectancy and health state desirability. The technique is based on an explicit and logical mathematical structure; thus, the results are objective, inferential and reproducible\textsuperscript{195,196}. Analytical strategies such as sensitivity analyses can be applied to address the uncertainties arising from heterogeneous, incomplete or biased data sources. In most cases, the different treatment strategies considered are easily identified\textsuperscript{191}. Furthermore, the assumptions and data are open to close scrutiny and easy revision.

3.1.2 Conventional Steps

The technique of decision analysis can be summarised in five steps\textsuperscript{196-198}. The first is to identify the question and to structure the problem. Doing so requires considering all important interventions and events. The second step is to assign a probability to each event in the model which quantifies the likelihood of its occurrence. These probabilities can be obtained from the literature, original
data collection, or pooling various sources. The third step is to assign a utility score to the relative desirability of each event. Typically, the utility is quantified using a linear scale from zero (equal to death) to one (equal to ideal health). The fourth step is to compile the data and thereby calculate the average expected utility for each intervention. The treatment with the highest utility is selected as the best option for the individual. The final step tests the effect of uncertainty using sensitivity analyses\(^{194,199}\). If the most preferred treatment strategy does not change when the data are varied, the model can be said to be robust and the degree of uncertainty to be not clinically relevant.

Patients may undergo repeated treatment or face multiple complications. In such cases, Markov models can be used to represent the costs and outcomes associated with each episode\(^{200}\). Unlike conventional decision trees, the Markov process allows patients to pass through a series of cycles each of a specified duration. To create a Markov model, the patient’s course is separated into a number of discrete health states. Each health state may have a unique quality of life, survival probabilities or financial cost. The probability of transition between states (for example transitioning from transplantation to dialysis) is quantified and may vary over time. The model can then be run over a large number of cycles and used to see how a cohort of patients would progress between states over time. The gains and losses of treatment can be estimated according to the time spent in each health state.

### 3.1.3 Classic Drawbacks

It is the logical nature of the method to which critics have common objections. No one tree, no matter how detailed, is able to fully describe a clinical situation or capture subtle clinical details. Assumptions are inevitable when data are incomplete. Even when data are available they may be of moderate or low quality. Often data transformation is necessary; for example, the conversion of
observed cumulative survival to annual mortality rates. Another classical drawback of modelling is the neglect of equity; namely, that a quality-adjusted life year gained is equally important regardless of who benefits\textsuperscript{201-203}. Thus, the methodology may not capture the most efficient use of limited organs or the urgent needs of unique individuals.

Decision analytical modelling also relies heavily on assumptions regarding time preference and perspective\textsuperscript{204,205}. In many cases, the model assumes that utilities are the same over time. In reality, adverse events occurring in the future are often less concerning to the individual than similar events occurring immediately. Although discounting can be used to modify the health state utility, the techniques available are limited and both under and over estimation is possible\textsuperscript{202,206,207}. The use of decision analysis to optimise clinical decision making is laborious and the results slow to arrive. Finally, the ultimate impact of decision analysis on improving patient care has never been verified by a rigorous clinical trial.

### 3.2 Construction Of The Specific Tree

#### 3.2.1 Treatment Strategies

The research design used was cost-utility analysis. The two treatment strategies compared were transplantation and continued haemodialysis. Peritoneal dialysis was not explicitly modelled. However, because survival with peritoneal dialysis and haemodialysis are comparable the results may be extrapolated to patients who are maintained on peritoneal dialysis.

#### 3.2.2 Economic Strategies

Outcomes are expressed as life expectancy in years (LE), both before and after quality-adjustment for a theoretical patient who may either continue on dialysis or undergo transplantation. Cost-
effectiveness is estimated in terms of the incremental cost incurred for each additional quality-adjusted life year gained. Both costs and health state utilities are discounted at a rate of 1% per three months (equal to about 4% per year). The perspectives taken are those of the third party payer. All costs are reported as 1997 Canadian dollars. As patients with end-stage renal failure are expected to be dialysis dependent for life, the time horizon for the analysis is the lifetime of the patient.

3.2.3 Overview

A decision tree was built using SMLTREE software. The first branch of the tree represents the option of transplantation and the second branch represents the option of continued dialysis (Figure 3.1). The next level introduces the two major comorbidities of diabetes and cardiovascular disease. Diabetic patients are at higher risk of death, post-operative complications and cardiovascular disease. Non-diabetic patients are at risk of developing glucose intolerance as a complication of steroid therapy and ensuing the attendant increased risks of infection and cardiovascular disease.

In the next level, the major events from transplantation are modelled using a Markov process. Specifically, patients continuing on dialysis are exposed to a constant risk of death over time while transplanted patients are exposed to the risk of acute rejection, of infection and of graft loss with return to dialysis (Figure 3.2). Death is the terminal event regardless of treatment choice. The possibility of cure is assumed to be zero.

3.2.4 Disease States in the Markov model

The clinical course with transplantation is characterised by six states: alive with a functioning graft; alive but with acute rejection; alive with acute rejection and a complication; alive with a complication but no acute rejection; alive on dialysis; and the absorbing health state, dead. The
transition probabilities vary with time since patients with a transplant can either continue to remain well with a functioning graft, develop acute rejection, have a complication or return to dialysis. At the end of each cycle (unless in the health state dialysis or death) the patient can re-enter the transplant state and again be at risk of acute rejection or complications. Patients developing acute rejection can fall into one of two health states: alive with acute rejection or alive with acute rejection plus a complication (Figure 3.3). The ratio between those with acute rejection who develop a complication and those with acute rejection who do not develop a complication is modelled as an independent variable to allow further exploration of the relationship between the rate of acute rejection, the rate of complication and the gains and losses associated with transplantation. The model is run until all patients are in the health state dead or for a maximum of 250 three month cycles.

3.3 Estimation Of Outcomes

3.3.1 Probability Values

Many probability values were derived from the literature. An extensive literature review was conducted using a MEDLINE search from 1980 through until August 1997. Search terms are listed in Table 3.1. All relevant papers were reviewed and data from the best study used to derive the probability values for the model\(^{129,210}\). When many studies of equal quality were found, the mean of all estimates was used. The remaining papers were reviewed to find the lowest and the highest published probabilities to set the clinically plausible range of probabilities.

When no single study determined the exact probability of the event occurring a probability was estimated by combining different sources. For example, the exact probability that a complication
will occur post-operatively is unknown. However, most studies which randomise patients to one of two immunosuppressive protocols document the number of complications occurring over a predefined period of time. Thus data were collected from such randomised control trials and a mean probability value calculated. Extreme values were used to define a clinically plausible range and thus included in the sensitivity analysis.

A second method was used to derive the probability of graft loss. Graft loss was assumed to follow an exponential curve similar to patient mortality. Therefore data from graft survival curves in the diabetic and non-diabetic population were used to estimate the relative risk ratio for graft loss in a diabetic subpopulation\textsuperscript{211,212}. Graft failure rates were calculated for both diabetic patients and non-diabetic patients using the formula

\[ \mu_{\text{Graft Loss}} = -\ln(S)/t \]

where \( \mu_{\text{Graft Loss}} \) equals graft failure rate and \( S \) the probability of graft survival at time \( t \). The ratio was then used as the relative risk of graft loss associated with diabetes. The same technique was used to derive the relative risk of death with cardiovascular disease (CVD) and the relative risk of death with diabetes. The probability values used, together with clinically plausible ranges are shown in Table 3.2.

3.3.2 Life expectancy with transplantation

Data from the United States Renal Data System (USRDS) and the Canadian Organ Replacement Register (CORR) were used to estimate patient survival at 1, 2 and 5 years post-transplantation\textsuperscript{1,52}. The USRDS database contains information about 9980 elderly patients transplanted over the period 1986-1992\textsuperscript{52}. The CORR database includes data for 333 elderly patients transplanted over the period 1981 to 1994\textsuperscript{1}. The relative risks of death of each health state was taken from the literature\textsuperscript{1,52,90,213}. Given that the American database was much larger than the Canadian database,
USRDS data were used to compare actual patient survival with that predicted by the model. Mortality rates with either a cadaveric or a living related transplant were considered equal.

Data from the USRDS database for survival beyond 10 years from transplantation was considered unreliable because of the small numbers of patients with long-term follow up (less than 300). Thus, the mortality rate at >10 years was estimated using methods of extrapolation. The excess mortality rate specific to transplantation \( \mu_{\text{Transplant}} \) was estimated as the difference between the overall mortality rate \( \mu_{\text{Overall}} \) at five years and the average mortality rate of an age and sex-matched general population \( \mu_{\text{ASR}} \). Similarly, if the patient was transplanted at age 65 years old, the mortality rate 10 years post-transplantation (\( \mu_{\text{Overall}} \)) was assumed to be equal to the sum of \( \mu_{\text{Transplant}} + \mu_{\text{ASR}} \) for a 75 yr. old.

\[
\mu_{\text{Overall}} = \mu_{\text{Transplant}} + \mu_{\text{ASR}}
\]

The assumption was that \( \mu_{\text{Transplant}} \) was constant and that \( \mu_{\text{ASR}} \) would vary with increasing age.

In the model, transplanted patients who remained well without acute rejection or complications tend to die at a rate of about 3.0 % per year for the first five years. Annual mortality rates tend to increase to 5.3% and 6.4 % at 5 and 10 years post-transplantation and further to 14.3% at 20 years, consistent with age-related increases. Patients who developed acute rejection or a complication have an increased risk of death of 1.22 and 1.80 respectively. Those patients who had both acute rejection and a complication were at further risk (cumulative relative risk of death after acute rejection and a complication of 2.20).
3.3.3 Life expectancy with dialysis

USRDS survival data for dialysis patients were not used because many patients included in the group would have been unsuitable for a transplant. Instead survival data were taken from the CORR database, that records comorbid conditions present at the time of starting renal replacement therapy. Therefore, dialysis patients with similar comorbidity profiles to those transplanted could be found.

All patients, aged 60 years or more, who received a transplant over the period 1986 to 1993 were identified from the CORR database\(^1\). These patients were then matched to a minimum of two dialysis patients. Matching criteria included age, sex, comorbidity profile at the onset of renal failure, and the time from starting renal replacement therapy. Over the six year period, 223 elderly patients were transplanted. These patients had spent an average of 701 days (median 589, quartiles 331 - 932 days) on dialysis prior to transplantation\(^1\). This was called the wait interval. A total of 446 dialysis patients, similar in age, sex and comorbidity profile to transplantation patients, were identified. A survival plot of the percentage of dialysis patients alive against the time from start of renal replacement. As dialysis patients must have survived a minimum period equal to the wait interval to have been selected, an arbitrary cut-off point was drawn at 932 days (75th quartile) after which the data were used to estimate the mortality rate (Appendix 1). The mortality rate was calculated from the slope of the curve at three different time points. These estimates were averaged and given as the percentage of deaths per year. Mortality was estimated at a rate of 11.5% per year, with an arbitrary clinically plausible range between 10 and 20 percent.
3.3.4 Utility Values

Utility values were derived from the literature based on studies of end-stage renal disease patients. Investigators who applied either the time trade-off method or the standard gamble method were chosen preferentially. Quality of life studies using other scoring systems, though relevant, were not included in the literature search because of the limitations in transforming quality of life data to utility values. One study was preferentially used because it specifically examined the time trade-off values of patients aged 60 years or more while on dialysis and then again within one year of both successful and unsuccessful transplantation.

In the reference study, patients were recruited from three clinical centres providing they had been stable on the transplant waiting list for at least three months. Prior to transplantation patients were interviewed every 6 months. Post-transplantation interviews were done at 1, 3, 6, 12, 18 and 24 months. Quality of life was assessed using the Kidney Disease Questionnaire, the Kidney Transplant Questionnaire, the Sickness Impact Profile and the time-trade off method. Although a total of 168 patients were studied, the utility values from 22 patients aged 60 years or more were used as the baseline utility values in the model. Utility values derived from the remaining studies were used to define a clinically plausible range.

The inclusion of short term dysutilities associated with surgery, acute rejection and complications are important in the model. Multiple adverse events were modelled as cumulative dysutilities. The dysutility of surgery was estimated from the mean time spent in hospital when initially admitted for transplantation. The key assumption was that the dysutility during hospitalisation and surgery was complete. The dysutilities associated with acute rejection and complications were similarly estimated using the mean duration of hospitalisation and the assumption of complete dysutility.
Each patient could only undergo surgery once. The expected duration of hospitalisation for transplant surgery was on average 18 days (range 7 - 53), for acute rejection 30 days (range 3 - 30) and for a complication 30 days (range 3 - 30)²¹⁶⁻²¹⁸. Dysutilities associated with acute rejection and complications were discounted in the same manner as all health state utilities. The utility values, together with their clinically plausible ranges are shown in Table 3.2.

3.3.5 Financial Costs

Costs were estimated using two methods. The first method was to derive estimates from published data. Studies were selected if they clearly identified the data source, specified the target population and prospectively gathered data. Studies from European centres were used only to establish the clinically plausible range. American and Canadian studies were considered together. All costs were converted to 1997 Canadian dollars using the Oanda exchange rate index and the Statistics Canada Consumer Price Index ²¹⁹,²²⁰.

Two studies were preferentially used to estimate the costs associated with different therapies ⁶⁵,¹⁴². Both studies were from Canadian centres and calculated the costs of care rather than charges. As both studies spanned a similar time period they were felt to be comparable. In the second study, the costs of transplantation were divided into four periods, the pretransplant period, the first 90 days after transplantation, the first year after transplantation after exclusion of the first 90 days, and the second year of transplantation ⁶⁵. Specific costs for acute rejection and complications were not given. The remaining data were used to estimate the clinically plausible range of costs.

Additional costs incurred because of acute rejection and complications were also included in the model. Costs were estimated from a previously published study which compared the effect of
different immunosuppressive regimens in the early post-transplant period and from studies reporting the difference in the cost of follow-up of a patient with a well functioning graft compared to that of a poorly functioning graft. In addition, each patient who returned to dialysis after transplantation incurred additional costs for the insertion of temporary venous access and acute dialysis therapy.

The second method used to determine costs was to identify the costs of transplantation incurred in the local University of Toronto transplant units. This was done using cost estimates from the Ontario Case Costing Project (OCCP). The OCCP is a government funded project which traces patient specific encounters with medical services. Overhead costs (for example laundry and administration costs) are allocated to clinical services using a model which estimates the average utilisation by each clinical department. Thus, individual patient costs can be estimated for each admission. This included the average cost of investigations, drugs, dialysis, surgical materials, staffing and per diem accommodation. Inpatient drug costs were included. Patients who had acute rejection or another complication incurred additional expenses not captured by this model. Professional fees and outpatient costs were not included.

Baseline cost estimates for the cost of surgery and initial hospitalisation, for each complicating event and for dialysis costs are given in Table 3.3. The mean costs estimated from the Ontario Case Costing Project are shown in Table 3.4. Each estimate is expressed in 1997 Canadian dollars.
3.4 Validation of the model

The estimated mortality rate was validated by comparing predicted patient survival data to expert opinion and to data from the USRDS and CORR databases using the Markov tracer function.

3.4.1 Survival

The accuracy with which the model predicted survival was first checked using a simple model where patients were not exposed to the risk of de novo cardiovascular disease or steroid induced diabetes. When plotted as a survival curve for patients receiving a transplant, the model predicted similar mortality to that reported by the USRDS and CORR (Figure 3.4). In contrast, patients continuing on dialysis (but otherwise suitable for a transplant) had significantly better predicted survival than the average age-matched dialysis patient (Figure 3.5). This was consistent with expert opinion (University of Toronto, transplant nephrology physicians).

3.4.2 Graft Survival

Graft survival was estimated by noting the number of patients who died or returned to dialysis using the Markov tracer function. Censored graft survival rates were estimated by censoring those patients who died with a functioning graft at the time of death. Graft survival was compared to that reported by the USRDS. The model predicted a similar rate of graft loss as that seen with current practice (Figure 3.6). Censored graft survival, estimated by censoring data at the time of death if a patient died with a functioning transplant, is also shown in the figure (dark grey line).

The transition from alive with a functioning transplant to alive but with acute rejection varied with time from transplantation falling to zero percent within two years. Maximal risk of a complication occurred early in the clinical course when immunosuppressive therapy was maximal. Subsequently the probability of a complication fell, to around 20% per 6 month period, with an annual increase of 0.5% per year.
3.5 Assumptions

The assumptions made during construction of the model include the following:

i. A patient entering the dialysis treatment limb will remain on haemodialysis throughout their clinical course

ii. Dialysis patients have a constant risk of death

iii. Annual cost and utility estimates for a patient continuing on dialysis implicitly include complications arising from vascular access problems and comorbid illnesses. Dialysis complications were not explicitly modelled because this select group of patients should have few comorbid conditions and a low risk of dialysis related complications.

iv. Surgery is performed once only

v. Surgical complications and peri-operative complications such as vascular leak, lymphocele, ureteric leak, wound infection and urinary tract infection are implicitly included in the terms for the average cost and average dysutility of surgery.

Assumptions made to estimate the probabilities and utilities include the following:

i. The cohort of patients entering the model are initially free of diabetes mellitus, free of symptomatic cardiovascular disease, but face a risk of developing problems while on the waiting list or as time progresses. This is consistent with current selection criteria.

ii. Most complications occur within the first two years post-transplantation and are related to infection or cardiovascular death.

iii. The rate of acute rejection falls exponentially with time so that most rejection episodes occur during the first six months post-transplant and no episodes occur after the first two years post-transplant.
iv. The relative risk of death is higher in patients with acute rejection than in patients who do not have acute rejection.

v. The relative risk of death after an infection is higher than after an episode of acute rejection.

vi. The relative risk of death is assumed to be additive when a patient has both acute rejection and an infection.

Three economic assumptions are also made when estimating costs:

i. The economic exchange rate between the American and Canadian dollar reflects the purchasing power of each of the two currencies.

ii. Studies using charges to estimate the financial outlay of an intervention are representative of true costs.

3.6 Other Methodological Details

3.6.1 Sensitivity analysis

The imprecision of the probability, utility and cost estimates was assessed using one-way analysis. Threshold levels are defined as the value of a probability, utility or cost estimate at which the outcome with either treatment strategy become equal. These were calculated using the two outcome measures: cost-benefit and quality-adjusted life expectancy. The Markov tracer function allows us to follow the proportion of the patient cohort in each of the health states at any one time. This was used to validate transition from different health states and the results compared to CORR and USRDS data. Multi-way sensitivity analyses were used to explore the effect of interacting variables. In particular: the effect of increasing probability of developing symptomatic cardiac disease while wait-listed and the relative risk of death if cardiovascular disease is present; the effect of increased utility from continued dialysis compared to decreased utility after transplantation; and
the effect of an increased complication rate and an increased relative risk of death as a result of complications. The effect of discounting was tested by establishing a threshold using one-way analysis, by measuring the effect of different discount rates using a 2-way cost-effectiveness analysis and by using a three-way sensitivity analysis was performed to describe the effect of increased dialysis and transplant follow-up costs at different discounting rates. The discount rate was varied between zero and five percent per three month cycle in the sensitivity analysis.

3.6.2 Societal Acceptability

Health policies should be acceptable to the community. With kidney transplantation, the main debate surrounds the limited number of organs available for harvesting. Thus, recommendations favouring transplantation for the elderly must be accompanied by identifiable acceptable donor sources. As the ideal source of transplantable organs is living related donation, we directed some attention to younger members of society as potential donors. The hypothesis was that younger members of society would be relatively willing to donate but that older members of society would be relatively unwilling to accept a kidney.

Respondents sampled had a target age range of about 30+ years (seen as potential living related donors) and about 65+ years (seen as potential recipients). This was achieved by selecting a group of nurses involved with dialysis in the Toronto area and a group of retired physicians living in the same geographical area. Nurses were identified from the lists of staff registered with the dialysis units across the city. Physicians were identified from the Canadian Medical Directory. A one-page questionnaire, with eight items was designed to assess the age, experience and attitudes of the respondent. A pilot project was performed in 10 young physicians and minor modifications were made to the questionnaire. The final version appears in Appendix 2.
The questionnaire assumed a basic understanding of transplantation and dialysis. Questions were closed-ended with respondents being asked to select one of four options to each item. To maximise the response rate, all individuals were sent a personalised hand-addressed cover letter explaining the study objectives and a reply paid return envelope. In addition, respondents were offered participation in a prize draw for a bouquet of flowers (physicians) or a $100 cash prize (nurses). Non-respondents were sent a second mailing after 4 weeks. The project was approved by the Research Ethics Committee at Sunnybrook Health Science Center.

3.6.3 Statistical Analysis of Questionnaire Data

Data from the societal surveys were analysed independently. The respondent’s age and experience level was stratified using frequency intervals. A one-way analysis of variance test was used to identify any relationship between the age of the respondent, their level of experience and their impressions about the value of transplantation, and their willingness to donate or accept. A Wilcoxon Signed Rank test was performed to see if there was a difference between the proportion of nurses who would agree to donate an organ and the proportion of physicians who would agree to accept an organ. Significance levels of 0.05 or lower were accepted as significant.
Table 3.1: Search Terms Used To Generate Literature Review

<table>
<thead>
<tr>
<th>Major Terms</th>
<th>Modifying Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td>Mortality</td>
</tr>
<tr>
<td>Renal Replacement Therapy</td>
<td>Morbidity</td>
</tr>
<tr>
<td>Kidney Transplantation</td>
<td>Survival</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Outcome</td>
</tr>
<tr>
<td></td>
<td>Graft Loss</td>
</tr>
<tr>
<td></td>
<td>Graft Rejection (Textword)</td>
</tr>
<tr>
<td></td>
<td>Infection (Textword)</td>
</tr>
<tr>
<td></td>
<td>Hospitalisation (Textword)</td>
</tr>
<tr>
<td></td>
<td>Complication (Textword)</td>
</tr>
<tr>
<td></td>
<td>Post-Transplant Diabetes (Textword)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressive Agents</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost-Utility</td>
</tr>
<tr>
<td></td>
<td>Cost Effectiveness</td>
</tr>
<tr>
<td></td>
<td>Cost-Benefit</td>
</tr>
<tr>
<td>Quality Of Life</td>
<td>Time Trade Off (Textword)</td>
</tr>
<tr>
<td></td>
<td>Standard Gamble (Textword)</td>
</tr>
</tbody>
</table>
### Table 3.2 Baseline probability and utility values used in the model (with clinically plausible range)

<table>
<thead>
<tr>
<th>Item</th>
<th>Baseline</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated annual mortality rate on dialysis (%)</td>
<td>11.5</td>
<td>10-20</td>
<td>1</td>
</tr>
<tr>
<td>Annual probability of post-transplantation diabetes</td>
<td>0.07</td>
<td>0.03-0.15</td>
<td>95-108,221</td>
</tr>
<tr>
<td>Relative risk of death if diabetes</td>
<td>2.67</td>
<td>1.2-5.0</td>
<td>1,213</td>
</tr>
<tr>
<td>Relative risk of a complication if diabetes</td>
<td>2.00</td>
<td>1.0-5.0</td>
<td>217*</td>
</tr>
<tr>
<td>Relative risk of cardiovascular disease if diabetes</td>
<td>3.25</td>
<td>2.0-5.0</td>
<td>88,222,223</td>
</tr>
<tr>
<td>Probability of acute rejection</td>
<td>0.40</td>
<td>0.2-0.6</td>
<td>13,77,78,87,90,111</td>
</tr>
<tr>
<td>Relative risk of death if acute rejection</td>
<td>1.22</td>
<td>1.0-2.0</td>
<td>90</td>
</tr>
<tr>
<td>Relative risk of a complication if acute rejection occurs</td>
<td>3.00</td>
<td>1.5-6.7</td>
<td>88,224-227</td>
</tr>
<tr>
<td>Probability of complication (per 6 month period)</td>
<td>0.20</td>
<td>0.1-0.5</td>
<td>92,216,218,228</td>
</tr>
<tr>
<td>Relative risk of death if a complication</td>
<td>1.80</td>
<td>1.5-4.0</td>
<td>1,92,213,216,218,228</td>
</tr>
<tr>
<td>Probability of de novo cardiovascular disease</td>
<td>0.12</td>
<td>0.1-0.55</td>
<td>222,229</td>
</tr>
<tr>
<td>Relative risk of death if cardiovascular disease present in a patient continuing dialysis</td>
<td>2.35</td>
<td>1.5-5.0</td>
<td>222</td>
</tr>
<tr>
<td>Relative risk of death if cardiovascular disease present in a transplanted patient</td>
<td>1.74</td>
<td>1.5-3.0</td>
<td>222</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Utilities</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Utility associated with dialysis</td>
<td>0.49</td>
<td>0.34-0.55</td>
<td>65,76</td>
</tr>
<tr>
<td>Utility associated with transplantation</td>
<td>0.78</td>
<td>0.45-0.82</td>
<td>65,76</td>
</tr>
<tr>
<td>Utility associated with rejection</td>
<td>0.00</td>
<td>0.0-0.30</td>
<td>*</td>
</tr>
<tr>
<td>Utility associated with complication</td>
<td>0.00</td>
<td>0.0-0.30</td>
<td>*</td>
</tr>
</tbody>
</table>

* = estimated clinically plausible range
Table 3.3 Baseline costs used in the model (with clinically plausible range)

<table>
<thead>
<tr>
<th>Costs (in 1997 $ CDN)</th>
<th>Baseline</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued dialysis (per year)</td>
<td>57,500</td>
<td>31,500-100,000</td>
<td>65,173,182,185- 190</td>
</tr>
<tr>
<td>Transplant follow up (per year)</td>
<td>15,000</td>
<td>7,800-30,000</td>
<td>65,173,179,186, 188-190</td>
</tr>
<tr>
<td>Transplant workup, surgery and recovery</td>
<td>43,800</td>
<td>40,000-126,000</td>
<td>65,179,185- 187,190</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>10,400</td>
<td>5,000-24,000</td>
<td>65,179,187-189</td>
</tr>
<tr>
<td>Complications</td>
<td>10,400</td>
<td>5,000-30,000</td>
<td>65,179,188,189</td>
</tr>
<tr>
<td>Costs associated with starting a patient back onto dialysis after a failed transplant</td>
<td>8,000</td>
<td>7,000-10,000</td>
<td>230</td>
</tr>
</tbody>
</table>
Table 3.4: Average costs for initial transplant surgery estimated using the Ontario Case Costing Project (>65 years old)

<table>
<thead>
<tr>
<th>Costs</th>
<th>(1997 $ CDN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating Room</td>
<td>1900</td>
</tr>
<tr>
<td>Recovery Room</td>
<td>600</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>400</td>
</tr>
<tr>
<td>Basic Laboratory Costs†</td>
<td>1780</td>
</tr>
<tr>
<td>Imaging studies*</td>
<td>982</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>2808</td>
</tr>
<tr>
<td>Rehabilitation Services</td>
<td>115</td>
</tr>
<tr>
<td>Tissue Typing and Electron Microscopy</td>
<td>700</td>
</tr>
<tr>
<td>Nursing Services</td>
<td>5500</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14,385</td>
</tr>
</tbody>
</table>

† Include biochemistry, haematology, surgical pathology & microbiology
* Radiology, Nuclear Medicine and Ultrasound
Figure 3.1: Overview of decision analysis model

CVD = cardiovascular disease
\(\infty\) = Markov model
Figure 3.2: Markov model.
Figure 3.3:
Subtree within Markov tree of acute rejection and of complication

Acute rejection

Complication

probability of acute rejection

HEALTH STATE 1
Alive with acute rejection and complication

prob complication x RR *

HEALTH STATE 2
Alive with acute rejection

No Complication

No rejection

Complication

probability of complication

HEALTH STATE 3
Alive with complication

HEALTH STATE 4
Alive, no rejection or complication

No Complication

* = probability of complication x relative risk of complications after acute rejection
Figure 3.4:
Predicted Patient Survival For Patients Receiving a Transplant

The heavy line shows the predicted survival after transplantation. The fine line show the survival estimates from 1997 USRDS data with standard error margins (shaded area).
The heavy line shows the survival as predicted by the decision analysis model. The fine line shows the survival estimates from 1997 USRDS data for age-matched dialysis patients (with standard error margins shown as the shaded area). The survival rate for the first 5 years on dialysis in a subset of patients without any comorbid illness is shown as a dotted line (unpublished data, with permission from CORR).
The predicted actuarial graft survival rate (black line) is similar to that reported by the USRDS (fine black line). The standard error for the USRDS survival curve is shown as the shaded area. If censored at the time of the death, the apparent graft survival is higher (dark grey line).
4. Results

The purpose of this chapter is to:

1. Describe the predicted survival for patients with a transplant and patients continuing on dialysis
2. Demonstrate the transition between states, and present the clinical, cost and cost-effectiveness results
3. Show the results of one-way, two way and three way sensitivity testing
4. Provide the survey results on the societal acceptability of transplantation in the elderly

4.1 Clinical Results

4.1.1 Estimated life expectancy

Table 4.1 shows the results of the different treatment strategies. The life expectancy for a 65 year old non-diabetic male, without cardiovascular disease, who received a transplant was estimated at about 6.5 years, compared to about 5.8 years if continuing on dialysis, a gain of almost 8.5 months of life. In a diabetic patient, the gain in life expectancy was the same as for a non-diabetic patient, although the estimated life expectancy was shorter both with transplantation and with continued on dialysis (2.8 vs. 2.1 years, respectively).

4.1.2 Estimated quality-adjusted life expectancy

When differences in the quality of life are considered in addition to survival, the quality-adjusted life expectancy (QALE) for a 65 year old non diabetic male who continued on dialysis was 2.8 years. With a transplant the predicted QALE was 4.2 years, equivalent to a gain of 1.4 quality-adjusted life years. In a diabetic patient, the gain in life expectancy with transplantation compared to dialysis was 0.8 QALYs (1.8 vs. 1.0, respectively).
4.2 Economic Results

4.2.1 Net Costs

The model predicted that transplantation was the cheaper treatment. Despite high initial costs, the overall expense associated with transplantation was lower because of significantly lower maintenance costs. After discounting, the net cost of care for a patient with transplantation was $249,440 CDN. For patients remaining on dialysis the estimated net cost was $338,335 CDN. Hence the savings amounted to $88,985 per patient transplanted.

The net discounted cost of transplantation for a diabetic patient was estimated around $128,294, and for dialysis around $123,498. Hence with discounting the cost amounted to about $4796 per patient transplanted. Diabetic patients incur greater expenses with transplantation because of a higher rate of complications. However, these additional costs were partly offset by the reduced costs of long-term follow up.

4.2.2 Cost per life-year

Transplantation is the dominant treatment strategy providing both a cheaper treatment option and a longer life expectancy. In diabetic patients transplantation cost $7,229 per life year gained.

4.2.3 Cost per quality-adjusted life year

After adjustment for quality of life transplantation remained the dominant strategy for non diabetic patients. In diabetic patients the estimated cost per QALY was about $6,093 (Table 4.1).
4.3 Sensitivity Analyses

4.3.1 One-way Sensitivity Analysis

Each probability was tested across a wide range of values. The threshold where QALE after transplantation was equal to that for patients remaining on dialysis was sought for each probability, utility and mortality estimate. The stability of the model to changes in input variables was shown (Tables 4.2 and 4.3). The model was robust to all estimates except the utility of transplantation (threshold value 0.47). Thus, transplanted patients who obtained utility scores less than 0.47 would have had a longer QALE had they remained on dialysis. Figure 4.1 shows how the life expectancy with transplantation was influenced by the estimated dialysis mortality rate because of the risk of graft failure. The threshold value for the dialysis mortality rate was lower than the clinically valid range (threshold 0.05). The results of sensitivity analyses for the utility of dialysis and of transplantation are shown in Tables 4.4 and 4.5.

One-way sensitivity analysis on the probability of de novo cardiovascular disease is shown in Table 4.6. Despite a higher cardiovascular mortality with dialysis than with transplantation (relative risk 2.35 vs. 1.79, respectively) transplanted patients showed a marginally steeper fall in QALE with an increasing risk of this comorbidity. This arose because transplanted patients were at risk of developing steroid-related diabetes and hence at higher risk of developing de novo cardiovascular disease. Both life expectancy and economic implications were estimated.

Cost estimates were also subjected to one-way analysis. The threshold was defined as the point at which the overall cost of transplantation was equal to that of dialysis. The model was highly sensitive to the average annual cost of dialysis (threshold $34,278). Threshold values for the cost estimates are shown in Table 4.7. Dialysis was the cheaper treatment when the annual mortality
rate was estimated to be more than 21%; however, this was at the cost of a significantly reduced QALE (Table 4.9). As transplantation was found to be a dominant strategy, the cost-effectiveness of each additional life year with transplantation was measured at the extremes of the plausible range (Tables 4.2 and 4.3).

4.3.2 Two-way sensitivity analysis

A two-way sensitivity analysis explored the relationship between the probability of a complication and the relative risk of death if a complication occurred. As the probability of a complication increased one would have predicted that the threshold value for the relative risk of death if a complication occurred would decrease. The results support this hypothesis but also show that when the probability of a complication was low (less than a 40% risk per 6 months) the relative risk of death does not reach a point at which the QALE of dialysis equals that of transplantation (no threshold). However if the probability of a complication was to rise beyond that predicted (i.e. more than a 40% risk) the threshold for the relative risk of death if a complication occurred was greater than 4.0 (Figure 4.2). A two-way sensitivity analysis examining the relationship between the discounting rate used for costs and health states showed no significant thresholds.

4.3.3 Three way Sensitivity analysis results

Three-way sensitivity analyses tested the relationship between the prevalence of cardiovascular disease and the relative risk of death in dialysis and transplant patients. The relationship between the relative risk of death if CVD occurs in a transplanted patient and that if CVD occurs in a dialysis patient and the probability of developing de novo CVD is shown in Table 4.9. The model remained robust over all plausible ranges of the variables suggesting that an increased risk of de novo CVD should not alter the benefits seen with transplantation. A similar stability was seen for the relationship between acute rejection and the effects of a complication (Table 4.10).
The results of a three-way analysis testing the relationship between the utility scores for transplantation and for dialysis at different estimates of the dialysis mortality rate is shown in Figure 4.3. Each line represents the threshold values at which the QALE of transplantation equals that of dialysis. The different lines show the threshold values for different estimates of the mortality rate for those continuing on dialysis. The best estimates of the utility of transplantation and of dialysis are shown as an asterix, with extreme values lying within the rectangle. The results show that as the dialysis mortality rate is increased, the threshold value at which the QALE of transplantation equals that of dialysis falls. A few of the threshold values transect the rectangle of plausible values suggesting that either overestimation of the utility scores for transplantation or underestimation of the dialysis mortality rate could be significant. A number of additional sensitivity analyses are shown in the Appendix.

4.3.4 Worst and Best Case Scenario

Worst and best case scenarios were developed using the plausible estimates of all probability, quality of life and economic variables. The worst case scenario was created by choosing the value of the variable which would minimise the expected outcome from transplantation compared to dialysis (Table 4.10). Dialysis was the dominant strategy with the worst case scenario, resulting in a life expectancy gain of 1.6 QALYs and a saving of $113,063 per patient. The best case scenario was developed using estimates which would minimise the expected outcome with dialysis. Transplantation was the dominant strategy in the best case scenario with a predicted QALE of 4.4 years at a net cost of $236,934 per patient. The gain in life-expectancy with transplantation using the best case scenario was somewhat modest because this treatment strategy includes a number of patients who return to dialysis after graft loss.
4.4 Acceptability Survey

Two groups of respondents were studied; namely, young nurses and old physicians. At the time of survey, the dialysis units within Metro Toronto employed a total of 211 nurses, of which 173 (82%) responded to the questionnaire. Questionnaires were also sent to 323 physicians, of which 108 returned completed questionnaires (33%). Most nurses were aged 35-49 years old (65%), a small number aged 20-34 years (15%) and 50-64 years (20%) and none aged more than 65 years. Most of the physicians were aged over 65 years (92%), the remaining 8% aged 50-64 years, and none below age 50.

The majority of nurses and physicians had more than 10 years experience in general clinical settings (84% vs. 91%, respectively). Relatively more nurses than physicians surveyed had direct clinical experience with dialysis (95% vs. 25%, respectively) or transplant patients (46% vs. 18%, respectively). Most of the nurses and physicians agreed that transplantation was superior to dialysis (94% vs. 89%, respectively). When asked about the risks of organ donation, more nurses than physicians felt that there were substantial risks to the donor (53% vs. 35% respectively, p<0.01).

Despite the perceived risk, the majority of both nurses and physicians indicated they would be willing to donate a kidney to a relative (60% vs. 83%, p<0.01). However, only a minority of nurses would be willing to accept an organ if they had renal failure requiring renal replacement therapy (45% vs. 72%, p<0.02). Based on the assumption that the nurses represented a potential donor pool of younger societal members and that the physicians represented a potential pool of older societal recipients, fewer nurses were willing to donate a kidney than physicians were to
willing to accept (60% vs. 72%, \( p<0.05 \)). Neither age nor the duration of clinical experience of
the respondent was significantly related to responses \( (p>0.20) \).
Table 4.1 Baseline Results

<table>
<thead>
<tr>
<th>Strategy</th>
<th>LE</th>
<th>QALE</th>
<th>Net Cost*</th>
<th>Δ LE</th>
<th>Δ QALE</th>
<th>Δ CE</th>
<th>Ratio‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>years</td>
<td>years</td>
<td>($1000)</td>
<td>years</td>
<td>years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>6.5</td>
<td>4.2</td>
<td>328</td>
<td>0.7†</td>
<td>1.4†</td>
<td></td>
<td>Dominant</td>
</tr>
<tr>
<td>(non-diabetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>5.8</td>
<td>2.8</td>
<td>443</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(non-diabetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>2.8</td>
<td>1.8</td>
<td>139</td>
<td>0.7†</td>
<td>0.8†</td>
<td>$6,093</td>
<td></td>
</tr>
<tr>
<td>(diabetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>2.1</td>
<td>1.0</td>
<td>137</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(diabetic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LE  Predicted Life Expectancy  
QALE Quality adjusted life expectancy  
* Undiscounted costs  
‡ Cost per additional QALY for transplantation compared to dialysis. Both the costs and the health state are discounted at a rate of 1% per 3 month cycle.  
† Additional life years gained with transplantation compared to dialysis
Table 4.2  Results of Sensitivity Testing (cost estimates)

<table>
<thead>
<tr>
<th>Cost Estimate</th>
<th>Range</th>
<th>LE Gain† yr</th>
<th>QALY Gain† yr</th>
<th>Cost Utility Ratio‡,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued dialysis (per year)</td>
<td>31,500</td>
<td>0.68</td>
<td>1.35</td>
<td>7.9</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>57,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Transplant workup, surgery and recovery</td>
<td>40,000</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>43,800</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>126,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>5,000</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>10,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Complications</td>
<td>5,000</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>10,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Transplant follow up (per year)</td>
<td>7,800</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>15,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
<tr>
<td>Re-starting dialysis after a failed graft</td>
<td>7,000</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td>8000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10,000</td>
<td>0.68</td>
<td>1.35</td>
<td></td>
<td>#</td>
</tr>
</tbody>
</table>

†  Gain from transplantation compared to dialysis
‡  Costs given as $1000 per QALE
#  Dominated strategy
Table 4.3  Results of Sensitivity Testing (probability and utility estimates)

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Range</th>
<th>LE Gain†, yr</th>
<th>QALY Gain† yr</th>
<th>Cost Utility Ratio‡,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk of death if diabetes</td>
<td>1.2</td>
<td>0.74</td>
<td>1.46</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>0.49</td>
<td>1.29</td>
<td>#</td>
</tr>
<tr>
<td>Relative risk of cardiovascular disease if diabetes</td>
<td>2.0</td>
<td>0.69</td>
<td>1.36</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>0.55</td>
<td>1.34</td>
<td>#</td>
</tr>
<tr>
<td>Probability of de novo cardiovascular disease</td>
<td>0.1</td>
<td>0.57</td>
<td>1.34</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>0.12</td>
<td>0.55</td>
<td>1.38</td>
<td>#</td>
</tr>
<tr>
<td>Probability of acute rejection</td>
<td>0.2</td>
<td>0.69</td>
<td>1.40</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.56</td>
<td>1.30</td>
<td>#</td>
</tr>
<tr>
<td>Relative risk of death if acute rejection</td>
<td>1.0</td>
<td>0.70</td>
<td>1.37</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>1.22</td>
<td>0.48</td>
<td>1.29</td>
<td>#</td>
</tr>
<tr>
<td>Probability of complication (per 6 month period)</td>
<td>0.1</td>
<td>0.69</td>
<td>1.47</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.36</td>
<td>1.08</td>
<td>#</td>
</tr>
<tr>
<td>Relative risk of death if a complication</td>
<td>1.5</td>
<td>0.74</td>
<td>1.47</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>0.43</td>
<td>0.68</td>
<td>#</td>
</tr>
<tr>
<td>Estimated annual mortality rate on dialysis (%)</td>
<td>10</td>
<td>0.15</td>
<td>1.14</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>0.68</td>
<td>1.35</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>11.5</td>
<td>2.0</td>
<td>2.05</td>
<td>#</td>
</tr>
</tbody>
</table>

† Gain from transplantation compared to dialysis
‡ Costs given as $1000 per QALE
# Dominated strategy
Table 4.4  One-way sensitivity analysis for various probabilities for the utility of dialysis

<table>
<thead>
<tr>
<th>Utility on Dialysis</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>3.26</td>
<td>0.0</td>
<td>Tx 3.26*</td>
</tr>
<tr>
<td>0.2</td>
<td>3.66</td>
<td>1.18</td>
<td>Tx 2.48*</td>
</tr>
<tr>
<td>0.4</td>
<td>4.05</td>
<td>2.35</td>
<td>Tx 1.70*</td>
</tr>
<tr>
<td>0.6</td>
<td>4.45</td>
<td>3.53</td>
<td>Tx 0.92*</td>
</tr>
<tr>
<td>0.8</td>
<td>4.85</td>
<td>4.71</td>
<td>Tx 0.14*</td>
</tr>
<tr>
<td>1.0</td>
<td>5.25</td>
<td>5.89</td>
<td>Dx 0.64*</td>
</tr>
</tbody>
</table>

* Tx = transplant strategy more effective
  Dx = dialysis strategy more effective
Table 4.5  One-way sensitivity analysis for various probabilities for the utility of transplantation

<table>
<thead>
<tr>
<th>Utility of transplantation</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>-0.11</td>
<td>2.88</td>
<td>Dx 2.99*</td>
</tr>
<tr>
<td>0.2</td>
<td>-0.04</td>
<td>2.88</td>
<td>Dx 2.92*</td>
</tr>
<tr>
<td>0.4</td>
<td>2.53</td>
<td>2.88</td>
<td>Dx 0.35*</td>
</tr>
<tr>
<td>0.6</td>
<td>3.43</td>
<td>2.88</td>
<td>Tx 0.55*</td>
</tr>
<tr>
<td>0.8</td>
<td>4.32</td>
<td>2.88</td>
<td>Tx 1.44*</td>
</tr>
<tr>
<td>1.0</td>
<td>5.22</td>
<td>2.88</td>
<td>Tx 2.34*</td>
</tr>
</tbody>
</table>

* Tx = transplant strategy more effective  
Dx = dialysis strategy more effective
Table 4.6  One-way cost effectiveness analysis for various probabilities of developing de novo CVD

<table>
<thead>
<tr>
<th>Probability of CVD</th>
<th>Cost of Transplantation Strategy ($ CDN)</th>
<th>Cost of Dialysis Strategy ($ CDN)</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>261,730</td>
<td>360,227</td>
<td>4.43</td>
<td>3.07</td>
<td>Tx* dominant</td>
</tr>
<tr>
<td>0.2</td>
<td>241,247</td>
<td>323,741</td>
<td>4.11</td>
<td>2.76</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>0.4</td>
<td>221,656</td>
<td>287,255</td>
<td>3.80</td>
<td>2.45</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>0.6</td>
<td>203,108</td>
<td>250,769</td>
<td>3.52</td>
<td>2.14</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>0.8</td>
<td>184,559</td>
<td>214,283</td>
<td>3.24</td>
<td>1.83</td>
<td>Tx dominant</td>
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<tr>
<td>1.0</td>
<td>166011</td>
<td>177,797</td>
<td>2.96</td>
<td>1.52</td>
<td>Tx dominant</td>
</tr>
</tbody>
</table>

* Tx = transplant strategy
Table 4.7: Threshold values for the costs used in the model

<table>
<thead>
<tr>
<th>Costs</th>
<th>Clinically Plausible Range ($)</th>
<th>Threshold for Cost Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs associated with continued dialysis (per year)</td>
<td>31,500-100,000</td>
<td>34,278</td>
</tr>
<tr>
<td>Cost associated with transplant workup, surgery and recovery</td>
<td>40,000-126,000</td>
<td>134,518</td>
</tr>
<tr>
<td>Costs associated with rejection</td>
<td>5,000-30,000</td>
<td>no threshold</td>
</tr>
<tr>
<td>Costs associated with complications</td>
<td>5,000-30,000</td>
<td>59,237</td>
</tr>
<tr>
<td>Costs associated with transplant follow up (per year)</td>
<td>7,800-30,000</td>
<td>36,390</td>
</tr>
<tr>
<td>Costs associated with starting a patient back onto dialysis after a failed transplant</td>
<td>7,000-10,000</td>
<td>no threshold</td>
</tr>
</tbody>
</table>
### Table 4.8  
Table showing increase in costs per additional QALE for extreme values

<table>
<thead>
<tr>
<th>Item</th>
<th>Extreme value</th>
<th>Cost per QALY</th>
<th>Effect at extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of transplantation</td>
<td>0.4</td>
<td>255,160</td>
<td>Dialysis more effective but at great cost</td>
</tr>
<tr>
<td>Dialysis mortality</td>
<td>4% per year</td>
<td>604,760</td>
<td>Dialysis more effective but at great cost</td>
</tr>
<tr>
<td></td>
<td>22% per year</td>
<td>2,105</td>
<td>Dialysis cheaper but less effective</td>
</tr>
<tr>
<td>Cost of dialysis</td>
<td>25,000 per year</td>
<td>51,020</td>
<td>Dialysis cheaper but less effective</td>
</tr>
<tr>
<td></td>
<td>30,000 per year</td>
<td>61,224</td>
<td>Dialysis cheaper but less effective</td>
</tr>
<tr>
<td>Cost associated with transplant workup, surgery and recovery</td>
<td>140,000</td>
<td>3,980</td>
<td>Dialysis cheaper but less effective</td>
</tr>
</tbody>
</table>
Table 4.9  Table showing three-way sensitivity analysis for different estimates of the effect of cardiovascular disease (CVD). The threshold values for the relative risk of death if CVD present and transplanted are given. The different columns represent different estimates for the risk of death if CVD present but patient remains on dialysis. The different rows show the thresholds across a range of prevalence rates.

<table>
<thead>
<tr>
<th>Probability of developing de novo CVD</th>
<th>Estimated value of RR of death in those with CVD if remaining on dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>0.0</td>
<td>No Threshold</td>
</tr>
<tr>
<td>0.2</td>
<td>No Threshold</td>
</tr>
<tr>
<td>0.4</td>
<td>No Threshold</td>
</tr>
<tr>
<td>0.6</td>
<td>3.24</td>
</tr>
<tr>
<td>0.8</td>
<td>2.41</td>
</tr>
<tr>
<td>1.0</td>
<td>2.03</td>
</tr>
</tbody>
</table>
Table 4.10: Table showing three-way sensitivity analysis for different estimates of the effect of complications. The threshold values for the relative risk of death if a complication was present are given. The different columns represent different estimates for the risk of death of a complication occurring (for each 6 month period). The different rows show the thresholds across a range of different rates of acute rejection.

<table>
<thead>
<tr>
<th>Probability of developing a complication</th>
<th>Estimated probability of developing acute rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>No Threshold</td>
</tr>
<tr>
<td>0.2</td>
<td>No Threshold</td>
</tr>
<tr>
<td>0.4</td>
<td>4.60</td>
</tr>
<tr>
<td>0.6</td>
<td>3.62</td>
</tr>
<tr>
<td>0.8</td>
<td>3.11</td>
</tr>
<tr>
<td>1.0</td>
<td>2.80</td>
</tr>
</tbody>
</table>
Table 4.1  Variables altered to create a best and worst case scenario

<table>
<thead>
<tr>
<th>Estimate</th>
<th>Value used for worst case</th>
<th>Value used for best case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated annual mortality rate on dialysis</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Costs associated with continued dialysis (per year)</td>
<td>30,000</td>
<td>100,000</td>
</tr>
<tr>
<td>Cost associated with transplant workup, surgery and recovery</td>
<td>126,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Costs associated with rejection</td>
<td>24,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Costs associated with complications</td>
<td>30,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Costs associated with transplant follow up (per year)</td>
<td>30,000</td>
<td>7,800</td>
</tr>
<tr>
<td>Costs associated with starting a patient back onto dialysis after a failed transplant</td>
<td>10,000</td>
<td>7,000</td>
</tr>
<tr>
<td>Annual probability of post-transplantation diabetes</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>Relative risk of death if diabetes</td>
<td>5.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Relative risk of a complication if diabetes</td>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Relative risk of cardiovascular disease if diabetes</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Relative risk of death if cardiovascular disease present in a patient continuing dialysis</td>
<td>1.0</td>
<td>unchanged</td>
</tr>
<tr>
<td>Relative risk of death if cardiovascular disease present in a transplanted patient</td>
<td>1.0</td>
<td>unchanged</td>
</tr>
<tr>
<td>Probability of acute rejection</td>
<td>0.56</td>
<td>0.2</td>
</tr>
<tr>
<td>Relative risk of death if acute rejection</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Relative risk of a complication if acute rejection occurs</td>
<td>5.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Relative risk of death if a complication</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Utility associated with dialysis</td>
<td>0.55</td>
<td>0.34</td>
</tr>
<tr>
<td>Utility associated with transplantation</td>
<td>0.45</td>
<td>0.82</td>
</tr>
</tbody>
</table>
Figure 4.1: One-way sensitivity analysis showing the QALE of transplantation and dialysis as the estimated mortality rate for dialysis patients is varied. The graph shows how the QALE of dialysis (grey line) and transplantation (black line) as the dialysis mortality rate is varied. The QALE for transplantation decreases because of those patients who return to dialysis after unsuccessful transplantation.
Figure 4.2: Two-way sensitivity analysis results showing the threshold for the relative risk of death if a complication occurred for increasing probability values for a complication.

Points lying within the shaded area indicate the clinically valid range, with the best estimate shown as an asterix.
Figure 4.3: Three-way sensitivity analysis

Graph shows the threshold values for the utility of transplantation for different estimates of the annual dialysis mortality rate expressed as a percentage (MRdx). The boxed area represents the range of values felt to be clinically valid and the asterisk the best estimate for the utility of dialysis and transplantation.
5. Discussion

The purpose of this chapter is to
1. Review the significant results of the study
2. Discuss the limitations
3. Discuss the policy implications of the results

5.1 Commentary

This study examined the benefits and risks of transplantation for elderly patients with renal failure. The principle finding was that transplantation was the preferred treatment modality, both in terms of better quality-adjusted life expectancy and lower expected medical costs. The model was robust to all variables except the utility of transplantation and the annual cost of dialysis. In particular, a lower quality-adjusted life expectancy was seen with transplantation only if the annual utility fell below 0.47. This utility value was equal to that given for the hypothetical clinical scenario describing a bad transplant\textsuperscript{65}. Thus, one may predict that the majority of elderly patients who had a functioning transplant would benefit in terms of QALE.

The model suggests that transplantation is cheaper than dialysis. Therefore, even in the event of a modest utility after transplantation, one would anticipate lower costs for a similar QALE. Yet the annual cost of dialysis was a significant variable in the sensitivity analysis. For instance, dialysis was found to be more cost-effective than transplantation if dialysis costs could be reduced to less than $34,000. Although peritoneal dialysis was estimated to cost around $35,000 per year, current recommendations to increase dialysis adequacy by using larger volumes of dialysate have increased the overall cost\textsuperscript{182,231,232}. 
Perhaps the most counter-intuitive finding of the study was that the model was not dependent upon the probability of acute rejection or complications within the clinically plausible range. Together these findings imply that kidney transplantation is both a desirable and an affordable intervention for well selected elderly patients with renal failure. Moreover the procedure need not be restricted to only a few elite hospitals.

The findings of this study are in accordance with other observational and comparative studies\(^7,138,233\). For example, when patients aged over 60 years were matched for age, sex, comorbidity and time from the onset of renal replacement therapy, transplantation offered better survival than those patients who remained on dialysis\(^77\). Similarly wait-listed dialysis patients appeared to have an overall higher mortality than those who received a transplant\(^138,233\).

Four differences are noted between the results of this study and other studies already published. First, the probabilities introduced into the decision analysis model were drawn from both the published literature and new analyses from the USRDS and CORR. As a result, the final model did not depend on only one series of patients but on the combination of all currently available data. Second, previous studies have not used quality adjustment techniques. Third, no other study has attempted to explicitly explore the consequences of post-transplantation diabetes or de novo cardiovascular disease in an older population. Lastly, the cost-effectiveness of transplantation in an older population has not been previously studied. Hence, this study is the first to suggest that transplantation both improves patient outcomes and decreases societal costs.

Perhaps the most controversial finding in this study is that a positive benefit was seen with transplantation even in the presence of de novo cardiovascular disease. Cardiovascular disease is more common in the elderly and can be accelerated by the immunosuppressive therapies used in
transplantation. Although the base case analysis focused on a 65 year old man who did not have myocardial ischaemia detected at the time of screening, the individual had some chance of developing clinically overt disease during the wait-listed period or around the time of surgery. The literature report a 12% chance of developing clinically overt disease while wait-listed or shortly after receiving a transplant. One may argue that this may be an under-estimate particularly in the elderly population where silent ischaemia is more prevalent. Similarly, the term used to describe the relative risk of death in the presence of cardiovascular disease was based on secondary analyses of data from patients recruited into two randomised controlled trials of different immunosuppressive regimens and its accuracy remains unknown. Consequently, the model may underestimate both the mortality rate at the time of surgery and for the subsequent few years. However, one-way and multi-way sensitivity analyses were robust suggesting that patients at risk of developing de novo cardiovascular disease may still benefit from transplantation.

Based on the results of this study, there are compelling reasons to suggest that transplantation should be widely adopted as the treatment of choice for selected elderly patients who have chronic renal failure. It is both more effective and cheaper than dialysis. Furthermore, despite the use of wide sensitivity analyses, the recommendation to adopt transplantation seems relatively robust. For example, even when an arbitrary lower estimate for the annual cost of dialysis was used ($30,000 per year) the additional cost of transplantation was estimated to be around $61,000 per QALY. This remains favourable when compared to other widely accepted therapies, for example, coronary artery bypass surgery ($113,000 US per QALY) and screening mammography ($168,000 US per QALY).

A further observation is that a positive survival benefit was seen from transplantation even in diabetic patients. A 65 year old man with diabetes, for example, would have a life expectancy of
2.7 years with transplantation and 1.5 years with dialysis. This increased survival was associated with an increase in costs of around $30,000 per QALY. These findings were not wholly unexpected. In a previous study of transplanted patients aged less than 65 years, the relative benefit of transplantation compared to wait-listed patients was seen to vary with the aetiology of end-stage renal disease\textsuperscript{233}. In particular, the benefits gained by transplantation were maximal in diabetic patients.

Traditionally, even young diabetic patients are not often offered transplantation\textsuperscript{1,52}. One of the possible reasons for this is that diabetics are more likely to suffer from silent myocardial ischaemia, undetected peripheral vascular disease, or steroid-induced hyperglycaemia. Our model did not account for the increased risk of accelerated systemic atherosclerosis related to diabetic hyperglycaemia and consequently we may have over-estimated the benefits and underestimated the costs in the diabetic subgroup. In addition, because simultaneous kidney-pancreas transplantation is still not widely available no attempt was made to consider it as an alternative treatment option for older diabetic patients. Of note, the additional risk of steroid-induced diabetes did not alter the model results.

An additional finding from the survey is that older individuals are more willing to accept an organ from a younger member of society than younger persons are willing to donate. This is contrary to our a priori hypothesis which proposed that younger individuals would be relatively willing to donate a kidney but that older persons would be relatively hesitant to accept. Public opinion on the allocation of organs has never been predictable\textsuperscript{236,237}. In a number of studies individuals have shown a preference to allocate therapy to the most seriously ill rather than to those with the best prognosis\textsuperscript{238-240}.
Special priority is sometimes given to those with the least personal responsibility for their illness, and the greatest need, or the longest time waiting\textsuperscript{241,242}. These preferences may reflect ignorance of prognostic data or may represent true equity\textsuperscript{236}. Interestingly, some respondents may be more willing to allocate organs (in this case transplantable livers) on the basis of the chances of success when patients were ranked as individuals rather than when they were grouped into those with a good or poor prognosis\textsuperscript{236,243}. The results presented from the current study differ from previously published studies in many respects. The questions used in the survey measure both attitudes towards organ allocation and personal risk preferences. Each respondent was asked if they would personally donate their kidney to a close, but older, relative. As a result those who were unwilling to donate included persons who did not agree with the allocation of living kidneys to older persons and those who were risk averse.

\textbf{5.2 Limitations of the study}

As with many decision analysis models, the main limitation of this study was the imperfect data used to estimate probabilities, utilities and costs. Probabilities were drawn from data collected from different populations, with different characteristics, and treated with different regimens. In the model, one-way analysis for each probability value was applied to tease out potential biases. For example, the threshold for the annual cost of dialysis was $34,278 with a clinically valid range between $31,500 and $100,000. However, this threshold was of limited clinical importance because of two points. First it is unlikely that the average cost of dialysis be this low even if patients are preferentially maintained on continuous ambulatory peritoneal dialysis; and second, the increase in the cost per additional QALY with transplantation would be comparable to other widely accepted medical interventions (Table 4.6).
The use of a mathematical model seldom portrays the true complexity of the clinical situation. Constructing a model requires making simplifying assumptions and excluding complications which are rare or transient. In this study, surgical complications including wound infection, urinary tract infection, leaky anastomosis, venous thrombosis or cyclosporin induced hypertension were not explicitly included. The assumption was that the dysutility and costs of such complications were included in the aggregate terms describing the dysutility of surgery and the cost of surgery. Other assumptions were explicit and open to sensitivity analysis, for example, haemodialysis and peritoneal dialysis were treated as having the same cost and survival implications and the mortality rate for patients continuing on dialysis was assumed to be constant.

To minimise the chances of wrongly promoting transplantation, a relatively conservative approach was taken. For example, Figure 3.4. shows how the model accurately predicts survival after transplantation. However, the predicted survival data included in this figure was taken from the simplified model where no additional risk of death was attributed to either de novo cardiac disease or post-steroid diabetes, thus causing a bias against transplantation. Similarly the range of costs associated with transplantation included extreme cases reported in the literature. For example, the average cost of a complication was estimated between $5,000 and $30,000. The data supporting a complication cost of $30,000 reflected the most severe clinical scenario where a patient developed a cytomegalovirus pneumonia requiring admission to an intensive care unit. In addition, the model favoured dialysis by estimating the annual cost of dialysis after excluding costs for hospitalisation. This was justified by the argument that a patient continuing on dialysis, but otherwise suitable for transplantation, would be significantly healthier than the average 65 year old dialysis patient.
Disparity between the predicted and observed clinical course is acknowledged. The model did not adjust for potential differences in survival and graft loss rates between cadaveric and living related organ transplants. All results reported were based upon cadaveric data. This is another bias against transplantation, justified only because most transplant kidneys are cadaveric. Similarly, the model assumed rates of acute rejection and complications consistent with published data. However, these estimates were based on reports from the mid-1990’s, shortly after cyclosporin and antilymphocyte immunosuppressive regimes were introduced. Recent data suggest further improvements in transplant outcome with newer immunosuppressive \textsuperscript{117,118,224}.

Each complication was allocated a complete dysutility for the duration of hospitalisation. Although older patients tend to have longer periods of hospitalisation than younger patients, the estimated duration applied in the model was unusually long (30 days). This would tend to over-estimate the dysutility of acute rejection or other complication and reduce the estimated quality-adjusted life expectancy following transplantation. However, as neither the duration of acute rejection nor the duration of a complication was sensitive to one-way analysis this is unlikely to be a significant bias. Finally, no attempt was made to modify the utility of transplantation if a person had experienced multiple episodes of acute rejection.

One significant clinical limitation was that all types of complications were considered equal. For example, complications in the earlier course of transplantation tend to be caused by infections while in the latter years tend to be caused by lymphoproliferative diseases and skin malignancies. Thus, the single term ‘complications’ was used to cover a heterogeneous group of diseases, each with a wide array of costs and dysutility assumptions. Although clinically this assumption is unrealistic, the robustness of the model (using both one-way and multi-way sensitivity testing
across a wide range of clinical and cost estimates) suggests that categorisation into different types of complications would not have altered the results.

One apparent strength of the model was that the predicted patient and graft survival rates closely matched the observed survival rates from both Canadian and American renal registries. The predicted survival on dialysis was somewhat longer than reported survival rates, however, registry data consider all patients regardless of clinical status. Thus, one would expect the survival statistics quoted by the CORR and USRDS to be too pessimistic for a patient continuing on dialysis but otherwise fit for transplantation.

The estimated mortality rate for those who continued on dialysis was derived from registry data. As with all registries, the strengths and limitations of the USRDS and CORR databases merit emphasis. Registry data are useful because they record long-term follow up of a large number of patients, are relatively free from recall bias, and do not infringe on the personal rights of an individual. However, registry data are often of lower quality than prospectively collected information because of incomplete records, coding and inputting errors, and other inaccuracies introduced at source e.g. poor data extraction. In addition, clinical information is often lacking.

Although no formal evaluation of CORR data was available, multiple mandatory fields and cross checks have been incorporated into the software making data quality acceptable. USRDS data has been reviewed in the past and suggests a 98% completion rate. In this study, we assumed that the group of dialysis patients, selected to match those transplanted in Canada during the period 1987 to 1993, were identical in all other ways to the transplant group. As the patients were matched using registry data, it is plausible that the dialysis patients had more severe comorbidities, differentiating them from those transplanted. As the predicted mortality rate was lower than that seen in dialysis
patients without comorbidity the estimate was felt to be accurate. Nevertheless, error could lead to
over-estimation of dialysis mortality and bias in favour of transplantation. However, one-way
sensitivity analysis suggested the mortality rate for the dialysis patients would need to be
dramatically lower to outweigh the survival advantage of transplantation. Furthermore, the
mortality rate of wait-listed patients aged less than 65 years, previously estimated at 10.7% per
year, was similar.233

Quality-adjusted life expectancy (QALE) was used as a composite measure of both the desirability
and the duration of a health state. Although frequently used to evaluate cost-effectiveness of
different health policies, the validity of QALE is debatable. In particular, error in estimating
utilities are worrisome as quality-adjusted life expectancy is highly dependent on the utility
attached to each health state. Moreover, different utility measures yield different results and
hence cost effectiveness studies may show different marginal cost effectiveness profiles. We
chose to derive the utility values used in our model from only one study because the time-trade off
method was used in an age-specific population both before and after transplantation. This had the
advantage of directly comparing the quality of life on dialysis with that after transplantation in
individuals who had experienced both health states. Moreover, the study measured health related
quality of life using different tools and on several occasions, minimising measurement error and
increasing precision.

The use of utilities to adjust for health preferences (though accepted and widely used) must be
viewed with scepticism. Numerous assumptions were necessary; for example, the use of QALYs
assumed that utility estimates were interval scores. That is, that a unit change at the lower end of
the scale was equal to a unit change at the higher end of the scale. This may not have been a valid
assumption and has not been established in older dialysis patients. In addition, the method used to
identify the population surveyed may influence utility estimates. This has been clearly demonstrated in a study which examined the utility assigned to having a colostomy. Patients who had previously had a colostomy and physicians specialising in colonic disease ranked the quality of life with a colostomy significantly higher than healthy subjects. Furthermore, the phrasing of the questions and the scoring method used influenced the results. Lastly, personal preferences are rarely predictable. In a study of laryngeal cancer, patients were willing to accept a shorter life span in return for retaining normal speech. Similarly, in a recent study of older hospitalised patients, few elderly participants were willing to trade more than one month (per year) for excellent health.

The methods used to estimate costs in the model are open to criticism. The data from the Ontario Case Costing project was drawn from a small number of patients admitted to two local hospitals and showed very wide variability. Outpatient costs, especially those associated with the pre-transplant work-up, were not captured using this method. In addition, the costs did not include professional medical fees, a large component of health care expenditures. Data drawn from the literature is open to similar criticisms. Variability can occur because of different methodologies (costs vs. charges), different treatment regimens, variation in hospital charges and limited information about the complications which were incurred. Occasionally, pre-transplant work-up costs were not discussed. The inclusion of data from all studies, including those which reported both costs and charges, resulted wide clinical ranges for all estimates. However, this conservative approach had the advantage of allowing interpretation of the results from alternative perspectives.

To standardise costs across the different studies, reported cost estimates were converted into 1997 Canadian dollars. Although frequently used in cost-effectiveness studies, the assumption was that the spending power of different currencies was equal. For example, the equivalent number of US
dollars may not buy the same amount of health care in the US as may Canadian dollars in Canada. Likewise, the use of Statistics Canada consumer price index to update costs to 1997 values may not be ideal because of different economic policies, health care priorities and available regional services. Moreover the general rate of inflation may differ in the health care sector relative to the more general economy.

Of note, use of the extreme estimates of costs altered the overall results only minimally. Transplantation went from a cheaper, more effective treatment to an acceptable level of cost-effectiveness\textsuperscript{252}. The results were was surprisingly robust throughout a relatively wide range of estimates. Together, the results suggested that transplantation in older patients may offer significant cost-savings to health care in Canada.

Both costs and life expectancies were discounted at approximately 5% per year. Cost discounting is well established and reflects a balance between any potential interest from invested money and the propensity to consume sooner rather that later\textsuperscript{206,253}. In contrast, discounting of health states remains controversial. Most experts in cost-effectiveness studies advise that QALYs be discounted at the same rate as costs\textsuperscript{202,206,207}. However, there may be situations when different discount rates for costs and health effects may be more appropriate, for example, if a change in the future cost of the intervention or in the availability of resources is anticipated. As no change in health care funding or in the costs of renal replacement therapy were envisioned, equal discount rates were applied.

One aspect of discounting not studied in the model was time preference. Time preference refers to how much value a person places on delayed events. For example, most individuals would accept a smaller amount of money in the present rather than a larger amount in the future. In terms of
health, the time preference theory would predict that patients would accept an increased risk of an event occurring providing it would delay the event. However, it is unclear if older patients with renal failure would agree or if their time preferences would differ. In fact, time preferences have been shown to vary with age, with a tendency for older patients to discount life at a greater rate than younger patients because they feel less secure about surviving to that particular time point.

Another limitation specific to this study is that the criteria for transplantation are not standardised. Guidelines for the screening and workup of potential transplant candidates have been published and address some of the issues relevant to older patients; for example, screening for cognitive impairment, malnutrition and both systemic and cardiac vascular disease. Yet the guidelines do not include specific criteria with regard to the acceptable level of investigation for older patients or those with asymptomatic cardiac disease. In addition, few of the studies included older patients, thereby limiting the generalizability of the data. Standardisation is difficult as each individual brings with them a unique constellation of comorbidity and clinical symptoms. The results of this study assume that clinicians will continue to select individuals using similar implicit criteria to those employed to date. A major change in selection criteria could alter the cost-effectiveness analysis in an unpredictable way.

The survey results offer a potential solution to the problem of organ shortage. They show that successful organ retrieval from younger family members is plausible. However, the survey results are limited by the imperfect respondent rate and the selected population. First, the respondents were highly selected for advanced medical experience and were not representative of the general public. The main reason for choosing this sample was that both the nurses and the physicians had a detailed understanding of the terms dialysis and kidney transplantation. Another limitation is that the comparison groups were not perfectly matched. Apart from possible differences in the ratio of
men to women, the two cohorts may have had different perspectives of dialysis therapy. In particular, nurses working in dialysis units would be more familiar with modern approaches to dialysis therapy (including the use of bicarbonate dialysate, newer high flux membranes and the use of erythropoietin) while retired physicians would recall cases without modern advances. This could affect the results and explain the relatively more favourable view of dialysis held by the nurses. Lastly, the response rates from the physicians were sufficiently low to introduce some concerns about participation bias. If however, one considers the worst case scenario and assumes that all non-responders would refuse a kidney from a younger relative, 24% of the cohort would still be willing to accept a kidney. The absolute number of patients who may consider accepting an organ from a younger relative remains impressive given that over one thousand elderly patients start dialysis therapy each year in Canada.

One final limitation of our study is that we have neither incorporated the societal costs of a limited cadaveric transplant pool nor the indirect costs of transplanting older patients. By concluding that older patients may benefit from transplantation we further increase the potential for a severe organ shortage. In practice, this would further lengthen the waiting time to transplantation, perhaps reducing the overall life expectancy for other patients with renal failure, despite offering them transplantation at some stage. In addition, the cost to society of increased waiting times for younger patients who may otherwise have returned to the workforce may be unacceptable. By including a small survey to determine societal values for living related donation we offer a potential solution for the problem of organ shortage. However, until societal values change and living related donation becomes much more acceptable, implementation of a more liberal transplantation policy may be limited.
5.3 *Impact on health care spending in Canada*

Assuming that all non diabetic patients aged 65 years or more who are free of comorbid illnesses are suitable for, and willing to undergo transplantation surgery the potential healthcare savings can be estimated. Over the 6 year period spanning 1987-1993, 552 suitable patients were identified. Assuming a cost saving of $88,895 per patient with transplantation (as shown with the base case analysis) health care savings may amount to $49.1 million per year in Canada alone.

5.4 *Future Directions*

Further research in the area of geriatric nephrology is greatly needed. In the field of transplantation little is known about the ideal regimen for immunosuppression and the true clinical significance of comorbid disease. Furthermore, the ideal method for screening and selection of recipients is unclear. At present, data examining the effect of different risk profiles on longevity is being collected.
6. Conclusion

This study examined the risks and benefits of kidney transplantation in elderly patients with end-stage renal disease and found that transplantation offered both better life expectancy and lower medical costs. The model was robust despite the use of wide sensitivity analyses and suggested a potential health care saving of over $49 million per year in Canada alone. However, the success of this strategy would be highly dependent on societal attitudes toward living-related donation of kidney organs.
7. References


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8. Appendices
Mortality was estimated from three areas of the curve and an average used in the model. All estimates were taken after a minimum survival time of 936 days (75% quartile for the transplant wait interval).
Appendix 2

Letters and Questionnaires used in Acceptability Survey
Dear Colleague,

We are inviting you to participate in research about kidney transplantation for patients with end-stage renal disease. We believe that this is an issue important to both the practice of medicine and society. We are asking you to complete the enclosed survey, which should take less than five minutes, and return it in the envelope provided.

The survey contains questions about yourself and your opinions about end-stage renal disease. There are no right or wrong answers. We are interested in your perspective. Please answer all questions using your best judgment.

Responses are confidential. If you have any questions about this study you may contact Dr. Vanita Jassal (pager 416-376-5273). If you wish, summary data can be sent to you. In appreciation of your time you can be entered into a lucky draw for a $100 cash prize. To participate in the lucky draw fill in the enclosed card and return it with the survey.

Yours truly,

\[Signature\]

Donald A. Redelmeier, MD
Associate Professor of Medicine

\[Signature\]

S. Vanita Jassal, MD
Nephrology Research Fellow
Kidney Transplantation Survey

1) How old are you? (circle one)
   20-34 years   35-49 years   50-64 years   >65 years

2) How many years of experience do you have looking after patients?
   < 1 year   1-5 years   5-10 years   >10 years

3) How many years of experience do you have looking after patients with renal failure on dialysis?
   < 1 year   1-5 years   5-10 years   >10 years

4) How many years of experience do you have looking after patients with renal transplants?
   < 1 year   1-5 years   5-10 years   >10 years

5) In your judgment, is transplantation superior or inferior to dialysis?
   definitely superior   tend to superior   tend to inferior   definitely inferior

6) In your judgment, are there substantial risks for those who donate a kidney?
   definitely yes   tend to yes   tend to no   definitely no

7) Suppose that a 68 year old relative of yours needed a kidney as a result of renal failure. Suppose that you were a suitable match. Would you donate?
   definitely yes   tend to yes   tend to no   definitely no

8) If a 68 year old relative was willing to donate a kidney to you (assuming you had renal failure and they were a suitable match) would you accept?
   definitely yes   tend to yes   tend to no   definitely no

Thank you
Dear Colleague,

We are inviting you to participate in a study about kidney transplantation for patients with end-stage renal disease. We believe that this is an important issue to both the practice of medicine and society. We are asking you to complete the enclosed survey, which should take less than five minutes, and return it in the envelope provided.

The survey contains questions about yourself and your opinions about end-stage renal disease. There are no right or wrong answers. We are interested in your perspective. Please answer all questions using your best judgment. You have been selected at random from the Canadian Medical Directory.

Responses are confidential. If you do have any questions about this study you may contact Dr. Vanita Jassal (pager 416-376-5273). If you wish, summary data can be sent to you. In appreciation of your time you can be entered into a draw for a bouquet of roses. To participate in the draw fill in the enclosed card and return it with the survey.

Yours truly,

Donald A. Redelmeier, MD
Associate Professor of Medicine

S. Vanita Jassal, MD
Nephrology Research Fellow
Kidney Transplantation Survey

1) How old are you? (circle one)
   20-34 years old        35-49 years old        50-64 years old   >65 years old

2) How many years of experience do you have looking after patients?
   < 1 year              1-5 years               5-10 years         >10 years

3) How many years of experience do you have looking after patients with renal failure on dialysis?
   < 1 year              1-5 years               5-10 years         >10 years

4) How many years of experience do you have looking after patients with renal transplants?
   < 1 year              1-5 years               5-10 years         >10 years

5) In your judgment, is transplantation superior or inferior to dialysis?
   definitely superior   tend to superior       tend to inferior   definitely inferior

6) In your judgment, are there substantial risks for those who donate a kidney?
   definitely yes         tend to yes            tend to no         definitely no

7) If a 42 year old relative needed a kidney (assuming they had renal failure and you were a suitable match) would you donate?
   definitely yes         tend to yes            tend to no         definitely no

8) Suppose you needed a kidney as a result of renal failure. Suppose a 42 year old relative was willing to donate and you were a suitable match. Would you accept?
   definitely yes         tend to yes            tend to no         definitely no

Thank you.
### Appendix 3: One-way cost effectiveness analysis for various probabilities of acute rejection

<table>
<thead>
<tr>
<th>Probability of rejection</th>
<th>Cost of Transplantation Strategy ($ CDN)</th>
<th>Cost of Dialysis Strategy ($ CDN)</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>241,529</td>
<td>338,335</td>
<td>4.33</td>
<td>2.88</td>
<td>Tx* dominant</td>
</tr>
<tr>
<td>0.2</td>
<td>245,542</td>
<td>338,335</td>
<td>4.28</td>
<td>2.88</td>
<td>Tx dominant</td>
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<tr>
<td>0.4</td>
<td>249,440</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>0.6</td>
<td>253,224</td>
<td>338,335</td>
<td>4.19</td>
<td>2.88</td>
<td>Tx dominant</td>
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<tr>
<td>0.8</td>
<td>256,894</td>
<td>338,335</td>
<td>4.15</td>
<td>2.88</td>
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</tr>
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<td>1.0</td>
<td>260,452</td>
<td>338,335</td>
<td>4.11</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
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</table>

* Tx = transplant strategy
Appendix 4: One-way cost effectiveness analysis for various estimates for the annual cost of dialysis treatment

<table>
<thead>
<tr>
<th>Estimates annual cost of dialysis</th>
<th>Cost of Transplantation Strategy ($ CDN)</th>
<th>Cost of Dialysis Strategy ($ CDN)</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>30,000</td>
<td>192,906</td>
<td>176,523</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx* 12,117</td>
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<tr>
<td>45,000</td>
<td>223,742</td>
<td>264,784</td>
<td>4.24</td>
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</tr>
<tr>
<td>60,000</td>
<td>254,579</td>
<td>353,045</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>75,000</td>
<td>285,416</td>
<td>441,307</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>90,000</td>
<td>316,253</td>
<td>529,568</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>100,000</td>
<td>336,810</td>
<td>588,409</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
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</tbody>
</table>

* Tx = transplant strategy more effective but at the increased annual cost shown
Appendix 5: One-way cost effectiveness analysis for various estimates for the annual cost of transplant follow-up

<table>
<thead>
<tr>
<th>Estimated annual cost of follow-up ($ CDN)</th>
<th>Cost of Transplantation Strategy ($ CDN)</th>
<th>Cost of Dialysis Strategy ($ CDN)</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,000</td>
<td>207,877</td>
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<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
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<td>228,659</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
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<tr>
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<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>20,000</td>
<td>270,222</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>25,000</td>
<td>291,003</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>30,000</td>
<td>311,785</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
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</table>
Appendix 6: One-way cost effectiveness analysis for various estimates for the annual cost of transplant workup, surgery and recovery

<table>
<thead>
<tr>
<th>Estimated annual cost of surgery</th>
<th>Cost of Transplantation Strategy ($ CDN)</th>
<th>Cost of Dialysis Strategy ($ CDN)</th>
<th>QALE with Transplantation Strategy (years)</th>
<th>QALE with Dialysis Strategy (years)</th>
<th>Marginal Cost-Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>40,000</td>
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<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
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<td>265,316</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
</tr>
<tr>
<td>80,000</td>
<td>284,916</td>
<td>338,335</td>
<td>4.24</td>
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<tr>
<td>100,000</td>
<td>304,516</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
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<tr>
<td>120,000</td>
<td>324,116</td>
<td>338,335</td>
<td>4.24</td>
<td>2.88</td>
<td>Tx dominant</td>
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</tbody>
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