Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

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LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

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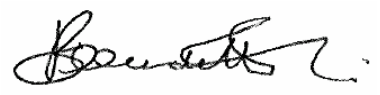
DECLARATION

I, Bernadette Li, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed



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ABSTRACT

In the United Kingdom, the number of patients waiting to receive a kidney transplant far outstrips the supply of donor organs, thereby making some form of rationing inevitable. The criteria for rationing can be made explicit in the design of a kidney allocation scheme, which typically aims to achieve a balance between efficiency, defined as maximising health benefits from a limited resource, and equity in the distribution of that resource. In the past, kidney allocation schemes have focussed on waiting time as one of the criteria to promote equity in access to transplantation. Over time, increasing emphasis has been placed on closer tissue matching between recipients and donors after this was shown to result in better post-transplant outcomes. More recently, there has been recognition of variability in the quality of donor kidneys such that not all donor kidneys will result in equally good survival outcomes and not all patients will derive the same benefit from a given donor kidney. This thesis describes the development of a patient-level simulation model that compares five different approaches to allocating kidneys from across the equity-efficiency spectrum. Emphasis is placed on characterising heterogeneity in the data inputs that are used to inform the simulation. This is achieved by using various regression modelling strategies to analyse patient-level data to facilitate prediction of costs, health-state utilities and survival conditional on covariates such as age, comorbidities and treatment modality. For each allocation scheme, the simulation model reports total costs, life years and quality-adjusted life years across the patient population. The simulation model can be used to quantify not only the magnitude of health gains associated with moving from one kidney allocation approach to another, but also the impact in terms of equity in access to transplantation and the distribution of outcomes across different patient groups. The outputs of the simulation can be used to inform discussions about equity-efficiency trade-offs in the design of a kidney allocation policy.

ACKNOWLEDGEMENTS

Thank you first and foremost to my supervisor, John Cairns, for the opportunity to undertake this research and for providing sage advice and patience in equal measure throughout the entire project. I would also like to thank my advisers John Forsythe and Matt Stevenson for their clinical and modelling expertise respectively. I am grateful to the entire steering committee of the NIHR-funded Access to Transplantation and Transplant Outcome Measures (ATTOM) study for their collaboration and support, and especially to Rommel Ravanan for always taking the time to answer my many questions.

This thesis would not have been possible without access to several important sources of data. I would like to acknowledge the team at NHS Blood & Transplant (Matthew Robb, Rachel Johnson and Lisa Bradbury) and the UK Renal Registry for facilitating data provision and James Fotheringham for restructuring and coding the UKRR/HES linked dataset for the analysis of hospital costs. I would like to thank SIMUL8 Corporation for providing a licence to use the software as part of the PhD Research Scheme and Tom Stephenson for technical advice on coding. Lastly, thank you to Sarah Willis for acting as a sounding board and providing constructive feedback and support from start to finish, not to mention many, many cups of tea to keep me going over the past few years.

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ABBREVIATIONS

AIC	Akaike information criterion
ATTOM	Access to Transplantation and Transplant Outcome Measures
cRF	calculated reaction frequency
EPTS	estimated post-transplant survival
ERF	established renal failure
ESRD	end-stage renal disease
GFR	glomerular filtration rate
GLM	generalised linear model
HES	Hospital Episode Statistics
HLA	human leukocyte antigen
ICER	incremental cost-effectiveness ratio
KDPI	kidney donor profile index
LYFT	life years from transplant
MAR	missing at random
MCDA	multi-criteria decision analysis
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NKAS	national kidney allocation scheme
OLS	ordinary least squares
OPTN	Organ Procurement and Transplantation Network
PbR	Payment by Results
QALY	quality-adjusted life year
QOL	quality of life
RMSE	root mean square error
RRT	renal replacement therapy

SPK	simultaneous pancreas and kidney
SRTR	Scientific Registry of Transplant Recipients
UKKDRI	UK kidney donor risk index
UKRR	UK Renal Registry
USRDS	US Renal Data System

1. INTRODUCTION

1.1. Background

Established renal failure (ERF) is a condition of abnormal kidney structure or function defined by a glomerular filtration rate (GFR) persistently below 15 mL/min per 1.73m^2.[1] Treatment of patients with ERF may involve renal replacement therapy (RRT) with dialysis or kidney transplantation. Mortality rates for patients with ERF are high, in part due to a lack of access to RRT.[2] The number of patients awaiting a transplant far exceeds the number of available donor kidneys while the costs of dialysis consume a disproportionate amount of the healthcare budget.[1] Because of this, interventions for the treatment of ERF are a frequent subject of interest for economic evaluation. There have been numerous comparisons of the costs and health outcomes associated with transplantation and dialysis (Appendix 1) and most of these have demonstrated that kidney transplantation results in improved survival and better quality of life at lower cost.[3-13] However, given the shortage of donor kidneys, increasing the rate of kidney transplantation is not a straightforward endeavour. In the United Kingdom, the number of deceased donor transplants carried out between 1 April 2014 and 31 March 2015 was 2069, while the number of patients registered on the kidney transplant list was 5686.[14]

1.2. Kidney allocation in the United Kingdom

The scarce supply of donor kidneys has given rise to the need to ration for reasons other than the constraints of a finite healthcare budget. In many countries including the UK, the criteria for rationing of kidneys is made explicit through the design of a national allocation scheme.

In 1989, transplant centres in the UK started to exchange kidneys retrieved from deceased adult donors to facilitate beneficial tissue matching on the basis of human leukocyte antigen (HLA) compatibility. The interest in tissue matching was motivated by evidence at the time that graft survival was superior in transplants with no mismatches between donors and

recipients on the three HLA groups (A, B and DR) or only one mismatch at the HLA-A or HLA-B loci and no mismatch at the HLA-DR locus.[15] While the introduction of HLA matching could potentially improve survival gains through a shared scheme for kidney allocation, one possible consequence of the focus on immunological compatibility was that patients with rare HLA types, especially those occurring in minority ethnic groups, could end up waiting longer for a transplant.[16]

A revised kidney allocation scheme was introduced at the national level in 1998. The emphasis on HLA matching was retained, but the scheme was expanded to include a number of other factors.[17] It included the introduction of three tiers based on the degree of HLA matching (zero mismatched, favourably matched, non-favourably matched). Within the first and second tiers, the scheme gave priority to paediatric patients and patients with rare HLA types. Other factors that formed part of the points-based scoring system were donor-recipient age difference, waiting time and a factor to control for the balance of exchange of kidneys between transplant centres. Approximately 50% of kidneys from deceased donors (following brain-stem death) were allocated through the 1998 national scheme.[17] However, improved data collection in the period following implementation of the 1998 scheme provided evidence of the unintended consequences of HLA matching on equity in access to transplantation. For example, a review of patients registered on the waiting list between January 1998 and December 2000 showed variations in median waiting times of patients from different ethnic groups, with Asian and black patients waiting approximately twice as long (4 years) as white patients (2 years).[18]

In 2006, a new national scheme was introduced, through which all kidneys from deceased donors following brain-stem death are now allocated. The primary objective of the 2006 scheme was to improve equity of access to transplant among all patients regardless of geographical location, ethnicity and rareness of HLA type and, so far as biologically possible, blood group and degree of sensitisation to HLA specificities.[19] The number of tiers under the 2006 scheme was expanded to five. Tiers A and B are designated for zero mismatched paediatric patients (with highly sensitised patients and HLA-DR homozygous

patients in Tier A). Within Tiers A and B, patients are prioritised on the basis of waiting time. Tier C includes zero mismatched adult patients (highly sensitised and HLA-DR homozygous), while remaining zero mismatched adult patients and favourably matched paediatric patients are in Tier D. Tier E contains all other patients. Within Tiers C through E, patients are prioritised using a points system based on seven factors[19]:

1. Waiting time
2. HLA match and age combined
3. Donor-recipient age difference
4. Location of patient relative to donor
5. HLA-DR homozygosity
6. HLA-B homozygosity
7. Blood group match (to achieve equity between group O and B patients)

Since 2014, kidneys from deceased donors following circulatory death which meet certain criteria are allocated regionally according to the same principles as the 2006 scheme for kidneys from deceased donors following brain-stem death.[20] At the time of preparation of this thesis, the 2006 national kidney allocation scheme was undergoing a review to assess the scope for making changes with respect to its underpinning philosophy, design and the criteria for HLA matching.[21]

1.3. Newer concepts in kidney allocation

Historically, the deceased donor kidney allocation system in the United States was primarily based on the principle of “first-come, first-served,” in which candidates were prioritised based on waiting time.[22] In 2003, the Organ Procurement and Transplantation Network (OPTN) charged the Kidney Transplantation Committee with reviewing the allocation system to better understand its limitations and identify possible approaches for improvement.[23] This precipitated a 10-year period of intensive research and public consultation to debate proposals for new concepts in kidney allocation. Of the proposed new concepts, there were two that garnered the most attention and scrutiny: life years from

transplant (LYFT) and longevity matching. LYFT is the concept of ranking transplant candidates by the estimated incremental years of life that are expected to be achieved with a transplant from a specific donor. The underlying calculation is computed as the difference in median lifespan with the transplant compared with remaining on dialysis.[24] Thus the objective of the LYFT concept is to achieve the best use of donated kidneys by allocating each one to the patient who is expected to gain the most. In contrast, the concept of longevity matching is meant to address the fact that donor kidneys are of variable quality, with organs from donors over the age of 60 at greater risk of graft failure.[25] Allocating high quality kidneys with long potential longevity to candidates with shorter potential longevity and vice versa can result in unrealised graft years and high re-transplant rates. Under the concept of longevity matching, the Kidney Donor Profile Index (KDPI) uses information on ten donor factors to estimate the quality of the kidney relative to other donors. Similarly, the Estimated Post-Transplant Survival (EPTS) score is calculated to risk-stratify transplant candidates (Table 1.1). The 20% of candidates with the highest EPTS scores are prioritised to receive the best 20% of kidneys according to the KDPI.[26,27]

Table 1.1 Variables included in the calculation of the KDPI and EPTS scores in the revised US kidney allocation system

Kidney Donor Profile Index[28]	**Estimated post-transplant survival[29]**
1. Age	1. Age
2. Height	2. Length of time on dialysis
3. Weight	3. Prior transplant
4. Ethnicity	4. Diabetes status
5. History of hypertension	
6. History of diabetes	
7. Cause of death	
8. Serum creatinine	
9. Hepatitis C virus status	
10. Circulatory death	

During the consultation process for the proposed new allocation concepts, the Committee received feedback and concerns that the LYFT approach was made up of too many

variables and that an allocation system which attempted to match each kidney and patient was too complicated and unpredictable to be feasible.[30] Concerns were also raised that a LYFT approach to kidney allocation would result in fewer older patients and those with diabetes receiving transplants.[31]

In June 2013, the OPTN Board of Directors approved a new kidney allocation policy for the US that incorporates the concept of longevity matching based on the KDPI and EPTS scores. This revised system became effective in December 2014.[31]

1.4. Simulation as a tool to study kidney allocation schemes

Given the complexity and far-reaching consequences of organ allocation schemes, it is useful to be able to test the impact of potential changes to a system prior to implementing a new policy. Computer-based simulation modelling offers a method of doing so. Using historical data, it is possible to imitate the process of kidney allocation and test the impact of making various changes to data inputs and assumptions on model outputs.

To be feasible, simulation modelling requires making simplifying assumptions in comparison to the real system that it is attempting to imitate.[19,32] Oversimplification of a model can give a misleading or inaccurate depiction of reality, but added complexity can lead to the requirement for more data. In the case of kidney allocation, where a randomised experimental study design is not possible to implement, simulation is potentially the only way to assess in advance the impact of making changes to the system.

The application of simulation modelling to study kidney allocation schemes is well established. However, the majority of the published literature is presented as an exploration or investigation of the impact of a single clinical factor on the allocation process or a description of a new allocation policy in which simulation methods or results are not the main feature, but are reported as supporting evidence. A summary of this body of literature, including the methods used to identify these papers, can be found in Appendix 2. Only four studies were identified in which the development of a model to simulate different approaches to deceased donor kidney allocation was the primary focus. These simulation

exercises have explored a variety of conceptual approaches to kidney allocation, with a common stated objective of exploring trade-offs between equity and efficiency.[33-36] Table 1.2 summarises the allocation approaches that were considered and the key results presented in each of these four simulation examples.

The most notable difference among these simulation studies is the extent to which they capture the consequences of the allocation process by reporting characteristics of patients who received a transplant by attempting to link these characteristics to post-transplant outcomes such as survival. The earliest of the studies by Yuan et al. was essentially a representation of the flow of patients through five different allocation algorithms. Results were presented as a snapshot of the number of patients arriving, the number of transplants performed and the number of patients still waiting at 1, 3, 6, and 10 years. Yuan et al. did not report individual patient characteristics such as age, but did report the distribution of HLA mismatches and the distribution of waiting time at each time point for each allocation algorithm.[33] The study by Jacquelinet et al. compared the results of a simulated allocation process to observed data in terms of transplantation access rates, but also described the transplant recipient population in terms of median waiting time, distribution of HLA mismatches, the distribution of donor and recipient ages and a measure of matched donor potential. However, no attempt was made to link these characteristics to post-transplant outcomes.[36]

The study by Higgins et al. compared three kidney allocation algorithms, including the national UK transplant algorithm that was introduced in 1998, an equality (lottery) algorithm and an efficiency algorithm that was designed to allocate kidneys based on greatest expected transplant survival time. Transplant survival was estimated as a prognostic risk score that reflected 5-year graft survival based on a Cox proportional hazards model and included recipient age, diabetes status and HLA mismatching as covariates. This results of this simulation study provided a more detailed comparison of patient characteristics for each of the three allocation schemes. For example, in addition to HLA matching and

Table 1.2 Summary of kidney allocation simulation models in the published literature

Author, year and country	Allocation concepts explored	Main results or outcomes
Yuan et al. [33] 1994, Canada	Comparison of 5 approaches: 1. HLA matching 2. Equal weight to HLA matching and waiting time 3. Equal weight to HLA matching and waiting time + priority if HLA match score above a certain threshold 4. First come, first transplanted 5. Minimum HLA match requirement + first come, first transplanted	• Number of patients arriving • Number of transplantations performed • Number of patients still waiting for transplant • Number of discarded kidneys • Mean HLA-match scores • Number of days from registration to transplantation • Number of days from registration for patients still waiting
Zenios et al. [34] 1999, United States	Comparison of 4 approaches: 1. First-come, first-transplanted 2. United Network of Organ Sharing algorithm in 1995 (points based on waiting time, rank in the waiting list, tissue mismatch, panel reactivity, priority to paediatric patients) 3. Efficiency-based algorithm to maximise quality-adjusted life expectancy 4. Distributive efficiency to promote equitable allocation among African-American candidates	• Patient survival rates (5-year) • Quality-adjusted life expectancy (at 10 years) • Median waiting time • Likelihood of transplantation
Higgins et al. [35] 2005, United Kingdom	Comparison of 3 approaches: 1. Equality method (lottery) 2. Efficiency algorithm (prioritise patients based on risk score reflecting 5-year graft survival) 3. 1998 UK national kidney allocation algorithm	• Characteristics of transplanted patients (e.g. HLA matching, waiting time, proportion paediatric, highly sensitised and diabetic) • Mean prognostic score (based on recipient age, diabetes and HLA match)
Jacquelinet et al. [36] 2006, France	Allocation according to a score based on: 1. Waiting time 2. Recipient matchability (prioritise patients with lowest potential to find a match) 3. HLA matching 4. Age match	• Characteristics of transplanted patients (HLA mismatch level, matched donor potential, waiting time, donor-recipient age distribution) • Transplantation access rates (number of transplanted patients among total number of candidates)

median waiting time, this study reported the proportion of paediatric, diabetic and highly sensitised transplant recipients. Furthermore, for each allocation scheme, the mean prognostic risk score for the population of transplant recipients was reported. The results demonstrated that based on prognostic risk scores, the efficiency algorithm would result in significantly better outcomes than the national UK transplant algorithm, and the national UK transplant algorithm would result in significantly better outcomes than the equity approach. Notably however, diabetic patients did not receive transplants under the efficiency allocation algorithm.[35]

Of the four simulation studies identified, Zenios et al. provided the most extensive exploration of post-transplant outcomes using United States Renal Data System (USRDS) reports to estimate 5-year survival and mean quality-adjusted life years (QALYs) in addition to median waiting time and likelihood of transplantation. However, in the base case, QALY estimates were restricted to the 10-year time horizon of the simulation rather than reflecting lifetime estimates. A 100-year simulation was performed as a sensitivity analysis. Both the 10-year and 100-year analyses showed that the efficiency-based allocation algorithm yielded the highest average QALYs, followed by the distributive efficiency approach, with the national algorithm (at the time) and the first-come, first-transplanted approaches producing the lowest average QALYs. Another notable contribution of the paper by Zenios et al. is that it demonstrated the ability to present simulation results such as median waiting time and survival by patient subgroups based on age, gender and ethnicity.[34]

1.5. Research problem and objective

The objective of this thesis is to use simulation modelling to compare the consequences of alternative approaches to kidney allocation from across the equity-efficiency spectrum in the UK context. It will differ from previously published simulation studies in the following four ways:

1. By exploring newer kidney allocation concepts of interest that have emerged since the simulation exercise reported by Higgins et al.

2. By estimating outcomes in terms of both life years and QALYs from a lifetime time horizon
3. By estimating costs associated with different approaches to kidney allocation
4. By quantifying the impact of the different allocation concepts in terms of equity in access to transplantation and equity in outcomes.

The simulation model in this thesis will compare five different allocation concepts. The current UK national kidney allocation scheme introduced in 2006 has been described in the literature as a compromise between efficiency (maximisation of outcomes) and equity (fair access to transplant).[19] Taking the current allocation scheme as a midpoint along the equity-efficiency spectrum, the simulation model will explore two alternative allocation concepts towards the equity end of the spectrum, namely random allocation and allocation based on waiting time. The simulation model will also explore the consequences of newer allocation concepts towards the efficiency end of the spectrum, namely longevity matching and QALY-maximisation. The five kidney allocation concepts of interest are briefly summarised in Table 1.3. By exploring different allocation concepts from opposite ends of the equity-efficiency spectrum, it will be possible to quantify the minimum and maximum health benefit that can be derived from a scarce supply of kidneys as well as the costs and health gains

Table 1.3 The five kidney allocation concepts that will be explored in the simulation exercise

Scheme	Allocation concept
1	Random allocation: subject to blood group and tissue compatibility, the kidney is randomly allocated to a patient on the waiting list
2	Waiting time: subject to blood group and tissue compatibility, the kidney is allocated to the patient with the longest waiting time
3	Current (2006) national kidney allocation scheme
4	Longevity matching: top 20% of patients with the longest expected post-transplant survival are prioritised to receive top 20% kidneys based on risk score
5	Utility-maximising: for each patient, calculate the difference between expected QALYs if the patient were to receive the transplant and expected QALYs if the patient were to remain on dialysis; allocate the kidney to the recipient with the greatest expected QALY gain

associated with moving from one allocation approach to another, while also considering the potential trade-off in terms of equity. It is anticipated that the results of this simulation exercise can be used to inform discussions about equity-efficiency trade-offs in the design of a national kidney allocation policy.

The intended objective and outputs of this simulation exercise have several important implications for the methods and overall modelling approach. Firstly, the allocation process takes place at the level of individual donor kidneys and patients, and therefore this simulation exercise will ideally be based on recent UK-specific sources of patient and donor characteristics to inform the matching process. Secondly, the more data that are available on patient characteristics, the greater the potential to capture variability in costs, survival and health-state utilities across patients. This will necessitate the use of various regression modelling techniques to generate estimates of costs, survival and health-state utilities conditional on patient characteristics of interest. Thirdly, in order to estimate post-transplant outcomes in terms of life years, QALYs and costs from a lifetime time horizon, some form of extrapolation of survival data will be necessary and will require consideration of different survival analysis methods to those that have been described in previous simulation exercises.

This emphasis of this thesis is on the application of data and methods from across a number of different disciplines to demonstrate the feasibility of modelling alternative approaches to kidney allocation and to estimate the consequences of these different approaches in terms of costs, health benefits and equity. It will draw on knowledge, concepts and methods from clinical transplantation, health economics, operations research and medical statistics. Given the interdisciplinary nature of this thesis, Box 1.1 provides clarification of some key terms with an explanation of how they will be used in context of this thesis.

Box 1.1 Explanation of key terms used in this thesis

Efficiency: this term has many different meanings in the published literature; in the context of this thesis, efficiency is used to refer to maximisation of health benefits (QALYs) from a scarce resource

Equity: this term has many different meanings in published literature; in the context of this thesis, equity is used to refer to the distributive consequences of a resource allocation decision and will specifically be considered in terms of equity in access to transplantation and equity in outcomes (QALYs) resulting from transplantation

QALY: the quality-adjusted life year is an outcome measure that combines mortality and morbidity into a single index and is a widely used measure of health improvement in the UK for guiding resource allocation decisions[37]

Simulation: a computer-based modelling exercise to imitate the process of matching donor kidneys with recipients under different allocation algorithms and to estimate the consequences of that process

1.6. Data sources

The inclusion of both costs and QALYs as outputs in this simulation has important repercussions for the data inputs required to inform the model. An individual patient simulation approach is necessary in this exercise because the process of kidney allocation takes place at the patient level. A number of different sources of patient-level data will be used to develop separate models to predict costs, survival and health-state utility values, as well as to simulate the transplant patient and donor kidney characteristics (Table 1.4). Each data source is described in more detail in subsequent chapters. A brief introduction to the Access to Transplantation and Transplant Outcome Measures (ATTOM) study is provided here.

Table 1.4 Summary of key data sources for the simulation exercise

Parameter	Source
Costs	
RRT costs (dialysis and transplantation)	Payment by Results tariff
Hospital costs for RRT patients	UK Renal Registry / Hospital Episode Statistics linked dataset
Survival	
Post-transplant survival	UK Transplant Registry (historical cohort)
Graft failure	UK Transplant Registry (historical cohort)
Waiting-list survival	UK Transplant Registry (historical cohort) with linkage to UK Renal Registry (for dialysis dates)
Health-state utility values	
EQ-5D-5L index scores	ATTOM study
Simulation inputs	
Waiting-list patient characteristics	ATTOM study
Donor characteristics	NHSBT (historical cohort)

1.7. The ATTOM study

The ATTOM study is a prospective observational study involving collection of demographic, treatment and health outcomes data from all 72 renal units (including 23 transplant units) in the UK.[38] The study recruited incident transplant patients aged 18-75 years between 1 November 2011 and 30 September 2013. Prevalent patients on the transplant waiting list were selected as matched controls on a 1:1 basis for every incident transplant patient according to the following criteria: transplant centre, age (within five years), time on the waiting list, type of transplant (kidney only or combined kidney and pancreas), diabetes status (as a primary renal diagnosis) and dialysis status at the time of listing.[38] The ATTOM study is a key data source for the simulation exercise, providing information on patient characteristics, as well as health-state utility values derived from the administration of the EQ-5D-5L questionnaire. The ATTOM study did not include collection of patient-level cost data. In addition, the maximum duration of follow-up for patients in the study is

approximately 4 years, therefore alternative sources of historical data from the UK Transplant Registry were needed to estimate long-term survival for the simulation exercise.

The work contained in this thesis forms the basis of one of the five main research aims of the ATTOM study.[38] The other four aims of the study were to:

1. Identify patient-specific and centre-specific factors that influence access to the transplant waiting list and to transplantation
2. Identify patient-specific and centre-specific factors that influence survival on the waiting list and after transplantation
3. Evaluate quality of life (QOL) for patients on dialysis and after transplantation and including detailed analysis of patient-reported outcomes measures in several patient subgroups
4. Utilise survival, health status, QOL, treatment satisfaction and costs to determine an optimal organ allocation policy.

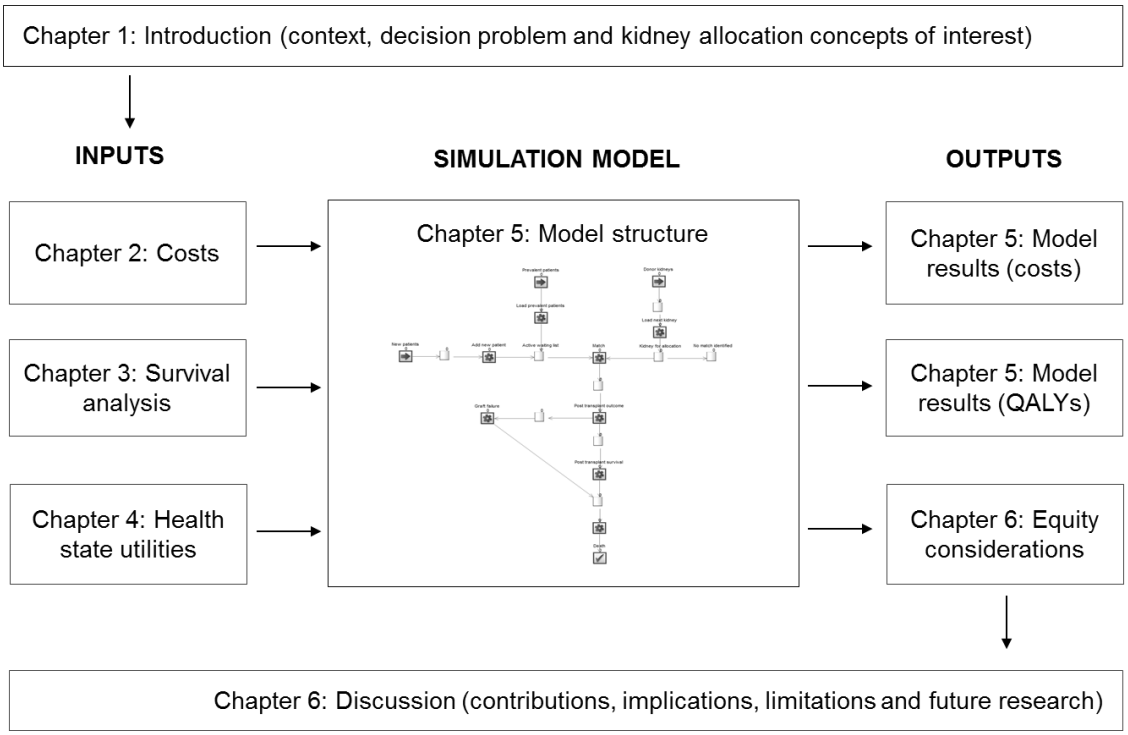
The ATTOM study is led by a multidisciplinary team of researchers who have met approximately every 6 months throughout the study to discuss progress and share results for each of the five workstreams. Work on this PhD commenced in July 2012, after patient recruitment for the ATTOM study had already begun. I was not directly involved in primary data collection but led on all other aspects of the research described in this thesis. This included:

1. Outlining the decision problem, including reviewing relevant literature and identifying which allocation concepts to include in the simulation exercise
2. Identifying data sources (costs, historical survival data) beyond the ATTOM study that were required to inform the simulation model
3. Conducting analyses of patient-level cost, survival and health-state utility data
4. Conceptualising, designing and coding the simulation model
5. Reporting results and drafting the research papers contained within this thesis.

1.8. Structure of the thesis

This thesis has been written as a series of individual research papers that can each be read as stand-alone pieces of work but are integrated in this thesis into a single document. Figure 1.1 provides an overview of what each chapter contributes to the development of the simulation model and to the overall thesis.

Figure 1.1 Contribution of each chapter to the thesis



The structure of the remainder of this thesis is as follows: Chapters 2, 3 and 4 describe the separate regression analyses of patient-level data to predict cost, survival and health-state utility values respectively. Estimates from these regression models are then used as data inputs in the simulation model. Chapter 5 describes the structure of the kidney allocation simulation model and presents key results in terms of total costs and QALYs associated with each allocation scheme. Chapter 6 highlights equity considerations, discusses the contributions, implications and limitations of this work and identifies potential areas for future research.

1.9. Funding and ethics approval

This PhD was funded by a National Institute for Health Research (NIHR) programme grant for the ATTOM study (RP-PG-0109-10116) and included tuition fees and an annual stipend over a period of 4 years.

The protocol for the ATTOM study was independently reviewed by the NIHR and approved by the East of England Research Ethics Committee (Ref 11/EE/0120). The simulation modelling work and patient-level data analyses for this thesis received additional approval by the Observational Research Ethics Committee of the London School of Hygiene and Tropical Medicine (Ref 6383).

2. COST ESTIMATES

2.1. Introduction

The simulation model comparing alternative allocation schemes will estimate lifetime costs for each patient from the perspective of the NHS as one of its main outcomes. This chapter of the thesis describes the data source, methods and final regression models that will be used to estimate annual costs for each patient during their time spent on the waiting list and following transplantation in the simulation model, dependent on individual characteristics such as age, gender and comorbidities.

2.2. Research Paper 1

The increasing cost of managing patients with ERF has received considerable attention and is an issue that many health systems around the world are facing.[1,39] A number of countries, including the UK, have developed systems of bundled payments or fixed tariffs for the reimbursement of dialysis services.[40] Given the high rate of comorbidities among patients with ERF, they are likely to incur additional costs beyond the provision of dialysis or, in the case of transplant recipients, beyond the transplant surgery itself.[41]

Robust patient-level data sources for analysing healthcare costs outside of the United States are somewhat scarce. Prospective collection of cost data is often prohibitively expensive or limited to short time periods and small sample sizes. However, one-time linkage of the UK Renal Registry and the Hospital Episode Statistics (HES) datasets in England presented a rare opportunity to analyse variations in hospital costs for a large cohort of patients starting RRT over a period of several years. The richness of the linked dataset has facilitated the development of regression models to predict variations in costs by treatment modality, number of years on treatment, age and comorbidities. Research Paper 1, entitled *Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation*, describes the characteristics of this dataset, highlights

some of the considerations and challenges encountered in the analysis of cost data and presents the final regression models.[42]

Appendix 3 contains an additional research paper, entitled *Understanding cost of care for patients on renal replacement therapy: looking beyond fixed tariffs,* which combines estimates of hospital costs from Research Paper 1 with fixed costs of RRT and illustrates how total costs vary for three hypothetical patient examples.[43]

RESEARCH PAPER COVER SHEET – Research Paper 1

SECTION A – Student Details

Student	Bernadette Li
Principal Supervisor	John Cairns
Thesis Title	Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	The European Journal of Health Economics		
When was the work published?	July 2016 (July 2015 online)		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

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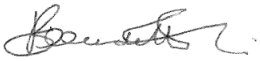
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had primary responsibility for obtaining the dataset, performing the statistical analysis and drafting the paper.

Student Signature:  **Date:** 27 July 2016

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Predicting hospital costs for patients receiving renal replacement therapy to inform an economic evaluation

Short title: Predicting hospital costs for patients receiving renal replacement therapy

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ABSTRACT

Objective: To develop a model to predict annual hospital costs for patients with established renal failure, taking into account the effect of patient and treatment characteristics of potential relevance for conducting an economic evaluation, such as age, comorbidities and time on treatment. The analysis focuses on factors leading to variations in inpatient and outpatient costs and excludes fixed costs associated with dialysis, transplant surgery and high cost drugs.

Methods: Annual costs of inpatient and outpatient hospital episodes for patients starting renal replacement therapy in England were obtained from a large retrospective dataset. Multiple imputation was performed to estimate missing costs due to administrative censoring. Two-part models were developed using logistic regression to first predict the probability of incurring any hospital costs before fitting generalised linear models to estimate the level of cost in patients with positive costs. Separate models were developed to predict inpatient and outpatient costs for each treatment modality.

Results: Data on hospital costs were available for 15,869 incident dialysis patients and 4,511 incident transplant patients. The two-part models showed a decreasing trend in costs with increasing number of years on treatment, with the exception of dialysis outpatient costs. Age did not have a consistent effect on hospital costs, however, comorbidities such as diabetes and peripheral vascular disease were strong predictors of higher hospital costs in all four models.

Conclusion: Analysis of patient-level data can result in a deeper understanding of factors associated with variations in hospital costs and can improve the accuracy with which costs are estimated in the context of economic evaluations.

Key words: hospital costs, established renal failure, regression, patient-level data, two-part model

INTRODUCTION

Analysts involved in carrying out economic evaluations in healthcare are accustomed to expending considerable effort and resources to identify, collect, extrapolate and synthesise data to fully quantify the health consequences associated with different treatment approaches. However, when it comes to estimating costs, it is not uncommon to rely on readily available average unit costs that are assumed to apply uniformly to all patients or remain constant over time. If appropriate data sources can be identified, it would be beneficial to develop more precise ways to estimate the costs of managing patients with specific diseases and to explore in greater detail whether costs vary with patient and treatment characteristics of interest.

Treatment options for patients with established renal failure (ERF) include dialysis and transplantation. For many patients, transplantation can result in increased life expectancy and better quality of life compared to chronic dialysis [1]. Treatment of ERF is resource intensive for the health service. While costs of dialysis and transplantation may be comparable in the first year of treatment, costs for transplant recipients following surgery drop considerably in subsequent years, while the cost of maintenance dialysis sessions remains constant [2]. In England, payment to providers for dialysis is covered under a fixed national tariff as part of the Payment by Results (PbR) system. A similar approach is underway to introduce a fixed tariff for kidney transplant surgery. However beyond the provision of dialysis and transplant surgery, patients with ERF may incur additional hospital costs for monitoring of their condition, management of comorbidities or infections, maintenance of vascular access or post-operative follow-up. More than half of patients starting renal replacement therapy (RRT) have one or more comorbidities [3] which, alongside other factors such as age, may lead to variations in hospitalisation rates [4].

As part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) study, an economic evaluation is being developed to compare alternative schemes for allocating kidneys to patients with ERF who are awaiting transplantation in the United Kingdom. Different approaches to kidney allocation can impact the length of time that

patients with different characteristics will spend on dialysis. This in turn can have an impact on the level of costs incurred. The objective of the current analysis is to develop a model to predict hospital inpatient and outpatient costs for patients with ERF, taking into account relevant patient and treatment characteristics such as age, comorbidities and time on treatment. The analysis will focus on characterising variations in hospital costs and therefore exclude fixed costs associated with routine dialysis, transplant surgery and high cost drugs. The approach to this analysis is guided by the intended use of the results as inputs for an economic evaluation that will compare the costs and consequences of alternative kidney allocation schemes.

METHODS

Data source

In England, all admissions to NHS hospitals are captured in the Hospital Episode Statistics (HES) dataset. Patient demographics and information about type and length of stay are collected during a patient's time at hospital and are submitted to allow hospitals to be paid for the care they deliver [5]. Data on inpatient admissions have been routinely captured in HES since 1998 and outpatient attendances since 2003 [6]. The UK Renal Registry (UKRR) collects data provided by renal centres on all incident renal replacement therapy (RRT) patients, including demographics, comorbidity and treatment information [7]. In 2011, a pilot study was carried out in which UKRR data was linked to HES data for incident patients ≥18 years of age who started dialysis or received a kidney transplant between 2002 and 2006. HES only began collection of outpatient attendances in April 2003, therefore the sample for this analysis was restricted to those patients who started RRT between April 2003 and December 2006. The linked dataset captured hospital episodes until the end of December 2009 [6].

Linkage of HES data to UKRR data enhances the variables available in the separate datasets and facilitates analysis of hospital episodes by RRT modality. Taking the start of dialysis or date of transplant surgery as the index date, annual costs for each patient were

generated by applying the appropriate 2011-12 PbR tariff to each inpatient admission (based on healthcare resource group) or outpatient appointment (based on treatment function code) [8]. Four separate datasets were created to capture dialysis inpatient, dialysis outpatient, transplant inpatient, and transplant outpatient costs in order to allow for the effect of explanatory variables to differ between regression models depending on treatment modality or type of hospital activity. The datasets included all inpatient admissions and outpatient appointments for any reason except routine dialysis or kidney transplant surgery. High cost drugs such as immunosuppressants following transplant surgery or drugs to treat renal anaemia were not captured in the dataset. The analysis therefore includes hospital costs that may not be specifically related to the management of patients' ERF. It was not considered feasible to distinguish between hospital episodes that were related versus those that were unrelated to the management of ERF in the current analysis. However in economic evaluations, the focus is on the difference in costs between alternative strategies, therefore the inclusion of both related and potentially unrelated costs is appropriate, provided the same approach is taken for both the dialysis and transplant datasets.

Administrative censoring

Linkage of the HES and UKRR datasets came to an end in December 2009 and therefore no further data on hospital episodes were available beyond this date. This means that in any given year, some patients may only have observed costs for a portion of the year due to administrative censoring. Rather than exclude these patients from the analysis, multiple imputation was performed to predict costs in the year that administrative censoring occurred under an assumption that data were missing at random (MAR). In the first instance, costs were imputed for the full year in which administrative censoring took place. However, since observed costs were available in these patients for part of the year up until the day of censoring, an additional step was taken to generate a hybrid imputed cost in order to make use of as much observed data as possible. Hybrid imputed costs were generated by using the imputed cost for the full year to calculate an imputed cost per day and multiplying this

by the number of unobserved days for that year, to which the observed costs up until the day of censoring were then added.

Model development

Hospital costs in all four datasets were positively skewed with a varying proportion of zero-cost patients who had no inpatient admissions or outpatient visits in a given year. In order to accommodate these characteristics of the data, a two-part model approach for the regression analyses was taken [9-11]. Part one involved using logistic regression analysis to predict whether or not patients would incur any hospital costs. Part two involved fitting a generalised linear model (GLM) for those patients with positive costs [12, 13]. The cluster option was used to take into account the dependence between multiple observations (years of cost data) for the same patient.

Initially age, sex, treatment modality, year since starting RRT, and co-morbidities were all entered into the regression models. Dummy variables were also entered for events including renal recovery, transplant and death in the dialysis models and for graft failure and death in the transplant models. Since costs are expected to be elevated for several months prior to death, inclusion of a dummy variable only in the year of death would not capture the full impact of this event on costs in patients who die at the beginning of the year. Therefore, an additional variable was created to indicate if death occurred in the first half of the following year. Backwards elimination was used to inform variable selection using a P-value threshold of 0.2 [14].

Model performance was assessed by comparing predicted and observed mean costs and calculating the root-mean-square error (RMSE) [10]. In addition, models that were developed based on multiply imputed values were compared to the results of complete-case analyses to provide reassurance of the validity of the MAR assumption.

All analyses were conducted in Stata (Version 13, Stata Corp, College Station, Texas, USA).

RESULTS

Data on inpatient admissions and outpatient appointments during the first year after initiation of RRT were available for 15,869 dialysis patients and 4,511 transplant patients. Administrative censoring occurred in approximately 11% of transplant patients in the first year after surgery and increased to more than 50% by year six. In contrast, no administrative censoring was present in the first three years of the dialysis patient sample, but ranged between 20% and 50% in years three through six. Tables 1a and 1b summarise the number of patients included in the dataset by number of years following initiation of RRT.

Table 1a Dialysis dataset: number of patients by years on dialysis

Dialysis patients						
Years on dialysis	With complete year costs	With part-year costs due to				TOTAL PATIENTS
		Death	Transplant	Recovered	Admin censoring	
1	11,894 (75%)	2,798 (17%)	750 (5%)	427 (3%)	0 (0%)	15,869
2	9,472 (80%)	1,488 (12%)	803 (7%)	123 (1%)	0 (0%)	11,886
3	7,501 (79%)	1,246 (13%)	634 (7%)	84 (1%)	0 (0%)	9,465
4	4,205 (56%)	1,063 (14%)	476 (6%)	40 (1%)	1,713 (23%)	7,497
5	1,932 (48%)	659 (16%)	248 (6%)	31 (1%)	1,188 (29%)	4,058
6	596 (33%)	274 (15%)	101 (6%)	5 (0%)	823 (46%)	1,799

Table 1b Transplant dataset: number of patients by years following transplant

Transplant patients					
Years following transplant	With complete year costs	With part-year costs due to			TOTAL PATIENTS
		Graft failure	Death	Admin censoring	
1	3,625 (80%)	266 (6%)	122 (3%)	498 (11%)	4,511
2	2,881 (80%)	116 (3%)	33 (1%)	585 (16%)	3,615
3	2,150 (75%)	48 (2%)	35 (1%)	644 (22%)	2,877
4	1,355 (63%)	38 (2%)	22 (1%)	735 (34%)	2,150
5	717 (53%)	16 (2%)	17 (1%)	605 (44%)	1,355
6	239 (33%)	9 (1%)	21 (3%)	448 (63%)	717

Part one: logistic regression analyses

Excluding patients with only part-year cost data, the proportion of patients with zero costs in the first year of RRT was lower in the outpatient setting (2% for dialysis patients and 1% for transplant patients) than in the inpatient setting (24% for dialysis patients and 27% for transplant patients). Logistic regression analyses showed that, compared to the first year of RRT, the odds of incurring any hospital costs in subsequent years was lower, with the exception of outpatient appointments for transplant patients (Tables 2a and 2b).

The presence of comorbidities was associated with higher odds of incurring inpatient costs in both dialysis and transplant patients, but the association was less consistent in the outpatient setting.

Part two: generalised linear models

Generalised linear models with an identity link function and gamma distribution were fitted to the subset of patients with non-zero costs. The model results shown in Tables 3a and 3b include imputed values that were generated using the hybrid approach to predict missing costs due to administrative censoring.

Mean inpatient costs were higher for dialysis patients compared to transplant patients with a trend towards decreasing costs in both patient groups over time. In contrast, mean outpatient costs were initially higher in the first year for transplant patients compared to dialysis patients, but decreased at a faster rate in subsequent years with dialysis outpatient costs overtaking those of transplant patients by the third year.

For dialysis patients, cost differed by treatment modality; haemodialysis was associated with higher costs in the inpatient setting, whereas peritoneal dialysis was associated with higher costs in the outpatient setting. Similarly in the transplant datasets, living donor transplants were associated with lower costs in the inpatient setting (although not statistically significant) and higher costs in the outpatient setting.

Table 2a Logistic regression analysis to predict whether or not dialysis patients incur any hospital costs

	n (%) patient-years	Dialysis inpatient		Dialysis outpatient	
		Odds ratio	95% CI	Odds ratio	95% CI
Constant		2.34*	(2.18, 2.51)	18.09*	(15.62, 20.95)
Age group					
< 50 years	10,608 (21%)	Reference		Reference	
50-64 years	13,330 (26%)	0.98	(0.91, 1.05)	1.26*	(1.08, 1.46)
65-75 years	15,393 (30%)	0.91*	(0.85, 0.97)	1.01	(0.88, 1.17)
> 75 years	11,243 (22%)	0.87*	(0.81, 0.94)	0.82*	(0.70, 0.96)
Sex					
Male	31,450 (62%)	Reference		-	-
Female	19,124 (38%)	1.10*	(1.05, 1.16)	-	-
Years on dialysis					
1	15,869 (31%)	Reference		Reference	
2	11,886 (23%)	0.59*	(0.56, 0.62)	0.80*	(0.73, 0.88)
3	9,465 (19%)	0.50*	(0.47, 0.52)	0.69*	(0.62, 0.76)
4	7,497 (15%)	0.58*	(0.54, 0.62)	0.76*	(0.67, 0.85)
5	4,058 (8%)	0.61*	(0.56, 0.67)	0.71*	(0.62, 0.82)
6	1,799 (4%)	0.65*	(0.57, 0.74)	0.72*	(0.59, 0.89)
Dialysis modality					
Haemodialysis	39,730 (79%)	Reference		Reference	
Peritoneal dialysis	10,844 (21%)	0.83*	(0.79, 0.88)	2.36*	(2.07, 2.69)
Comorbidities					
Myocardial infarction	8,347 (17%)	1.22*	(1.14, 1.31)	-	-
Congestive heart failure	8,801 (17%)	1.11*	(1.04, 1.19)	0.88*	(0.79, 0.98)
Peripheral vascular disease	8,204 (16%)	1.33*	(1.24, 1.42)	1.25*	(1.12, 1.41)
Cerebrovascular disease	5,459 (11%)	1.15*	(1.07, 1.24)	0.86*	(0.76, 0.97)
Pulmonary	7,351 (15%)	1.26*	(1.17, 1.35)	1.13*	(1.01, 1.27)
Liver	393 (1%)	-	-	-	-
Diabetes	19,167 (34%)	1.27*	(1.21, 1.34)	1.64*	(1.48, 1.81)
Cancer	4,092 (8%)	1.22*	(1.11, 1.33)	1.40*	(1.20, 1.63)
Hypertension	31,245 (62%)	1.09*	(1.04, 1.14)	1.36*	(1.23, 1.49)
Transplant	3,012 (6%)	1.11*	(1.02, 1.21)	0.25*	(0.21, 0.29)
Recovered renal function	710 (1%)	0.82*	(0.69, 0.96)	0.12*	(0.10, 0.15)
Death	7,528 (15%)	1.94*	(1.81, 2.07)	0.16*	(0.15, 0.18)
Death first half following year	2,521 (5%)	2.61*	(2.34, 2.92)	1.16	(0.93, 1.44)

*p<0.05

Table 2b Logistic regression analysis to predict whether or not transplant patients incur any hospital costs

	n (%) patient-years	Transplant inpatient		Transplant outpatient	
		Odds ratio	95% CI	Odds ratio	95% CI
Constant		1.89*	(1.65, 2.16)	104.02*	(72.08, 150.12)
Age group					
< 35 years	3,352 (22%)	Reference		-	-
36-45 years	3,950 (26%)	0.81*	(0.72, 0.92)	-	-
46-55 years	3,886 (25%)	0.73*	(0.64, 0.82)	-	-
> 55 years	4,037 (27%)	0.76*	(0.67, 0.87)	-	-
Sex					
Male	9,575 (63%)	Reference		Reference	
Female	5,650 (37%)	1.35*	(1.22, 1.49)	1.53*	(1.09, 2.16)
Years following transplant					
1	4,511 (29%)	Reference		Reference	
2	3,615 (24%)	0.21*	(0.19, 0.23)	1.17	(0.85, 1.62)
3	2,877 (19%)	0.18*	(0.16, 0.20)	1.60*	(1.06, 2.43)
4	2,150 (14%)	0.19*	(0.17, 0.22)	1.79*	(1.06, 3.04)
5	1,355 (9%)	0.19*	(0.16, 0.23)	1.08	(0.64, 1.84)
6	717 (5%)	0.18*	(0.14, 0.22)	1.06	(0.45, 2.51)
Transplant type					
Deceased donor	9,874 (65%)	Reference		Reference	
Living donor	5,351 (35%)	0.82*	(0.75, 0.90)	0.71	(0.49, 1.03)
Comorbidities					
Myocardial infarction	1,238 (8%)	1.47*	(1.24, 1.73)	-	-
Congestive heart failure	932 (6%)	1.48*	(1.22, 1.79)	-	-
Peripheral vascular disease	1,676 (11%)	1.87*	(1.62, 2.16)	1.56*	(1.00, 2.42)
Cerebrovascular disease	975 (6%)	1.38*	(1.16, 1.65)	-	-
Pulmonary	2,050 (13%)	1.24*	(1.09, 1.40)	-	-
Liver	119 (1%)	2.18*	(1.37, 3.47)	-	-
Diabetes	4,000 (26%)	1.62*	(1.46. 1.80)	1.80*	(1.21, 2.66)
Cancer	614 (4%)	1.62*	(1.31, 2.01)	3.45*	(1.32, 8.99)
Hypertension	11,251 (74%)	1.33*	(1.21, 1.46)	-	-
Graft failure	493 (3%)	-	-	0.02*	(0.02, 0.03)
Death	250 (2%)	1.62*	(1.14, 2.31)	0.02*	(0.01, 0.03)
Death first half following year	79 (0.5%)	4.55*	(2.47, 8.39)	-	-

*p<0.05

Table 3a Mean annual costs (£) for dialysis patients (generalised linear model)

	Dialysis inpatient		Dialysis outpatient	
	Coeff	95% CI	Coeff	95% CI
Constant	7782*	(7423, 8140)	1379*	(1331, 1428)
Age group				
< 50 years	Reference		Reference	
50-64 years	-170	(-489, 149)	-25	(-79, 29)
65-75 years	-181	(-513, 151)	-167*	(-219, -115)
> 75 years	-444*	(-806, -83)	-320*	(-376, -264)
Sex				
Male	Reference		-	-
Female	208*	(-23, 439)	-	-
Years on dialysis				
1	Reference		Reference	
2	-1189*	(-1487, -891)	-159*	(-186, -131)
3	-1434*	(-1729, -1140)	-112*	(-145, -80)
4	-1848*	(-2166, -1530)	-438*	(-85, -1)
5	-1709*	(-2099, -1319)	-13	(-66, 40)
6	-2270*	(-2774, -1767)	134*	(36, 232)
Dialysis modality				
Haemodialysis	Reference		Reference	
Peritoneal dialysis	-612*	(-838, -385)	334*	(296, 373)
Comorbidities				
Myocardial infarction	390*	(96, 683)	-	-
Congestive heart failure	321*	(58, 584)	-40	(-81, 0)
Peripheral vascular disease	721*	(423, 1019)	117*	(66, 168)
Cerebrovascular disease	506*	(174, 838)	-	-
Pulmonary	412*	(128, 696)	46	(0, 93)
Liver	1682*	(-161, 3524)	-	-
Diabetes	1191*	(929, 1453)	248*	(211, 284)
Cancer	-	-	139*	(72, 206)
Hypertension	-	-	-	-
Transplant	-1863*	(-2140, -1585)	-552*	(-602, -501)
Recovered renal function	1293*	(513, 2073)	-348*	(-454, -243)
Death	2403*	(2152, 2654)	-377*	(-414, -341)
Death first half following year	4415*	(3926, 4904)	200*	(138, 262)

*p<0.05

Table 3b Mean annual costs (£) for transplant patients (generalised linear model)

	Transplant inpatient		Transplant outpatient	
	Coeff	95% CI	Coeff	95% CI
Constant	4735*	(4331, 5138)	4053*	(3961, 4145)
Age group				
< 35 years	Reference		Reference	
36-45 years	-318	(-664, 29)	-123*	(-193, -53)
46-55 years	-310	(-676, 56)	-151*	(-224, -78)
> 55 years	-91	(-487, 306)	-126*	(-195, -57)
Sex				
Male	Reference		Reference	
Female	190	(-76, 455)	126*	(76, 175)
Years following transplant				
1	Reference		Reference	
2	-1576*	(-1881, -1271)	-2671*	(-2731, -2610)
3	-1919*	(-2228, -1611)	-2935*	(-3000, -2869)
4	-2138*	(-2485, -1790)	-3018*	(-3088, -2948)
5	-2061*	(-2502, -1620)	-3089*	(-3166, -3011)
6	-2654*	(-3212, -2096)	-3105*	(-3204, -3006)
Transplant type				
Deceased donor	Reference		Reference	
Living donor	-223	(-486, 39)	130*	(78, 182)
Comorbidities				
Myocardial infarction	641*	(145, 1138)	130*	(17, 242)
Congestive heart failure	1248*	(646, 1851)	159*	(35, 284)
Peripheral vascular disease	1222*	(729, 1715)	256*	(157, 354)
Cerebrovascular disease	898*	(271, 1524)	88	(-21, 197)
Pulmonary	264	(-87, 616)	179*	(99, 258)
Liver	2093*	(30, 4155)	524*	(200, 849)
Diabetes	1046*	(734, 1359)	593*	(515, 671)
Cancer	485*	(2, 969)	273*	(134, 411)
Hypertension	324*	(56, 592)	144*	(91, 197)
Graft failure	2438*	(1723, 3152)	-309*	(-451, -167)
Death	4924*	(3726, 6123)	-216*	(-426, -5)
Death first half following year	5725*	(3350, 8100)	629*	(321, 936)

*p<0.05

The increase in mean annual costs associated with various comorbidities ranged between £321 - £1,682 in the dialysis inpatient setting and between £264 and £2,093 in the transplant inpatient setting. Of the comorbidities included in the final models, peripheral vascular disease and diabetes were the only two that were consistently associated with significantly higher costs in both dialysis and transplant patients as well as in both inpatient and outpatient settings. The proportion of patients in both the dialysis and transplant datasets who had peripheral vascular disease was approximately 12% and the proportion who had diabetes was approximately 30%.

Model performance and predicted costs

Table 4 summarises observed and predicted mean annual cost estimates for each of the final two-part models. The results were compared with models that were developed based on complete-case analyses, in which patients who were administratively censored were

Table 4 Observed and predicted mean annual costs

	Number of observations (patient-years)	Mean costs (std dev)	RMSE
Dialysis inpatient			
Observed	46850	£ 5581 (9440)	
Two-part model complete-case analysis		£ 5576 (2120)	9202.92
Two-part model hybrid imputed costs		£ 5578 (2136)	9204.73
Dialysis outpatient			
Observed	46850	£ 1202 (1348)	
Two-part model complete-case analysis		£ 1196 (343)	1291.19
Two-part model hybrid imputed costs		£ 1203 (345)	1291.22
Transplant inpatient			
Observed	11710	£ 2398 (4675)	
Two-part model complete-case analysis		£ 2390 (1931)	4278.45
Two-part model hybrid imputed costs		£ 2468 (1958)	4279.87
Transplant outpatient			
Observed	11710	£ 2388 (2007)	
Two-part model complete-case analysis		£ 2383 (1332)	1459.10
Two-part model hybrid imputed costs		£ 2447 (1386)	1458.98

removed from the dataset. In each case, RMSE was found to be similar between the model based on complete-case analysis and the model that was developed using multiply imputed values.

As the motivation for the analysis was to predict annual hospital costs that can be used as inputs in an economic evaluation, the appendix provides a worked example of how the regression results presented above can be used for this purpose.

DISCUSSION

Previous examples of economic evaluations that have compared dialysis and transplantation as treatment alternatives for patients with ERF have taken a variety approaches to estimating costs. For transplant costs, it is common practice to estimate a cost for the first year of treatment that reflects the cost of surgery, and then assume a constant annual cost to capture resource use such as immunosuppressive therapy or outpatient visits in subsequent years [15-20]. For dialysis costs, some studies restrict the analysis to the cost of routine dialysis only, while others include the cost of hospitalisations, management of complications or drugs. Other than taking into account the cost of vascular access at the start of dialysis, annual costs for dialysis patients are often assumed to be constant [16, 18]. However, there are examples of economic evaluations that have introduced an element of variation in costs among dialysis patients by considering factors such as age or time on treatment: de Wit et al [19] presented separate estimates of hospital costs by age group based on data collected at 13 Dutch dialysis centres; Haller et al [15] analysed patient-level cost data from a hospital in Austria and presented separate cost estimates for dialysis patients in the first year, second year and subsequent years of treatment. None of these previous studies have simultaneously considered the impact of treatment modality, length of time on treatment, age and comorbidities on costs.

Collection of patient-level cost data is a resource intensive exercise. The linkage of HES data to UKRR data provides a rare opportunity to analyse a large existing dataset to explore variations in hospital costs specifically among patients receiving RRT in England. HES is,

to our knowledge, the most complete source of routinely collected information on admissions and attendances at NHS hospitals in England and linkage to UKRR data facilitates simultaneous exploration of multiple patient and treatment-related factors that may affect costs. The approach to analysing the linked dataset was guided by both the features of the data and the intended use of the results. In this case, the primary objective of the analysis was to predict annual costs for patients with different characteristics for use as inputs in an economic evaluation. Additionally, there were three main features of the cost data that needed to be addressed: 1) missing data due to administrative censoring, 2) the proportion of observations with zero costs and 3) positively skewed distributions.

Multiple imputation was carried out to address the issue of administrative censoring. Multiple imputation has the advantage of making use of all available observed data, while allowing for uncertainty about the missing values [21, 22]. In this analysis, the models based on complete cases and the models that included imputed values were very similar, providing confidence that missing data due to administrative censoring did not bias the estimates of cost. This suggests that a complete-case analysis would have been sufficient, but it is unclear if this conclusion can be generalised beyond our dataset. There is a growing body of literature describing other methods to address the common issue of censoring of cost data [23-27]. However, given that the primary objective of the current analysis was to estimate annual (as opposed to lifetime) costs and that cost histories detailing the timing of individual hospital events were not available in the current extract of the dataset, approaches based on survival analysis techniques were not pursued.

The issues of zero costs and positively skewed distributions were addressed by adopting a two-part approach in which a logistic regression was fitted to predict the probability of incurring any hospital costs, followed by fitting a GLM to estimate the level of cost for patients with at least one admission or visit. A potential advantage of the two-part approach is that covariates that are determined to be significant in part one of the model do not have to be the same as those that determine the level of cost in part two. In the present analyses, there was general consistency in terms of the covariates that were included in part one and

part two of the final inpatient cost models, but less agreement in the outpatient setting where the percentage of zero costs was lower.

The results of this analysis highlight a number of findings that are relevant when considering variations in hospital costs for patients on RRT in the context of economic evaluation. Firstly, while the cost of transplant surgery can be viewed as a one-time event and the cost of maintenance dialysis sessions generally remains constant from week to week and year to year, hospital costs for patients on RRT showed a decreasing trend over time that extended beyond the first two years on RRT. A plausible explanation for this trend is that patients who survive longer on therapy are on average fitter and healthier and required fewer hospital visits. Secondly, age did not have a consistent effect on costs across all treatment modalities and hospital settings and, in contrast to the approach taken in the economic evaluation by de Wit et al [19], the current analysis suggests that, controlling for other factors, increasing age alone may be associated with lower rather than higher costs. Thirdly, many of the comorbidities included in the analysis were found to be significant predictors of hospital costs and had a bigger impact than age in the estimation of costs for patients on RRT.

In the absence of evidence to the contrary, it is perhaps most natural to adopt an assumption that costs remain constant either over time or between subgroups of patients with different characteristics. However, if appropriate patient-level data sources can be identified, a more detailed understanding of patient characteristics and treatment factors that influence costs can help improve the accuracy with which costs are estimated in the context of economic evaluations.

APPENDIX: A WORKED EXAMPLE TO PREDICT HOSPITAL COSTS BASED ON THE FINAL TWO-PART MODEL

To estimate annual inpatient costs for a 55-year-old male patient with diabetes who has been on haemodialysis for three years:

Part 1: probability of incurring any inpatient cost > £0

Taking the natural log of the odds ratios in Table 2a, calculate log odds of incurring any inpatient cost

$$\text{CONSTANT} + (\beta 1 \times \text{AGEGROUP50} - 64) + (\beta 2 \times \text{YEAR3}) + (\beta 3 \times \text{DIABETES})$$

$$= 0.850 + (-0.022 \times 1) + (-0.702 \times 1) + (0.242 \times 1) = 0.368$$

Calculate probability from log odds

$$e^{x\beta} / \left(1 + e^{x\beta}\right) = e^{0.368} / (1 + e^{0.368}) = 0.591$$

Part 2: estimate level of inpatient cost based on coefficients in Table 3a

$$\text{CONSTANT} + (\beta 1 \times \text{AGEGROUP50} - 64) + (\beta 2 \times \text{YEAR3}) + (\beta 3 \times \text{DIABETES})$$

$$= 7782 + (-170 \times 1) + (-1434 \times 1) + (1191 \times 1) = 7368$$

Combine parts 1 and 2: multiply estimated level of inpatient cost by probability of incurring any cost

$$7368 \times 0.591 = £4{,}354$$

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3. SURVIVAL ESTIMATES

3.1. Introduction

Survival estimates are the main building blocks for the simulation model in two important ways:

1. The longevity matching and QALY-maximising allocation schemes both require a method to predict expected post-transplant survival for each patient on the waiting list in order to inform prioritisation of patients as part of the kidney allocation process
2. For all allocation schemes, estimates of post-transplant survival and time to graft failure are required to calculate lifetime costs and QALYs for all transplant recipients and estimates of waiting-list survival are required to calculate lifetime costs and QALYs for all patients who do not receive a transplant.

This chapter of the thesis describes the approach to fitting survival models to a historical cohort of patients from the UK Transplant Registry. Survival analysis in kidney transplantation is dominated by the use of Cox regression models.[16,44-47] While this approach is useful for quantifying treatment effects or determining factors that influence relative survival, its usefulness in extrapolating survival beyond the period of observed data is limited. Methods to extrapolate and estimate mean patient survival using parametric models are becoming increasingly important for informing the development of prognostic models and conducting cost-effectiveness analyses.[48] Depending on the shape of the hazard function, standard parametric models such as the Weibull or exponential may be appropriate, but early exploration of the UK Transplant Registry data revealed that standard parametric models were unlikely to provide an appropriate fit. This led to the decision to explore flexible parametric modelling techniques in order to predict post-transplant survival, time to graft failure and waiting-list survival.[49]

3.2. Research Paper 2

Research Paper 2, entitled *Predicting patient survival after deceased donor kidney transplantation using flexible parametric modelling,* describes the dataset containing 20 years of historical transplant data and discusses the methodological considerations that were encountered in the application of a flexible parametric modelling approach to analyse post-transplant survival.[50] The richness of the dataset made it possible to develop a survival model that included both donor and recipient characteristics, meaning that predictions of post-transplant survival in the simulation model reflect the combination of each donor-recipient pairing.

The flexible parametric modelling approach described in Research Paper 2 was also used to analyse time to graft failure and waiting-list survival. The final fitted models for these events are provided in Appendix 4.

RESEARCH PAPER COVER SHEET – Research Paper 2

SECTION A – Student Details

Student	Bernadette Li
Principal Supervisor	John Cairns
Thesis Title	Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	BMC Nephrology		
When was the work published?	May 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had primary responsibility for obtaining the dataset, performing the statistical analysis and drafting the paper.

Student Signature:  **Date:** 27 July 2016

Supervisor Signature:  **Date:** 27 July 2016

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TECHNICAL ADVANCE Open Access

Predicting patient survival after deceased donor kidney transplantation using flexible parametric modelling

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Abstract

Background: The influence of donor and recipient factors on outcomes following kidney transplantation is commonly analysed using Cox regression models, but this approach is not useful for predicting long-term survival beyond observed data. We demonstrate the application of a flexible parametric approach to fit a model that can be extrapolated for the purpose of predicting mean patient survival. The primary motivation for this analysis is to develop a predictive model to estimate post-transplant survival based on individual patient characteristics to inform the design of alternative approaches to allocating deceased donor kidneys to those on the transplant waiting list in the United Kingdom.

Methods: We analysed data from over 12,000 recipients of deceased donor kidney or combined kidney and pancreas transplants between 2003 and 2012. We fitted a flexible parametric model incorporating restricted cubic splines to characterise the baseline hazard function and explored a range of covariates including recipient, donor and transplant-related factors.

Results: Multivariable analysis showed the risk of death increased with recipient and donor age, diabetic nephropathy as the recipient's primary renal diagnosis and donor hypertension. The risk of death was lower in female recipients, patients with polycystic kidney disease and recipients of pre-emptive transplants. The final model was used to extrapolate survival curves in order to calculate mean survival times for patients with specific characteristics.

Conclusion: The use of flexible parametric modelling techniques allowed us to address some of the limitations of both the Cox regression approach and of standard parametric models when the goal is to predict long-term survival.

Keywords: Kidney transplantation, Survival, Multivariable analysis, Flexible parametric model, Extrapolation

Background

Outcomes following kidney transplantation are commonly analysed using Cox regression models. Such analyses have been instrumental for understanding the influence of both donor and recipient factors on post-transplant events, such as graft failure and patient mortality [1–5]. However, the Cox regression approach places emphasis on estimating relative risk and does not make any distributional assumptions about the absolute risk of an event. Therefore, its usefulness in predicting survival beyond the period of observed data is limited [6]. Following kidney transplantation, the risk of death is highest in the period immediately after surgery, but decreases sharply and then changes direction when the risk of death starts to gradually increase over time. While a number of standard parametric models (such as the exponential, Weibull or loglogistic) are available and

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could facilitate extrapolation of survival data, they are not flexible enough to accommodate hazard functions that change direction.

In some situations, we not only want to understand what factors influence relative survival, but we also want to predict long-term survival for patients with given characteristics. Estimates of life expectancy following transplant are important as a basis for having informed discussions with individual patients and their relatives. For decision-making at a population level, estimates of mean survival are needed to inform cost-effectiveness evaluations that compare two or more treatment alternatives in terms of both lifetime health gains and costs. There has also been considerable interest in the development of survival prediction models and scoring tools for use in kidney allocation systems. A number of predictive models have been proposed, such as the Recipient Risk Score (RRS), Life Years From Transplant (LYFT) and the Expected Post Transplant Survival (EPTS) score, the latter which was adopted as a measure alongside the Kidney Donor Profile Index (KDPI) to facilitate longevity matching in the revised kidney allocation system approved by the Organ Procurement and Transplantation Network in the United States in 2013 [7–11]. The primary motivation for the current analysis is to develop a predictive model to estimate post-transplant survival as a potential approach to inform the design alternative allocation schemes for deceased donor kidneys in the United Kingdom.

In order to estimate mean patient survival from observed data, it is desirable to have complete information about when most or all patients have died. If the data are not complete, estimates of mean survival will not reflect the full distribution of survival times and will likely underestimate true survival [12]. For recipients of kidney transplants, waiting to observe post-transplant mortality for a complete cohort of patients would require several decades of follow-up. To circumvent this problem, predictive models such as the aforementioned LYFT approach used estimates of median rather than mean survival times [8]. In contrast to the mean, median survival only requires sufficient follow-up to observe when 50 % of patients have died. However, with gradual improvements in post-transplant survival, even median survival can exceed 15 years. The survival models for LYFT were developed based on transplant recipient data spanning the period 1987 to 2006, thus highlighting another dilemma: predicting survival times based on data from patients who received transplants as many as 20 years ago may not accurately reflect the current clinical situation and the data often need to be further adjusted to reflect improvements in survival over time. For example, advances in surgical technique, organ preservation technology, immunosuppressive therapy and changes in the age and comorbidity profiles of both donors and recipients all have the potential to influence post-transplant outcomes.

Unlike the Cox regression approach, flexible parametric models characterise the baseline hazard directly and can therefore provide smooth estimates of the hazard and survival functions for any combination of covariates and can be used to extrapolate survival beyond the observed data [6]. The ability to extrapolate also means that it is not necessary to rely on older historical data simply to have sufficient long-term follow-up to observe enough deaths. By choosing to focus on data from transplants that have been carried out more recently, a parametric modelling approach offers the advantage of allowing us to generate predictions of mean patient survival that are more reflective of the characteristics of the current transplant population and of current clinical practice.

In this analysis, we demonstrate the application of the flexible parametric modelling approach proposed by Royston and Parmar [6, 13] to predict mean patient survival among recipients of kidney transplants from deceased donors in the United Kingdom. We begin by describing the dataset and explaining the approach we took to determine how many years of historical data we should use to inform model development. We then present the fitted flexible parametric model and demonstrate agreement between observed and predicted survival. Finally, we use the model to extrapolate beyond the observed data in order to predict mean survival for patients with a given set of characteristics.

Methods

Data source

NHS Blood and Transplant is the central authority responsible for managing the UK Transplant Registry, which records mandatory data for kidney transplants performed in all transplant centres across the UK [3]. Anonymised data on all first-time kidney and combined kidney and pancreas transplants performed between 1993 and 2012 were obtained from the registry. Patients <18 years old at the time of transplant, recipients of kidneys from living donors, en bloc and double transplants were excluded from the analysis, as were recipients of kidneys transplanted with organs other than the pancreas.

Determining how many years of transplant data to include in model development

Kaplan-Meier curves and log-rank tests were used to explore if there was any evidence of notable shifts in mortality rates over the 20-year period that would justify controlling for change over time or potentially restricting the analysis to more recent years of data. Several approaches for dividing the dataset into cohorts based on year of transplant were explored, including 5-year intervals, 10-year intervals

and intervals that coincided with changes to the UK national kidney allocation scheme in 1998 and 2006. The list of variables that were routinely recorded in the UK Transplant Registry changed between 1993 and 2012 and so the availability of key variables was also an important consideration in deciding whether to model survival using all of the data or to limit the analysis to a more recent subset. Based on a combination of the above factors, a decision was made to restrict the development of the flexible parametric model to patients who received transplants between 2003 and 2012; however, longer-term data from transplants performed between 1993 and 2002 were used to check the plausibility of extrapolated survival based on the fitted model.

Explanatory variables

Previous published analyses and prognostic models were reviewed to identify potential factors for inclusion in the development of the model to predict post-transplant patient survival [3, 8, 9]. Recipient factors of interest included age, gender, ethnicity, primary renal diagnosis, pre-emptive transplant, waiting time, kidney only versus combined kidney and pancreas transplant and the calculated reaction frequency of antibodies to human leukocyte antigen (HLA). Calculated reaction frequency (cRF) is a measure of the sensitisation level for each patient and is calculated as the percentage of donors in a pool of 10,000 UK donors with whom the patient is HLA antibody incompatible, similar to the concept of calculated panel reactive antibody [2]. Patients with a cRF between 0 and 9 % were considered non-sensitised, whereas patients with a cRF ≥ 85 % were classed as highly sensitised [14]. Donor factors of interest included age, ethnicity, weight, history of hypertension, diabetes, circulatory-death versus brain-death donor and cause of death. Cold ischaemia time and the level of HLA mismatch were also included. HLA mismatch was graded from level 1 (000-mismatched) to level 4 (poorly matched) as described in the UK 2006 National Kidney Allocation Scheme [15].

Categorical variables were created for each of these factors and the univariate effect of each factor on survival was explored using log-rank tests [16]. After making the decision to restrict model development to patients who received transplants between 2003 and 2012, most variables had either complete or only a small amount of missing data (<2 %) and therefore we did not perform imputation in order to facilitate the model fitting process. However, data for two donor factors, hypertension and diabetes, were missing in approximately 8 % of cases. For these variables, two approaches to handling missing data were explored. First, in order to retain these cases during model fitting, additional categories for missing donor hypertension and donor diabetes status were created. Second, multiple imputation using chained equations was performed and results were compared for consistency with the non-imputed dataset.

Fitting the multivariable flexible parametric model

We followed the Royston-Parmar approach to fitting a flexible parametric model, in which the baseline distribution is modelled as a restricted cubic spline function of log time [6, 17]. The first step in the development of the prognostic model was to determine the appropriate complexity or number of knots to characterise the baseline spline function and choose a suitable scale (proportional hazards, proportional odds or probit) [6]. We initially fitted models on each of the three scales while varying the number of interior knots from 0 to 4 and inspected the Akaike information criterion (AIC) to determine the optimal fit.

For the multivariable model, the data were then split 2:1 into derivation and validation subsets and variable selection was performed on the derivation dataset using backward elimination and a p-value threshold of 0.10. We tested selectively for clinically plausible interactions and explored the possibility of time-dependent effects for specific covariates if log-log plots suggested any departures from proportionality of hazards over time. We used the model fitted to the derivation subset to predict survival curves in the validation subset and compared these graphically. The final model was then refitted to the combined derivation and validation dataset and results are reported with the index of concordance (c index) as a measure of discrimination. The c index estimates the probability of concordance between predicted and observed outcomes with a value of 0.5 indicating no predictive discrimination and a value of 1.0 indicating perfect separation of patients with different outcomes [18]. The fitted model was then used to extrapolate survival curves for patients with given characteristics in order to generate predictions of mean survival by calculating the area under the curve.

All analyses were conducted in Stata (Version 13, Stata Corp, College Station, Texas, USA). The flexible parametric model was fitted using the *stpm2* command [17].

Results

Restricting model development to transplants carried out between 2003 and 2012

The initial dataset included 23,729 patients who received a transplant between 1993 and 2012. Kaplan-Meier curves were plotted for groups defined by year of transplant to explore if there have been any notable shifts in mortality rates over the 20-year period of available data. Visual inspection showed clear separation of survival curves for patients who received a transplant between 1993 and 2002 versus patients who received a transplant between 2003 and 2012, and this difference was confirmed by a log-rank test (Fig. 1a). Alternative approaches to dividing the time period into 5-year intervals (Fig. 1b) or intervals that coincided with changes to the national kidney allocation scheme (Fig. 1c) confirmed that mortality rates did not differ significantly within the last 10 years (between 2003 and 2012) of the dataset; however, improvements in

survival were seen when comparing mortality rates within the first 10 years (between 1993 and 2002). In addition to shifts in survival curves, another important consideration for the multivariable analysis was the availability of data for key covariates of interest. For example, data on cold ischaemia time has only been consistently recorded in the registry since 2000 and there were considerable differences in the proportion of circulatory-death donors between the years 1993 and 2002 (3.7 %) and the years 2003 and 2012 (28.4 %). Therefore based on the observed improvements in survival and availability of data, a decision was made to restrict the development of the survival model to those patients who received transplants between 2003 and 2012.

Univariate analysis

Table 1 summarises the results of univariate survival analyses by recipient, donor and transplant factors. At a *p*-value threshold of 0.05, only three of the factors investigated did not yield statistically significant differences in patient survival: cRF, cold ischaemia time and whether the patient received a kidney only or combined kidney and pancreas transplant.

Shape of the hazard function and choice of spline function

Based on AIC, the preliminary flexible parametric model with the optimal fit was found to be on a proportional

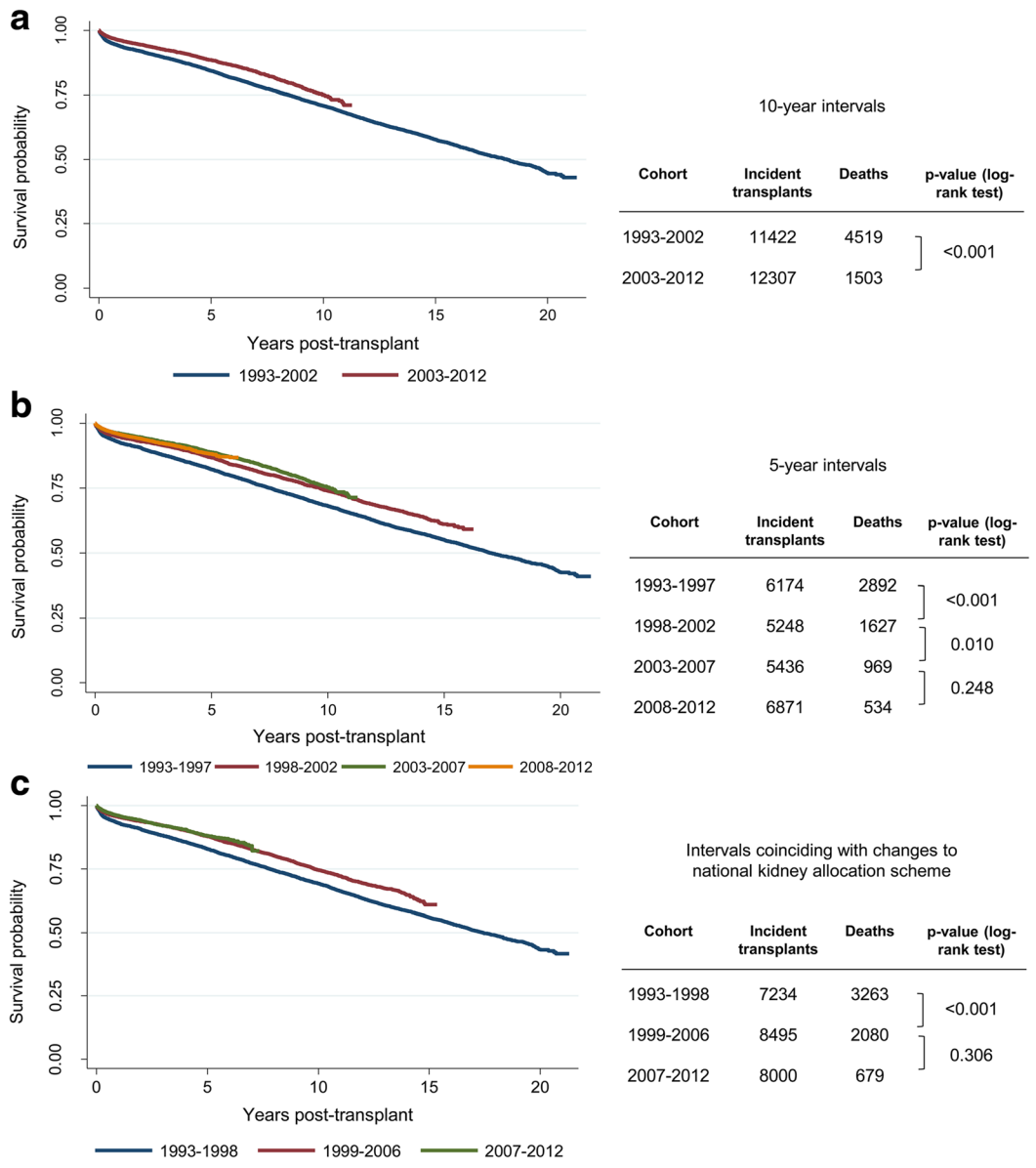

Fig. 1 Kaplan-Meier curves and log-rank tests to explore changes in patient survival between different cohorts based on year of transplant: (**a**) 10-year intervals (**b**) 5-year intervals and (**c**) intervals that coincide with changes to the national kidney allocation scheme

Table 1 Univariate survival analysis by recipient, donor and transplant factors for transplants carried out between 2003 and 2012 ($N = 12,307$)

	n	%	Observed deaths	Crude mortality rate %	*p*-value (log-rank test)
Recipient age					
18-29	997	8.1	43	4.3	<0.001*
30-39	2034	16.5	115	5.7	
40-49	3185	25.9	256	8.0	
50-59	3110	25.3	407	13.1	
> 60	2981	24.2	682	22.9	
Recipient gender					
Male	7628	62.0	984	12.9	0.002
Female	4673	38.0	517	11.1	
Not reported	6	0.1	-	-	
Recipient ethnicity					
White	9871	80.2	1248	12.6	0.033
Asian	1376	11.2	164	11.9	
Other	1049	8.5	90	8.6	
Not reported	11	0.1	-	-	
Transplanted organs					
Kidney only	11013	89.5	1368	12.4	0.253
Kidney and pancreas	1294	10.5	135	10.4	
Pre-emptive transplant					
No	11019	89.5	1406	12.8	<0.001
Yes	1270	10.3	92	7.2	
Not reported	18	0.2	-	-	
cRF					
0-9 %	10026	81.5	1229	12.3	0.356
10-29 %	523	4.3	55	10.5	
30-84 %	1357	11.0	171	12.6	
85-100 %	401	3.3	48	12.0	
Waiting time					
< 6 months	1941	15.8	243	12.5	0.003*
6 months to <2 years	4129	33.6	538	13.0	
> 2 years	6237	50.7	722	11.6	
Primary renal disease					
Glomerulonephritis	1849	15.0	186	10.1	<0.001
Diabetic nephropathy (type 1)	1705	13.9	230	13.5	
Diabetic nephropathy (type 2)	380	3.1	71	18.7	
Renal vascular disease	545	4.4	78	14.3	
Polycystic kidney disease	1513	12.3	147	9.7	
Pyelonephritis	804	6.5	95	11.8	
Other	1573	12.8	181	11.5	
Not reported	3938	32.0	515	13.1	
Donor age					
< 40	3650	29.7	306	8.4	<0.001*
40-49	2754	22.4	324	11.8	

Table 1 Univariate survival analysis by recipient, donor and transplant factors for transplants carried out between 2003 and 2012 ($N = 12,307$) *(Continued)*

50-59	3200	26.0	416	13.0	
> 60	2703	22.0	457	16.9	
Donor type					
Brain-death donor	8812	71.6	1117	12.7	0.003
Circulatory-death donor	3495	28.4	386	11.0	
Donor hypertension					
No	8688	70.6	938	10.8	<0.001
Yes	2525	20.5	386	15.3	
Not reported	1094	8.9	179	16.4	
Donor diabetes					
Negative	10790	87.7	1268	11.8	0.021
Positive	541	4.4	69	12.8	
Not reported	976	7.9	166	17.0	
Donor weight					
< 55 kg	3150	25.6	380	12.1	0.036
55-65 kg	723	5.9	62	8.6	
65-75 kg	1721	14.0	215	12.5	
75-85 kg	3234	26.3	411	12.7	
85-95 kg	1973	16.0	226	11.5	
> 95 kg	1342	10.9	168	12.5	
Not reported	164	1.3	-	-	
Donor cause of death					
Trauma	1510	12.3	158	10.5	<0.001
Intracranial	7954	64.6	1059	13.3	
Other	2843	23.1	286	10.1	
HLA mismatch					
Level 1 [000]	1485	12.1	193	13.0	0.001*
Level 2 [0 DR + 0/1 B]	4002	32.5	467	11.7	
Level 3 [0 DR + 2 B] or [1 DR + 0/1 B]	5192	42.2	624	12.0	
Level 4 [1 DR + 2 B] or [2 DR]	1628	13.2	219	13.5	
Cold ischaemia time					
< 12 hrs	2061	16.8	177	8.6	0.310*
12 to <18 hrs	5859	47.6	691	11.8	
18 to <24 hrs	2930	23.8	427	14.6	
> = 24 hrs	1264	10.3	186	14.7	
Not reported	193	1.6	-	-	

*log-rank test for trend

hazards scale with 2 interior knots for the spline function. Before fitting the multivariable model, we compared the preliminary model based on the chosen scale and number of knots without covariates to the observed data by examining the shape of the hazard and survival functions.

The risk of death is highest in the period immediately following surgery, then drops sharply before it starts to gradually increase at approximately 2 years post-transplant. Figure 2 demonstrates the ability of the flexible parametric model to accommodate a hazard function that is consistent with the shape of the observed data. This provides reassurance of the improved fit that can be obtained when using splines instead of standard parametric models such as the Weibull or loglogistic shown in Fig. 2 for comparison.

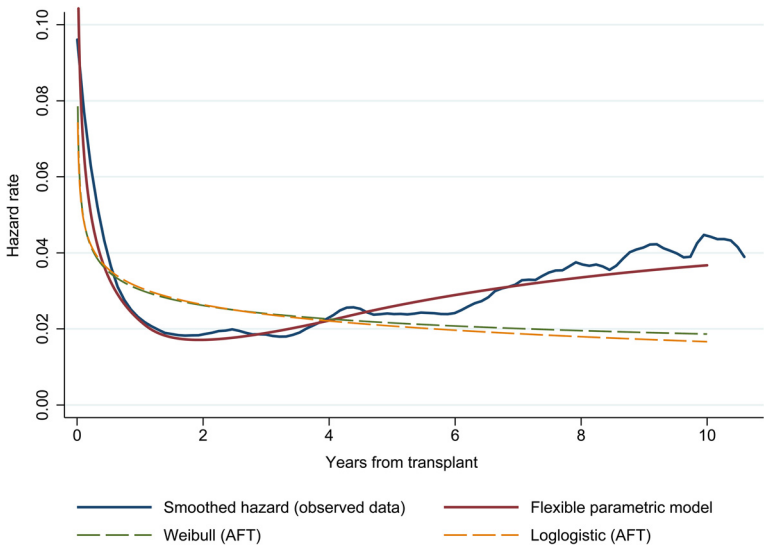

Fig. 2 Comparison of smoothed hazard function based on observed data and preliminary flexible parametric model (no covariates) fitted with spline function (2 interior knots); Weibull and loglogistic models in the accelerated-failure time (AFT) metric are also shown for comparison

Fitting the multivariable flexible parametric model

The variable selection process to identify significant predictors of post-transplant survival resulted in the model shown in Table 2. The results in Table 2 reflect the final model fitted to the combined derivation and validation subsets. The risk of death increased with increasing age of both the recipient and the donor, with a primary renal diagnosis of diabetic nephropathy (type 1 or type 2 diabetes) in the recipient and with the presence of hypertension in the donor. The risk of death was lower for female transplant recipients, patients with polycystic kidney disease and patients who received a pre-emptive transplant. Excluding age, type 1 diabetic nephropathy was associated with the highest increase in the risk of death among transplant recipients.

Interaction terms for recipient age and gender, recipient age and diabetic nephropathy as the primary renal diagnosis, and donor age and hypertension history were tested, but none were found to be significant. To allow for the possibility of time-dependent effects for any of the covariates in the model, we first examined log-log plots for any potential departures from the proportional hazards assumption and identified pre-emptive transplant, type of transplant (kidney only versus combined kidney and pancreas transplant) and cold ischaemia time as potentially varying over time. We tested time-dependent effects for these variables in the flexible parametric model, but again none were found to improve the fit of the model.

Agreement between observed and predicted survival

The c index for the final model was 0.70, comparable to the value reported in the development of the LYFT model (0.68) [19]. To assess the predictive performance of the model, we created five prognostic groups and used the final flexible parametric model to generate a mean survival curve for each group and compared this to the Kaplan-Meier survival curves based on the observed data. Figure 3 shows broad agreement between predicted mean survival curves and the observed Kaplan-Meier curves, although there is less agreement in later years when heavier censoring occurs. The separation of the curves in Fig. 3 also provides insight into the magnitude of survival differences among transplant recipients across the risk spectrum.

Extrapolation beyond the observed time period to predict mean survival

To demonstrate the value of flexible parametric models for extrapolation beyond the period of observed data, we created three hypothetical patient profiles and generated complete survival curves for each of them. Figure 4 shows the differences in survival curves and predicted mean survival by calculating the area under the curve for each patient profile.

Discussion

There are many examples in the transplant literature of analyses that have examined the influence of various factors on patient survival following kidney transplantation, most of which are based on Cox regression models [3–5]. The objective of the current analysis was to revisit post-transplant mortality using a different modelling technique that facilitates extrapolation of survival curves beyond the period of observed data and allows us to predict mean patient survival times.

Table 2 Final flexible parametric model fitted to combined derivation and validation dataset showing coefficients for each of the 3 spline terms for the baseline hazard function and hazard ratios for significant predictors of post-transplant patient survival ($N = 12,283$)

Baseline hazard (log hazard scale)	Coefficient	*p*-value	95 % CI
Restricted cubic spline 1	1.03	<0.001	0.97 - 1.09
Restricted cubic spline 2	-0.08	0.001	-0.12 - -0.03
Restricted cubic spline 3	-0.14	<0.001	-0.16 - -0.12
Constant	-3.97	<0.001	-4.31 - -3.63
	Hazard ratio	*p*-value	95 % CI
Recipient age			
18-29	Baseline		
30-39	1.15	0.423	0.81 - 1.64
40-49	1.79	<0.001	1.29 - 2.48
50-59	3.22	<0.001	2.35 - 4.43
> = 60	6.56	<0.001	4.79 - 8.98
Recipient gender			
Male	Baseline		
Female	0.89	0.028	0.80 - 0.99
Pre-emptive transplant			
No	Baseline		
Yes	0.66	<0.001	0.53 - 0.82
Primary renal diagnosis			
Glomerulonephritis	Baseline		
Diabetic nephropathy (type 1)	2.24	<0.001	1.84 - 2.73
Diabetic nephropathy (type 2)	1.59	0.001	1.21 - 2.09
Polycystic kidney disease	0.81	0.056	0.65 - 1.01
Other	1.28	0.007	1.07 - 1.53
Not reported	1.28	0.004	1.08 - 1.52
Donor hypertension			
No	Baseline		
Yes	1.27	<0.001	1.12 - 1.44
Not reported	1.20	0.023	1.03 - 1.42
Donor age			
< 40	Baseline		
40-49	1.26	0.004	1.08 - 1.48
50-59	1.26	0.003	1.08 - 1.47
> = 60	1.48	<0.001	1.26 - 1.74

Before fitting a flexible parametric model, we felt it was important to first consider how much historical data to include in the development of our model. A conventional approach might be to try and maximise sample size and number of years of follow-up in order to capture any changes in the hazard rate over as long a period as possible; however, we felt that this needed to be balanced with the objective of developing a predictive model that reflects current expectations of post-transplant survival. Although 20 years of historical data on transplants were available for analysis, we chose to restrict model development to the most recent 10 years for two main reasons. First, our exploratory analysis of Kaplan-Meier curves indicated that there had been significant improvements in survival for patients who received transplants between 2003 and 2012 in comparison to patients who received transplants between 1993 and 2002. Second, a wider number of variables that were of potential interest as predictors in the survival model were only available in the more recent subset of the data, including sufficient sample sizes to facilitate a comparison between recipients of organs from circulatory-death donors and brain-death donors. Although restricting model development to transplants performed between 2003 and 2012 reduced the overall sample size and limited the maximum duration of follow-up to 10 years, it was judged that on balance, an analysis based on the more recent subset of data would be a better reflection of current clinical practice and more appropriate given the intended use of the model for predicting survival. Quite often the decision about how much historical data to include in model development is determined primarily by availability of and access to information sources. While the decision that we took to only use the most recent 10 years of transplant data is not widely generalisable beyond our analysis, we advocate considering changes in the clinical context that might influence survival and using exploratory analysis to provide empirical guidance to inform this decision prior to model fitting.

A range of potential explanatory variables were considered during the model development process, but the final model was reduced to just four recipient factors (age, gender, primary renal diagnosis and pre-emptive transplant) and two donor factors (age and hypertension). Notably, we found no difference in death rates between recipients of kidneys from circulatory-death donors in comparison to brain-death donors. In addition, controlling for type 1 diabetic nephropathy as the primary renal diagnosis, we found no difference in death rates for recipients of kidney only transplants compared to recipients of combined kidney and pancreas transplants. These findings are broadly consistent with previous UK analyses based on Cox regression models. For example, Johnson et al identified recipient age, donor age and diabetes to be significant predictors of 5-year patient survival [3]. However, Johnson et al. found that a waiting time of 2 years or more and hypertension as the primary renal diagnosis in transplant recipients also significantly increased the risk of death at 5 years. In the present analysis, hypertension was grouped with other forms of renal vascular disease as a

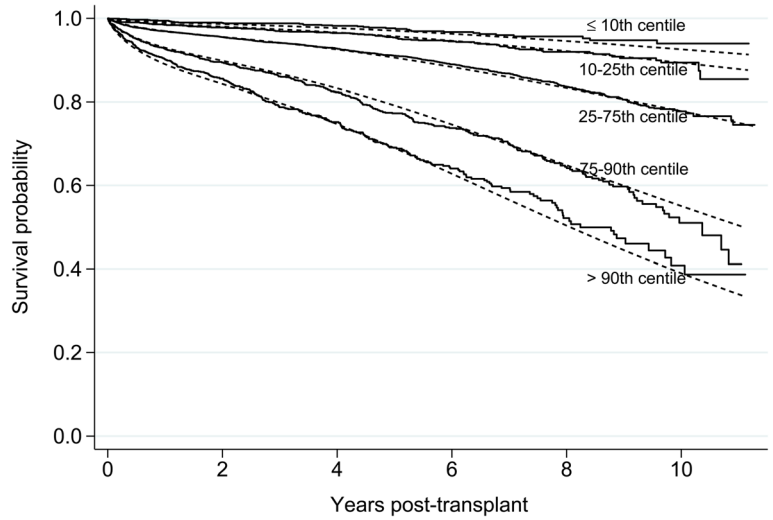

Fig. 3 Comparison of Kaplan-Meier curves based on observed data (solid lines) and predicted mean survival curves based on final flexible parametric model (dotted lines) by prognostic group

primary diagnosis, the latter which was also not found to be a significant predictor of survival by Johnson et al. The analysis by Johnson et al. was based on a slightly earlier time period and included patients who received transplants in the UK between 1995 and 2001; it did not include recipients of combined kidney and pancreas transplants or recipients of organs from circulatory-death donors. With respect to donor factors, the current analysis reaches similar conclusions to the findings of Watson et al. in the development of the UK Kidney Donor Risk Index (KDRI), which identified donor age group and donor hypertension as the two most

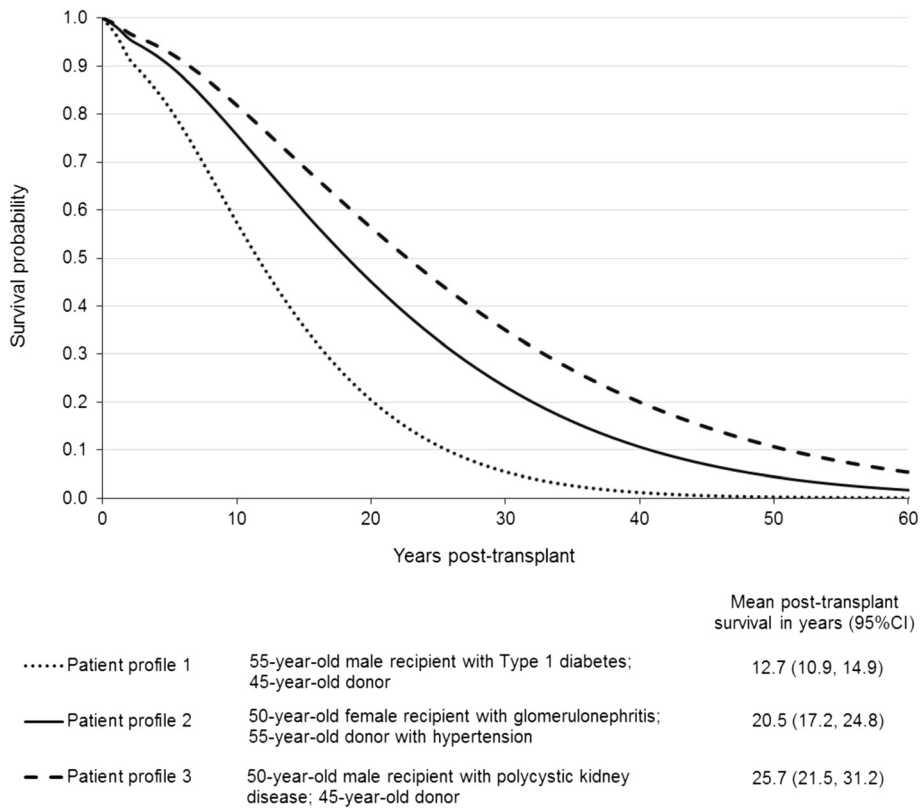

Fig. 4 Extrapolated survival curves with mean predicted survival for three different patient profiles

important variables with the largest influence on transplant outcomes [20].

The UK Transplant Registry is a rich source of historical data and among patients who received transplants after 2002, many of the variables that we explored in our model had either complete or only small amounts of missing data. However, the amount of missing data for variables such as recipient primary renal diagnosis and donor hypertension potentially introduce an additional source of uncertainty into our final predictive model. For donor hypertension, we performed multiple imputation and confirmed that this did not change the effect of this variable on post-transplant survival estimates. Nonetheless, information on donor hypertension in the registry is obtained from various sources, ranging from medical records to family members, and we were unable to control for consistency with respect to the definition of donor hypertension in the dataset. The prominence of donor hypertension in post-transplant survival models highlights the importance of improving the completeness and consistency with which this variable is recorded. In addition, the registry does not contain information on other factors such as comorbidities or dialysis history for transplant recipients, so we were unable to explore the potential effect of these variables on patient survival in the current analysis.

Conclusion

The flexible parametric approach to modelling survival offers several advantageous features. In comparison to semi-parametric approaches such as the Cox regression model, fully parametric models characterise the baseline hazard, which facilitates extrapolation beyond the period of observed data. In comparison to standard parametric models such as the Weibull, the use of restricted cubic splines allows for greater flexibility to accommodate more complex hazard functions that increase and decrease over time and are commonly encountered in medical research. The objective of this analysis was to demonstrate the application of a flexible parametric modelling approach to predict mean survival times for recipients of kidney transplants. The application of flexible parametric techniques to estimate mean survival in patients who are receiving dialysis would facilitate comparisons of survival differences between alternative treatment modalities. In addition to informing cost-effectiveness analyses, this approach may have a variety of applications, from the development of prognostic models for informing discussions with patients about treatment outcomes to the use of scoring tools as part of organ allocation schemes. Given the advantages of flexible parametric models, we feel that it is a particularly useful approach for conducting multivariable analysis of patient-level observational data when the goal is to predict long-term survival.

Abbreviations

AIC, Akaike information criterion; cRF, calculated reaction frequency; EPTS, expected post transplant survival; HLA, human leukocyte antigen; KDPI, kidney donor profile index; KDRI, kidney donor risk index; LYFT, life years from transplant; RRS, recipient risk score.

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Availability of data and materials

Data for this analysis were obtained from the UK Transplant Registry held by NHSBlood and Transplant, whose Data Access Policy is available from: http://www.odt.nhs.uk/uk-transplantregistry/data/data-access-policy/

Authors' contributions

All authors contributed to the design of the study. MLR obtained the registry data. BL performedthe analysis and drafted the manuscript. All authors read, revised and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Observational Research Ethics Committee of the London School of Hygieneand Tropical Medicine (Ref 6383).

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4. HEALTH-STATE UTILITY ESTIMATES

4.1. Introduction

A number of sources of health-state utility estimates among ERF patients have been reported in the published literature.[51,52] As a large, prospective study involving all renal and transplant centres in the UK, the ATTOM study was an important opportunity to collect additional health-state utility estimates that can add to existing knowledge in the following ways:

1. Collection of data using the newer 5-level version of the EQ-5D questionnaire, the EQ-5D-5L
2. Measurement of EQ-5D-5L responses in both transplant patients and matched controls from the waiting list
3. Collection of patient and treatment characteristics to facilitate multivariable regression analysis to identify factors that may lead to variations in health-state utility values.

4.2. Research Paper 3:

Research Paper 3, entitled *Estimating health-state utility values in kidney transplant recipients and waiting-list patients using the EQ-5D-5L*, describes the characteristics of transplant recipients and matched controls recruited into the ATTOM study and their EQ-5D-5L responses converted into index scores. In this paper, because of the structure of the simulation model, separate multivariable regression models were fitted to predict health-state utility values for transplant recipients and matched controls. Note that due to the international audience of the target journal for Research Paper 3, the term end-stage renal disease (ESRD) is used in place of ERF.

The health-state utility estimates captured in the ATTOM study will be used to quality adjust survival in the simulation model comparing alternative allocations schemes. These values will be used not only to estimate pre- and post-transplant QALYs for all patients under all

allocation schemes, but also to calculate QALY differences between transplantation and dialysis to inform prioritisation of patients on the waiting list under the QALY-maximising approach. Box 4.1 provides a worked example to demonstrate the application of the health-state utility estimates presented in Research Paper 3 to the simulation model. This example calculates the expected QALY gain from transplant for two hypothetical patients and determines which patient will receive a given donor kidney under the QALY-maximising approach to allocation.

In recognition of the fact that not all covariates captured in the ATTOM study will be relevant to other researchers wishing to undertake cost-effectiveness analyses in the ERF patient population, Appendix 5 provides a summary of alternate regression models that can be used for predicting health-state utility estimates with different combinations of predictor variables.

Box 4.1 Worked example to compare QALY gains from transplant for two hypothetical patients on the waiting list

In this example, we consider how to allocate a kidney from a 45-year-old donor with no history of hypertension to one of two hypothetical patients on the transplant waiting list under the QALY-maximisation allocation scheme.

Patient 1: 55-year-old Asian female, primary renal diagnosis diabetes
Patient 2: 60-year-old White male, primary renal diagnosis pyelonephritis

Expected post-transplant survival and expected survival on the waiting list for each patient can be derived using the predictive models described in Research Paper 2 and Appendix 4. Survival estimates in this example are rounded to the nearest full year for simplicity.

Estimates of health-state utility values for each patient can be derived using the models presented in Research Paper 3.

First, we calculate QALYs if Patient 1 receives the transplant:

Expected post-transplant survival in years = 9

Using the regression model from Table 4.3 in Research Paper 3:

Calculate post-transplant health-state utility value:
= Constant + (EQ-5D at 6 months) + Female + Asian + Diabetes
= 0.809 + 0.053 – 0.019 – 0.030 – 0.086
= 0.727

Assuming post-transplant health-state utility remains constant over time, calculate total QALYs if patient receives the transplant:
= 9 x 0.727
= 6.543

Next, we calculate QALYs if Patient 1 remains on the waiting list (dialysis):

Expected survival on waiting list in years = 4 years

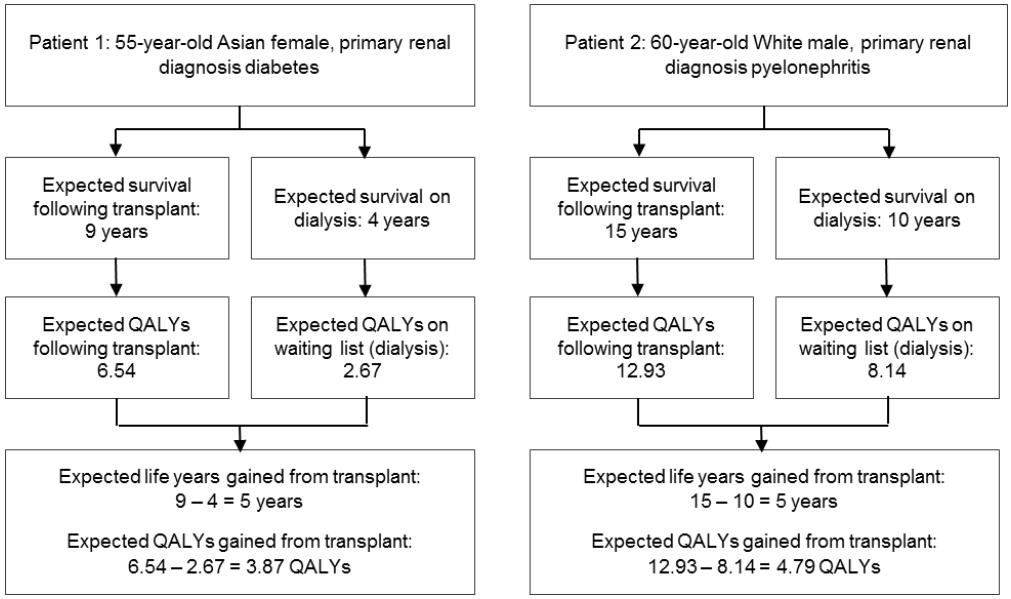
Using the regression model from Table 4.4 in Research Paper 3:

Calculate dialysis health-state utility < year 1:
= Constant + (Time on dialysis < 1 year) + Female + Asian + Diabetes
= 0.878 – 0.053 – 0.048 – 0.054 – 0.055
= 0.668

Calculate dialysis health-state utility year 1-3:
= Constant + (Time on dialysis 1-3 years) + Female + Asian + Diabetes
= 0.878 – 0.055 -0.048 -0.054 – 0.055
= 0.666

Calculate total QALYs if patient remains on the waiting list:
= (1 x 0.668) + (3 x 0.666)
= 2.666

Repeat the same process to calculate QALYs for Patient 2 and then compare the expected QALY gain from transplant for Patient 1 and Patient 2:



Under a QALY-maximisation approach to kidney allocation, Patient 2 would be prioritised to receive the kidney.

RESEARCH PAPER COVER SHEET – Research Paper 3

SECTION A – Student Details

Student	Bernadette Li
Principal Supervisor	John Cairns
Thesis Title	Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Value in Health
Please list the paper's authors in the intended authorship order:	Bernadette Li, John A. Cairns, Heather Draper, Christopher Dudley, John L. Forsythe, Rachel J. Johnson, Wendy Metcalfe, Gabriel C. Oniscu, Rommel Ravanan, Matthew L. Robb, Paul Roderick, Charles R. Tomson, Christopher J. E. Watson, J. Andrew Bradley
Stage of publication	Submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had primary responsibility for reviewing the relevant literature, performing the statistical analysis and drafting the paper.

Student Signature:  **Date:** 27 July 2016

Supervisor Signature:  **Date:** 27 July 2016

Estimating health-state utility values in kidney transplant recipients and waiting-list patients using the EQ-5D-5L

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Key words: EQ-5D-5L, health-state utility values, kidney transplantation, multivariable regression

Running title: Utility values in kidney transplantation

ABSTRACT

Objectives: Previous studies have shown that recipients of kidney transplants have higher health utility scores than patients receiving dialysis, but how scores vary in relation to patient-level characteristics or treatment factors such as comorbidities and time on dialysis has not been well characterized.

Methods: As part of the prospective observational study entitled Access to Transplantation and Transplant Outcomes Measures (ATTOM), we captured information on patient and treatment characteristics for a cohort of incident adult kidney transplant recipients and a cohort of matched controls from the kidney transplant waiting list in the United Kingdom. We assessed patients' health status using the EQ-5D-5L questionnaire and conducted multivariable regression analyses of index scores in each cohort.

Results: EQ-5D-5L responses at study recruitment were available for 1807 transplant recipients and 1704 patients on the waiting list. Mean index scores were higher in transplant recipients at six months following transplant surgery (0.827) compared with patients on the waiting list (0.772). In multivariable analyses, age was not a significant predictor of index scores. Female gender, Asian ethnicity, a primary renal diagnosis of diabetic nephropathy, smoking and the presence of comorbidities such as mental illness or ischemic heart disease were associated with lower utility scores in both cohorts. For patients on the waiting list, increasing time on dialysis was associated with lower utility scores.

Conclusions: The current study provides new insights into variations in health-state utility values from a single source that can be used to inform future cost-effectiveness evaluations in patients receiving kidney transplants or dialysis.

INTRODUCTION

Estimates of health-state utility values are required to undertake cost-effectiveness evaluations in which quality-adjusted life years (QALYs) are the outcome of interest. Utility estimates can be captured using patient-reported questionnaires as part of a clinical trial or observational study but in the absence of primary data, estimates are often sourced from published literature

End-stage renal disease (ESRD) is a chronic condition that has been shown to impact patients' health status. Numerous studies have been conducted to measure utility values among patients receiving renal replacement therapy. Meta-analyses of published studies suggest that higher utility values are generally observed among patients who receive kidney transplants in comparison to dialysis [1, 2]. Pooling results across studies can be an appealing approach to obtain a summary estimate (weighted average with associated uncertainty) of a utility value for each health state of interest that can be used to quality adjust survival in a cost-effectiveness model. However caution is required when undertaking meta-analyses of health-state utility values because there is often considerable variability in utility scores as a result of using different valuation methods across studies [3]. A further limitation of pooled utility estimates is that they may not be able to take into account heterogeneity of patient characteristics, treatment or measurement factors that could explain variations in utility scores for a given condition. Individual utility studies often have small sample sizes and each study may collect only a limited number of covariates that are not comparable across studies.

Datasets that enable analysis of the effect of covariates such as age, gender or comorbidities on health-state utility values are increasingly important in order to facilitate the use of patient-level simulation techniques in economic evaluations. The Access to Transplantation and Transplant Outcomes Measures (ATTOM) study is a prospective observational study that involved collection of demographic, treatment and health outcomes data from all 72 renal units in the United Kingdom. As part of this study, we recruited a cohort of incident kidney transplant and combined (simultaneous) pancreas and kidney

(SPK) transplant recipients as well as a cohort of prevalent waiting-list patients selected as controls for transplanted patients [4]. Collection of health-state utility values as part of the ATTOM study has facilitated the following objectives of the current analysis:

1. To report health-state utility values for a large sample of kidney transplant recipients and prevalent waiting-list patients using the 5-level version of the EQ-5D questionnaire.
2. To conduct multivariable regression analyses to understand patient and treatment factors that lead to variations in health-state utility values among kidney transplant recipients and patients on the waiting list that can then be used to inform quality adjustment of life years in cost-effectiveness evaluations.

METHODS

The EQ-5D is a widely used generic instrument for describing and valuing health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The original version of the EQ-5D has three levels of response categories for each dimension, ranging from no problems to extreme problems [5]. More recently, a 5-level version of the questionnaire (EQ-5D-5L) has been developed in an attempt to improve the instrument's sensitivity and to reduce ceiling effects [6].

Patients aged 18-75 years who received a kidney or SPK transplant in the UK between November 1, 2011 and September 30, 2013 were approached for recruitment into the ATTOM study. EQ-5D-5L questionnaires were administered to transplant recipients at recruitment and were supposed to be captured within 90 days of transplantation, although we noted a proportion of patients completed the questionnaire prior to surgery. Transplant recipients who were recruited during the first 6 months of the study were asked to complete the EQ-5D-5L again approximately 6 months after transplantation. We aimed to collect EQ-5D-5L assessments at 6 months in 50% of all transplant patients; we were unable to collect data at 6 months in all patients because study nurses were only on site and available to administer questionnaires over a total period of 12 months.

Prevalent patients on the waiting list were selected as matched controls on a 1:1 basis for every incident transplant recipient based on the following criteria: transplant center, age (within five years), time on the waiting list, type of transplant (kidney only or SPK), diabetes status (as a primary renal diagnosis) and dialysis status (at the time of listing) [4]. For matched controls, the EQ-5D-5L responses were captured within 90 days of recruitment. Matched controls were recruited from prevalent patients who had been on the waiting list and on dialysis for varying periods of time. Therefore, the EQ-5D-5L assessment at recruitment in matched control patients did not represent the start of dialysis as a treatment modality.

Questionnaire responses were converted to index scores using the EQ-5D-5L value set for England reported by Devlin et al [7]. We used logistic regression to explore if there were any factors that increased the likelihood of having a missing EQ-5D-5L index score at recruitment in both the transplant and waiting-list cohorts and identified Asian ethnicity as a potential predictor of missing responses in both cohorts. We performed multiple imputation creating 20 imputed datasets using predictive mean matching drawing from 3 nearest neighbors for missing EQ-5D-5L index scores in transplant recipients at recruitment. Among patients on the waiting list, in addition to 13% with missing EQ-5D-5L index scores, approximately 30% had missing information about duration of dialysis and therefore multiple imputation in this cohort was performed using predictive mean matching and chained equations. Due to the extent of missing EQ-5D-5L responses at 6 months in the transplant cohort, we did not feel it was appropriate to attempt imputation of these scores; instead we performed chi-squared tests for equality of proportions to provide reassurance that the characteristics of the patients with EQ-5D-5L index scores at 6 months were broadly representative of the overall population of transplant recipients recruited into the study.

For the multivariable regression analysis of EQ-5D-5L index scores in transplant patients, we considered the following covariates that were collected in the ATTOM study: age, gender, ethnicity, deceased versus living donor, kidney alone versus SPK transplant, primary renal diagnosis, smoking status and comorbidities that occurred in at least 5% of patients. Initially we fitted separate ordinary least squares (OLS) regression models to

estimate EQ-5D-5L index scores among transplant recipients at recruitment and at 6 months. However, given the lower than expected number of EQ-5D-5L responses at 6 months, we then conducted a combined analysis of EQ-5D-5L index scores using an indicator variable for time of assessment (recruitment versus 6 months) and the cluster option to take into account dependence between multiple EQ-5D-5L responses in the same patient. For patients on the transplant waiting list, the multivariable regression model explored the following covariates: age, gender, ethnicity, dialysis modality, primary renal diagnosis, smoking status, comorbidities that occurred in at least 5% of patients and time on dialysis. Backwards elimination was used to inform variable selection using a threshold P-value of 0.15 as a proxy to performing an all-subsets procedure and selecting the model based on the Akaike Information Criterion (AIC) [8].

As the main objective of this analysis is to estimate health-state utility values for use as inputs in cost-effectiveness models, we compared mean predicted index scores based on the final fitted multivariable regression models to mean observed index scores in various subgroups containing at least 20 patients each.

Previous studies have reported that OLS regression models tend to overestimate index scores at low values and underestimate index scores at high values. Using complete cases only, we explored a number of alternative approaches including Tobit regression and fitting an adjusted limited dependent variable mixture model. However, neither of these approaches led to notable reductions in root mean squared error (RMSE) and were not pursued any further within the current analysis.

All analyses were conducted in Stata (Version 13, Stata Corp, College Station, Texas, USA).

RESULTS

A total of 2252 transplant recipients and 1959 patients on the transplant waiting list were recruited into the ATTOM study. Figure 1 shows the number of completed EQ-5D-5L assessments that were available for analysis for each cohort. The proportion of patients

who completed the questionnaire at recruitment was 80% and 87% in the transplant recipient and waiting-list cohorts respectively. Among transplant recipients, the proportion of patients who completed the questionnaire at 6 months was 23%, less than half of the target of 50%.

Among transplant recipients who completed the EQ-5D-5L at recruitment, 134 (7.4%) completed the questionnaire prior to transplantation rather than in the 90-day period following transplantation. Of the 134 patients who completed the questionnaire prior to transplantation, 117 were recipients of kidneys from living donors. Mean EQ-5D-5L index scores in patients who completed the questionnaire prior to transplantation were higher than those who completed the questionnaire after transplantation, although the difference we observed was not statistically significant (0.803 vs. 0.772, P-value = 0.078). When we simultaneously controlled for other patient and treatment characteristics, the timing of the EQ-5D-5L assessment (before versus after transplantation) was not found to be a significant predictor of index score. Therefore, we retained the 134 questionnaire responses that had been completed prior to transplantation in our analysis of index scores at recruitment so as not to bias the sample by removing a large number of recipients of living donor transplants.

Table 1 provides a univariate summary of EQ-5D-5L index scores by patient and treatment characteristics in each cohort. Among transplant recipients, we observed a statistically significant difference between mean EQ-5D-5L index scores at recruitment and at 6 months (0.774 vs. 0.827, P-value < 0.001). For the multivariable analysis in the transplant cohort, we initially fit separate regression models to estimate index scores at recruitment and at 6 months. We noted consistency between the two models in the direction and magnitude of coefficients for most covariates before proceeding to a combined analysis of scores from both time-points. Table 2 shows the variables that were retained in the final model fitted to the combined sample. The following variables were associated with lower index scores in transplant recipients: female gender, Asian ethnicity, a primary renal diagnosis of diabetic nephropathy, current or ex-smoking status and the presence of comorbidities including ischemic heart disease, respiratory disease, malignancy or mental illness, which included

psychosis, bipolar disorder or depression as recorded in case notes. Higher index scores were seen in recipients of living donor transplants compared with deceased donor transplants.

The final multivariable regression model of EQ-5D-5L index scores for patients on the transplant waiting list is shown in Table 3. Similar to the findings of the analysis for transplant recipients, female gender, Asian ethnicity, a primary diagnosis of diabetic nephropathy and the presence of ischemic heart disease or mental illness were significant predictors of lower scores among patients on the waiting list. In addition, the model showed that patients who were pre-emptively listed for transplantation before starting dialysis had higher utility scores and health status appeared to decline the longer patients remain on dialysis.

To assess the performance of the final multivariable regression models, Table 4 summarizes mean predicted and mean observed EQ-5D-5L index scores for each cohort in all possible subgroups with a sample size of at least 20 patients. For transplant recipients, we only summarized comparisons of scores at 6 months post-transplant as these are more likely to be of relevance for use in cost-effectiveness models than scores measured at recruitment. Table 4 shows that the magnitude of error between predicted and observed mean scores varies across subgroups up to a maximum of ±0.042.

DISCUSSION

Primary collection of data on health-state utility values to inform cost-effectiveness evaluations can be a time consuming and resource-intensive exercise. In situations where primary data collection is not feasible, estimates of health-state utility values are often sourced from the published literature. As the volume of published utility estimates for many disease areas continues to grow, analysts undertaking cost-effectiveness evaluations increasingly need to justify their approach for selecting what values to use as inputs in their models [9, 10]. One strategy is to select a single study from the published literature that most closely reflects the patient population (inclusion/exclusion criteria), disease stage and health states defined in the model. In contrast, if multiple studies estimating health-state

utility values for the same disease state have been published, another strategy is to pool estimates across studies using meta-analytic techniques. However in some cases, neither of these strategies is entirely satisfactory; a single study may not report utility estimates for the full range of health states of interest in the cost-effectiveness model but meta-analysis may be unsuitable due to high levels of heterogeneity arising from differences in the methods used to elicit and value health states [3, 11]. This has given rise to the practice of selecting health-state utility estimates from separate studies to inform the different comparator arms in a cost-effectiveness model, to distinguish between patient subgroups or to capture decrements in utility due to adverse events and comorbidities. Drawing on data from disparate sources to inform the same cost-effectiveness model can potentially lead to inconsistent or implausible values and raises additional questions about how utility values should be combined [11, 12].

Published systematic reviews have identified a large number of studies capturing health-state utility values among patients receiving renal replacement therapy. In both Liem et al. and Wyld et al., health-state utility values were more extensively studied in dialysis than in transplant patients and only a minority of studies evaluated health status in both dialysis and transplant patients at the same time [1, 2]. Both reviews concluded that higher utility values are seen in transplant recipients compared to dialysis patients but these pooled comparisons do not explicitly take into account adjustments between these groups for potential differences in patient demographics such as age, gender and ethnicity or comorbidities.

The ATTOM study recruited incident kidney and SPK transplant recipients and also identified a cohort of prevalent patients on the transplant waiting list as matched controls. In addition to administering the EQ-5D-5L questionnaire, we collected data on a range of patient and treatment characteristics to allow us to explore their effects on utility scores. Our analysis confirms previous findings that transplant recipients have higher utility scores than dialysis patients. The mean utility score at 6 months for transplant recipients in our study was similar to the values reported in meta-analyses by Liem at al. (0.81) and Wyld et al. (0.82) [1, 2]. Where longitudinal studies were available, both of these meta-analyses

examined utility scores that were measured at or closest to 12 months post-transplant rather than 6 months. Our study also provides a source of utility estimates for a cohort of patients on the transplant waiting list that reflects the subset of ESRD patients who were considered suitable candidates for transplantation. The mean utility score for patients on the transplant waiting list in our study was 0.772, higher than the mean values reported among dialysis patients by Liem et al. (0.56 for hemodialysis, 0.68 for peritoneal dialysis patients) and Wyld et al. (0.71) [1, 2]. The waiting-list population in our study was a prevalent cohort that included patients who had been receiving dialysis for varying periods of time and also included some patients who had not yet commenced dialysis. This provided an important opportunity to quantify the magnitude of decline in health status associated with time spent on dialysis.

We made a number of other notable observations based on multivariable regression analyses: Firstly, age was not found to be a significant predictor of index scores. Although the background effect of age on health state valuations using the time trade-off method has been established [13], the current analysis suggests that when controlling for other factors affecting health status such as comorbidities, primary renal diagnosis and time on treatment, age did not appear to have any additional explanatory effect. Secondly, gender and Asian ethnicity were associated with lower scores among both transplant recipients and patients on the waiting list, although the effect was more pronounced for those on the waiting list. Thirdly, diabetic nephropathy as a primary renal diagnosis was associated with lower index scores in both cohorts. Taken together, these results provide insight into how much health status can vary, particularly for patients on the transplant waiting list. In our comparison of mean utility scores across patient subgroups, we observed differences in index scores of almost 0.20 and this does not even include subgroups of patients with comorbidities such as mental illness that were shown to be associated with the largest decrements in health status. A greater understanding of which types of patients experience poorer health status while on the transplant waiting list compared to health status following transplant could provide a basis for assessing the impact of prioritizing different types of patients for transplantation within the context of organ allocation schemes.

The main strengths of this study are the large sample sizes combined with comprehensive collection of data on patient and treatment factors that allowed us to explore their influence on health status among both transplant recipients and patients on the transplant waiting list. In the meta-analysis conducted by Liem et al., EQ-5D scores for a given treatment modality were based on studies with sample sizes ranging from as few as 27 patients to a maximum of 455 patients [1]. In our analysis, we assessed the final multivariable regression models by comparing mean observed and mean predicted index scores and demonstrated that they performed satisfactorily overall across most patient subgroups.

A limitation of the present study is the lower number of EQ-5D-5L responses captured among transplant recipients at 6 months. Although we were primarily interested in estimating health status at 6 months rather than at the time of transplant surgery, we included questionnaire responses collected at both time-points in the multivariable analysis because the large sample size at recruitment could help improve the precision of the coefficient estimates in the regression model. More complete data at 6 months as well as additional longitudinal assessments would have been desirable to explore if utility values change over time. For the multivariable analyses, we restricted our approach to the use of OLS regression. While several regression modelling approaches have been proposed in the literature to deal with the bounded and skewed nature of health state utility data [14-17], we believe that OLS regression is justified in this case because the primary objective was to estimate mean utility scores and, even with missing EQ-5D-5L responses, the sample sizes were relatively large. Exploration of alternative modelling approaches using Tobit regression or mixture models did not appear to reduce RMSE. Nonetheless, there are a number of other approaches that could be applied to our dataset to facilitate a more comprehensive comparison of different methods in future research.

When conducting cost-effectiveness evaluations of ESRD patients receiving dialysis or transplantation, careful consideration should be given to the treatment strategies under comparison and selection of the most appropriate utility values that reflect the characteristics of the patient populations of interest. The current study provides new insights

into variations in health-state utility values from a single source that can be used to inform such evaluations in the future.

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EQ-5D™ is a trade mark of the EuroQol Group. The EQ-5D-5L was used in the ATTOM study with permission from the EuroQol Group Foundation.

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Table 1 Univariate summary of EQ-5D-5L index scores by patient and treatment characteristics

	Incident transplant recipients at recruitment			Incident transplant recipients at 6 months			Prevalent waiting list patients at recruitment		
Patients with EQ-5D-5L responses	1807			512			1704		
EQ-5D-5L index score									
Mean (SD)	0.774 (0.192)			0.827 (0.213)			0.772 (0.219)		
Interquartile range	0.698 - 0.898			0.766 -1.003			0.682 - 0.944		
	n (%)		EQ-5D-5L index Mean (SD)*	n (%)		EQ-5D-5L index Mean (SD)*	n (%)		EQ-5D-5L index Mean (SD)*
Age group									
18-29	187	(10.4%)	0.805 (0.179)	41	(8.0%)	0.910 (0.167)	137	(8.0%)	***0.801 (0.209)***
30-39	253	(14.0%)	0.770 (0.206)	62	(12.1%)	0.854 (0.192)	224	(13.2%)	***0.757 (0.193)***
40-49	441	(24.4%)	0.769 (0.187)	128	(25.0%)	0.817 (0.222)	412	(24.2%)	***0.766 (0.230)***
50-59	473	(26.2%)	0.767 (0.196)	140	(27.3%)	0.809 (0.225)	481	(28.2%)	***0.757 (0.232)***
>60	453	(25.0%)	0.778 (0.189)	141	(27.5%)	0.818 (0.212)	450	(26.4%)	***0.792 (0.207)***
Gender									
Male	1,127	(62.4%)	***0.783 (0.193)***	307	(60.0%)	0.827 (0.221)	984	(57.8%)	***0.791 (0.211)***
Female	680	(37.6%)	***0.761 (0.190)***	205	(40.0%)	0.827 (0.202)	720	(42.3%)	***0.747 (0.227)***
Ethnicity									
White	1,523	(84.3%)	0.778 (0.188)	452	(88.3%)	0.827 (0.212)	1,299	(76.2%)	***0.780 (0.213)***
Asian	146	(8.1%)	0.737 (0.213)	28	(5.5%)	0.848 (0.166)	192	(11.3%)	***0.725 (0.257)***
Black	104	(5.8%)	0.781 (0.206)	24	(4.7%)	0.800 (0.277)	178	(10.5%)	***0.768 (0.208)***
Other	34	(1.9%)	0.745 (0.212)	8	(1.6%)	0.824 (0.237)	35	(2.1%)	***0.764 (0.227)***

Primary renal diagnosis									
Glomerulonephritis	318	(17.6%)	***0.791 (0.190)***	96	(18.7%)	***0.865 (0.176)***	251	(14.7%)	***0.792 (0.210)***
Diabetic nephropathy	248	(13.7%)	***0.691 (0.226)***	60	(11.7%)	***0.718 (0.267)***	195	(11.5%)	***0.708 (0.228)***
Renal vascular disease	111	(6.2%)	***0.801 (0.165)***	26	(5.1%)	***0.856 (0.180)***	112	(6.6%)	***0.769 (0.236)***
Polycystic kidney disease	275	(15.2%)	***0.797 (0.160)***	67	(13.1%)	***0.851 (0.195)***	288	(16.9%)	***0.793 (0.200)***
Pyelonephritis	217	(12.0%)	***0.783 (0.186)***	63	(12.3%)	***0.828 (0.208)***	195	(11.4%)	***0.770 (0.239)***
Other	638	(35.3%)	***0.781 (0.190)***	200	(39.1%)	***0.829 (0.216)***	663	(38.9%)	***0.776 (0.215)***
Transplanted organs									
Kidney only	1,694	(93.7%)	***0.779 (0.189)***	489	(95.5%)	0.830 (0.210)	-		-
Kidney and pancreas	113	(6.3%)	***0.706 (0.221)***	23	(4.5%)	0.756 (0.273)	-		-
Donor type									
Brain-death donor	579	(32.0%)	***0.746 (0.201)***	155	(30.3%)	***0.784 (0.236)***	-		-
Circulatory-death donor	562	(31.1%)	***0.765 (0.195)***	165	(32.2%)	***0.818 (0.205)***	-		-
Living donor	666	(36.9%)	***0.808 (0.176)***	192	(37.5%)	***0.868 (0.195)***	-		-
Dialysis modality (at listing)									
Haemodialysis	-		-	-		-	1,140	(66.9%)	***0.753 (0.228)***
Peritoneal dialysis	-		-	-		-	255	(15.0%)	***0.786 (0.201)***
Pre-dialysis	-		-	-		-	298	(17.5%)	***0.833 (0.188)***
Missing	-		-	-		-	11	(0.7%)	***0.824 (0.167)***
Time on dialysis (at EQ-5D completion)									
Pre-dialysis	-		-	-		-	98	(5.8%)	***0.827 (0.213)***
<1 year	-		-	-		-	224	(13.2%)	***0.777 (0.220)***
1-3 years	-		-	-		-	389	(22.8%)	***0.768 (0.219)***
>3 years	-		-	-		-	457	(26.8%)	***0.741 (0.228)***
Missing	-		-	-		-	536	(31.5%)	***0.789 (0.208)***
Ischemic heart disease									
No	1,646	(91.1%)	***0.778 (0.189)***	462	(90.2%)	***0.838 (0.195)***	1,519	(89.1%)	***0.779 (0.217)***

Yes	154	(8.5%)	***0.735 (0.224)***	48	(9.4%)	***0.730 (0.321)***	166	(9.7%)	***0.716 (0.220)***
Missing	7	(0.4%)	***0.777 (0.092)***	2	(0.4%)	***0.616 (0.547)***	19	(1.1%)	***0.703 (0.309)***
Respiratory disease									
No	1,651	(91.4%)	***0.779 (0.188)***	464	(90.6%)	0.830 (0.209)	1,565	(91.8%)	0.773 (0.219)
Yes	150	(8.3%)	***0.728 (0.227)***	47	(9.2%)	0.794 (0.255)	119	(7.0%)	0.772 (0.203)
Missing	6	(0.3%)	***0.773 (0.100)***	1	(0.2%)	1.003 (0.000)	20	(1.2%)	0.707 (0.301)
Malignancy									
No	1,687	(93.4%)	***0.777 (0.190)***	466	(91.0%)	0.829 (0.214)	1,563	(91.7%)	0.773 (0.218)
Yes	114	(6.3%)	***0.731 (0.225)***	45	(8.8%)	0.807 (0.210)	122	(7.2%)	0.770 (0.213)
Missing	6	(0.3%)	***0.773 (0.100)***	1	(0.2%)	1.003 (0.000)	19	(1.1%)	0.703 (0.309)
Mental illness									
No	1,697	(93.9%)	***0.781 (0.189)***	483	(94.3%)	***0.835 (0.209)***	1,559	(91.5%)	***0.783 (0.211)***
Yes	104	(5.8%)	***0.673 (0.214)***	28	(5.5%)	***0.685 (0.248)***	125	(7.3%)	***0.654 (0.264)***
Missing	6	(0.3%)	***0.773 (0.100)***	1	(0.2%)	***1.003 (0.000)***	20	(1.2%)	***0.695 (0.303)***
Smoking status									
Non-smoker	970	(53.7%)	***0.785 (0.181)***	277	(54.1%)	***0.848 (0.201)***	854	(50.1%)	***0.785 (0.222)***
Current smoker	184	(10.2%)	***0.759 (0.209)***	43	(8.4%)	***0.778 (0.242)***	238	(14.0%)	***0.743 (0.226)***
Unknown	156	(8.6%)	***0.791 (0.181)***	41	(8.0%)	***0.877 (0.175)***	225	(13.2%)	***0.756 (0.220)***
Ex-smoker	497	(27.5%)	***0.755 (0.208)***	151	(29.5%)	***0.788 (0.230)***	387	(22.7%)	***0.772 (0.204)***

*Bold / italics denote P<0.05 for comparison of means using two-sample t-test / one-way analysis of variance. SD, standard deviation.

Table 2 Multivariable regression model for EQ-5D-5L index scores in transplant recipients at study recruitment and at 6 months (multiply imputed dataset at baseline only, n = 2,241 patients with 2,750 observations)

	Coefficient	Std. Error	P-value	95% CI
Constant	0.809	0.008	<0.001	(0.793, 0.824)
EQ-5D assessment at study recruitment	Reference			
EQ-5D assessment at 6 months	0.053	0.009	<0.001	(0.035, 0.071)
Male	Reference			
Female	-0.019	0.009	0.026	(-0.036, -0.002)
Ethnicity White, Black or Other	Reference			
Ethnicity Asian	-0.030	0.017	0.092	(-0.064, 0.005)
Deceased donor transplant	Reference			
Living donor transplant	0.034	0.009	<0.001	(0.017, 0.051)
Primary renal diagnosis other	Reference			
Diabetic nephropathy	-0.086	0.015	<0.001	(-0.115, -0.057)
Presence of comorbidities				
Ischemic heart disease	-0.040	0.020	0.052	(-0.079, 0.000)
Respiratory disease	-0.045	0.018	0.016	(-0.081, -0.008)
Malignancy	-0.040	0.018	0.026	(-0.075, -0.005)
Mental illness	-0.098	0.022	<0.001	(-0.141, -0.056)
Non-smoker / unknown status	Reference			
Current smoker	-0.025	0.015	0.099	(-0.056, 0.005)
Ex-smoker	-0.029	0.010	0.004	(-0.049, -0.009)

Table 3 Multivariable regression model for EQ-5D-5L index scores (multiply imputed dataset) in patients on the transplant waiting list (n=1931)

	Coefficient	Std. Error	P-value	95% CI
Constant	0.878	0.015	<0.001	(0.850, 0.907)
Male	Reference			
Female	-0.048	0.010	<0.001	(-0.069, -0.028)
Ethnicity White, Black or Other	Reference			
Ethnicity Asian	-0.054	0.017	0.002	(-0.088, -0.020)
Primary renal diagnosis other	Reference			
Diabetic nephropathy	-0.055	0.016	0.001	(-0.087, -0.023)
Time on dialysis				
Pre-dialysis	Reference			
<1 year	-0.053	0.019	0.005	(-0.090, -0.016)
1-3 years	-0.055	0.017	0.001	(-0.088, -0.022)
>3 years	-0.071	0.016	<0.001	(-0.103, -0.039)
Presence of comorbidities				
Ischemic heart disease	-0.048	0.018	0.007	(-0.082, -0.013)
Mental illness	-0.118	0.021	<0.001	(-0.158, -0.077)
Non-smoker / ex-smoker / unknown	Reference			
Current smoker	-0.027	0.012	0.029	(-0.051, -0.003)

Table 4 Mean predicted versus mean observed EQ-5D-5L index scores (all subgroups with ≥20 patients)

(A) Transplant recipients

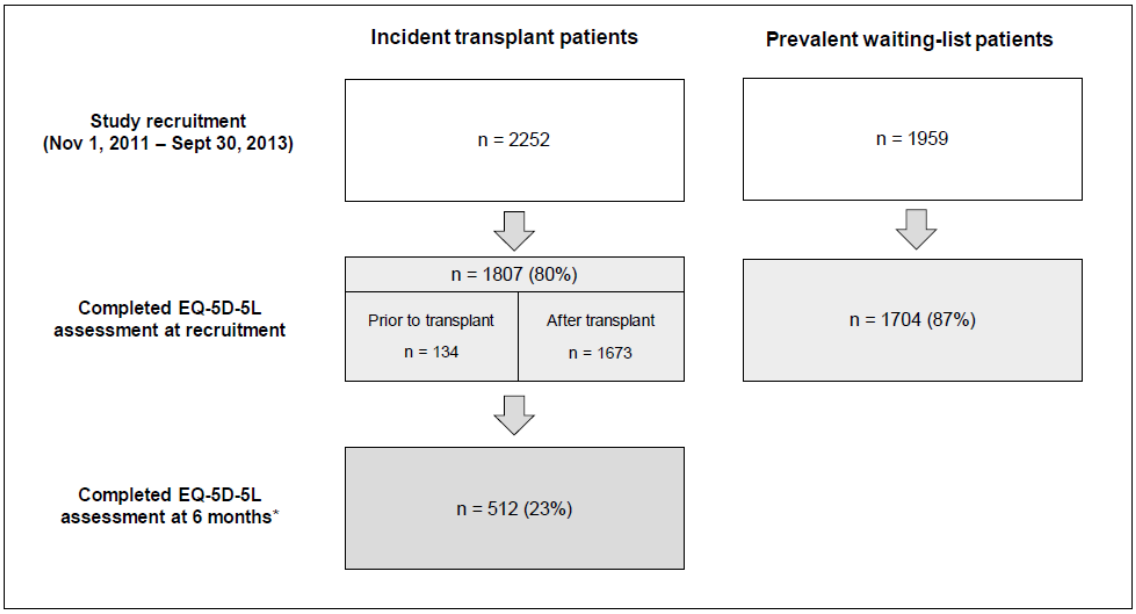
	n	Predicted	Observed	Error
Male, non-Asian, deceased donor transplant, primary renal diagnosis other, none of listed comorbidities, non-smoker	60	0.862	0.888	-0.026
Male non-Asian, living donor transplant, primary renal diagnosis other, none of listed comorbidities, non-smoker	61	0.896	0.900	-0.004
Female, non-Asian, deceased donor transplant, primary renal diagnosis other, no ne of listed comorbidities, non-smoker	44	0.843	0.844	-0.001
Female non-Asian living donor transplant, primary renal diagnosis other, none of listed comorbidities, non-smoker	34	0.877	0.889	-0.012

(B) Waiting-list patients

	n	Predicted	Observed	Error
Male, non-Asian, primary renal diagnosis other, pre-dialysis, none of listed comorbidities, non-smoker	30	0.878	0.886	-0.008
Male, non-Asian, primary renal diagnosis other, dialysis <1 year, none of listed comorbidities, non-smoker	64	0.825	0.825	0.000
Male, non-Asian, primary renal diagnosis other, dialysis 1-3 years, none of listed comorbidities, non-smoker	87	0.824	0.864	-0.040
Male, non-Asian, primary renal diagnosis other, dialysis >3 years, none of listed comorbidities, non-smoker	112	0.808	0.816	-0.008
Male, non-Asian, primary renal diagnosis other, dialysis 1-3 years, none of listed comorbidities, smoker	55	0.797	0.755	0.042
Male, non-Asian, primary renal diagnosis other, dialysis >3 years, none of listed comorbidities, smoker	44	0.781	0.773	0.008
Male, non-Asian, primary renal diagnosis diabetic nephropathy, dialysis 1-3 years, none of listed comorbidities, non-smoker	20	0.769	0.750	0.019

Female, non-Asian, primary renal diagnosis other, pre-dialysis, none of listed comorbidities, non-smoker	28	0.830	0.852	-0.022
Female, non-Asian, primary renal diagnosis other, <1 year, none of listed comorbidities, non-smoker	60	0.777	0.779	-0.002
Female, non-Asian, primary renal diagnosis other, 1-3 years, none of listed comorbidities, non-smoker	60	0.776	0.803	-0.027
Female, non-Asian, primary renal diagnosis other, >3 years, none of listed comorbidities, non-smoker	99	0.759	0.753	0.006
Female, non-Asian, primary renal diagnosis other, 1-3 years, none of listed comorbidities, smoker	34	0.749	0.728	0.021
Female, non-Asian, primary renal diagnosis other, >3 years, none of listed comorbidities, smoker	24	0.733	0.692	0.041

Figure 1 Number of completed EQ-5D-5L assessments in each cohort



*Incident transplant patients who were recruited during the first 6 months of the study were asked to complete an EQ-5D-5L assessment at approximately 6 months after surgery

5. KIDNEY ALLOCATION SIMULATION MODEL

5.1. Introduction

The main objective of this thesis is to compare the costs and consequences associated with alternative approaches to allocating kidneys from deceased donors to patients on the transplant waiting list in the UK. Previous chapters have described the sources of data used to characterise variations in costs, survival and health-state utility values at the patient level which will serve as inputs in the simulation model. This chapter describes the structure and key assumptions for the simulation model and reports total costs and QALYs across the patient population for each allocation scheme.

5.2. Research Paper 4

The simulation model described in Research Paper 4 was constructed in two phases. The first phase involved translating each of the allocation criteria into code to perform the matching process in which one patient from the waiting list is selected for every kidney that becomes available. Once all five allocation schemes had been coded and tested, the second phase was to incorporate the predictive regression models from Chapters 2, 3 and 4 to estimate lifetime costs and QALYs for each patient who receives a transplant and then to sum these across all patients. The simulation model was constructed using the software package SIMUL8. A detailed explanation of the approach to structuring and coding the simulation model is beyond the scope of Research Paper 4, however interested readers may wish to refer to Appendix 6, which provides additional documentation to describe how the model was constructed.

Although the simulation exercise described in this thesis was designed to estimate total lifetime costs and QALYs associated with different approaches to kidney allocation, special care has been taken in Research Paper 4 not to draw any formal conclusions or recommendations about which of the five allocation schemes under comparison is considered optimal. Part of the reason for this will become more evident in Chapter 6, when

equity considerations are discussed. However, another challenge in trying to determine which allocation scheme is optimal is that it requires an informed answer to the following question: whose outcomes should we be seeking to maximise? Given a limited supply of kidneys, the different approaches to kidney allocation will result in different patients being prioritised to receive a transplant, while other patients will be more likely to remain on the waiting list for longer periods of time. Taking a lifetime time horizon for estimating costs and QALYs in the simulation model introduces a particular challenge, namely how to account for the lifetime costs and outcomes for those patients who do not receive a transplant during the simulation period. A number of approaches were considered, including:

1. Continue to run the model with an infinite stream of donor kidneys, however this was not considered feasible because SIMUL8 requires the model to terminate in order to trigger code at the end of a run to produce results (total costs and QALYs)
2. For all patients who remained on the waiting list at the end of the model run, predict which patients will receive a transplant in the future and estimate their costs and QALYs, however this would require a reliable method to predict which patients would receive a transplant (dependent on the characteristics of future donor kidneys) and when they would receive a transplant under each of the different allocation schemes
3. Assume that all patients who remained on the waiting list at the end of the model run never receive a transplant and assign them costs and QALYs equivalent to remaining on the waiting list until death, however this assumption is unlikely to be met in practice.

The first two options were not considered feasible to implement within the structure of the simulation model that had been developed or within the time constraints of the PhD. Consequently, the third approach outlined above was adopted. Given the limitations of the assumption that none of the patients on the waiting list would receive a transplant in the future, Research Paper 4 presents results (total costs and QALYs) for transplant recipients only as well as for the combined population of transplant recipients and patients who did not receive a transplant during the simulation.

Note that due to the target journal and intended audience for Research Paper 4, the term *utility-maximisation* has been used interchangeably with the term *QALY-maximisation*.

RESEARCH PAPER COVER SHEET – Research Paper 4

SECTION A – Student Details

Student	Bernadette Li
Principal Supervisor	John Cairns
Thesis Title	Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

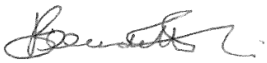
Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Medical Decision Making
Please list the paper's authors in the intended authorship order:	Bernadette Li will be first author, remaining intended authorship order to be confirmed
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had primary responsibility for developing the model, producing results and drafting the paper.

Student Signature:  **Date:** 27 July 2016

Supervisor Signature:  **Date:** 27 July 2016

Title: Individual patient simulation of alternative approaches to kidney allocation: how can we maximise health gains from a scarce resource?

Running title: Simulating alternative approaches to kidney allocation

Key words: patient-level simulation, kidney transplant, allocation, quality-adjusted life year, cost

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ABSTRACT

Introduction: In the United Kingdom, the number of patients waiting to receive a kidney transplant far outstrips the supply of donor organs thereby making some form of rationing inevitable. There is increasing recognition that not all donor kidneys will result in equally good survival outcomes and that not all patients will derive the same benefit from a given donor kidney. We sought to explore the feasibility of designing a kidney allocation scheme to match recipients and donors in a manner that would maximise the benefit derived from each donor organ.

Methods: An individual patient simulation was developed to compare a utility-maximising approach to kidney allocation with alternative allocation concepts from across the equity-efficiency spectrum. We used various sources of patient-level data to develop separate multivariable regression models to predict survival, health state utilities and costs. We simulated the allocation of kidneys from 2200 donors to a waiting list of 5500 patients and produced estimates of total lifetime costs and quality-adjusted life years (QALYs) for each allocation scheme.

Results: Among patients who received a transplant, the utility-maximising approach to kidney allocation resulted in the highest total QALYs and costs (47,613 QALYs, £665 million) while waiting-time allocation resulted in the lowest (39,496 QALYs, £584 million). However, when taking into consideration outcomes for those patients who did not receive a transplant, the utility-maximising scheme no longer produced the highest total QALYs across the entire patient population.

Discussion: This simulation exercise demonstrates the feasibility of designing a utility-maximising approach to kidney allocation and provides insight into the magnitude of QALY and cost differences to inform the discussion about trade-offs associated with alternative allocation concepts from across the equity-efficiency spectrum.

INTRODUCTION

In 2015, there were approximately 5700 patients waiting to receive a kidney transplant in the United Kingdom [1]. Because the number of patients waiting to receive a transplant far outstrips the supply of organs from deceased donors, some form of rationing is inevitable. In many countries, the approach to rationing is made explicit through the design of a national kidney allocation scheme. In the UK, a matching system between recipients and donors has been in place since 1989 [2]. The approach to kidney allocation in this country is subject to continuous audit and review and over the decades, the national scheme has been revised twice in order to address and balance considerations of both improving transplant outcomes and promoting equity in access to transplant [3, 4].

Simulation modelling is a practical tool that can be used to evaluate or prospectively test the impact of potential changes to kidney allocation schemes [5-7]. As part of the Access to Transplantation and Transplant Outcomes Measure (ATTOM) study, we conducted a simulation exercise to explore and compare alternative approaches to allocating kidneys in the UK context. Building a simulation model can be a time-consuming and data-intensive exercise. Before constructing a simulation, it is therefore important to define the decision problem and intended outputs of the model as these can influence the required data inputs and vice versa. We approached the development of the simulation model described in this paper with three key objectives in mind:

1. To simulate a number of different approaches to kidney allocation that reflect varying degrees of emphasis on the competing objectives of maximising transplant outcomes on the one hand and promoting equity on the other
2. To report outcomes for each kidney allocation scheme in terms of both quality-adjusted life years (QALYs) and costs
3. To maximise use of information on individual patient and donor characteristics to inform the allocation process and to account for between-patient variability in the estimation of outcomes.

Kidney allocation concepts of interest

The current UK kidney allocation scheme was introduced in 2006 [4]. In this simulation exercise, we compared the 2006 national kidney allocation scheme (NKAS) to several alternative approaches, with a particular interest in exploring the feasibility of designing an allocation scheme that would maximise health gains among transplant recipients from a fixed supply of donor kidneys. The design of a utility-maximising allocation scheme was predicated on the following assumptions:

1. For patients awaiting a transplant, there is a treatment alternative, namely dialysis
2. Not all donor kidneys will result in equally good survival outcomes
3. Not all potential recipients will derive the same survival benefit from a given donor kidney.

In the utility-maximising scheme, for each donor kidney that becomes available, the simulation model estimates expected QALYs following transplant for each patient on the waiting list given the characteristics of both that patient and the donor kidney to be allocated. Next, the simulation model estimates expected QALYs for each patient on the waiting list if that patient were to remain on dialysis. Taking the difference between expected QALYs following transplant and expected QALYs on dialysis, each kidney is allocated to the patient with the biggest expected QALY gain as a result of receiving the transplant. Over the population of transplant recipients, this approach to allocation should yield the maximum total QALY gains for a fixed number of donor kidneys. This utility-maximising scheme is conceptually similar to the Life Years from Transplant (LYFT) calculation previously described by Wolfe et al., however in the current simulation exercise, we applied different methods and used UK data sources to estimate survival and health state utilities in order to calculate QALY gains [8].

Another allocation concept that we wanted to explore in our simulation exercise can be broadly referred to as longevity matching, which was a key feature of the new kidney allocation scheme implemented in the United States in 2014. Under this concept, donor kidneys are risk-stratified using a scoring system in order to identify which kidneys are associated with better post-transplant survival. Similarly, potential recipients on the waiting

list are risk-stratified based on estimates of their expected post-transplant survival (EPTS) score. The allocation policy then prioritises candidates in the top 20th percentile of EPTS scores to receive kidneys from the top 20% of donor kidneys [9]. To test the concept of longevity matching in the UK context, we used a UK-specific kidney donor risk index (UKKDRI) [10] and developed a multivariable parametric model to estimate mean post-transplant survival for potential recipients based on an analysis of historical UK Transplant Registry data [11]. A key difference between our approach to estimating recipient post-transplant survival and the EPTS score used in the US kidney allocation scheme is that our survival predictions also take into account relevant donor characteristics, namely age and history of hypertension. Thus, in our simulation exercise, recipient post-transplant survival estimates for both the utility-maximising and longevity matching allocation schemes are recalculated for each potential donor-recipient combination.

In addition to exploring the concepts of utility-maximisation and longevity matching, we included two other allocation concepts in our simulation exercise that were intended to reflect greater emphasis on equity: random allocation and allocation based on waiting time. Table 1 provides an overview of all five allocation concepts explored in our simulation exercise.

Table 1 Description of the five kidney allocation schemes included in the simulation exercise

Allocation concept	Description of allocation criteria considered in each scheme
Scheme 1: random	• Blood group compatibility and HLA match • Priority for HLA mismatch level 1 (000) • Taking the above criteria into account, allocate the kidney randomly
Scheme 2: waiting time	• Blood group compatibility and HLA match • Priority for HLA mismatch level 1 (000) • Taking the above criteria into account, allocate the kidney to the patient with the longest waiting time
Scheme 3: 2006 NKAS [12]	• Priority for HLA mismatch level 1 (000), taking into account whether or not patients are highly sensitised or HLA-DR homozygous • Within tiers, prioritise patients according to a points-based system based on: ○ waiting time

	○ HLA match and age combined ○ donor-recipient age difference ○ location of patient relative to donor ○ HLA-DR homozygosity ○ HLA-B homozygosity ○ blood group match
Scheme 4: longevity matching	• For each donor kidney, estimate expected post-transplant survival for each patient on the waiting list • If the donor kidney has a UKKDRI score in the top 20%, then 20% of patients with the longest expected post-transplant survival are prioritised to receive the kidney • Taking the above criteria into account, allocate the kidney according to the 2006 NKAS scheme points-based system
Scheme 5: utility-maximising	• Blood group compatibility and HLA match • Priority for HLA mismatch level 1 (000) • For each donor kidney, estimate expected post-transplant QALYs for each patient and expected QALYs if each patient were to remain on the waiting list • Taking the above criteria into account, allocate the kidney to the patient with the biggest expected QALY gain from transplant

METHODS

Characteristics of waiting list patients and donor kidneys

To simulate the composition of the transplant waiting list, we obtained data on 1948 prevalent listed patients who were recruited into the ATTOM study between November 2011 and September 2013 [13]. Of these patients, 513 had received a previous transplant. In the absence of predictive survival models that would allow us to account for prior transplants, we excluded these patients from the simulation exercise leaving a sample of 1435 patients, whose characteristics were replicated to make up a total waiting list of 5500 patients. During the simulation exercise, each time a patient received a transplant, a replacement was added to the waiting list to keep it constant at 5500 patients. For the donor dataset, we obtained characteristics of 2200 donors (4400 kidneys) based on a representative historical cohort from NHS Blood and Transplant.

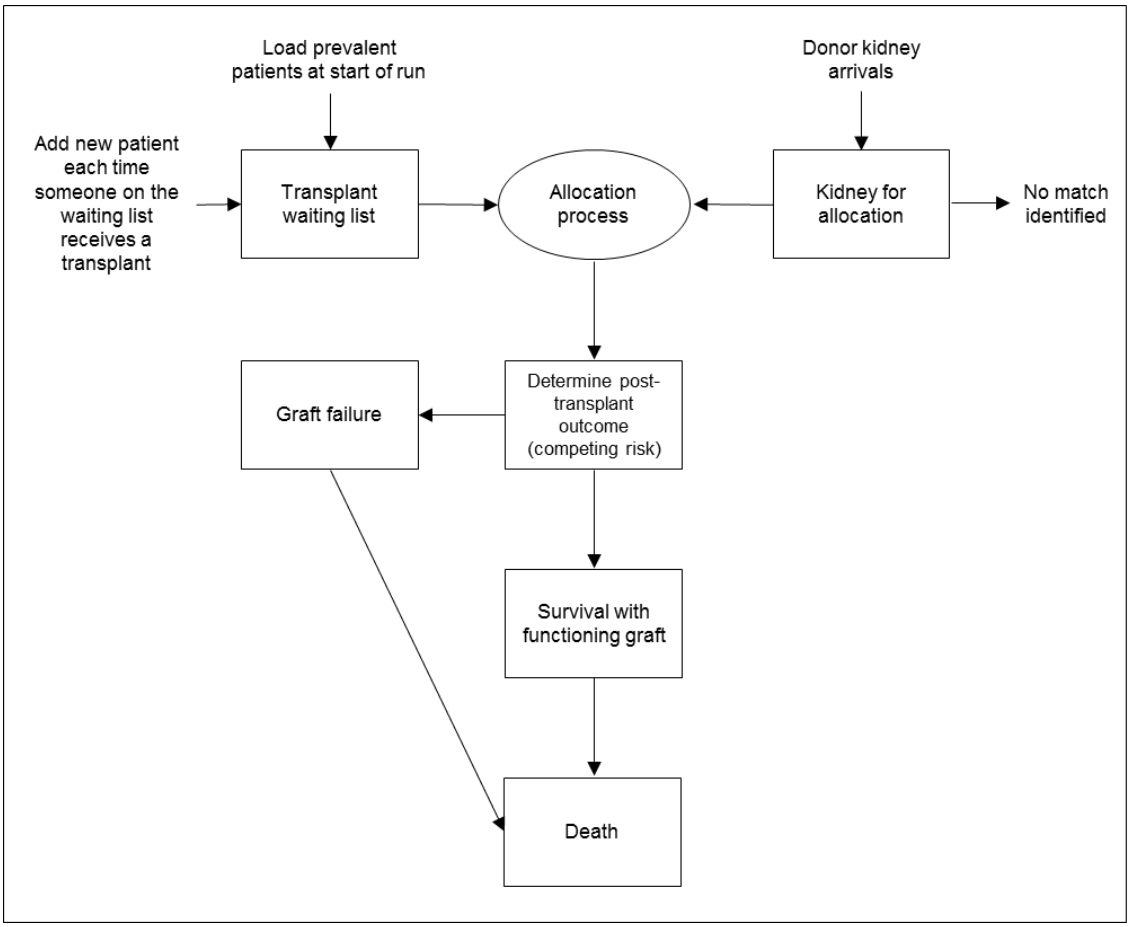
Characteristics of individual patients and donors were assigned at the point of entry into the model so that these characteristics could be used throughout the simulation to inform the allocation process as well as to estimate survival, costs and health state utilities. Most patient characteristics, including comorbidities, were kept constant throughout the

simulation, however three characteristics were updated as simulation time progressed; waiting time and time on dialysis were incremented on a daily basis, while patient age was incremented annually.

Model structure and assumptions

The simulation model was constructed using the software package SIMUL8 2015 Professional version (SIMUL8 Corporation, Boston, MA, USA). At the start of the simulation, prevalent waiting list patients are loaded and held in a queue while donor kidneys are assumed to arrive at a fixed rate equivalent to 1200 deceased donors per year (Figure 1).

Figure 1 Structure of the simulation model



The allocation process is triggered by the arrival of each donor kidney. Using Visual Logic, SIMUL8's internal programming language, we are able to loop through patients on the waiting list to evaluate blood group and tissue compatibility for each potential donor-recipient combination and perform the necessary calculations and scoring algorithms relevant to each allocation scheme of interest. In the model, we allowed for the possibility that no appropriate match is identified for a donor kidney. This is expected to occur in only a small proportion of cases, usually due to incompatibility with a rare donor blood or tissue type. In the current UK allocation scheme, tissue matching between the donor and recipient is determined on the basis of human leukocyte antigens (HLA); patients are separated into one of four possible HLA mismatch levels from level 1 (000-mismatched) to level 4 (poorly matched). In current practice, patients with a level 4 HLA mismatch are not eligible to receive the donor kidney through the national allocation scheme [12]. In order to maintain consistency and comparability between allocation schemes, we applied this same criterion to all five allocation schemes in our simulation exercise.

Once a match has been identified, the recipient and donor kidney are assembled into a single entity to simulate the transplantation event and moved to the next step in the simulation process to determine post-transplant survival and to estimate lifetime QALYs and costs. The model assumes only two events are possible following transplantation: graft failure, in which the transplanted kidney stops working, or patient death. These events are modelled as competing risks in which we randomly sample from the survival curve for each event and move the patient to the event with the earliest sampled time [14]. If a patient experiences graft failure, we have assumed the patient returns to dialysis and faces the same mortality risk as a patient who has been on the waiting list and receiving dialysis for >3 years. However, if the sampled value for time to death following graft failure is longer than the time the patient would have survived based on the previously sampled value to determine initial post-transplant outcomes, we replaced it with the lower value so as not to paradoxically award patients who experienced graft failure with better survival prospects than those who did not experience graft failure. We made a decision not to model repeat transplants in this simulation in the absence of survival models specific to these patients.

The model was built by developing separate sections of Visual Logic code for each step in the allocation process so that, for example, the same procedure to evaluate blood group compatibility could be called at any point in the simulation for any of the five allocation schemes. Internal spreadsheets were used extensively to perform interim calculations at the patient level, which also facilitated model checks and step-by-step verification of the simulation process.

Estimating life years, QALYs and costs

Survival models

There are three survival models underpinning time-to-event calculations to estimate post-transplant patient survival, post-transplant graft failure and waiting list survival at various points in the simulation. Each of these models was developed based on analysis of historical UK Transplant Registry data. Data on dialysis start dates were additionally obtained through linkage to the UK Renal Registry to inform the waiting list survival model. Models were fitted using flexible parametric survival analysis in order to facilitate [15]:

1. Extrapolation of survival curves to allow calculation of mean survival in years
2. Inclusion of relevant patient and donor characteristics as covariates to capture variability in our predictions of survival and by extension in our estimates of costs and QALYs.

A more detailed description of the method used to fit the post-transplant patient survival model is described elsewhere [11]. Table 2 summarises the various points in the simulation where each of the survival models was applied and Table 3 summarises the patient and donor characteristics that were included as covariates in each of the models. When the survival models were used as part of the allocation process to match recipients and donor kidneys (longevity matching and utility-maximisation), they were applied deterministically to produce mean survival estimates. When the survival models were used to inform competing risks following transplantation in order to estimate lifetime QALYs and costs, we allowed for stochastic variation.

Table 2 Description of survival models used in the simulation

	Where used	How used	Post-transplant patient survival	Waiting list survival	Post-transplant graft failure
1.	Allocation scheme 4: longevity matching	To calculate expected post-transplant survival for each patient on the waiting list; 20% of patients with the longest expected post-transplant survival are prioritised to receive kidneys with top 20% UKKDRI scores	Deterministic	-	-
2.	Allocation scheme 5: utility-maximisation	To calculate expected QALYs for each patient on the waiting list if (1) the patient were to receive the transplant (2) the patient were to remain on the waiting list	Deterministic	Deterministic	-
3.	Competing risk to determine post-transplant outcomes after the kidney has been allocated (all allocation schemes)	Following allocation of the kidney to a recipient on the waiting list, sample times for (1) graft failure event and (2) patient death event; take the minimum	Stochastic	-	Stochastic
4.	Time from graft failure to death (all allocation schemes)	If the patient experiences graft failure, sample time from graft failure to death assuming the survival rate is equivalent to a patient on the waiting list who has been on dialysis >3 years; compare this with the difference between time to death less time to graft failure from #3; take the minimum	-	Stochastic	-
5.	Waiting list survival for patients who did not receive a transplant (all allocation schemes)	For patients on the waiting list at the end of the simulation, assume survival rate is equivalent to a patient who remains on the waiting list and does not receive a transplant	-	Deterministic	-

Table 3 Summary of covariates in survival models used in the simulation

Covariate	Categories	Post-transplant patient survival	Waiting list survival	Post-transplant graft failure
Recipient age	18-29, 30-39, 40-49, 50-59, >60	✓	✓	✓
Recipient gender	Male / Female	✓	✓	-
Recipient ethnicity	White, Asian, Black, Other	-	✓	-
Recipient primary renal diagnosis				
Diabetic nephropathy	Yes / No	✓	✓	-
Polycystic kidney disease	Yes / No	✓	-	✓
Recipient years on dialysis at the time of listing for transplant	Pre-dialysis, <1 year, 1-3 years, > 3 years	-	✓	-
Pre-emptive transplant	Yes / No	✓	-	✓
HLA mismatch level	Level 1 [000], Level 2 [0 DR + 0/1 B], Level 3 [0 DR + 2 B] or [1 DR + 0/1 B], Level 4 [1 DR + 2B] or [2 DR]	-	-	✓
Donor age	<40, 40-49, 50-59, >=60	✓	-	✓
Donor history of hypertension	Yes / No / Unknown	✓	-	-

Health-state utility estimates

Health-state utility estimates for transplant recipient and patients on the waiting list were captured in the ATTOM study using the EQ-5D-5L questionnaire. We developed multivariable regression models to identify patient characteristics that led to variations in utility scores to inform quality-adjustment of survival estimates in the simulation model (citation to ATTOM EQ-5D paper pending publication). Table 4 provides a summary of characteristics that were included as covariates for each of the patient groups.

Table 4 Summary of covariates in regression models to predict health state utilities used in the simulation model

Covariate	Categories	Waiting list	Transplant
Gender	Male / Female	✓	✓
Ethnicity	White, Black, Other, Asian	✓	✓
Primary renal diagnosis: diabetic nephropathy	Yes / No	✓	✓
Comorbidities			
Ischaemic heart disease	Yes / No	✓	✓
Respiratory disease	Yes / No	-	✓
Malignancy	Yes / No	-	✓
Mental illness	Yes / No	✓	✓
Smoking status	Non-smoker. Ex-smoker, Current smoker	✓	✓
Time on dialysis	Pre-dialysis, <1 year, 1-3 years, >3 years	✓	-

Costs

The costs of maintenance dialysis and transplant surgery were estimated in the simulation by applying fixed national tariffs [16]. We estimated annual hospital costs using two-part regression models that were developed by analysing patient-level data from linkage of the Hospital Episode Statistics dataset to UK Renal Registry data [17]. Hospital costs were captured by treatment modality (dialysis vs. transplantation) and by hospital setting (inpatient vs. outpatient) and regression models included a number of patient characteristics as covariates summarised in Table 5. For transplant recipients, the annual cost of maintenance immunosuppression assumed that patients received a combination of corticosteroids, a calcineurin inhibitor (50/50 split between ciclosporin and tacrolimus) and an antiproliferative agent (50/50 split between mycophenolate mofetil and azathioprine) [18].

Table 5a Summary of covariates in regression models to predict hospital costs for dialysis patients in the simulation model

Covariate	Categories	Dialysis inpatient	Dialysis outpatient
Age	< 50, 50-64, 65-75, >75	✓	✓
Gender	Male / Female	✓	✓
Years on dialysis	1 to 6	✓	✓
Dialysis modality	Haemodialysis / Peritoneal dialysis	✓	✓
Comorbidities			
Myocardial infarction	Yes / No	✓	-
Congestive heart failure	Yes / No	✓	✓
Peripheral vascular disease	Yes / No	✓	✓
Cerebrovascular disease	Yes / No	✓	✓
Respiratory disease	Yes / No	✓	✓
Liver disease	Yes / No	✓	-
Diabetes	Yes / No	✓	✓
Malignancy	Yes / No	✓	✓
Hypertension	Yes / No	✓	✓
Year of death	Yes / No	✓	✓

Table 5b Summary of covariates in regression models to predict hospital costs for transplant patients in the simulation model

Covariate	Categories	Transplant inpatient	Transplant outpatient
Age	<35, 36-45, 46-55, >55	✓	✓
Gender	Male / Female	✓	✓
Years following transplant	1 to 6	✓	✓
Comorbidities			
Myocardial infarction	Yes / No	✓	✓
Congestive heart failure	Yes / No	✓	✓
Peripheral vascular disease	Yes / No	✓	✓
Cerebrovascular disease	Yes / No	✓	✓

Respiratory disease	Yes / No	✓	✓
Liver disease	Yes / No	✓	✓
Diabetes	Yes / No	✓	✓
Malignancy	Yes / No	✓	✓
Hypertension	Yes / No	✓	✓
Year of graft failure	Yes / No	✓	✓
Year of transplant surgery	Yes / No	✓	✓
Year of death	Yes / No	✓	✓

Running the simulation

For each allocation scheme, we performed three runs using a separate random number stream for each run. A single run ends when all 4400 donor kidneys have been allocated or removed from further consideration if no match has been identified. Although we are primarily interested in comparing total costs and QALYs across all transplant recipients resulting from the different allocation schemes, it is also important to consider the outcomes of those patients who did not receive a transplant within the time frame of the simulation. For these patients, we made a simplifying assumption that they face a mortality risk equivalent to remaining on the waiting list until death and used this as the basis for projecting their lifetime costs and QALYs at the end of the simulation. For each allocation scheme, we present total discounted life years, QALYs and costs for all transplant recipients averaged across the three runs (with 95% confidence intervals) using a discount rate of 3.5%.

RESULTS

A summary of the main results for all transplant recipients for each of the five allocation schemes is shown in Table 6. The proportion of donor kidneys for which no match was identified was approximately 1% across all simulation runs and therefore the number of patients who received a transplant was similar across allocation schemes. Reassuringly, the utility-maximising scheme generated the most QALYs for transplant recipients but also led to the highest costs. Waiting-time allocation resulted in the lowest total QALYs and costs. Table 7 orders the allocation schemes by increasing total costs relative to waiting-time as the baseline option and reports incremental cost-effectiveness ratios (ICERs). Figure 2 plots the five allocation schemes on the cost-effectiveness plane, showing how closely all of them are positioned to the cost-effectiveness frontier.

Given the objective of maximising health gains from a scarce resource, the utility-maximising allocation scheme produced results that were in line with expectations for transplant recipients, but a complete assessment of the consequences of an allocation scheme should also consider the outcomes for those patients who did not receive a transplant. For the purposes of estimating lifetime QALYs and costs, we applied a simplifying assumption that all patients who did not receive a transplant during the simulation remained on the waiting list until death. If we add these estimates to the total QALYs and costs for transplant recipients (Table 8), we see that the relative positions of the allocation schemes on the cost-effectiveness plane change (Figure 3). Longevity matching now produces the lowest total QALYs and costs, while the 2006 NKAS leads to the highest total QALYs and costs. Incremental analysis (Table 9) shows that random allocation and waiting-time allocation are dominated as they produce both fewer QALYs and higher costs compared to the utility-maximising allocation scheme. While the longevity matching and utility-maximising schemes both generated more QALYs for transplant recipients than the current national allocation scheme, they generated far fewer QALYs for those patients who we have assumed remain on the waiting list.

Table 6 Total discounted life years, QALYs and costs for all transplant recipients averaged across 3 runs (with 95% confidence interval)

	Total discounted life years	Total discounted QALYs	Total discounted costs (millions)
Allocation scheme 1: random	49,773 (48,860, 50,687)	40,236 (39,434, 41,038)	£ 591 (574, 607)
Allocation scheme 2: waiting time	48,848 (47,464, 50,233)	39,496 (38,390, 40,602)	£ 584 (568, 601)
Allocation scheme 3: 2006 NKAS	54,320 (52,956, 55,684)	44,040 (42,882, 45,198)	£ 625 (619, 631)
Allocation scheme 4: longevity matching	55,061 (53,476, 56,646)	44,704 (43,316, 46,092)	£ 632 (627, 638)
Allocation scheme 5: utility-maximising	58,951 (58,276, 59,625)	48,045 (47,542, 48,549)	£ 681 (667, 694)

Table 7 Incremental cost-effectiveness analysis based on total costs and QALYs for transplant recipients

	Discounted costs	Discounted QALYs	Comparison	Incremental cost	Incremental QALY	ICER
Allocation scheme 2: waiting time	£ 0	0	-	-	-	-
Allocation scheme 1: random	£ 6,167,585	739	1 vs. 2	£ 6,167,585	739	£ 8,342 / QALY
Allocation scheme 3: 2006 NKAS	£ 40,375,355	4544	3 vs. 2	£ 34,207,771	3804	£ 8,992 / QALY
Allocation scheme 4: longevity matching	£ 47,893,249	5208	4 vs. 3	£ 7,517,894	664	£ 11,317 / QALY
Allocation scheme 5: utility-maximising	£ 80,033,713	8117	5 vs. 4	£ 48,170,081	3341	£ 14,418 / QALY

Figure 2 Cost-effectiveness plane showing incremental costs and QALYs for transplant recipients only

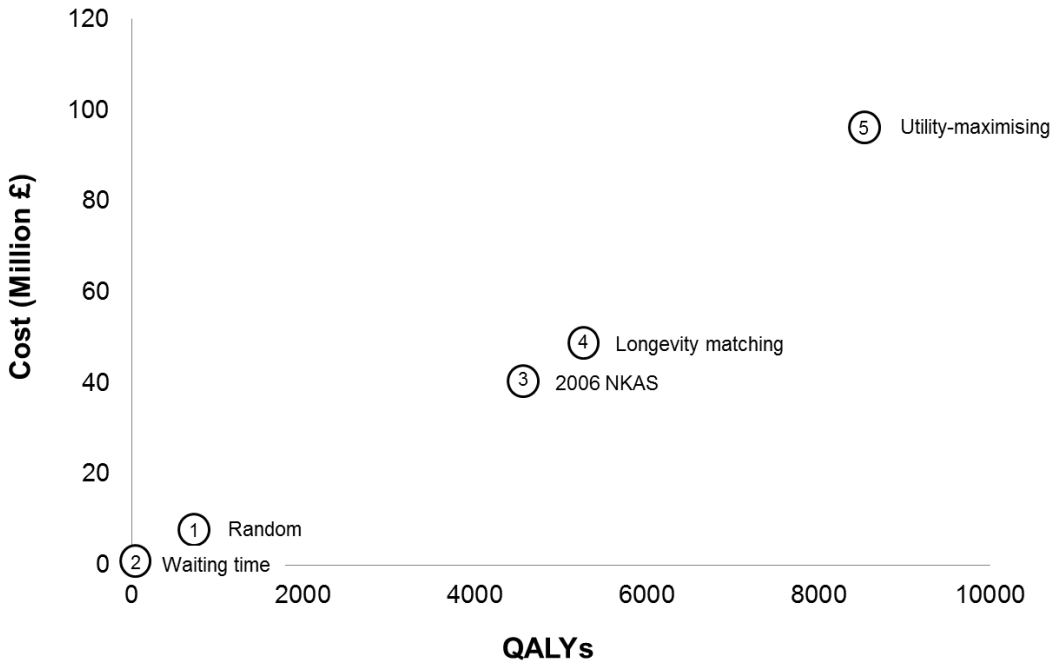


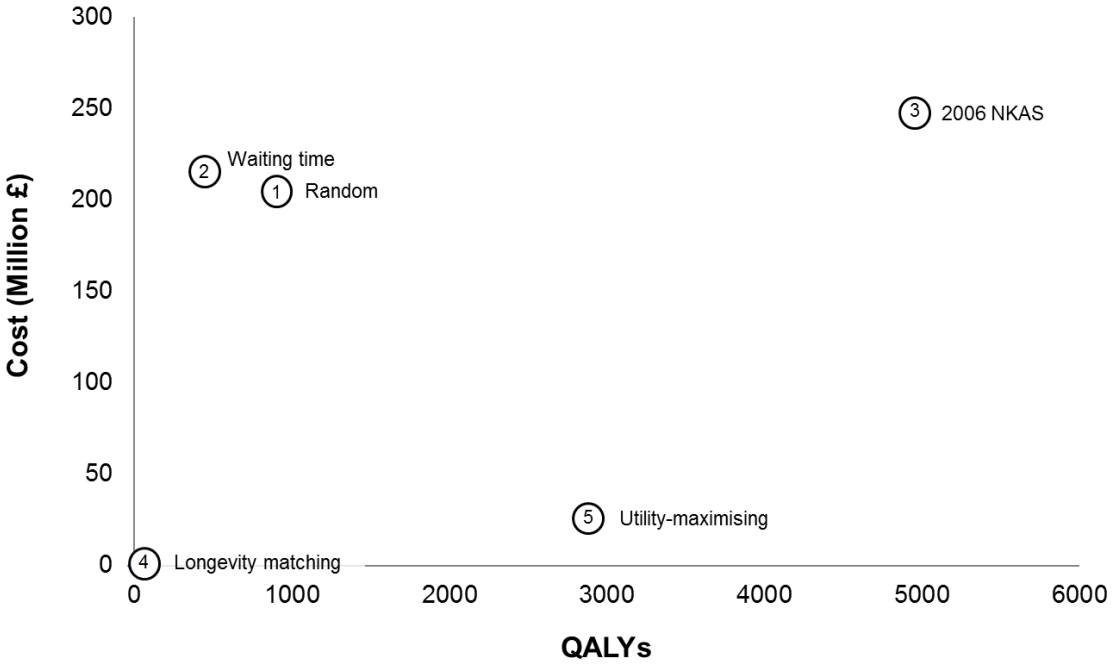
Table 8 Total discounted life years, QALYs and costs for all transplant recipients and waiting-list patients who did not receive a transplant averaged across 3 runs (with 95% confidence interval)

	Total discounted life years	Total discounted QALYs	Total discounted costs (million)
Allocation scheme 1: random	83,983 (82,866, 85,100)	66,563 (65,607, 67519)	£ 1,679 (1,669, 1,690)
Allocation scheme 2: waiting time	83,328 (81,938, 84,718)	66,068 (64,957, 67,179)	£ 1,684 (1,665, 1702)
Allocation scheme 3: 2006 NKAS	88,776 (87,627, 89,925)	70,569 (69,591,71,547)	£ 1,722 (1,710, 1,735)
Allocation scheme 4: Longevity matching	82,258 (80,754, 83,761)	65,665 (64,367, 66,964)	£ 1,473 (1,469, 1,478)
Allocation scheme 5: utility-maximising	85,506 (84,675, 86,336)	68,549 (67,915, 69,184)	£ 1,499 (1,480, 1,518)

Table 9 Incremental cost-effectiveness analysis identifying dominated alternatives based on total costs and QALYs for transplant recipients and waiting-list patients who did not receive a transplant combined

	Discounted costs	Discounted QALYs	Comparison	Incremental cost	Incremental QALY	ICER
Allocation scheme 4: longevity matching	£ 0	0	-	-	-	-
Allocation scheme 5: utility-maximising	£ 25,236,780	2,884	5 vs. 4	£ 25,236,780	2884	£ 8,752
Allocation scheme 1: Random	£ 206,020,093	898	1 vs. 5	£ 180,783,313	-1986	Dominated
Allocation scheme 2: waiting time	£ 210,422,609	403	2 vs. 5	£ 185,185,829	-2481	Dominated
Allocation scheme 3: 2006 NKAS	£ 248,891,110	4,904	3 vs. 5	£ 223,654,330	2020	£110,720

Figure 3 Cost-effectiveness plane showing incremental costs and QALYs for transplant recipients and patients who did not receive a transplant combined



DISCUSSION

There are a number of examples from across the clinical, decision modelling and operations research literature that have described the application of simulation to evaluate different approaches to kidney allocation [4, 5, 7, 19, 20]. While these examples differ in terms of data sources, model structure, outcomes and allocation schemes of interest, all of them acknowledge the tension that exists between the competing objectives of equity in access to transplantation and efficient use of a limited supply of donor kidneys.

The motivation for the simulation exercise described in this paper was not only to explore a number of newer allocation concepts in the UK context, but also to improve our ability to estimate variability in outcomes resulting from different approaches to allocation at the individual patient level. If alternative approaches to kidney allocation result in different patients receiving transplants, then an accurate comparison of the consequences of alternative allocation schemes depends on our ability to predict variability in outcomes dependent on individual patient characteristics. This simulation exercise relied on the availability of a number of rich sources of patient-level data including the ATTOM study, the UK Transplant Registry, Hospital Episode Statistics and the UK Renal Registry in order to develop predictive regression models to estimate survival, health state utilities and costs. These predictive models were not only used to estimate QALYs and costs for transplant recipients in all five allocation schemes, but were also used as part of the criteria to inform the kidney allocation process for the longevity matching and utility-maximising schemes.

In our simulation, we demonstrated the feasibility of designing an allocation scheme that maximised total QALYs among transplant recipients by allocating each kidney to the patient on the waiting list who would gain the most QALYs compared to remaining on dialysis. However, when we also took into account outcomes for patients who were not prioritised to receive a transplant under the utility-maximising scheme, it was clear that this allocation scheme was no longer utility-maximising across the total patient population. The assumption that patients on the waiting list at the end of the simulation would never receive a transplant is unlikely to be met in practice. Survival on the waiting list is on average poorer than survival following transplant, so the likely effect of this assumption is that we have

underestimated total QALYs for all allocation schemes. However, it is difficult to anticipate the net impact of this assumption on the relative positions of the five allocation schemes on the cost-effectiveness plane in Figure 3. Different allocation criteria will result in different types of patients receiving transplants and by corollary, the composition of patients who remain on the waiting list will also differ between schemes. Under the waiting time allocation scheme, patients who remain on the waiting list at the end of the simulation would in practice still have a reasonable prospect of receiving a future transplant as their likelihood of being prioritised for transplant increases with time. In contrast, under the utility-maximising scheme, patients who remain on the waiting list at the end of the simulation may be less likely to receive a future transplant if their expected QALY gains from transplant decrease over time relative to new patients joining the waiting list. Rather than attempt to apply different assumptions to each allocation scheme to project what proportion or which types of patients on the waiting list are likely to receive a future transplant at the end of the simulation, we chose to implement a standardised assumption so as not to confound our ability to observe and compare the effect of the different allocation schemes themselves. Given the importance of this assumption on estimates of QALYs and costs for the total patient population, further modelling efforts should focus on testing alternative assumptions and, for example, explore if a non-terminating model could achieve a steady-state outcome that can be compared across allocation schemes over a long enough period of time.

As with all simulation exercises, it was necessary to make a number of other simplifying assumptions that limit the generalisability and direct applicability of the results to the real world context. The ATTOM study recruited prevalent waiting list patients aged 18-75 years and therefore our analysis did not include any paediatric recipients. We also restricted the simulation to first-time transplant recipients and did not consider the impact of combined kidney and pancreas offers, which fall under a separate national allocation policy in the UK. With these caveats in mind, simulation modelling is still an important tool that can help increase our understanding of the potential consequences of different approaches to kidney allocation in relation to one another.

Although we chose to report lifetime QALYs and costs as the main outcomes of interest, this simulation exercise was not specifically designed with standard methods for cost-effectiveness modelling at the forefront of our approach [21]. There were both technical and philosophical reasons that contributed to this decision. During development of the simulation model, primary emphasis was placed on the design, feasibility and coding of the different allocation schemes. Each scheme requires the simulation model to loop through all patients on the waiting list in order to evaluate donor-recipient compatibility. In the case of the utility-maximising and longevity matching schemes, survival predictions take into account both recipient and donor characteristics and therefore need to be recalculated for all patients on the waiting list each time a donor kidney enters the simulation. The computational burden of the allocation process itself led to long model running times even in the absence of introducing parameter uncertainty and therefore we were unable to perform probabilistic sensitivity analysis. On a more philosophical note, kidney allocation represents a somewhat unique resource allocation problem constrained not only by a finite healthcare budget, but more fundamentally by a limited supply of organs. Conventional cost-effectiveness methods focus on maximising health gains [22], but in the case of kidney allocation it is clear that maximising health gains is not the only objective. For this reason, we presented all five allocation schemes on the cost-effectiveness planes and refrained from comparing ICERs with respect to a specific willingness-to-pay threshold.

The results of this simulation exercise cannot answer the question about what the objectives of a national kidney allocation scheme *should* be, but nonetheless provide insight into the magnitude of QALY and cost differences to inform the discussion about trade-offs associated with alternative allocation concepts from across the equity-efficiency spectrum.

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6. DISCUSSION

6.1. Research objective

This thesis sought to use simulation modelling to compare the costs and consequences of alternative approaches to kidney allocation in the UK context from across the equity-efficiency spectrum. The primary emphasis of this research was on feasibility, sourcing of data inputs and design of the modelling approach rather than on any attempt to define in a normative sense what the objectives of an allocation scheme should be. There is no shortage of discussion in the literature about the tension that exists between the competing priorities of ensuring equity in access to transplantation and making the most efficient use of a scarce resource.[19,23,26,35] So far in this thesis, any attempt to define equity and efficiency has been limited to the use of these terms as anchors on either end of the spectrum to describe the relative positions of the allocation concepts of interest. Deeper insight into how trade-offs between equity and efficiency should be valued would require further research that is beyond the scope of this thesis. However, this concluding section will highlight some potential considerations arising from the simulation exercise.

6.2. Key findings of simulation modelling results

Reassuringly, the results of the simulation exercise demonstrated that the QALY-maximising approach to kidney allocation generated the most QALYs among transplant recipients. The QALY-maximising scheme also generated the highest total costs for transplant recipients. This result is not entirely unexpected because the longer transplant recipients survive, the longer they will continue to incur costs. Allocation based on waiting time generated the fewest QALYs and costs. Although formal threshold analysis was not used to determine the optimal allocation strategy, ICERs for the 2006 NKAS, longevity matching and QALY-maximising approaches relative to waiting-time allocation were all well below the commonly referenced threshold of £30,000 / QALY. In the UK, this is the threshold below which the National Institute for Health and Care Excellence (NICE) generally

considers a technology, service or treatment strategy to be a cost effective use of NHS resources.[53,54]

While the simulation exercise has clearly demonstrated the benefits of a QALY-maximising approach for patients who receive a transplant, less thorough consideration has been given to the implications for patients who are not prioritised to receive a transplant. Each run of the model simulated the allocation of kidneys from 2200 donors. As the model was designed to estimate lifetime costs and QALYs, an assumption had to be made about the lifetime costs and QALYs for those patients who did not receive a transplant during the simulation and therefore remained on the waiting list at the end of each run. To be consistent across allocation schemes, a simplifying assumption was made that patients who did not receive a transplant during the simulation would face a mortality risk equivalent to remaining on the waiting list until death. When the costs and QALYs for patients who remained on the waiting list were combined with those for transplant recipients, the relative positions of the allocation schemes on the cost-effectiveness plane changed, with longevity matching producing the lowest total costs and QALYs and the 2006 NKAS producing the highest.

6.3. Equity considerations

Although it is often stated that kidney allocation schemes should be designed to balance both efficiency and equity considerations, in practice there is a lack of clarity about how to define equity and a lack of data to inform discussions about the potential trade-offs between efficiency and equity that would be acceptable to society. Conventional cost-effectiveness methods aim to maximise efficiency, but do not explicitly consider equity. In order to supplement the results of the simulation model presented in Chapter 5, Tables 6.1 and 6.2 demonstrate how the simulation model can also be used to explore the distributional consequences of each of the kidney allocation schemes in terms of equity in access to transplantation and equity in outcomes for example by patient age, gender, ethnicity and diabetes status.

Table 6.1 summarises the characteristics of the patients who received a transplant under each scheme alongside the prevalent waiting list at the start of the simulation. Allocation schemes that generated more total QALYs resulted in a lower proportion of kidneys being allocated to patients aged 50 years and over, as well as a lower proportion of male patients, diabetic patients and patients of white ethnicity.

Table 6.2 summarises post-transplant outcomes in terms of mean undiscounted life years and QALYs. Compared to allocation based on waiting time, which produced the fewest total QALYs, the QALY-maximising approach to kidney allocation resulted in an average increase in life expectancy of 6.5 years (17.1 versus 23.6 years) and an average increase of 5.4 QALYs (13.9 versus 19.3 QALYs) for each transplant recipient. When considering the distribution of health outcomes by patient characteristics within each allocation scheme, Table 6.2 suggests that in comparison to the 2006 NKAS, the QALY-maximising approach resulted in larger differences in average life years and QALYs by gender and diabetes status, but smaller differences in average life years and QALYs by age group and ethnicity.

There are many other possible ways of defining equity and many other patient characteristics that could be considered beyond the examples given here. Once again, the intention is not to use these results on the distributional consequences of the different kidney allocation schemes to try and draw a conclusion or make a recommendation about which of the allocation approaches is optimal. Rather, the motivation behind presenting these results is to highlight the richness of outputs that can be generated from the patient-level simulation model and, alongside the results presented in Chapter 5, can be used to inform future discussions about trade-offs between equity and efficiency in the design of a kidney allocation policy.

Table 6.1 Characteristics of transplant recipients for each allocation scheme and the initial prevalent waiting list

	Waiting list (n = 5500)		Random allocation (n = 4352)		Waiting time (n = 4376)		2006 NKAS (n = 4341)		Longevity matching (n = 4346)		QALY-maximising (n = 4355)	
Age, mean years (SD)	51·1	(12·7)	51·4	(12·8)	52·6	(12·3)	46·7	(12·5)	46·4	(12·6)	41·8	(10·7)
Age group, n (%)												
18-29	369	(7%)	299	(7%)	210	(5%)	442	(10%)	461	(11%)	645	(15%)
30-39	708	(13%)	541	(12%)	486	(11%)	846	(19%)	886	(20%)	1204	(28%)
40-49	1245	(22%)	957	(22%)	940	(21%)	1216	(28%)	1251	(29%)	1562	(36%)
50-59	1576	(29%)	1229	(28%)	1316	(30%)	1075	(25%)	986	(23%)	779	(18%)
>60	1602	(29%)	1326	(31%)	1424	(33%)	762	(18%)	762	(18%)	165	(4%)
Gender, n (%)												
Male	3180	(58%)	2529	(58%)	2511	(57%)	2431	(56%)	2422	(56%)	2175	(50%)
Female	2320	(42%)	1823	(42%)	1865	(43%)	1910	(44%)	1924	(44%)	2180	(50%)
Ethnicity, n (%)												
White	4017	(73%)	3146	(72%)	3128	(72%)	3003	(69%)	3005	(69%)	2904	(67%)
Asian	727	(13%)	634	(15%)	602	(14%)	659	(15%)	666	(15%)	738	(17%)
Black	616	(11%)	465	(11%)	535	(12%)	555	(13%)	552	(13%)	571	(13%)
Other	140	(3%)	107	(2%)	111	(2%)	124	(3%)	123	(3%)	142	(3%)
Diabetes, n (%)												
No	4674	(85%)	3680	(85%)	3715	(85%)	3714	(86%)	3749	(86%)	3879	(89%)
Yes	826	(15%)	672	(15%)	661	(15%)	627	(14%)	597	(14%)	476	(11%)

Table 6.2 Average undiscounted post-transplant life years and QALYs per patient for each allocation scheme and by patient characteristics

	Random allocation			Waiting time			2006 NKAS			Longevity matching			QALY-maximising		
	Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)		
All patients															
Life years	18·0 (16·6)			17·1 (15·6)			21·1 (19·5)			21·2 (19·1)			23·6 (20·8)		
QALYs	14·6 (13·6)			13·9 (12·8)			17·1 (16·0)			17·2 (15·7)			19·3 (17·2)		
Life years	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**
By age															
18-29	27·2	(25·5, 29·0)	<0·0001	27·2	(25·2, 29·1)	<0·0001	32·8	(31·1, 34·5)	<0·0001	31·5	(29·9, 33·1)	<0·0001	29·2	(27·7, 30·8)	<0·0001
30-39	26·5	(25·2, 27·8)		25·4	(24·1, 26·7)		29·2	(28·0, 30·5)		30·2	(29·0, 31·3)		27·5	(26·3, 28·6)	
40-49	23·5	(22·5, 24·4)		22·2	(21·2, 23·1)		23·4	(22·4, 24·4)		22·6	(21·7, 23·6)		23·4	(22·4, 24·4)	
50-59	15·2	(14·4, 16·1)		15·0	(14·2, 15·8)		14·5	(13·4, 15·6)		14·5	(13·4, 15·6)		15·6	(14·2, 17·1)	
>60	11·2	(10·3, 12·0)		11·4	(10·7, 12·2)		10·7	(9·5, 12·0)		11·0	(9·8, 12·3)		13·2	(10·1, 16·3)	
By gender															
Male	18·0	(17·3, 18·6)	0·7986	17·0	(16·4, 17·7)	0·7329	21·0	(20·3, 21·8)	0·9126	21·5	(20·7, 22·2)	0·3349	24·5	(23·8, 25·4)	0·0069
Female	18·1	(17·3, 18·9)		17·2	(16·5, 17·9)		21·1	(20·2, 22·0)		20·9	(20·1, 21·8)		22·8	(21·9, 23·6)	
By ethnicity															
White	17·6	(17·1, 18·2)	0·0097	16·8	(16·3, 17·3)	0·1442	20·8	(20·1, 21·5)	0·0143	20·7	(20·1, 21·4)	0·0112	23·6	(22·9, 24·4)	0·1385
Asian	18·8	(17·5, 20·0)		18·3	(17·0, 19·5)		21·7	(20·2, 23·2)		23·0	(21·5, 24·4)		24·7	(23·2, 26·2)	
Black	18·7	(17·2, 20·2)		17·7	(16·4, 19·0)		20·5	(18·9, 22·1)		21·0	(19·4, 22·6)		22·9	(21·1, 24·6)	
Other	22·5	(19·3, 25·6)		16·8	(13·9, 19·7)		26·3	(22·9, 29·7)		24·4	(21·1, 27·8)		20·7	(17·3, 24·2)	
By diabetes															
No	18·7	(18·2, 19·3)	<0·0001	17·9	(17·4, 18·4)	<0·0001	22·0	(21·4, 22·7)	<0·0001	22·2	(21·5, 22·8)	<0·0001	24·6	(24·0, 25·3)	<0·0001
Yes	14·3	(13·3, 15·3)		12·9	(12·0, 13·8)		15·4	(14·3, 16·5)		15·3	(14·2, 16·5)		15·4	(14·1, 16·6)	
QALYs	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**	**Mean**	**95% CI**	**p-value**
By age															
18-29	22·4	(21·0, 23·9)	<0·0001	22·4	(20·7, 24·0)	<0·0001	27·1	(25·7, 28·5)	<0·0001	26·0	(24·6, 27·3)	<0·0001	24·1	(22·8, 25·4)	<0·0001
30-39	21·4	(20·3, 22·5)		20·6	(19·6, 21·7)		23·8	(22·8, 24·8)		24·5	(23·6, 25·5)		22·4	(21·5, 23·4)	

40-49	18·9	(18·1, 19·7)		17·9	(17·1, 18·7)		18·9	(18·1, 19·8)		18·3	(17·5, 19·1)		19·1	(18·2, 19·9)	
50-59	12·3	(11·6, 13·0)		12·1	(11·2, 12·8)		11·7	(10·8, 12·6)		11·7	(10·8, 12·6)		12·7	(11·5, 13·9)	
>60	9·0	(8·4, 9·7)		9·2	(8·6, 9·8)		8·7	(7·6, 9·7)		8·9	(7·9, 10·0)		10·7	(8·1, 13·2)	
By gender															
Male	14·7	(14·1, 15·2)	0·6211	13·9	(13·4, 14·4)	0·6494	17·3	(16·6, 17·9)	0·5030	17·6	(17·0, 18·2)	0·0864	20·2	(19·5, 21·0)	0·0004
Female	14·5	(13·8, 15·1)		13·8	(13·2, 14·3)		16·9	(16·2, 17·7)		16·8	(16·1, 17·5)		18·4	(17·7, 19·0)	
By ethnicity															
White	14·3	(13·8, 14·8)	0·0068	13·7	(13·2, 14·1)	0·3586	17·0	(16·4, 17·5)	0·0170	16·9	(16·3, 17·5)	0·0575	19·4	(18·7, 20·0)	0·4163
Asian	14·7	(13·7, 15·8)		14·3	(13·3, 15·4)		17·1	(15·9, 18·4)		18·2	(17·0, 19·4)		19·6	(18·4, 20·9)	
Black	15·4	(14·2, 16·6)		14·5	(13·5, 15·6)		16·9	(15·6, 18·3)		17·4	(16·1, 18·7)		18·9	(17·5, 20·4)	
Other	18·6	(16·0, 21·1)		13·6	(11·3, 16·0)		21·6	(18·8, 24·4)		20·0	(17·3, 22·8)		17·1	(14·3, 19·9)	
By diabetes															
No	15·3	(14·9, 15·8)	<0·0001	14·6	(14·2, 15·1)	<0·0001	18·1	(17·5, 18·6)	<0·0001	18·2	(17·7, 18·7)	<0·0001	20·3	(19·7, 20·8)	<0·0001
Yes	10·4	(9·7, 11·2)		9·5	(8·8, 10·1)		11·4	(10·6, 12·1)		11·3	(10·5, 12·1)		11·4	(10·5, 12·3)	

6.4. Policy implications

If the explicit objective of a kidney allocation scheme is to maximise health gains from a limited supply of kidneys, then this simulation exercise demonstrates how this can be achieved through the QALY-maximising scheme. However, the simulation also provides insight into some of the potential unintended consequences of a QALY-maximising approach:

1. Although it produces the most QALYs, it also generates the highest costs
2. Inequity in access: similar to the LYFT concept, a QALY-maximisation approach can negatively impact access to transplantation for patients with lower expected QALY gains, such as diabetic patients and older patients
3. Inequity in outcomes: while health gains for transplant recipients are maximised, patients who are not prioritised for a transplant may have worse outcomes.

Before making changes to a kidney allocation scheme, the underlying policy objectives need to be understood and made explicit. This simulation exercise on its own cannot be used as the basis for recommending a change in policy, but it quantifies the magnitude of potential gains and losses associated with moving from one allocation strategy to another. It also reveals some of the complexities of the decision problem. This information can help inform the debate about trade-offs between allocation approaches. The simulation exercise presented in this thesis only compared five different allocation concepts from across the equity-efficiency spectrum, but there are many more potential approaches or combinations of approaches that could be explored using the same data inputs and model structure.

6.5. Contributions of this research to the field

There are a number of ways in which this research contributes to the field of kidney transplantation and allocation:

1. New insight into variations in hospital costs for RRT patients

Linkage of the UK Renal Registry and HES datasets provided a rare opportunity to analyse variations in hospital costs over time for RRT patients in relation to age, treatment modality and comorbidities. The regression models that were developed in Chapter 2 can also be used as cost inputs in other cost-effectiveness analyses involving RRT patients.

2. *Application of flexible parametric modelling techniques to analyse post-transplant survival*

While the use of standard parametric models to extrapolate survival data in economic evaluation is well established, there are still relatively few applied examples of flexible parametric modelling techniques in the literature. The survival models described in Chapter 3 have two important features that were crucial for the simulation of alternative kidney allocation schemes. Firstly, the flexible parametric modelling approach facilitates extrapolation of the data in order to predict mean survival. This allowed survival estimates to be used both deterministically (for the calculation of expected post-transplant survival in the longevity matching allocation scheme and for the calculation of QALY differences in the utility-maximising scheme) and stochastically to model competing risks after each kidney had been allocated to a specific patient. Secondly, the survival model was based on a historical cohort of patients from the UK Transplant Registry and allowed for inclusion of both donor and recipient characteristics as covariates in the analysis, thus facilitating the prediction of expected post-transplant survival for each patient taking into consideration the characteristics of a given donor, namely age and hypertension status.

3. *Updated health-state utility estimates for transplant recipients and waiting list patients*

The ATTOM study presented an opportunity to collect utility values in a large, representative population of ERF patients in the UK using the EQ-5D-5L questionnaire. Using data collected on patient and treatment factors, regression models were fitted to provide insight into variations in health-state utility values, including characterisation of the decline in health status in relation to time on dialysis. Similar to the models for estimating hospital costs, the

regression models in Chapter 4 and Appendix 4 can be used as inputs to inform other cost-effectiveness analyses involving RRT patients.

4. *Exploration of newer allocation concepts that have not previously been studied in the UK context*

The concepts of longevity matching and utility-maximisation emerged in the last 10 years as part of the proposals to revise the kidney allocation scheme in the US, but these concepts have not previously been studied in the UK context. The simulation exercise undertaken for this thesis tested these newer concepts using UK data and allowed for a comparison of outcomes with the current national allocation scheme. In addition, this thesis demonstrated the feasibility of designing an allocation system that can estimate post-transplant survival for each potential recipient for a given donor kidney. In theory, this should further optimise the matching process in comparison to predictive models that are based on an average donor or an average patient. Interestingly in the US, when the OPTN was considering LYFT as a potential allocation concept, matching each kidney and patient was deemed too complicated and unpredictable to be feasible.[30] This is likely because the LYFT calculation attempted to simultaneously model graft failure and patient survival and included a much larger number of covariates than the final predictive models presented in this thesis, highlighting the trade-off between complexity and feasibility that is inherent in the modelling process.[24]

5. *Quantification of the consequences of different allocation schemes in terms of both costs and QALYs*

None of the previously identified simulation studies (Chapter 1) that have compared different approaches to deceased donor kidney allocation have quantified outcomes in terms of both lifetime costs and QALYs. Although the supply of donor kidneys is often seen as the primary resource constraint that limits the rate of transplantation, all decision-making in healthcare is subject to a budget constraint and therefore cost should be a relevant

consideration. Going beyond survival to report quality-adjusted survival or QALYs recognises the fact that there are disparities in health status associated with different RRT modalities. Although a decision was made not to evaluate the ICERs from the simulation exercise by applying a specific willingness-to-pay threshold, policy makers may wish to do so alongside equity and distributional considerations.

6.6. Limitations

As a simulation exercise, there are several ways in which the model and results presented here may not accurately reflect the kidney allocation process in the real world. The waiting list population in the simulation model was based on patients recruited into the ATTOM study and therefore did not include any paediatric candidates. Elements on the 2006 NKAS give priority to paediatric patients, and this has not been directly modelled here. Structurally, the model also made a number of important simplifying assumptions. For example, the model did not allow for re-transplantation and the waiting list was maintained at a constant size throughout. In terms of data inputs and assumptions, health-state utility estimates for transplant patients only reflected data that were captured at a single point in time in the ATTOM study (6 months after transplant) as the study design and resources did not allow for longitudinal measurement. However, given that all of the allocation schemes were run using the same data inputs and subject to the same set of assumptions, these limitations reinforce the fact that, as with any simulation modelling exercise, the outputs should be interpreted in terms of the costs and consequences of the five allocation schemes in relation to one another, rather than the absolute value of any one output in isolation.

The most important limitation of this simulation exercise is the assumption that was made regarding the outcomes for those patients who did not receive a transplant. Factoring in the costs and QALYs for these patients had a dramatic effect on the relative positions of the allocation schemes on the cost-effectiveness plane. This also raises questions about the objectives and principles underpinning allocation concepts. For example, is an allocation strategy still QALY-maximising if it only maximises outcomes among patients who receive

a transplant? Whose outcomes matter? This simulation exercise cannot provide the answers, but brings to light some of the questions that require further consideration.

Finally, although the patient-level analyses of costs, survival and health-state utility values all provided estimates of uncertainty, it was not possible to consider parameter uncertainty in the simulation process as this would have had profound implications for model running time. It is possible that if the coding of the allocation process itself could be made more efficient, parameter uncertainty could be incorporated to allow for a fully probabilistic analysis.

6.7. Areas for future research

There are two main areas of future research that have emerged as priorities resulting from this thesis:

1. *Explore alternate assumptions and modelling approaches to determine outcomes for patients who are not prioritised to receive a transplant*

Using information about which types of patients received a transplant under each of the allocation schemes, predictive models could be developed to estimate time to transplantation for each of the patients who remains on the waiting list at the end of the simulation run, from which more accurate estimates of lifetime costs and QALYs could be generated. Alternatively, if the model could be run continuously by repeating the sequence of arriving donor kidneys many times, it may be possible to achieve a steady-state that can be compared across allocation schemes.

2. *Determine priorities and societal preferences in trading off equity and efficiency in the design of a national kidney allocation scheme*

Conventional methods for economic evaluation place emphasis on informing decisions that maximise efficiency but do not give consideration to distributional effects. Implicitly each QALY is assigned equal value irrespective of the characteristics of the recipients or how the

health gains are achieved, thereby overlooking the equity dimension of resource allocation decisions.[55-57]

Alternative methods exist to help make resource allocation decisions when faced with multiple and sometimes conflicting objectives. Multi-criteria decision analysis (MCDA) methods are increasingly being applied to healthcare decision making and can provide a structured, explicit approach that can also improve transparency in decision making processes.[58] This thesis has demonstrated the range of outputs that can be generated from the simulation model, including total costs and QALYs associated with each approach to allocation and the impact of different allocation schemes in terms of equity in access to transplantation and the distribution of outcomes among patients. An MCDA approach could be used in a deliberative process that brings together relevant stakeholders in order to identify which attributes of a kidney allocation scheme are important by considering some of the questions that have emerged in this thesis, including:

- In which patient population should we be seeking to maximise outcomes, transplant recipients or all ERF patients (including those who do not receive transplants)?
- How should equity be defined? In terms of access to transplantation? In terms of outcomes of transplantation? What patient characteristics are relevant to consider? What distribution of outcomes would be considered equitable?
- Are there other attributes beyond efficiency and equity that are important in the design of a national kidney allocation policy?

If it is possible to reach agreement on the relative importance of these attributes through a deliberative process, then each of the allocation schemes could be scored in relation to these attributes to produce an overall ranking and identify the preferred approach to allocating deceased donor kidneys in the UK.

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8. APPENDICES

APPENDIX 1: Summary of economic evaluation literature comparing transplantation and dialysis

APPENDIX 2: Summary of literature on the use of simulation as a tool to study kidney allocation

APPENDIX 3: Supplementary costing paper

APPENDIX 4: Final flexible parametric models for graft failure and waiting-list survival

APPENDIX 5: Additional regression models to estimate health-state utility values

APPENDIX 6: Description of Visual Logic code in the simulation model

APPENDIX 1: Summary of economic evaluation literature comparing transplantation and dialysis

Table 1 Economic evaluations comparing dialysis and transplantation – basic study characteristics

	Author	Year	Title	Journal	Country	Population	Intervention	Comparator	Modelling approach	Patient characteristics and co-morbidities	Perspective	Time horizon	Outcomes and key health events
1	Klarman	1968	Cost effectiveness analysis applied to the treatment of chronic renal disease	Medical Care	USA	Chronic renal disease	Haemodialysis	Transplantation	Cumulative costs and life expectancy analysis (decision tree)	Age	Health service	Lifetime	Life years
2	Stange	1978	Predicting treatment costs and life expectancy for end-stage renal disease	New England Journal of Medicine	USA	ESRD patients	Transition from facility dialysis to home dialysis	Transition from facility dialysis to cadaveric transplantation; transition from home dialysis to cadaveric transplantation	Cumulative costs and life expectancy analysis (decision tree)	Not specified	Health service (Medicare)	10 years	Dialysis survival, graft and transplant survival
3	Roberts	1980	Cost-effective care of end-stage renal disease: a billion dollar question	Annals of Internal Medicine	USA	ESRD patients	Home haemodialysis, centre haemodialysis	Cadaver donor transplantation, live related donor transplantation	Simulation (INS language)	Age	Medicare	Lifetime	Transplantation, dialysis, death

4	Ludbrook	1981	A cost-effectiveness analysis of the treatment of chronic renal failure	Applied Economics	UK	Patients with chronic renal failure	Hospital dialysis, home dialysis	Dialysis and transplantation	Markov (1 month cycle)	Age	Department of Health	Lifetime	Dialysis training, hospital dialysis, home dialysis, first transplant, rejection, death
5	Ohi	1986	Why are cadaveric renal transplants so hard to find in Japan?	Health Policy	Japan	ESRD patients	Haemodialysis	Transplantation	Cumulative costs and life expectancy analysis	Not specified	Payer (health insurance)	Lifetime	Survival, graft loss rate for transplantation, % on dialysis after graft failure
6	Garner	1987	Cost-effectiveness analysis of end-stage renal disease treatments	Medical Care	USA	ESRD patients	Home dialysis, in-centre dialysis	Living-related donor transplant, cadaveric transplant	Cumulative costs and life expectancy analysis (decision tree)	Age, sex	Health service (gross social costs model) and societal (net social costs model)	20 years	Life years x (value of a life year); assumed dialysis patients continue on same modality for entire period, transplant patients could experience graft failure, second transplant and dialysis
7	Laupacis	1996	A study of the quality of life and cost-utility of renal transplantation	Kidney International	Canada	Clinically stable patients on transplant list for at least 3 months	Transplantation	Dialysis	Prospective within-trial analysis (decision tree)	Age, gender, time on dialysis, employment status, type of renal disease	Societal	2 years after transplantation	Survival at 2 years (patient and graft), quality of life, employment outcome
8	Hornberger	1997	Cost-effectiveness of repeat medical procedures: kidney transplantation as an example	Medical Decision Making	USA	ESRD patients who are candidates for transplantation	Re-transplantation policy in event of graft failure	No re-transplantation policy	Markov (monthly cycle)	None	Societal	Lifetime	On dialysis (pre-transplant), first transplant, failed first transplant, repeat transplant, failed repeat transplant, death

9	de Wit	1998	Economic evaluation of end stage renal disease treatment	Health Policy	Netherlands	Patients receiving ESRD treatment	5 forms of dialysis (home HD, limited care HD, in-centre HD, CAPD, CCPD)	Renal transplant	Markov (1 year cycle)	Age, gender, number of comorbid diseases, months on dialysis	Societal	5 years	Death, technical failure,
10	Douzdjian	1998	Treatment strategies for insulin0dependent diabetics with ESRD: a cost-effectiveness decision analysis model	American Journal of Kidney Diseases	USA	Patients with type 1 diabetes and ESRD	Dialysis	Transplant from cadaver donor, transplant from living donor, simultaneous pancreas-kidney transplant	Decision tree	None	Medicare	5 years	Dialysis, graft failure, death and 4 health states for pancreas-kidney transplant recipients: dialysis-free/insulin-free, dialysis-free/insulin-dependent, dialysis dependent/insulin-free, dialysis-dependent/insulin-dependent
11	Kalo	2001	Economic evaluation of kidney transplantation versus haemodialysis in patients with end-stage renal disease in Hungary	Progress in Transplantation	Hungary	ESRD patients	Cadaveric kidney transplantation	Haemodialysis	Retrospective analysis of patient files (decision tree)	Age, gender, time on dialysis	National health insurer	3 years	
12	Kaminota	2001	Cost-effectiveness analysis of dialysis and kidney transplants in Japan	Keio J Med	Japan	ESRD patients who are candidates for dialysis or transplantation	Transplantation	Dialysis	Decision tree (implied)	Age	Health insurer	Lifetime	Duration on dialysis, survival

13	Greiner	2001	Socio-economic evaluation of kidney transplantation in Germany	Archives of Hellenic Medicine	Germany	ESRD patients on wait list for kidney transplant	Transplantation	Dialysis	Prospective single centre study (decision tree)	None	Societal	Not specified	Survival status and transplant function in first year, quality of life (EQ-5D and NHP), survival between dialysis and transplant assumed to be equal
14	Jassal	2003	Kidney transplantation in the elderly: a decision analysis	J Am Soc Nephrol	Canada	Patients stable on dialysis aged 65 yrs or more	Transplantation	Dialysis	Markov (3 month cycle)	Separate analyses for patients with diabetes or cardiovascular disease	Third-party payer	Lifetime	Dialysis, transplant, acute rejection, transplant-related complication, acute rejection and transplant-related complication, death
15	Mutinga	2005	Consequences of eliminating HLA-B in deceased kidney allocation to increase minority transplantation	American Journal of Transplantation	USA	ESRD patients on dialysis awaiting transplantation	Allocation policy with HLA antigen matching	Allocation policy without HLA antigen matching, allocation policy with HLA matching by partial priority to minorities	Markov (1 year cycle)	Costs adjusted for (patient age, race, gender, degree of immunologic sensitization, cause of renal disease, insulin dependence, length of time on dialysis, number of HLA mismatches); survival adjusted for (age, race, gender, cause of renal disease, blood type)	Medicare	20 years	Functioning transplant (alive), functioning transplant (death), return to dialysis (retransplantation not explicitly modelled, but included as part of patients who return to dialysis), death after return to dialysis
16	Lee	2006	A simulation model to estimate the cost and effectiveness of alternative dialysis initiation strategies	Medical Decision Making	USA	ESRD patients	Current practice	Early initiation, late initiation, no dialysis (wait for transplant only)	Simulation (ANSI C programming)	Demographics: age, gender, race, blood type (correlates with waiting time for transplant); cormorbid conditions: diabetes, CV disease, CHF, cancer; disease markers: eGFR,	Payer (Medicare)	Lifetime	eGFR deterioriation, transplant, graft failure, hospitalization, death (all hazard rates)

										serum albumin; clinical flags: previously hospitalised, currently on transplant			
17	Kontodimopoulos	2008	An estimate of lifelong costs and QALYs in renal replacement therapy based on patients' life expectancy	Health Policy	Greece	ESRD patients	In-center haemodialysis, peritoneal dialysis	Transplantation	Cumulative costs and life expectancy analysis (decision tree)	Age, gender	Health service (implied)	Lifetime	Life expectancy (90-day, 1, 2 and 5-year survival curves)
18	Howard	2009	The cost-effectiveness of increasing kidney transplantation and home-based dialysis	Nephrology	Australia	New ESKD patients	Service provision model (1) increase rate of kidney transplantation by 10% and 50% (2) increase number of new dialysis patients receiving home-based care (by 50% on PD, by 2-35% depending on age for HHD)	Current practice	Markov (multiple cohort, 1 year cycle)	Stratified by age group, time-dependent probabilities used for first 5 cycles	Central healthcare funder	Lifetime	Pre-emptive transplant (does not differentiate between live or deceased), dialysis (hospital HD, home HD, satellite HD, PD), transplant (does not differentiate between live or deceased), graft failure, re-graft, death ESKD, death other causes
19	Perovic	2009	Renal transplantation vs haemodialysis: cost-effective analysis	Vojnosanitetski Pregled	Serbia	ESRD patients	Haemodialysis	Transplantation	Cumulative costs and life expectancy analysis	None	Health insurer	10 years	Not clearly described

20	Haller	2011	Cost-effectiveness analysis of renal replacement therapy in Austria	Nephrol Dial Transplant	Austria	Incident ESRD disease patients	Strategy 1: current assignment to haemodialysis (90.6%) peritoneal dialysis (7.2%), transplantation (living donor 0.1%), transplantation (deceased donor 2.1%)	Strategy 2: increase PD by 20%; Strategy 3: increase PD by 20% and increase living donor transplantation by 10%	Markov (monthly cycle)	Reported age, gender, co-morbidities at baseline but not used in model	Health service	10 years	Haemodialysis (first 12 mths, 13-24 mths, beyond 25 mths), peritoneal dialysis (first 12 mths, 13-24 mths, beyond 25 mths), living donor transplanation (first 12 mths), deceased donor transplantation (first 12 mths), transplantation (13-24 mths), transplantation (beyond 25 mths), death
21	Wong	2012	Comparative survival and economic benefits of deceased donor kidney transplantation and dialysis in people with varying ages and co-morbidities	PLoS One	Australia, New Zealand	Potential transplant candidates	Listing on deceased kidney donor waiting list and transplanting (approx 10 health states)	Non waitlisting on dialysis (approx 5 health states)	Markov (1 year cycle) in Treeage/Excel	Cardiovascular disease, diabetes, cerebrovascular disease, obesity, smoking status, age at listing and transplantation	Third-party payer	Lifetime	Allograft failure, dialysis, death, post-transplant complications, delayed graft function, wound infection
22	Villa	2012	Cost-effectiveness analysis of the Spanish renal replacement therapy program	Peritoneal Dialysis International	Spain	ESRD patients	Strategy 1: current situation (with respect to scheduled dialysis patients i.e. to avoid non-planned or urgent start patients)	Strategy 2: increase in scheduled incident patients; Strategy 3: constant scheduled incidence, increase PD, lower HD; Strategy 4: increase in scheduled incident patients and increase PD	Markov (1 year cycle)	Not specified	Societal	5, 10 and 15 years	Haemodialysis, peritoneal dialysis, transplantation, death

Table 2 Economic evaluations comparing dialysis and transplantation – data sources and results

	Author	Year	Source of clinical data	Modelling outcomes	Cost categories	Source of cost data	Outputs reported	Sensitivity analysis	Key conclusion
1	Klarman	1968	Death rate on dialysis, transplantation and failures (Committee on Chronic Kidney Disease, Bureau of the Budget), quality adjustment for life after transplantation vs. dialysis (source or assumptions not specified)	Assume constant death rate for subsequent years	Transplantation, re-transplantation, maintenance drugs, dialysis	Not specified	Life years gained, cost per life year for dialysis vs. transplantation	None	Maximising transplantation is the more effective way to increase life expectancy at a given cost
2	Stange	1978	Dialysis survival (National Dialysis Registry), graft and transplant survival (Human Renal Transplant Registry NIH)	Linear extrapolation	Annual cost of facility dialysis, annual cost of home dialysis, cost of cadaveric transplantation (1st year, subsequent years for stable vs. unstable patients), rejection costs	Medicare (Health Care Financing Administration)	Discounted life years and costs for 1000 patient cohort for each treatment and then for shifting patients from one treatment to another ('incremental')	Low and high assumptions for cadaveric transplantation cost and survival	Shifting patients from facility to home dialysis leads to similar life expectancy and lower costs. Shifting patients from dialysis to transplant may reduce life expectancy (associated with higher first-year mortality) and also reduce costs

3	Roberts	1980	Survival on dialysis (National Dialysis Registry), patient and graft survival on transplant (Human Renal Transplant Registry)	Assumed constant survival after Year 1 post-transplant	Home haemodialysis (first year training, physician fees, modifications to home, equipment purchase, supplies; subsequent years including declotting and access revisions, hospitalizations, routine lab work); in-centre haemodialysis (Medicare charge and medical costs similar to home); transplantation (first year including kidney retrieval, hospitalisation, physician fees, complications, immunosuppressive therapy); follow-up for subsequent years after transplantation (including hospitalisations), graft rejection	Dialysis (Medicare charge data), General Accounting Office, literature	Life expectancy (survival), average cost per patient, average cost per life year for each treatment	Survival probability on dialysis, proportion of patients treated, survival probability after cadaver transplantation, discounting	In-centre dialysis is not cost effective
4	Ludbrook	1981	Transition probabilities (unpublished data from regional health authority), patient and graft survival (European Dialysis and Transplant Society, including by age group)	Not applicable	Not described	Unpublished Department of Health and Social Security study, age effect (assumptions)	Cost per life year gained	Discount rate	Transplantation is most cost-effective, however selection criteria such as age may affect outcome of the cost-effectiveness analysis
5	Ohi	1986	Survival rates (published literature), quality of life adjustment (assumed 25% better in transplanted patients based on Klarman 1968)	Not applicable	Annual cost of dialysis (cost per session x number of sessions, training fees, miscellaneous costs), cost of transplantation (and miscellaneous costs)	Annual medical insurance coverage	Total life expectancy, total cost, average cost/life year	Evaluated increased cost if increased patients on haemodialysis or increased patients receiving cadaveric transplant	Renal transplantation is more cost effective than haemodialysis

6	Garner	1987	Survival (NIH)	Not applicable	Labour costs, materials, capital, imputed earnings (for net social costs model as offset to gross social costs)	ESRD treatment costs (US HHS Medicare charge data), probability of working (National Kidney Dialysis and Kidney Transplant Study), earnings (US Bureau of the Census)	Cost per life year gained, no ICERs presented	Survival probability, costs past 20 years	The most cost-effective treatment is living-related donor transplant, followed by home dialysis.
7	Laupacis	1996	Trial data (survival, QALY by TTO in patients); n=168	Not applicable	In-patient hospitalizations, outpatient visits (dialysis, transplant clinic visits, medications, lab tests, physician fees), nephrectomy of living related donor, transplant program (organ retrieval and cross-matching), patient costs (transportation, accommodation, child care and time)	Patient charts (hospitalizations and outpatient visits), provincial billing system (physician fees, diagnostics), patient interview (cost to patient and family), time spent receiving care (provincial industrial sector rate)	Total and incremental costs, QALYs, ICER	None	Renal transplantation is more effective and less costly than dialysis
8	Hornberger	1997	Patient and graft survival (USRDS, HCFA), QOL adjustment from literature	Not applicable	Dialysis and never transplanted, first or second transplant procedure, functioning first or second graft, dialysis after graft failure, patient costs (copayments for immunosuppressive drugs, transplant therapies)	HCFA, published literature	Total life expectancy, QALYs, costs, ICER	Median waiting time, age group, discount rate, probability of survival on dialysis, effect of disallowing retransplantation on average median time until first transplant, effect of longer median time until first transplant when retransplantation allowed	ICER = $9,656 /QALY: retransplantation policy is cost effective

9	de Wit	1998	Dialysis outcomes and utility assessment from patients in prospective clinical study (NECOSAD), transplant outcomes from renal replacement registry (RENINE)	Not applicable	Resource use (days hospitalisations, medication use), costs of work force at dialysis centres by questionnaire (nephrologist services, overheads), cost of materials, cost of lab services from recent published study, patient travel cost and primary care costs outside of hospital, transplant costs	NECOSAD study (resource use, costs), patient interviews (travel and primary care costs), published clinical trial (transplant costs)	Total costs, life years gained, QALYs, appears to present average cost/LYG and average cost/QALY	One-way scenarios for cost reduction, substitution of patients to less expensive modalities	Transplantation is less costly than dialysis. Among dialysis modalities, CAPD is cost-effective.
10	Douzdjian	1998	Probability of graft and patient survival (USRDS, UNOS, literature), preference measures using Standard Gamble for simultaneous pancreas-kidney transplant from 17 patients	Not applicable	Hospital charge fees, professional fees, organ acquisition fees	Dialysis and kidney transplantation (Medicare), pancreas-kidney transplant (literature and assumptions)	Total costs, QALYS, average and incremental cost/QALY	One-way sensitivity analyses varying patient and graft survival probabilities, health state utility values, costs	For patients with insulin-dependent diabetes and ESRD, simultaneous pancreas-kidney transplantation is cost effective compared to kidney alone transplantation and dialysis
11	Kalo	2001	Mortality data from Hungarian subset of European database	Cox regression analysis to control for effect of age, gender, time on dialysis	Cost of dialysis, transplantation, transportation	National Health Insurance Fund database	Total costs, cost per life year saved	Discount rate	Kidney transplantation provides survival benefits at a reduced cost compared to haemodialysis
12	Kaminota	2001	Disability weights (questionnaire of Japanese Govt officials), duration dialysis (Japanese Society for Dialysis Therapy), graft survival (Japanese Society for Transplantation), abridged life table for Japan	Disease duration / survival (Weibull)	Cost of dialysis (excluding transportation, opportunity cost of time), cost of kidney transplants	Health insurance payments (National Sakura Hospital)	Costs, DALYs, ICER	Discount rate, age, disability weight	Transplantation is cost effective compared to dialysis

13	Greiner	2001	QOL (questionnaire), graft loss past first year (Eurotransplant)	Not described in detail	Transplant operation, immunosuppressive drugs, hospital stay, organ acquisition, evaluation costs, indirect work productivity loss, dialysis equipment, lab tests, drugs	Personnel (questionnaire), drugs, catheters, administrative expenses (from hospital accounting system), capital costs (estimated), productivity loss (estimated based on GDP)	Total QALYs, costs and average cost per QALY	Discount rate	Dialysis is more expensive and of lower value concerning patient quality of life
14	Jassal	2003	Mortality, acute rejection, graft survival (USRDS); utility data (literature)	Not applicable	Annual cost of dialysis, cost of transplantation, cost of immunosuppressive medication, cost associated with acute rejection and complications	Dialysis and transplantation costs (Medicare), immunosuppressive therapy(literature), rejection and complications (literature)	Total and incremental life expectancy, QALYs, and costs	One-way sensitivity analyses for all probabilities, utility and mortality estimates	In older patients, transplantation offers gains in both life years and QALYs, but also increases costs
15	Mutinga	2005	Clinical outcomes, patient and graft survival (USRDS), utility weights (Laupacis 1996); for new policy with no HLA allocation, 2% increase in graft loss was based on Roberts 2004	Multivariate Cox regression to estimate graft survival at 1, 2, 3, and 4 years post-transplant and graft survival at year 4 post-transplant, given survival at year 2	Initial hospitalization cost, organ procurement cost, first year cost transplantation, maintenance cost transplantation (month 12-24), cost first year post-graft loss, maintenance cost on dialysis	Medicare, kidney acquisition cost (CMS estimate)	QALYs, costs, average cost/QALY	PSA on parameters with distributions, utility values (± 30%), discount rate, number of organs that would be redistributed (± 50%)	Eliminating HLA-B matching is likely to increase allocation of deceased donor kidneys to minorities and save costs, but at a loss of QALYs (to Caucasions)

16	Lee	2006	Hospitalisation rates (USRDS, Kaiser Permanente Northern California), transplant and graft failure rate (United Network for Organ Sharing), eGFR (San Fran Department of Public Health)	Simulation based on hazard rates calculated from historical data	Dialysis, hospitalization, graft failure, transplantation (cost for procedure and annual cost for each subsequent year)	Medicare claims data	Costs, life years, QALYs, hospital admissions	Used Approximate Dynamic Programming to assess whether perturbations in the dialysis strategy (number of sessions per week, duration of each session) led to an improvement	Earlier initiation strategy is incrementally less cost-effective compared to other strategies
17	Kontodimopoulos	2008	Life expectancy (Annual Report of European Registries), utilities (SF-6D collected from patients selected from Hellenic Renal Registry)	Estimated from survival curves (not described in detail)	Annual cost HD (equipment/infrastructure, diagnostic services, drugs and consumables, staff salaries, operational costs/overheads); PD (also included staff hours per month for training and visits); transplantation (preoperative diagnostic and histological), postoperative hospitalization (diagnostics, drugs, materials, consumables, staff), subsequent years costs (immunosuppressive drugs)	PD and HD (micro-costing), transplantation (published report)	QALYs, annual and total costs, average cost/QALY	Discount rates	Transplantation results in greater QALYs and lower costs; PD is less costly than HD

18	Howard	2009	Incidence and transition probabilities for RRT modalities (ANZDATA), utility data (from Laupacis 1996 pre and post-transplant weights)	Not applicable	Annual cost of dialysis (equipment, buildings, maintenance, salaries, consumables, access, drugs including epo, calcitriol, iron, hospitalizations, due to infection and complications, cost of switching modalities, specialist consultations and reviews, work-up associated with transplant waiting list), transplantation (surgery, hospitalization, immunosuppressive drugs, specialist review and consultations), organ procurement cost	Previous published costing study, transplantation and dialysis (AR DRG), drugs (PBS), medical services (MBS), organ procurement cost (expert opinion)	QALYs, LYS, ICERs	Discount rate, increases to cost of dialysis and transplantation	Increasing rate of transplantation is dominant (less costly and more effective). Increasing PD and home HD rates is as effective and less costly.
19	Perovic	2009	Not clear, quality of life measured using McGill Questionnaire but not clear how utility weights were derived	Not clearly described	Haemodialysis (consumables, drugs, other, operation); transplantation (drugs, operation cost)	Not clear	Total and incremental costs and QALYs	None	Haemodialysis is more costly than transplantation
20	Haller	2011	Austrian Dialysis and Transplant Registry, utilities for dialysis (from de Wit 1998, EQ-5D, SG, TTO) and literature-based estimates for transplantation (Laupacis 1996)	Incidence (Poisson regression); transition prob and survival (multinomial model)	Cost of transplantation to renal unit, costs of medication, costs of non-ESRD-related hospital admissions (inpatient, outpatient, investigations, blood tests, medications received in hospital including epo and immunosuppressants, radiological imaging, consultations, nursing, supplies and overhead costs for maintenance, hospital admin, laundry, equipment and building acquisition). Excluded 'reimbursements and charges for cost data collection' as well as societal costs such as ability to work	Patient-level cost data from electronic records. Cost of outpatient prescription medication and transportation for dialysis (Upper Austrian Health Insurance); all other medical treatment including haemodialysis cost, cost or organ harvesting from live donor including health checks and follow up (Elisabethinen Hospital Linz); cost of organ harvesting from deceased donor based on expert assumptions about length	Total costs, total life years saved, total years free of dialysis, total QALYs (no ICERs both Strategy 2 and 3 dominated)	Policy parameters (different values for PD proportion and living-donor proportion), one-way sensitivity analysis individual parameters including cost, QALY, transition prob and prevalence	Increasing PD and kidney transplantation compared to current practice increases QALYs and reduces costs

						of ICU stay for brain-dead donor			
21	Wong	2012	Transplant registry, organ matching service, published literature	Multivariate Cox proportional hazard models for association of co-morbidities	Unit costs for initial and maintenance dialysis, annual resource use for patients with comorbidities (diabetes, cardiovascular disease), maintenance costs for kidney transplantation	DRGs, Medicare benefits schedule, published literature	Total and incremental costs, life years gained, ICER, varied age and co-morbidities (one at a time) in sensitivity analyses	Scenario analysis for age at time of listing and waiting time and comorbidities; PSA	Wait-listing and transplantation increases life years and saves cost
22	Villa	2012	Transition prob (Spanish Society of Nephrology registry), utilities from proprietary database (SF-36 converted to SF-6D) and from literature	Not applicable	Direct (scheduled HD, PD, transplantation, non-scheduled HD, PD, transplantation), indirect costs	From previous published costing study by same first author	Average annual cost, QALYs, ICER, net health benefit at WTP threshold or EURO 35,000 per QALY	Univariate by changing by changing costs and utilities for PD, bivariate by both lowering PD utilities by 10% and increasing PD costs by 10%	Increasing the number of scheduled incident patients receiving PD would result in greater QALYs at lower costs

APPENDIX 2: Summary of literature on the use of simulation as a tool to study kidney allocation

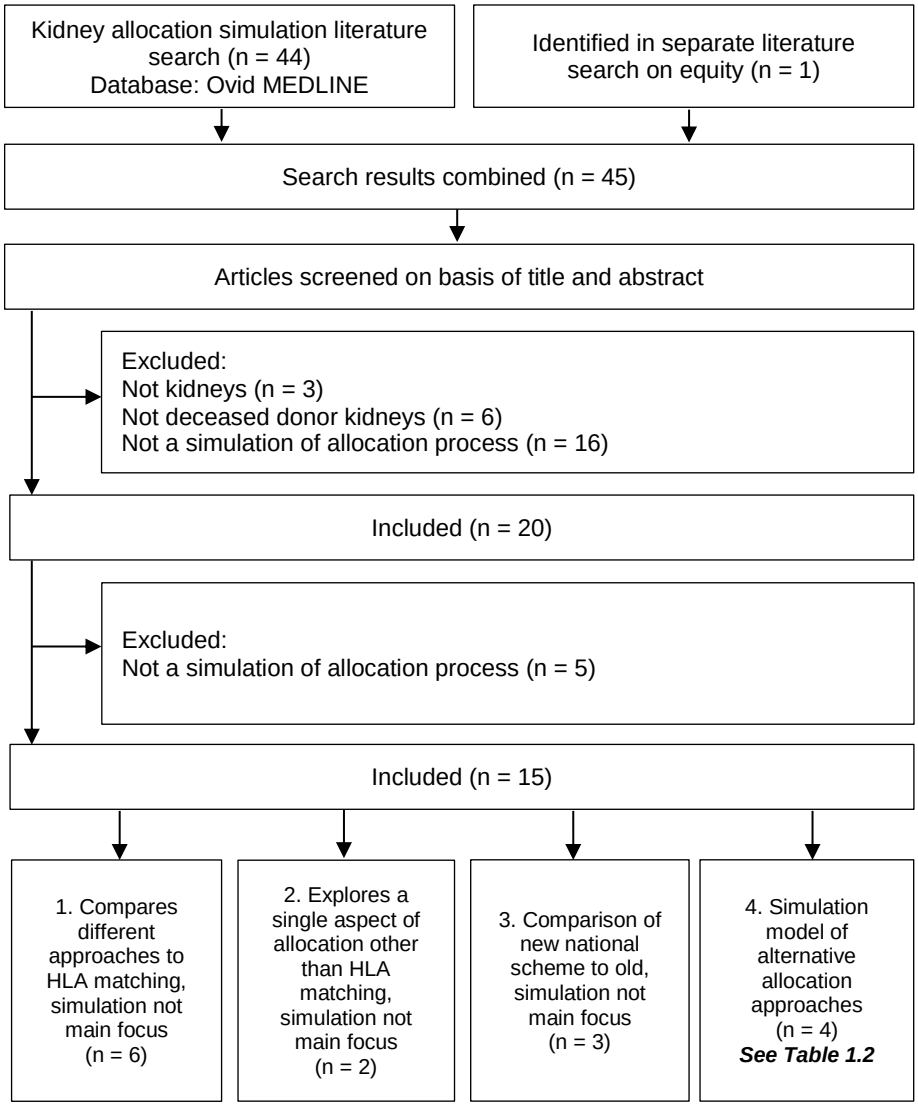
A literature review was undertaken to identify examples of simulation studies that compared different approaches to kidney allocation in the clinical literature. This appendix contains a summary of the search strategy and studies that were identified. After applying inclusion/exclusion criteria, a total of 15 papers were deemed eligible, however for the majority of these (8 papers), the simulation evidence was of secondary consideration and the primary emphasis of the paper was on exploring the impact of a single clinical factor (for example HLA matching) on the allocation process. A further 3 papers reported on the introduction of a new national kidney allocation policy in which the emphasis of the paper was on explaining how the new and old kidney allocation schemes differed, with some supporting evidence from simulations presented. Only 4 studies were identified in which the simulation model of a deceased donor allocation process was the primary focus of the paper and in which simulation methods were described in some level of detail that made it possible to understand the general approach taken. These 4 simulation modelling studies are discussed in Chapter 1 of the thesis (see Table 1.2). A brief summary of the main characteristics of the other 11 studies that were identified is provided below.

Search strategy

Database: Ovid MEDLINE

1	kidney.mp.	709977
2	allocat$.mp.	169921
3	simulat$.mp.	384410
4	transplant$.mp.	581411
5	1 and 2 and 3 and 4	48
6	limit 5 to (english language and humans and yr=”1960 – 2015”)	44

Flow diagram



Use of simulation in the kidney allocation literature - study characteristics

1. Comparing different approaches to HLA matching, simulation not main focus

Author, year and country / region	Allocation schemes	Main results or outcomes considered
Wujciak et al. 1993a, Europe and North America	1. HLA-A, -B, -DR matching only 2. FIFO ("first in, first out" based on waiting time) 3. HLA-FIFO (longest waiting patient among equivalent matches) and HLA-MMP (patient is selected with lowest mismatch probability) 4. COMB: different weighted combinations of mismatch grade, waiting time and mismatch probability	• % HLA-A, -B, -DR mismatches • One-year graft survival (%) • Waiting time
Wujciak et al. 1993b, Europe	1. HLA1 (longest waiting patient is selected among patients with same mismatch grade 2. LOCAL1: HLA1 plus local allocation 3. LOCAL2: 25% HLA mismatch, 25% waiting time, 50% at random 4. XCOMB: combination of HLA mismatch grade, mismatch probability, waiting time, local transplant rate, center import/export balance	• HLA mismatch • Waiting time • DR homozygous (%) • Mismatch probability • Exchange balance • Local transplants (%)
Ichikawa et al. 1994, Japan	Comparison of different degrees of histocompatibility based on zero mismatches (repeated taking blood type into consideration): 1. 6-antigen (HLA-A, -B, -DR) 2. 4-antigen (HLA-B, -DR) 3. DRB1	• Number of donors who had a certain number of possible recipients under each matching criterion • Possibility of finding 1 or more recipients for each matching grade and blood type
Held et al. 1994, United States	1. Actual kidney-graft allocation system in 1989 2. Allocation under maximal HLA matching	• Patient characteristics (age, gender, ethnicity) • 5-year graft survival
Wujciak et al. 1999, Western Europe	1. Allocation based on conventional HLA-A, -B, -DR matching 2. Allocation based on cross-reactive antigen groups (CREG) matching	• Distribution of HLA-A and HLA-B mismatches and impact on graft survival rate
Schnitzler et al. 1999, United States	1. Current allocation system (in 1999) 2. Local allocation based on minimal HLA mismatching 3. National allocation based on minimal HLA mismatching	• 3-year graft survival rate • Average cumulative costs 3 years after transplantation

2. Explores single aspect of allocation, simulation not main focus

Author, year and country	Allocation schemes	Main results or outcomes considered
Moers et al. 2009, United States	1. To explore influence of donor age on transplant (graft) outcome: 2. Old-to-young (allow allocation of kidneys from donors over 65 to recipients under 65) 3. Old-to-old (allow allocation of kidneys from donors over 65 to selected recipients over 65) 4. Young-to-old (allow allocation of kidneys from donors under 65 to selected recipients over 65) 5. Young-to-young (allow allocation of kidneys from donors under 65 to recipients under 65 who original received a 65+ graft)	• Delayed graft function • Graft loss within 3 months posttransplant • Graft survival up to 10 years posttransplant
Barnett et al. 2012, United Kingdom	1. To explore change in allocation to allow blood group incompatible transplants in paediatric patients: 2. Current 2006 National Kidney Allocation Scheme (no antibody-incompatible deceased-donor transplants) 3. Allocation to any suitable antibody-incompatible patient 4. Allocation to antibody-incompatible patient with preferential allocation for blood group B donor kidneys to blood group A recipients	• Number of paediatric transplant recipients • HLA mismatch level • Waiting time

3. Comparison of new national scheme to old, simulation not main focus

Author, year and country	Allocation schemes	Main results or outcomes considered
Johnson et al. 2010, United Kingdom	1. 1998 national kidney allocation scheme 2. 2006 national kidney allocation scheme	• Characteristics of transplanted patients (waiting time, HLA mismatch, age, location, homozygosity, blood group, ethnicity) • Estimated 5-year survival (%)
Dominguez et al. 2013, Chile	1. Older allocation policy (blood group matching, medical priority, then points based on HLA match, waiting time, panel-reactive antibodies and paediatric recipients) 2. Newer allocation policy (blood group matching, medical priority, previous living donor, 0 mismatch, paediatric recipients then points based on recipient age, HLA match, panel-reactive antibodies and waiting time)	• Characteristics of patients (age, waiting time, panel-reactive antibody, HLA mismatch) for both transplant recipients and patients who remained on the waiting list
Israni et al. 2014, United States	1. Existing national deceased donor kidney allocation policy 2. New national deceased donor kidney allocation policy approved introduced in 2014 (incorporates the concept of longevity matching based on the KDPI and EPTS)	• Number of transplant recipients • Median lifespan posttransplant • Median extra life-years for transplant versus waiting-list candidates • Number of death on the waiting list by age • Characteristics of transplant recipients (e.g. age, blood type, ethnicity, pre-emptive transplant, HLA mismatch, local or shared kidney, primary cause of disease, time on dialysis)

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APPENDIX 3: Supplementary costing paper

RESEARCH PAPER COVER SHEET – Supplementary costing paper

SECTION A – Student Details

Student	Bernadette Li
Principal Supervisor	John Cairns
Thesis Title	Patient-level simulation of alternative deceased donor kidney allocation schemes for patients awaiting transplantation in the United Kingdom

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Nephrology Dialysis Transplantation		
When was the work published?	October 2015 (June 2015 online)		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	No	Was the work subject to academic peer review?	Yes

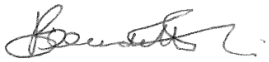
**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I had primary responsibility for obtaining the dataset, performing the statistical analysis and drafting the paper.

Student Signature:  **Date:** 27 July 2016

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Understanding cost of care for patients on renal replacement therapy: looking beyond fixed tariffs

Running headline: Hospital costs for patients on RRT

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ABSTRACT

Background. In a number of countries, reimbursement to hospitals providing renal dialysis services is set according to a fixed tariff. While the cost of maintenance dialysis and transplant surgery are amenable to a system of fixed tariffs, patients with established renal failure commonly present with comorbid conditions that can lead to variations in the need for hospitalisation beyond the provision of renal replacement therapy.

Methods. Patient-level cost data for incident renal replacement therapy patients in England was obtained as a result of linkage of the Hospital Episode Statistics dataset to UK Renal Registry data. Regression models were developed to explore variations in hospital costs in relation to treatment modality, number of years on treatment and factors such as age and comorbidities. The final models were then used to predict annual costs for patients with different sets of characteristics.

Results. Excluding the cost of renal replacement therapy itself, inpatient costs generally decreased with number of years on treatment for haemodialysis and transplant patients, whereas costs for patients receiving peritoneal dialysis remained constant. Diabetes was associated with higher mean annual costs for all patients irrespective of treatment modality and hospital setting. Age did not have a consistent effect on costs.

Conclusions. Combining predicted hospital costs with the fixed costs of renal replacement therapy showed that the total cost differential for a patient continuing on dialysis rather than receiving a transplant is considerable following the first year of renal replacement therapy, thus reinforcing the longer-term economic advantage of transplantation over dialysis for the health service.

Key words: comorbidities, dialysis, established renal failure, hospital costs, regression, transplantation

INTRODUCTION

In an attempt to control rising costs, several countries have introduced a system of fixed reimbursement rates for the provision of chronic dialysis for patients with established renal failure (ERF) [1]. Since 2010, reimbursement to hospitals providing renal dialysis services in England has been set according to a national tariff under the Payment by Results (PbR) system [2]. There are plans to introduce a similar national tariff for kidney transplantation in the near future, with separate currencies being developed to capture three stages of the transplant pathway: preparation for transplant, the inpatient episode including the transplant procedure, and post-transplant outpatient activity [3].

While the annual cost of chronic maintenance dialysis and the cost of transplant surgery are amenable to fixed tariffs, patients with ERF commonly present with comorbidities such as diabetes, ischaemic heart disease and vascular disease, which can lead to variations in the use of healthcare resources beyond renal replacement therapy (RRT) itself [4]. A number of previous studies have explored hospitalisation rates or costs among dialysis patients, however, given the challenges of collecting patient-level resource use data, these studies have typically been restricted to a time horizon of one year or less [5-7].

Linkage of the Hospital Episode Statistics (HES) dataset to UK Renal Registry (UKRR) data for patients who started RRT for ERF in England between 2003 and 2006 provides an opportunity to explore hospital inpatient and outpatient costs over a number of years among both dialysis and transplant patients. HES captures demographic information, comorbid conditions and data on all inpatient and outpatient care delivered in NHS hospitals in England, including treatment specialty and length of stay. The UKRR reports on the demography of incident RRT patients using data provided by renal centres. Linkage of these two datasets enhances the variables available for analysis and provides an opportunity to analyse a rich data source on hospitalisations for a cohort that represents >95% of all patients who started RRT during a defined period in England [8]. The aim of the current study is to analyse the linked dataset to explore variations in inpatient and outpatient

hospital costs, separately from the fixed cost of RRT, and in relation to treatment modality, number of years on treatment and factors such as age and comorbidities.

METHODS

The linked dataset comprised patients who started dialysis or received a kidney transplant in England between 1 April 2003 and 31 December 2006. The date of starting RRT was taken as the index date. If a patient on dialysis subsequently received a transplant, this patient then became part of the incident transplant cohort and the date of transplant was taken as the new index date for measuring subsequent hospitalisations. Comorbidity information in HES was determined from discharge codes from hospitalisations prior to starting RRT. Comorbidities were defined using International Classification of Disease version 10 (ICD10) codes applying algorithms previously described in the literature [9]. Inpatient costs were generated by grouping hospital episodes by Healthcare Resource Group (HRG) and applying the relevant 2011/12 PbR tariff associated with each HRG. Costs for outpatient appointments were assigned according to treatment function code [10]. Hospital episodes for the purpose of receiving maintenance dialysis or for undergoing transplant surgery were specifically excluded, but hospital episodes for any other reason, including procedures such as vascular access surgery, were included. This is because the aim of the present analysis is to explore variations in hospital costs separately from the costs associated with the fixed tariffs for dialysis and transplant surgery.

Linkage of the HES and UKRR datasets ended in December 2009 and therefore no further hospitalisation data were available beyond this point. Over the observation period, an increasing proportion of patients were therefore administratively censored part-way through a given year due to the end of data availability. The proportion of patients who were administratively censored ranged from 0% in year one to 47% in year six for haemodialysis patients, from 0% in year one to 38% in year six for peritoneal dialysis patients and from 11% in year one to 63% in year six for transplant patients. A comparison of patient characteristics and annual costs in the years prior to administrative censoring did not identify

any systematic differences between those patients who had been censored and those who had not. Therefore for the purposes of the current analysis, data from any year in which a patient was administratively censored were excluded under the assumption that these data were missing at random.

Patient characteristics and hospital costs in the first year after starting RRT are summarised by treatment modality using percentages and mean values as appropriate. Results of significance tests are presented to compare mean hospital costs between groups of patients with different characteristics of interest. Although cost data are typically not normally distributed, sample sizes in this dataset were sufficiently large for the use of t-tests or ANOVA to be robust to violations of the assumption of normality [11, 12]. In cases of unequal variances, Satterthwaite's approximation for standard errors was computed. To explore changes in hospital costs over time, mean annual costs and standard errors are presented by number of years on RRT.

Multiple regression was carried out to further determine which patient and treatment characteristics are important predictors of hospital costs. As cost data were positively skewed with a high proportion of patients with zero costs in the inpatient setting in any particular year, a two-part approach to the regression model was taken. Logistic regression was used to predict the probability of incurring any costs, followed by fitting generalised linear models to predict costs in patients who had at least one hospital episode in a given year. The effects of comorbidities on costs were explored using two approaches. In the first approach, individual comorbidities were included as covariates in the regression model and in the second approach, only the number of comorbidities was included as a covariate. Initially, all variables that were available in the dataset were included in the regression models and a process of backward elimination was used to inform variable selection using a P-value threshold of 0.2 [13]. Events such as transplant, renal recovery, death, or graft failure were included as covariates. In addition, a new variable was created to indicate if a patient died in the first half of the following year in order to adequately capture increased costs in the period prior to death.

All analyses were conducted in Stata (Version 13, Stata Corp, College Station, Texas, USA).

RESULTS

Descriptive analysis

Data on hospitalisations for 12 068 incident haemodialysis patients (Table 1a), 4 018 incident peritoneal dialysis patients (Table 1b) and 4 149 incident transplant patients (Table 1c) were available for analysis. The mean age for haemodialysis patients was 68.3 years compared with 56.0 years for peritoneal dialysis patients and 45.4 years for transplant patients. The two most common comorbidities were diabetes and hypertension and, of the nine comorbidities included in the scope of the analysis, the average number of comorbidities per patient at baseline was approximately 1.60 for haemodialysis patients, 1.26 for peritoneal dialysis patients and 1.56 for transplant patients.

Mean costs for patients during their first year of dialysis showed differences by modality, with haemodialysis patients incurring higher inpatient costs and peritoneal dialysis patients incurring higher outpatient costs. According to bivariate analysis, the presence of most comorbidities was associated with higher costs in the inpatient setting, but only diabetes was associated with significantly higher costs in both inpatient and outpatient settings and among both haemodialysis and peritoneal dialysis patients. Among transplant patients, congestive heart failure, peripheral vascular disease, diabetes and hypertension were all associated with higher costs in both inpatient and outpatient settings, whereas myocardial infarction, liver disease, cerebrovascular disease and deceased donor transplants were associated with higher costs only in the inpatient setting.

Table 2 summarises mean annual costs for patients receiving each type of RRT over the six years of available data. Combined inpatient and outpatient costs in the first year of RRT were similar for haemodialysis and transplant patients, however costs for transplant patients decreased more rapidly in subsequent years. Peritoneal dialysis patients had lower total

hospital costs compared to haemodialysis patients in the first year, but higher average costs in year six.

Multiple regression

Bivariate analysis of year 1 costs (Tables 1a, 1b and 1c) showed that events such as death can have opposite effects on inpatient and outpatient costs. Therefore it was important to control for these in multiple regression analyses and to keep the development of models for inpatient and outpatient costs separate. Two-part regression models were developed to determine which patient and treatment characteristics are important predictors of hospital costs. The final two-part models for each treatment modality are provided as supplementary material (available online at http://ndt.oxfordjournals.org). Key findings can be summarised as follows:

In the inpatient setting, logistic regression results (Supplementary Table 1a) showed that the probability of incurring any inpatient costs generally decreased as the number of years on haemodialysis increased. Female gender and presence of comorbidities, with the exception of liver disease, increased the probability of incurring inpatient costs. The effect of comorbidities on the probability of incurring outpatient costs for haemodialysis patients was less consistent.

Compared to the first year on RRT, patients on peritoneal dialysis had a lower probability of incurring inpatient and outpatient costs in subsequent years (Supplementary Table 1b), however there was not a consistent trend in the probability of incurring costs over time as seen among haemodialysis patients.

For transplant patients, logistic regression results indicated that the probability of incurring inpatient costs, but not outpatient costs, generally decreased over time (Supplementary Table 1c). Female gender and comorbidities were again associated with a higher probability of incurring inpatient costs, whereas living donor transplants were associated with a lower probability of incurring inpatient costs compared to deceased donor transplants.

Following logistic regression, generalised linear models were fitted to model costs in the subset of patients who had at least one inpatient or outpatient episode in a given year (Supplementary Tables 2a, 2b and 2c). For haemodialysis and transplant patients, inpatient costs tended to decrease as number of years on RRT increased, however this pattern was not seen among peritoneal dialysis patients. Age did not have a consistent effect on costs across hospital settings and treatment modalities, however where significant differences were noted, higher age was associated with lower costs. Of the comorbidities, only diabetes was consistently associated with higher mean annual costs for all patients irrespective of treatment modality and hospital setting.

Inpatient costs in the year of death were higher across all three RRT modalities, whereas outpatient costs in the year of death were lower. With the exception of the first year of the dataset, death events were fairly evenly distributed throughout the year, meaning that patients who died incurred significantly higher costs despite only being alive, on average, for approximately half of the year.

Alternative regression models based on the total number of comorbidities as a covariate, rather than on the presence or absence of individual comorbidities, yielded similar results, but were associated with slightly higher root-mean-square errors (RMSE). The number of comorbidities had a larger effect on hospital costs among transplant patients than among dialysis patients.

Application of regression models for predicting costs

A useful application of the regression models developed here is to predict hospital costs for patients with a given set of characteristics over time. Applying the models that have been developed, we can predict and compare costs for patients with different characteristics and by treatment modality. For illustrative purposes, Table 3 shows predicted inpatient and outpatient costs over a period of four years on each of the forms of RRT for three hypothetical patients: a 25-year-old female with no comorbidities, a 50-year-old male with

diabetes and a 65-year-old male with peripheral vascular disease. Table 3 also shows the fixed costs associated with national tariffs for RRT (maintenance haemodialysis, peritoneal dialysis or deceased heart-beating donor transplant) [10, 14]. When comparing combined RRT and hospital costs over the four years among the three patients on the same modality, costs are similar on haemodialysis and transplant, however larger variations in costs are seen with peritoneal dialysis (range £101 938 to £109 213), mostly attributable to differences in inpatient costs. In all three patient examples, total costs are highest on haemodialysis and in each case, are approximately four times the total costs compared with a scenario in which each of these patients had received a transplant from a deceased donor.

DISCUSSION

Many health systems around the world are grappling with the need to contain the increasing costs of providing care for patients with ERF and in recent years this has led to the emergence of bundled payments or fixed tariffs for reimbursement to providers of dialysis services. Considerable attention has been focused on determining what costs should be included or excluded within a fixed rate of payment and there is variation between countries especially with respect to drug costs, laboratory tests and physician fees [1]. Less attention has been directed at characterising the magnitude of other hospital costs beyond the fixed tariffs for RRT that are incurred by patients with ERF. These costs can be considerable given the high rate of comorbidities among this patient population. Insight into variable hospital costs in addition to the fixed costs of RRT is important for having an overall understanding of the costs of managing ERF. Linkage of the United States Renal Data System (USRDS) and Medicare data allows for extensive analysis of costs in relation to patient characteristics and treatment factors, however such data sources outside the US are limited [15].

One-time linkage of the HES and UKRR datasets has provided a rare opportunity to analyse variations in hospital costs beyond RRT in a large cohort of patients with ERF in England

and to explore changes in costs over several years, as well as in relation to treatment modality and comorbidities. As no attempt was made to distinguish renal-related resource use from non-renal-related resource use, the findings presented here are most relevant for looking at incremental costs between inpatient and outpatient settings, or between patients receiving different forms of RRT.

Excluding the fixed costs of RRT, our analysis showed that hospital costs were highest for all treatment modalities in the first year but hospital inpatient costs for both haemodialysis and transplant patients generally decreased with number of years on RRT, with transplant patients incurring lower annual costs than dialysis patients. A possible explanation for higher inpatient costs among incident haemodialysis patients could be access-related complications such as catheter-related infections, the need for catheter replacement or fistuloplasty and other forms of attention to dialysis access. In the UK, during the time period reflected in our analysis, a national audit showed that 69% of incident haemodialysis patients commenced treatment using venous catheters [16]. For transplant patients, higher costs in the first year reflect the need for frequent monitoring in the post-operative phase to manage immunosuppression, including detection and management of complications such as new onset diabetes after transplant (NODAT) [17-19].

In the current analysis there was little evidence to suggest that hospital costs increased with age or number of years on RRT. In some cases, older age was in fact associated with lower costs. However, a pattern of increasing costs was seen with many comorbidities and it is plausible that the patients who remained alive for longer on RRT were on average healthier and required fewer hospitalisations. The possibility of unobserved confounding could not be ruled out, but we believe this highlights the importance of controlling for comorbidities when exploring the effect of age on costs in the ERF population. Outpatient costs for transplant patients were highest in the first year of RRT, but dropped considerably in subsequent years and fell below average outpatient costs for haemodialysis patients by year six. In comparison, hospital costs for patients on peritoneal dialysis remained relatively constant over time, except for a slight decrease in years 2 and 3. These findings challenge the

commonly held assumption that costs increase with both age and time on RRT although caution should be exercised in extrapolating the findings beyond the 6-year period of our analysis. As with most retrospective datasets, there are several limitations to our analysis. In the HES dataset, coding practices meant that patients with missing comorbidity information could only be recorded as having no comorbidities, so the true extent of missing data was not known. However, the UKRR dataset also contained information on comorbidities at the start of RRT for approximately half of the patients in the sample. Where comorbidity data were available from both HES and UKRR data sources, concordance was 93% [8]. This high level of concordance between two independently collected data sources increases our confidence that missing data on comorbidities is unlikely to be a source of systematic bias in our analysis. Due to the structure of our dataset, another limitation is that we were unable to explore in more detail the specific reasons for variations in hospital costs as this would have required a more granular breakdown of admission codes and procedures. In addition, the current analysis did not take into account drug costs, which fall outside both the fixed tariff for RRT and the hospital reimbursement codes in England.

Although differences in currency, reimbursement rates for RRT and the organisation of healthcare systems varies from country to country, a deeper understanding of the relationship between factors such as age, comorbidities, treatment modality and hospital costs is likely to cut across different countries with varied healthcare delivery paradigms. Looking beyond fixed tariffs for RRT, hospital costs make up approximately 20-25% of the overall cost of managing patients on chronic dialysis. Taking into account both the fixed costs of RRT and variations in hospital costs characterised in the current analysis, it is readily apparent that although the total costs of treating dialysis and transplant patients may be similar in the first year of RRT, the cost differential in subsequent years is considerable. This reinforces the longer-term economic advantage of transplantation over dialysis for the health service.

SUPPLEMENTARY DATA

Supplementary data have been submitted with this manuscript.

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CONFLICT OF INTEREST STATEMENT

None to declare.

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Table 1a Haemodialysis patient characteristics and mean inpatient and outpatient costs (excluding the costs of maintenance dialysis) during the first year of renal replacement therapy

	n (%)	Mean inpatient cost (£) (95% CI)	p	Mean outpatient cost (£) (95% CI)	p
Age group					
<50 years	2 384 (19.8%)	7 452 (6 951 , 7 954)	0.319	1 342 (1 288 , 1 396)	<0.0005
50-64 years	2 900 (24.0%)	7 122 (6 667 , 7 577)		1 340 (1 291 , 1 389)	
65-75 years	3 911 (32.4%)	7 423 (7 032 , 7 815)		1 121 (1 079 , 1 163)	
>75 years	2 873 (23.8%)	6 934 (6 477 , 7 391)		893 (844 , 942)	
Gender					
Male	7 478 (62.0%)	7 084 (6 797 , 7370)	0.079	1 185 (1 153 , 1 216)	0.026
Female	4 590 (38.0%)	7 495 (7 140 , 7 850)		1 128 (1 090 , 1 165)	
Death					
No	9 530 (79.0%)	7 087 (6 821 , 7 354)	0.009	1 309 (1 280 , 1 337)	<0.0005*
Yes	2 538 (21.0%)	7 814 (7 467 , 8 160)		616 (578 , 655)	
Transplant					
No	11 644 (96.5%)	7 336 (7 106 , 7 566)	<0.0005*	1 169 (1 145 , 1 194)	0.009
Yes	424 (3.5%)	4 606 (4 110 , 5 103)		995 (858 , 1 131)	
Recovered renal function					
No	11 715 (97.1%)	7 270 (7 042 , 7 499)	0.127	1 178 (1 153 , 1 203)	<0.0005*
Yes	353 (2.9%)	6 241 (5 368 , 7 114)		664 (544 , 785)	
Myocardial infarction					
No	10 120 (85.1%)	7 185 (6 939 , 7 430)	0.033	1 183 (1 157 , 1 210)	0.019
Yes	1 774 (14.9%)	7 872 (7 302 , 8 443)		1 101 (1 041 , 1 162)	
Congestive heart failure					
No	9 630 (81.0%)	7 085 (6 827 , 7 344)	<0.0005*	1 187 (1 160 , 1 214)	0.010
Yes	2 264 (19.0%)	8 145 (7 707 , 8 585)		1 105 (1 050 , 1 160)	
Peripheral vascular disease					
No	10 285 (86.5%)	7 104 (6 859 , 7 349)	<0.0005*	1 170 (1 144 , 1 196)	0.854*
Yes	1 609 (13.5%)	8 459 (7 888 , 9 030)		1 177 (1 107 , 1 248)	
Cerebrovascular disease					
No	10 812 (90.9%)	7 241 (7 002 , 7 480)	0.205	1 180 (1 154 , 1 205)	0.034
Yes	1 082 (9.1)	7 749 (7 089 , 8 408)		1 087 (1011 , 1 164)	
Pulmonary disease					
No	10 293 (86.5%)	7 186 (6 937 , 7 435)	0.026	1 168 (1 142 , 1 194)	0.550*
Yes	1 601 (13.5%)	7 938 (7 434 , 8 443)		1 192 (1 118 , 1 265)	
Liver disease					
No	11 785 (99.1%)	7 260 (7 035 , 7 484)	0.143*	1 169 (1 145 , 1 194)	0. 180*
Yes	109 (0.9%)	10 263 (6 233 , 14 293)		1 379 (1 072 , 1 687)	
Diabetes					
No	7 846 (66.0%)	6 685 (6 415 , 6 956)	<0.0005*	1 081 (1 051 , 1 110)	<0.0005*
Yes	4 048 (34.0%)	8 454 (8 049 , 8 858)		1 346 (1 303 , 1 389)	
Cancer					
No	10 885 (91.5%)	7 248 (7 010 , 7 487)	0.266	1 167 (1 142 , 1 193)	0.311
Yes	1 009 (8.5%)	7 708 (7 045 , 8 370)		1 213 (1 119 , 1 307)	
Hypertension					
No	6 372 (53.6%)	7 525 (7 180 , 7 870)	0.024*	1 153 (1 122 , 1 184)	0.118
Yes	5 522 (46.4%)	7 013 (6 734 , 7 291)		1 192 (1 154 , 1 230)	

*Unequal variances

Table 1b Peritoneal dialysis patient characteristics and mean inpatient and outpatient costs (excluding the costs of maintenance dialysis) during the first year of renal replacement therapy

	n (%)	Mean inpatient cost (£) (95% CI)	p	Mean outpatient cost (£) (95% CI)	p
Age group					
<50 years	1 395 (34.7%)	4 874 (4 463 , 5 286)	0.003	1 712 (1 642 , 1 782)	<0.0005
50-64 years	1 217 (30.3%)	5 266 (4 825 , 5 707)		1 748 (1 674 , 1 823)	
65-75 years	967 (24.1%)	4 762 (4 267 , 5 257)		1 600 (1 516 , 1 684)	
>75 years	439 (10.9%)	6 321 (5 587 , 7 055)		1 320 (1 195 , 1 444)	
Gender					
Male	2 505 (62.3%)	5 200 (4 878 , 5 522)	0.428	1 647 (1 595 , 1 699)	0.696
Female	1 513 (37.7%)	4 998 (4 633 , 5 362)		1 664 (1 596 , 1 732)	
Death					
No	3 709 (92.3%)	4 755 (4 514 , 4 996)	<0.0005*	1 694 (1 651 , 1 738)	<0.0005
Yes	309 (7.7%)	9 553 (8 380 , 10 725)		1 158 (1 022 , 1 294)	
Transplant					
No	3 643 (90.7%)	5 275 (5 010 , 5 540)	<0.0005*	1 707 (1 663 , 1 751)	<0.0005*
Yes	375 (9.3%)	3 659 (3 316 , 4001)		1 130 (1 033 , 1 226)	
Recovered renal function					
No	3934 (97.9%)	5 158 (4 911 , 5 405)	0.060	1 673 (1 631 , 1 714)	<0.0005*
Yes	84 (2.1%)	3 528 (2 307 , 4 748)		745 (517 , 972)	
Myocardial infarction					
No	3 608 (90.8%)	5 057 (4 804 , 5 310)	0.021*	1 666 (1 622 , 1 710)	0.466
Yes	367 (9.2%)	6 191 (5 261 , 7 120)		1 613 (1 492 , 1 734)	
Congestive heart failure					
No	3 577 (90.0%)	4 963 (4 704 , 5 221)	<0.0005*	1 652 (1 609 , 1 695)	0.269*
Yes	398 (10.0%)	6 951 (6 202 , 7 670)		1 743 (1 587 , 1 899)	
Peripheral vascular disease					
No	3 656 (92.0%)	5 063 (4 806 , 5 320)	0.008	1 647 (1 604 , 1 689)	0.046*
Yes	319 (8.0%)	6 292 (5 500 , 7 084)		1 828 (1 655 , 2001)	
Cerebrovascular disease					
No	3 740 (94.1%)	5 043 (4 799 , 5 288)	0.006*	1 648 (1 605 , 1 690)	0.028*
Yes	235 (5.9%)	7 044 (5 631 , 8 458)		1 873 (1 677 , 2 070)	
Pulmonary disease					
No	3605 (90.7%)	5 026 (4 770 , 5 282)	0.001*	1 647 (1 604 , 1 691)	0.054*
Yes	370 (9.3%)	6 480 (5 641 , 7 319)		1 798 (1 651 , 1 945)	
Liver disease					
No	3 957 (99.6%)	5 152 (4 907 , 5 398)	0.275	1 661 (1 619 , 1 703)	0.794
Yes	18 (0.4%)	7 187 (3 361 , 10 743)		1 743 (812 , 2 674)	
Diabetes					
No	2 829 (71.2%)	4 492 (4 215 , 4 770)	<0.0005*	1 798 (1 453 , 1 543)	<0.0005*
Yes	1 146 (28.8%)	6 814 (6 321 , 7 307)		2 064 (1 976 , 2 152)	
Cancer					
No	3 810 (95.9%)	5 160 (4 907 , 5 413)	0.944	1 663 (1 621 , 1 706)	0.644
Yes	165 (4.1%)	5 204 (4 288 , 6 120)		1 614 (1 432 , 1 796)	
Hypertension					
No	1 986 (50.0%)	5 200 (4 840 , 5 561)	0.757	1 720 (1 659 , 1 782)	0.005*
Yes	1 989 (50.0%)	5 123 (4 790 , 5 456)		1 602 (1 546 , 1 658)	

*Unequal variances

Table 1c Transplant patient characteristics and mean inpatient and outpatient costs (excluding the costs of transplant surgery) during the first year of renal replacement therapy

	n (%)	Mean inpatient cost (£) (95% CI)	P	Mean outpatient cost (£) (95% CI)	P
Age group					
< 35 years	1 026 (25%)	3 941 (3 580 , 4 302)	<0.0005	4 111 (3 978 , 4 246)	0.914
36 - 45 years	1 110 (27%)	3 915 (3 568 , 4 263)		4 125 (3 996 , 4 254)	
46 - 55 years	973 (23%)	4 087 (3 716 , 4 458)		4 086 (3 948 , 4 224)	
> 55 years	1 040 (25%)	4 987 (4 628 , 5 346)		4 061 (3 928 , 4 195)	
Gender					
Male	2 589 (62.4%)	4 129 (3 908 , 4 350)	0.161*	4 073 (3 988 , 4 158)	0.373
Female	1 560 (37.6%)	4 400 (4 092 , 4 707)		4 136 (4 027 , 4 244)	
Donor type					
Deceased	2 660 (64.1%)	4 540 (4 306 , 4 774)	<0.0005*	4 095 (4 015 , 4 176)	0.131*
Living	1 367 (32.9%)	3 646 (3 373 , 3 919)		4 208 (4 086 , 4 331)	
Death					
No	4020 (96.9%)	4 160 (3 981 , 4 339)	0.004*	4 175 (4 108 , 4 241)	<0.0005
Yes	129 (3.1%)	6 424 (4 906 , 7 942)		1 657 (1 292 , 2 023)	
Graft failure					
No	3 874 (93%)	4 211 (4 027 , 4 395)	0.484*	4 279 (4 213 , 4 345)	<0.0005
Yes	275 (7%)	4 508 (3 695 , 5 321)		1 526 (1 294 , 1 758)	
Myocardial infarction					
No	3 758 (91.0%)	4 015 (3 834 , 4 195)	<0.0005*	4 110 (4 040 , 4 179)	0.637*
Yes	370 (9.0%)	6 666 (5 859 , 7 472)		4 170 (3 930 , 4 409)	
Congestive heart failure					
No	3 836 (93.9%)	4 051 (3 872 , 4 231)	<0.0005*	4 094 (4 026 , 4 163)	0.051*
Yes	292 (7.1%)	6 892 (5 952 , 7 832)		4 385 (4 101 , 4 669)	
Peripheral vascular disease					
No	3 625 (87.8%)	3 862 (3 683 , 4 040)	<0.0005*	4 070 (4 000 , 4 139)	0.001*
Yes	503 (12.2%)	7 067 (6 372 , 7 762)		4 443 (4 230 , 4 655)	
Cerebrovascular disease					
No	3 848 (93.2%)	4 082 (3 905 , 4 258)	<0.0005*	4 110 (4 041 , 4 179)	0.552
Yes	280 (6.8%)	6 597 (5 534 , 7 661)		4 190 (3 937 , 4 443)	
Pulmonary disease					
No	3 562 (86.3%)	4 194 (4 002 , 4 385)	0.112	4 114 (4 042 , 4 186)	0.962
Yes	566 (13.7%)	4 620 (4 087 , 5 153)		4 119 (3 946 , 4 292)	
Liver disease					
No	4 088 (99.0%)	4 220 (4 040 , 4400)	0.024*	4 115 (4 049 , 4 182)	0.919*
Yes	40 (1.0%)	7 530 (4 677 , 10 384)		4 068 (3 143 , 4 994)	
Diabetes					
No	3 002 (72.7%)	3 626 (3 439 , 3 813)	<0.0005*	3 963 (3 890 , 4 036)	<0.0005*
Yes	1 126 (27.3%)	5 921 (5 499 , 6 343)		4 520 (4 376 , 4 665)	
Cancer					
No	3 960 (95.9%)	4 255 (4 070 , 4441)	0.866	4 111 (4 043 , 4 179)	0.553
Yes	168 (4.1%)	4 176 (3 381 , 4 972)		4 213 (3 876 , 4 550)	
Hypertension					
No	1 003 (24.3%)	3 300 (3 021 , 3 579)	<0.0005*	3 845 (3 722 , 3 968)	<0.0005*
Yes	3 125 (75.7%)	4 558 (4 338 , 4 778)		4 202 (4 123 , 4 280)	

*Unequal variances

Table 2 Mean annual hospital costs by modality and number of years on renal replacement therapy (excluding the costs of maintenance dialysis and transplant surgery)

Haemodialysis patients				
Year	**n**	**Inpatient cost (£) Mean (SE)**	**Outpatient cost (£) Mean (SE)**	**Total cost (£) Mean (SE)**
1	12,068	7 240 (114)	1 163 (12)	8 403 (116)
2	9,096	5 340 (95)	1 044 (13)	6 384 (98)
3	7,614	4 844 (93)	1 069 (15)	5 913 (96)
4	4,830	5 020 (105)	1 070 (20)	6 090 (111)
5	2,452	5 325 (169)	1 091 (27)	6 416 (176)
6	846	4 866 (231)	1 218 (62)	6 084 (248)
Peritoneal dialysis patients				
Year	**n**	**Inpatient cost (£) Mean (SE)**	**Outpatient cost (£) Mean (SE)**	**Total cost (£) Mean (SE)**
1	4,018	5 124 (124)	1 653 (21)	6 777 (129)
2	2,897	4 140 (118)	1 407 (23)	5 547 (125)
3	1,934	4 198 (147)	1 514 (30)	5 712 (157)
4	1,000	4 830 (259)	1 541 (46)	6 371 (274)
5	440	4 433 (329)	1 510 (72)	5 943 (358)
6	137	4 859 (541)	1 484 (143)	6 343 (609)
Transplant patients				
Year	**n**	**Inpatient cost (£) Mean (SE)**	**Outpatient cost (£) Mean (SE)**	**Total cost (£) Mean (SE)**
1	4 149	4 231 (92)	4 097 (34)	8 327 (106)
2	3 136	1 695 (77)	1 662 (21)	3 357 (88)
3	2 307	1 334 (65)	1 403 (22)	2 738 (77)
4	1 447	1 209 (77)	1 308 (27)	2 517 (91)
5	759	1 368 (130)	1 234 (36)	2 603 (148)
6	271	1 145 (205)	1 152 (53)	2 296 (225)

Table 3 Comparison of predicted inpatient and outpatient costs and renal replacement therapy costs by treatment modality over a four-year period for three hypothetical patients

Patient 1: 25-year-old female patient with no comorbidities

	Haemodialysis (HD)				Peritoneal dialysis (PD)				Transplant (TX)			
	Cost of HD (£)*	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined HD and hospital costs (£)**	**Cost of PD (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined PD and hospital costs (£)**	**Cost of TX surgery (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined TX and hospital costs (£)**
Year 1	24 804	6 204	1 295	32 303	20 440	4 250	1 745	26 435	14 832	3 452	4 019	22 302
Year 2	24 804	4 335	1 148	30 287	20 440	3 190	1 481	25 112	0	1 206	1 472	2 678
Year 3	24 804	3 750	1 162	29 716	20 440	3 223	1 626	25 289	0	995	1 228	2 223
Year 4	24 804	3 699	1 202	29 705	20 440	3 417	1 673	25 530	0	908	1 139	2 047
Total	99 216	17 989	4 807	**122 011**	81 760	14 080	6 526	**102 366**	14 832	6 561	7 858	**29 251**

Patient 2: 50-year-old male patient with diabetes

	Haemodialysis (HD)				Peritoneal dialysis (PD)				Transplant (TX)			
	Cost of HD (£)*	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined HD and hospital costs (£)**	**Cost of PD (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined PD and hospital costs (£)**	**Cost of TX surgery (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined TX and hospital costs (£)**
Year 1	24 804	6 739	1 504	33 047	20 440	5 677	2 140	28 257	14 832	3 637	4 319	22 788
Year 2	24 804	4 811	1 359	30 974	20 440	4 463	1 877	26 780	0	1 223	1 770	2 993
Year 3	24 804	4 197	1 379	30 380	20 440	4 501	2 022	26 963	0	1 013	1 526	2 539
Year 4	24 804	4 144	1 422	30 370	20 440	4 703	2 070	27 213	0	940	1 437	2 377
Total	99 216	19 891	5 664	**124 771**	81 760	19 344	8 109	**109 213**	14 832	6 813	9 052	**30 697**

Patient 3: 65-year-old male patient with peripheral vascular disease

	Haemodialysis (HD)				Peritoneal dialysis (PD)				Transplant (TX)			
	Cost of HD (£)*	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined HD and hospital costs (£)**	**Cost of PD (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined PD and hospital costs (£)**	**Cost of TX surgery (£)***	**Inpatient cost (£)**	**Outpatient cost (£)**	**Combined TX and hospital costs (£)**
Year 1	24 804	6 512	1 249	32 564	20 440	4 174	1 719	26 333	14 832	4 263	4 008	23 103
Year 2	24 804	4 627	1 104	30 535	20 440	3 113	1 454	25 007	0	1 498	1 461	2 959
Year 3	24 804	4 034	1 121	29 960	20 440	3 145	1 598	25 183	0	1 104	1 216	2 320
Year 4	24 804	3 980	1 163	29 947	20 440	3 330	1 645	25 415	0	1 045	1 127	2 172
Total	99 216	19 154	4 636	**123 006**	81 760	13 762	6 417	**101 938**	14 832	7 910	7 812	**30 554**

*Fixed costs for renal replacement therapy were estimated using the following assumptions and sources:

Haemodialysis: 2011-12 PbR tariff (HRG code LD06A = £159 per session) for satellite haemodialysis with access via arteriovenous fistula or graft 19 years and over = £159 x 3 times per week x 52 weeks = £ 24 804 per year

Peritoneal dialysis: 2011-12 PbR tariff (HRG code LD12A = £56 per day) for automated peritoneal dialysis 19 years and over = £56 x 365 days = £ 20 440 per year

Transplant surgery: NHS Reference Costs Spell Schedule 2011-12 (currency code LA02A) for kidney transplant, 19 years and over, from cadaver heart-beating donor = £ 14 832

APPENDIX 4: Final flexible parametric models for graft failure and waiting-list survival

Table 1 Final fitted flexible parametric model for graft failure

n = 12,289

Scale: odds scale

Degrees of freedom: 5

c index = 0.61

Baseline hazard (log odds scale)	**Coeff**	**p-value**	**95% CI**		
Restricted cubic spline 1	0.658	<0.001	0.630	-	0.686
Restricted cubic spline 2	-0.149	<0.001	-0.169	-	-0.128
Restricted cubic spline 3	-0.124	<0.001	-0.136	-	-0.112
Restricted cubic spline 4	-0.041	<0.001	-0.055	-	-0.027
Restricted cubic spline 5	-0.028	<0.001	-0.039	-	-0.016
Constant	-2.468	<0.001	-2.501	-	-2.036
Covariates	**Odds ratio**	**p-value**	**95% CI**		
Recipient age 18-29	Reference				
Age 30-39	0.680	<0.001	-0.586	-	-0.184
Age 40-49	0.592	<0.001	-0.717	-	-0.332
Age 50-59	0.558	<0.001	-0.781	-	-0.384
Age >=60	0.632	<0.001	-0.662	-	-0.257
HLA mismatch level 1	Reference				
Level 2	1.222	0.032	0.017	-	0.384
Level 3	1.388	<0.001	0.148	-	0.507
Level 4	1.485	<0.001	0.181	-	0.610
Pre-emptive transplant					
No	Reference				
Yes	0.721	0.001	-0.520	-	-0.133
Primary renal diagnosis other	Reference				
Polycystic kidney disease	0.646	<0.001	-0.618	-	-0.256
Donor age <40	Reference				
40-49	1.588	<0.001	0.309	-	0.616
50-59	1.885	<0.001	0.483	-	0.784
> 60	2.579	<0.001	0.787	-	1.107

Table 2 Final fitted parametric model for death on waiting list

n = 4366

Scale: odds scale

Degrees of freedom: 2

c index = 0.67

Baseline hazard (log odds scale)	**Coeff**	**p-value**	**95% CI**		
Restricted cubic spline 1	1.128	<0.001	1.080	-	1.176
Restricted cubic spline 2	-0.155	<0.001	-0.195	-	-0.115
Constant	-2.442	<0.001	-2.829	-	-2.055
Covariates	**Odds ratio**	**p-value**	**95% CI**		
Age 18-29	Reference				
Age 30-39	1.476	0.062	0.980	-	2.222
Age 40-49	1.370	0.103	0.938	-	1.999
Age 50-59	1.697	0.005	1.174	-	2.455
Age >=60	2.093	<0.001	1.454	-	3.012
Pre-emptive listing	Reference				
Dialysis <1 year at activation	2.863	<0.001	2.214	-	3.253
Dialysis 1-3 years at activation	3.523	<0.001	2.913	-	4.261
Dialysis >3 years at activation	4.959	<0.001	3.921	-	6.273
Male	Reference				
Female	0.732	<0.001	0.642	-	0.835
White	Reference				
Asian	0.493	<0.001	0.412	-	0.591
Black	0.366	<0.001	0.283	-	0.473
Other	0.337	<0.001	0.223	-	0.510
Primary renal diagnosis other	Reference				
Diabetic nephropathy	2.405	<0.001	2.067	-	2.799

APPENDIX 5: Additional regression models to estimate health-state utility values

This appendix contains a summary of additional OLS regression models to predict EQ-5D-5L index scores in a combined population of waiting-list patients (constant, n = 1704) and transplant recipients at 6 months only (n = 512) from the ATTOM study. Eight different regression models were fitted with various combinations of predictor variables so that researchers undertaking cost-effectiveness analyses in ERF patients can select the appropriate model for their own needs based on data availability.

	Coefficient	Robust Std Error	P-value	95% CI
Model 1: transplant vs. waiting list				
Waiting list (constant)	0.773	0.005	<0.001	(0.762, 0.783)
Transplant	+0.054	0.011	<0.001	(0.032, 0.075)
Model 2: transplant vs. waiting list, age				
Waiting list, aged 18-29 (constant)	0.814	0.015	<0.001	(0.784, 0.844)
Age				
30-39	-0.046	0.019	0.015	(-0.084, -0.009)
40-49	-0.049	0.018	0.008	(-0.084, -0.013)
50-59	-0.057	0.018	0.001	(-0.092, -0.022)
>60	-0.027	0.017	0.123	(-0.061, 0.007)
Transplant	+0.053	0.011	<0.001	(0.032, 0.075)
Model 3: transplant vs. waiting list, gender				
Waiting list, male (constant)	0.787	0.006	<0.001	(0.775, 0.800)
Female	-0.034	0.010	<0.001	(-0.052, -0.015)
Transplant	+0.053	0.011	<0.001	(0.031, 0.074)

Model 4: transplant vs. waiting list, diabetes

Waiting list, non-diabetic (constant)	0.782	0.006	<0.001	(0.771, 0.793)
Diabetic	-0.083	0.016	<0.001	(-0.115, -0.052)
Transplant	+0.054	0.011	<0.001	(0.033, 0.075)

Model 5: transplant vs. waiting list, age, gender

Waiting list, male aged 18-29 (constant)	0.829	0.016	<0.001	(0.798, 0.860)
Age				
30-39	-0.047	0.019	0.014	(-0.084, -0.010)
40-49	-0.048	0.018	0.008	(-0.083, -0.013)
50-59	-0.058	0.018	0.001	(-0.093, -0.023)
>60	-0.029	0.017	0.100	(-0.063, 0.006)
Female	-0.034	0.009	<0.001	(-0.052, -0.015)
Transplant	+0.053	0.011	<0.001	(0.031, 0.074)

Model 6: transplant vs. waiting list, age, diabetes

Waiting list, non-diabetic aged 18-29 (constant)	0.816	0.015	<0.001	(0.785, 0.846)
Age				
30-39	-0.036	0.019	0.060	(-0.073, 0.002)
40-49	-0.040	0.018	0.028	(-0.076, -0.004)
50-59	-0.050	0.018	0.005	(-0.085, -0.015)
>60	-0.019	0.017	0.273	(-0.053, 0.015)
Diabetic	-0.081	0.016	<0.001	(-0.113, -0.050)
Transplant	+0.054	0.011	<0.001	(0.032, 0.075)

Model 7: transplant vs. waiting list, age, gender, diabetes

Waiting list, male non-diabetic aged 18-29 (constant)	0.830	0.016	<0.001	(0.800, 0.861)
Age				
30-39	-0.036	0.019	0.055	(-0.073, 0.001)
40-49	-0.039	0.018	0.029	(-0.075, -0.004)
50-59	-0.051	0.018	0.004	(-0.086, -0.017)
>60	-0.021	0.017	0.233	(-0.055, 0.013)
Diabetic	-0.081	0.016	<0.001	(-0.112, -0.049)
Female	-0.033	0.009	<0.001	(-0.052, -0.015)
Transplant	+0.053	0.011	<0.001	(0.032, 0.074)

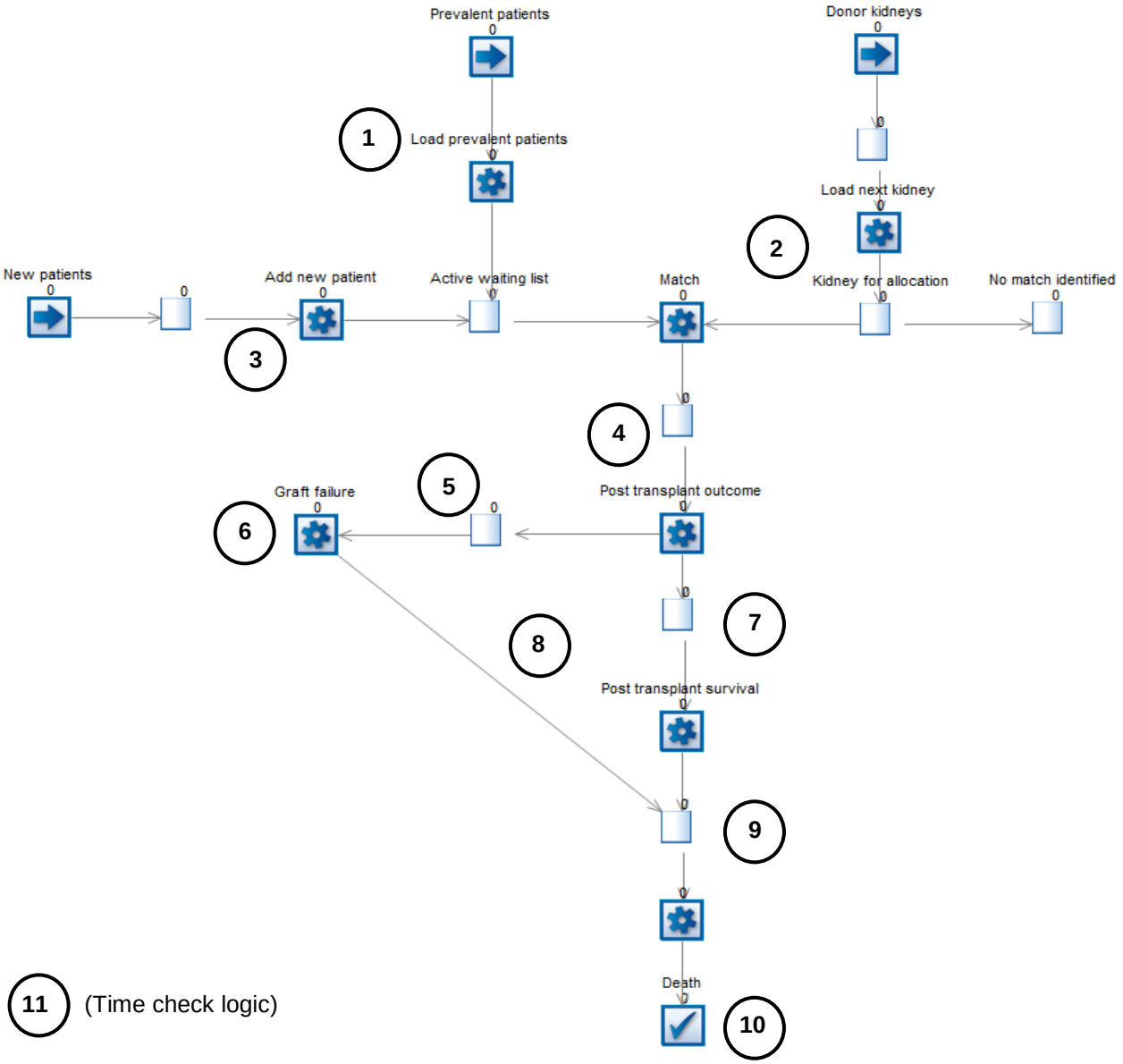
Model 8: transplant vs. waiting list, age, gender, diabetes, ethnicity

Waiting list, male non-diabetic, non-Asian aged 18-29 (constant)	0.837	0.016	<0.001	(0.807, 0.868)
Age				
30-39	-0.038	0.019	0.045	(-0.075, -0.001)
40-49	-0.043	0.018	0.018	(-0.078, -0.007)
50-59	-0.054	0.018	0.002	(-0.089, -0.020)
>60	-0.025	0.017	0.152	(-0.059, 0.009)
Female	-0.033	0.009	<0.001	(-0.051, -0.015)
Diabetic	-0.078	0.016	<0.001	(-0.110, -0.046)
Asian ethnicity	-0.040	0.018	0.024	(-0.074, -0.005)
Transplant	+0.051	0.011	<0.001	(0.029, 0.072)

APPENDIX 6: Description of Visual Logic code in the simulation model

SIMUL8, the software used to develop the kidney allocation model described in Chapter 5 of this thesis, is based on its own proprietary internal programming language known as Visual Logic. For interested readers, this appendix contains a summary of how Visual Logic code has been used in the simulation model. Rather than reproducing all of the Visual Logic code here (which would be over 100 pages and not very informative without the model and data inputs to hand), this appendix provides a summary of the comments that were documented to describe how the model was constructed and the purpose of each section of code. The figure on the following page indicates where each section of Visual Logic code has been applied in the model.

SIMUL8 model of kidney allocation schemes indicating where Visual Logic code applies



1. **Load prevalent patients Route In After Logic**

- ‘At the beginning of the simulation run, load 5500 patients from spreadsheet containing one patient per row with labels in columns for each characteristic
- ‘For each patient record waiting time at start
- ‘For each patient record time on dialysis at start
- ‘For each patient record age at start

2. **Kidney for allocation On Entry Logic**

- 'Obeyed just after a work item (kidney) enters the Queue
- 'Capacity of queue is 1 so that only one kidney is allocated at a time
- IF gbl_allocation_scheme = 1
    - 'Random allocation
    - CALL Proc_hla_matching
    - CALL Proc_blood_group_matching
    - CALL Proc_location_matching
    - CALL Proc_all_scheme1 ***(see section 2.1)***
- IF gbl_allocation_scheme = 2
    - 'Waiting time
    - CALL Proc_hla_matching
    - CALL Proc_blood_group_matching
    - CALL Proc_location_matching
    - CALL Proc_all_scheme2 ***(see section 2.2)***
- IF gbl_allocation_scheme = 3
    - 'Current national kidney allocation scheme
    - CALL Proc_hla_matching
    - CALL Proc_blood_group_matching
    - CALL Proc_location_matching
    - CALL Proc_hla_age_combined
    - CALL Proc_age_difference
    - CALL Proc_all_scheme3 ***(see section 2.3)***
- IF gbl_allocation_scheme = 4
    - 'Longveity matching (top 20% KDRI restricted to top 20% EPTS)
    - CALL Proc_hla_matching
    - CALL Proc_blood_group_matching
    - CALL Proc_location_matching
    - CALL Proc_hla_age_combined
    - CALL Proc_age_difference
    - CALL Proc_epts_calculation ***(see section 2.4a)***
    - CALL Proc_all_scheme4 ***(see section 2.4b)***
- IF gbl_allocation_scheme = 5
    - 'QALY maximisation
    - CALL Proc_hla_matching
    - CALL Proc_blood_group_matching
    - CALL Proc_qaly_max_calculation ***(see section 2.5a)***
    - CALL Proc_all_scheme5 ***(see section 2.5b)***

2.1 Proc_all_scheme1 (random)

- 'Loop through all patients on the waiting list to identify which patients are eligible for matching based on HLA and blood group compatibility
- 'Set priority based on combination of HLA mismatch level and location
- 'If patient is blood group incompatible (0) and/or hla incompatible (1), set priority to 0 (not eligible to receive kidney)
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Identify the number of patients with the highest score and store this in a global variable
- 'For patient(s) with highest score, set lbl_match = 1
- 'In the event that no match on the waiting list is found (e.g. rare blood or HLA type), move kidney to “No match identified”
- 'Otherwise create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible recipient ids based on current allocation scheme and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney
- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

2.2 Proc_all_scheme2 (waiting time)

- 'Identify all patients who are eligible for matching based on HLA and blood group compatibility
- 'Set priority based on combination of HLA mismatch level and location
- 'If patient is blood group incompatible (0), hla incompatible (1), set priority to 0 (not eligible to receive kidney)
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Identify the number of patients with the highest score (lbl_priority) and longest waiting time (lbl_rwait) store this in a global variable
- 'For patient(s) with highest priority, set lbl_match = 1
- 'Identify the longest waiting time for patients with lbl_match = 1
- 'Identify all patients that have the maximum value for waiting time
- 'In the event that no match on the waiting list is found (e.g. rare blood or HLA type), move kidney to “No match identified”
- 'Otherwise create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible patients based on current allocation criteria and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney
- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

2.3 Proc_all_scheme3 (current national kidney allocation scheme)

- 'Assign indicator for HSP and/or HLA-DR homozygosity
- 'Assign 500 points for HLA-DR homozygosity but not 000 mismatch
- 'Assign 100 points for HLA-B homozygosity but not 000 mismatch
- 'Create tiers C to E (no paediatric patients)
- 'Assign lbl_priority = 3 to patients in Tier C (000 mismatch, HSP or HLA-DR homozygous)
- 'Assign lbl_priority = 2 to patients in Tier D (000 mismatched other)
- 'Assign lbl_priority = 1 to all other patients in Tier E
- 'Assign lbl_priority = 0 to patients who are blood group and/or HLA incompatible
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Calculate total points for each patient within each tier
- 'Identify most favourable tier and highest points
- 'Loop through all patients on the waiting list to identify those in preferred tier with maximum score and set lbl_match = 1
- 'In the event that no match on the waiting list is found (e.g. rare blood or HLA type), move kidney to “No match identified”
- 'Otherwise create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible patients based on current allocation criteria and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney
- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

2.4a Proc_epts_calculation

- 'Convert donor age into categorical variable
- 'Copy current donor characteristics to EPTS calculation spreadsheet
- 'Calculate linear predictor for donor variables to use in regression to predict EPTS for each patient on the waiting list
- 'Calculate EPTS score for each patient on the waiting list and store in separate spreadsheet
- 'Calculate linear predictor for each patient according to flexible parametric post-transplant survival regression model
- 'After looping through all waiting list patients for a given kidney, determine which recipients have top 20% EPTS scores and reassign lbl_epts20 = 1

2.4b Proc_all_scheme4

- 'If donor kidney is in the top 20% KDPI, only allocate to waiting list patients with top 20% EPTS
    - CALL Proc_all_scheme4_kdri20_yes ***(see section 2.4b.1)***
- 'If donor kidney is not in top 20% KDPI (or if no match can be found in patients with top 20% EPTS), consider all patients irrespective of EPTS score
    - CALL Proc_all_scheme4_kdri20_no ***(see section 2.4b.2)***

2.4b.1 Proc_all_scheme4_kdri20_yes

- 'Assign indicator for HSP and/or HLA-DR homozygosity
- 'Assign 500 points for HLA-DR homozygosity but not 000 mismatch
- 'Assign 100 points for HLA-B homozygosity but not 000 mismatch
- 'Create tiers C to E (no paediatric patients)
- 'Assign lbl_priority = 3 to patients in Tier C (000 mismatch, HSP or HLA-DR homozygous)
- 'Assign lbl_priority = 1 to all other patients in Tier E
- 'Assign lbl_priority = 0 to patients who are blood group and/or HLA incompatible and/or who do not have top 20% EPTS score
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Only allow patients with top 20% EPTS score to receive kidney
- 'Identify most favourable tier and highest points
- 'Loop through all patients on the waiting list to identify those in preferred tier with maximum score and set lbl_match = 1
- 'In the event that no match among patients with top 20% is found on waiting list, expand to all patients
- 'Otherwise create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible patients based on current allocation criteria and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney
- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

2.4b.2 Proc_all_scheme4_kdri20_no

- 'Assign indicator for HSP and/or HLA-DR homozygosity
- 'Assign 500 points for HLA-DR homozygosity but not 000 mismatch
- 'Assign 100 points for HLA-B homozygosity but not 000 mismatch
- 'Create tiers C to E (no paediatric patients)
- 'Assign lbl_priority = 3 to patients in Tier C (000 mismatch, HSP or HLA-DR homozygous)
- 'Assign lbl_priority = 2 to patients in Tier D (000 mismatched other)
- 'Assign lbl_priority = 1 to all other patients in Tier E
- 'Assign lbl_priority = 0 to patients who are blood group and/or HLA incompatible
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Set one label value for each patient to reflect score in any tier
- 'Identify most favourable tier and highest points
- 'Loop through all patients on the waiting list to identify those in preferred tier with maximum score and set lbl_match = 1
- 'In the event that no match on the waiting list is found (e.g. rare blood or HLA type), move kidney to “No match identified”

- 'Otherwise create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible patients based on current allocation criteria and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney
- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

2.5a Proc_qaly_max_calculation

- 'Convert donor age into categorical variable
- 'Copy current donor characteristics to transplant QALY calculation spreadsheet
- 'Calculate linear predictor for donor variables to use in regression to predict QALYs for each patient
- 'Loop through each potential recipient on waiting list
    - 'Calculate linear predictor for each patient according to flexible parametric post-transplant survival regression model
    - 'Calculate health state utility for each patient according to transplant regression model
    - 'Calculate expected QALYs following transplant for each patient
    - 'Calculate linear predictor for each patient according to flexible parametric waiting list survival regression model
    - 'Calculate health state utility for each patient according to waiting list regression model allowing utility to change with time on dialysis
- 'For each patient, calculate QALY gain from transplant vs. remaining on waiting list and output to a separate spreadsheet

2.5b Proc_all_scheme5

- 'This version of the QALY maximisation scheme prioritises Level 1 (000) mismatches vs all other levels
- 'If patient is blood group incompatible (0), hla incompatible (1), set priority to 0 (not eligible to receive kidney)
- 'Exclude Level 4 HLA mismatches (NHSBT)
- 'Identify the top tier with patients who are potential matches
- 'Identify value of maximum QALY gain for each tier
- 'Loop through all patients on the waiting list to identify those in preferred tier with maximum QALY gain and set lbl_match = 1
- 'Create a distribution in which all patients with highest score have equal probability of receiving the kidney
- 'Create a spreadsheet with list of all eligible patients based on current allocation criteria and number rows consecutively
- 'Sample from distribution and match to row number in spreadsheet to select one patient from all eligible patients to receive kidney

- 'Loop through waiting list and change lbl_match_select = 1 for the patient who will receive the kidney; this label is used to match recipient and donor kidney

3. Active waiting list On Exit Logic

- 'Obeyed just after a work item exits the Queue but before it begins travelling to the next object
- 'Each time a patient on the waiting list receives a kidney, add one new patient selected at random (with waiting time set to zero)

4. Post transplant outcome Route In After Logic

- 'Recipient and donor characteristics now combined into single work item
- 'Record running total of number of transplants
- 'Record patient age at time of transplant
- 'Record cost of surgery
- 'Record HLA mismatch level
- 'Calculate time to next event (graft failure or death)
    - CALL Proc_post_tx_competing_risk ***(see section 4.1)***

4.1 Proc_post_tx_competing_risk

- 'Generate patient-specific survival curves for graft failure and death events to sample from in order to determine which event will happen first
- 'Calculate linear predictor for each time point on the graft failure survival curve (proportional odds scale)
- 'Calculate linear predictor for each time point on the patient death survival curve (proportional hazards scale)
- 'Sample from uniform distribution for graft failure event
- 'Loop through survival probabilities for graft failure event until the sample value is less than or equal to survival probability; take corresponding time as the time to graft failure event
- 'Sample from uniform distribution for patient death event
- 'Loop through survival probabilities for patient death event until the sample value is less than or equal to survival probability; take corresponding time as the time to patient death
- 'Determine which event occurs first (graft failure or death) and route patient accordingly

5. Queue graft failure On Entry Logic

- 'If patient experiences graft failure, assume patient returns to dialysis / waiting list (in absence of robust model to estimate death after graft failure)
- ‘Calculate survival after graft failure by sampling from waiting list (dialysis) survival curve; compare this to previously sampled estimate of transplant to death and use the smaller of the two values
    - 'Calculate patient age at time of graft failure (lbl_rage only updated while patient remains in Waiting List Queue)

    - 'Re-categorise into age groups based on age updated at time of graft failure
    - 'Assume all patients equivalent to having been on dialysis >3 years
- 'Sample from uniform distribution for death after graft failure
- 'Loop through survival probabilities for patient death on waiting list until the sample value is less than or equal to survival probability; take corresponding time as the time to patient death
- 'Calculate discounted life years (using continuous discounting assuming utility equivalent to >3 years on dialysis)
- 'Calculate QALYs and discounted QALYs for period between graft failure and death

6. Graft failure Route In After Logic

- 'Calculate QALYs and discounted QALYs prior to transplant
    - CALL Proc_qalys_pre_tx ***(see section 8.1)***
- 'Calculate QALYS and discounted QALYs between transplant and graft failure
- 'Calculate costs and discounted costs prior to transplant
    - CALL Proc_cost_pre_tx ***(see section 8.2)***
- 'Calculate costs and discounted costs after transplant but before graft failure
    - CALL Proc_cost_tx_graft ***(see section 8.3)***
- 'Calculate costs and discounted costs after graft failure until death
    - CALL Proc_cost_post_graft ***(see section 8.4)***

7. Queue post transplant survival On Entry Logic

- 'Calculate QALYs and discounted QALYs for period on dialysis prior to transplant
    - CALL Proc_qalys_pre_tx ***(see section 8.1)***
- 'Calculate QALYs and discounted QALYs for period between transplant and death
- 'Calculate costs and discounted costs for period on dialysis prior to transplant
    - CALL Proc_cost_pre_tx ***(see section 8.2)***
- 'Calculate costs and discounted costs for period between transplant and death
    - CALL Proc_cost_post_tx ***(see section 8.5)***

8.1 Proc_qalys_pre_tx

- 'Calculate time spent on waiting list prior to transplant
- 'Calculate time spent on dialysis prior to transplant
- 'Quality adjust time while on the waiting list prior to transplant using health state utility regression model
- 'Calculate total QALYs and discounted QALYs prior to transplant

8.2 Proc_cost_pre_tx

- 'Use two-part models to estimate hospital costs while on waiting list prior to transplant (for all transplant recipients)
- 'Create label to increment age for calculating costs during pre-transplant period

- 'Calculate non-varying components of linear predictor using logistic regression for inpatient costs
- 'Calculate non-varying components of linear predictor using glm for inpatient costs
- 'Calculate non-varying components of linear predictor using logistic regression for outpatient costs
- 'Calculate non-varying components of linear predictor using glm for outpatient costs
- 'Determine modality for calculating annual dialysis costs
- 'If time on waiting list prior to transplant is less than 1 year, calculate portion of year alive
    - 'If patient has not yet started dialysis, set pre-transplant cost multiplier = 0
    - 'Calculate time on dialysis component of linear predictor
    - 'Categorise age into groups using age at entry to waiting list
    - 'Calculate total pretx inpatient costs (assuming patient receives transplant the same year)
    - 'Calculate total pretx outpatient costs (assuming patient receives transplant the same year)
    - 'Write local variable values to spreadsheet
    - 'Calculate costs and discounted costs during pretx period
- 'If time on waiting list is more than one year, create one row to estimate costs for each year prior to transplantation
    - 'If patient has not yet started dialysis, set pre-transplant cost multiplier = 0
    - 'Calculate time on dialysis component of linear predictor
    - 'Categorise age into groups using age at entry to waiting list
    - 'Calculate age component of linear predictor
    - 'Calculate total pretx inpatient costs
    - 'Calculate total pretx outpatient costs
    - 'Write local variable values to spreadsheet
    - 'Calculate costs for each row (year)
    - 'Calculate discounted costs for each row (year)
    - 'Before calculating utility for next row (year), increment time on dialysis by 365 days
    - 'Before calculating utility for next row (year), increment recipient age by 1 year
    - 'In the final row, calculate costs for the portion of the year before transplant
    - 'Calculate costs and discounted costs during pretx period

8.3 Proc_cost_tx_graft

- 'Use two-part models to estimate hospital costs between transplant and graft failure
- 'Set age to age at time of transplant and then increment this label with each year
- 'Calculate non-varying components of linear predictor using logistic regression for inpatient costs
- 'Calculate non-varying components of linear predictor using glm for inpatient costs
- 'Calculate non-varying components of linear predictor using logistic regression for outpatient costs

- 'Calculate non-varying components of linear predictor using glm for outpatient costs
- 'If patient experiences graft failure less than 1 year after transplant, calculate portion of year
    - 'Calculate age component of linear predictor
    - 'Calculate inpatient costs (assuming graft failure occurs that year)
    - 'Calculate outpatient costs (assuming graft failure occurs that year)
    - 'Write local variable values to spreadsheet
    - 'Calculate costs and discounted costs between transplant and graft failure
- 'If time to graft failure is more than one year, create one row to estimate costs for each year until graft failure
    - 'Calculate time since transplant component of linear predictor
    - 'Categorise age into groups using age at time of transplant
    - 'Calculate post-transplant inpatient costs for the year
    - 'Write local variable values to spreadsheet
    - 'Calculate costs for each row (year)
    - 'Calculate discounted costs for each row (year)
    - 'Before calculating costs for next row (year), increment recipient age by 1 year
    - 'In the final row, calculate costs for the portion of the year before death
    - 'Add in the graft failure component of the linear predictor to the final full year of costs
    - 'Calculate costs and discounted costs between transplant and graft failure

8.4 Proc_cost_post_graft

- 'Use two-part models to estimate hospital costs between graft failure and death
- 'Use expected post-graft failure time to death to calculate costs by year
- 'Set age to age at time of transplant and then increment this label with each year
- 'Calculate non-varying components of linear predictor using logistic regression for inpatient costs
- 'Calculate non-varying components of linear predictor using glm for inpatient costs
- 'Calculate non-varying components of linear predictor using logistic regression for outpatient costs
- 'Calculate non-varying components of linear predictor using glm for outpatient costs
- 'Determine modality for calculating annual dialysis costs
- 'If patient dies less than 1 year after graft failure, calculate proportion of year alive
    - 'Following graft failure, assume all patients incur costs equivalent to the greatest number of years on dialysis in the regression model
    - 'Categorise age into groups using age at time of graft failure
    - 'Calculate total inpatient costs (assuming patient dies the same year)
    - 'Calculate total outpatient costs (assuming patient dies the same year)
    - 'Write local variable values to spreadsheet
    - 'Calculate costs and discounted costs between graft failure and death
- 'If time to death is more than one year, create one row to estimate costs for each year until death

    - 'Following graft failure, assume all patients incur costs equivalent to the greatest number of years on dialysis in the regression model
    - 'Categorise age into groups using age at time of graft failure
    - 'Calculate total post-graft failure inpatient costs
    - 'Calculate total post-graft failure outpatient costs
    - 'Write local variable values to spreadsheet
    - 'Calculate costs for each row (year)
    - 'Calculate discounted costs for each row (year)
    - 'Before calculating costs for next row (year), increment recipient age by 1 year
    - 'In the final row, calculate costs for the portion of the year before death
    - 'Add in the death component of the linear predictor to the final full year of costs
    - 'Calculate costs and discounted costs between graft failure and death

8.5 Proc_cost_post_tx

- 'Use two-part models to estimate hospital costs between transplant and death (for patients who do not experience graft failure)
- 'Set age to age at time of transplant and then increment this label with each year
- 'Calculate non-varying components of linear predictor using logistic regression for inpatient costs
- 'Calculate non-varying components of linear predictor using glm for inpatient costs
- 'Calculate non-varying components of linear predictor using logistic regression for outpatient costs
- 'Calculate non-varying components of linear predictor using glm for outpatient costs
- 'If patient dies less than 1 year after transplant, calculate portion of year alive
    - 'Categorise age into groups using age at time of transplant
    - 'Calculate age component of linear predictor
    - 'Calculate inpatient costs (assuming patient dies the same year)
    - 'Calculate outpatient costs (assuming patient dies the same year)
    - 'Write local variable values to spreadsheet
    - 'Calculate costs and discounted costs between transplant and death
- 'If time to death is more than one year, create one row to estimate costs for each year until death
    - 'Categorise years since transplant as dummy variables
    - 'Categorise age into groups using age at time of transplant
    - 'Calculate post-transplant inpatient costs for the year
    - 'Calculate post-transplant outpatient costs for the year
    - 'Write local variable values to spreadsheet
    - 'Calculate costs for each row (year)
    - 'Calculate discounted costs for each row (year)
    - 'Before calculating costs for next row (year), increment recipient age by 1 year
    - 'In the final row, calculate costs for the portion of the year before death
    - 'Add in the death component of the linear predictor to the final full year of costs
    - 'Calculate costs and discounted costs between transplant and death

9. Queue for Death On Entry Logic

- 'Obeyed just after a work item enters the Queue
- 'For each transplant recipient, record individual patient characteristics to spreadsheet to facilitate checks and report results
- 'For each transplant recipient, calculate total pathway life years, costs and QALYs

10. End Run Logic

- 'Obeyed when the simulation reaches end of "Results Collection Period"
- 'Calculate QALYs for patients who remain on the waiting list at the end of the model
- 'Calculate costs for patients who remain on the waiting list at the end of the model
    - CALL Proc_cost_no_tx ***(see section 10.1)***
- 'For each patient who did not receive a transplant, record individual patient characteristics to spreadsheet to facilitate checks and report results
- 'For each patient who did not receive a transplant, calculate life years, costs and QALYs
- 'Generate KPIs, life years, QALYs and costs for patients who received a transplant
    - CALL Proc_results_tx ***(see section 10.2)***
- 'Generate KPIs, life years, QALYs and costs for patients who did not receive a transplant
    - CALL Proc_results_no_tx ***(see section 10.3)***
- 'Generate combined life years, QALYs and costs for tx and no tx patients

10.1 Proc_cost_no_tx

- 'Use two-part models to estimate hospital costs for patients who remain on the waiting list
- 'Create label to increment age for calculating costs until death
- 'Calculate non-varying components of linear predictor using logistic regression for inpatient costs
- 'Calculate non-varying components of linear predictor using glm for inpatient costs
- 'Calculate non-varying components of linear predictor using logistic regression for outpatient costs
- 'Calculate non-varying components of linear predictor using glm for outpatient costs
- 'Determine modality for calculating annual dialysis costs
- 'If time to death is less than 1 year
    - 'If patient has not yet started dialysis, set pre-transplant cost multiplier = 0
    - 'Calculate time on dialysis component of linear predictor
    - 'Categorise age into groups using age at entry to waiting list
    - 'Calculate age component of linear predictor
    - 'Calculate total inpatient costs (assuming the patient dies the same year)
    - 'Calculate total outpatient costs (assuming patient dies the same year)
    - 'Write local variable values to spreadsheet

    - 'Calculate costs and discounted costs assuming patient never receives transplant
- 'If time to death is more than one year, create one row to estimate costs for each year prior to death
    - 'If patient has not yet started dialysis, set pre-transplant cost multiplier = 0
    - 'Calculate time on dialysis component of linear predictor
    - 'Categorise age into groups using age at entry to waiting list
    - 'Calculate age component of linear predictor
    - 'Calculate total pretx inpatient costs
    - 'Write local variable values to spreadsheet
    - 'Calculate costs for each row (year)
    - 'Calculate discounted costs for each row (year)
    - 'Before calculating utility for next row (year), increment time on dialysis by 365 days
    - 'In the final row, calculate costs for the portion of the year before transplant
    - 'Add in the death component of the linear predictor to the final full year of costs
    - 'Calculate costs and discounted costs assuming patient never receives transplant

10.2 Proc_results_tx

- 'Record summary characteristics for all patients who received a transplant in a spreadsheet
    - 'Average recipient age
    - 'Recipient blood group
    - ‘Recipient ethnicity
    - 'Proportion recipient HSP
    - 'Proportion recipient diabetic (PRD)
    - 'Proportion top 20% EPTS (allocation scheme 4 only)
    - 'Average QALY gain (allocation scheme 5 only)
    - 'Average waiting time
    - 'Average time on dialysis
    - 'Proportion HLA mismatch level 1
    - 'Proportion HLA mismatch level 2
    - 'Proportion HLA mismatch level 3
    - 'Proportion HLA mismatch level 4
    - 'Proportion pre-emptive transplant
    - 'Proportion graft failure
    - 'Average time to transplant within simulation time
    - 'Average time to graft failure
    - 'Average graft failure to death
    - 'Average time to death
    - 'Average inpatient cost
    - 'Average outpatient cost
    - 'Average dialysis cost
    - 'Average drug cost
    - 'Average total cost
    - 'Average total life years

- 'Average total QALYs
- 'Total life years
- 'Total QALYs
- 'Total costs
- 'Total discounted life years
- 'Total discounted QALYs
- 'Total discounted costs

10.3 Proc_results_no_tx

- 'Record summary characteristics for all patients who did not receive a not receive a transplant in a spreadsheet
  - ‘Average recipient age
  - 'Recipient blood group
  - 'Recipient ethnicity
  - 'Proportion recipient female
  - 'Proportion recipient HSP
  - 'Proportion recipient diabetic (PRD)
  - 'Average waiting time
  - 'Average time on dialysis
  - 'Average inpatient cost
  - 'Average outpatient cost
  - 'Average dialysis cost
  - 'Average total costs
  - 'Average life years
  - 'Average total QALYs
  - 'Total life years
  - 'Total QALYs
  - 'Total costs
  - 'Total discount life years
  - 'Total discounted QALYs
  - 'Total discounted costs

11. Time Check Logic

- 'For all patients on the waiting list, increment waiting time and time on dialysis each day
- 'For all patients on the waiting list, increment age by 1 year after 365 days