THE EFFECTIVENESS AND COST-EFFECTIVENESS OF METHODS OF STORING DONATED KIDNEYS FROM DECEASED DONORS:

A SYSTEMATIC REVIEW AND ECONOMIC MODEL

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ABOUT THE PENINSULA TECHNOLOGY ASSESSMENT GROUP (PenTAG)

The Peninsula Technology Assessment Group is part of the Institute of Health Service Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme, systematic reviews and economic analyses for the NICE Centre for Public Health Excellence, and systematic reviews as part of the Cochrane Collaboration Heart Group, as well as for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme. Projects to date include:

- The Effectiveness And Cost-Effectiveness Of Imatinib (STI 571) In Chronic Myeloid Leukaemia - A Systematic Review (2002)
- Screening For Hepatitis C Among Injecting Drug Users And In Genitourinary Medicine (GUM) Clinics - Systematic Reviews Of Effectiveness, Modelling Study And National Survey Of Current Practice (2002)
- Systematic Review Of Endoscopic Sinus Surgery For Nasal Polyps (2003)
- The Effectiveness And Cost-Effectiveness Of Imatinib For First Line Treatment Of Chronic Myeloid Leukaemia In Chronic Phase (2003)
- The Effectiveness And Cost-Effectiveness Of Microwave And Thermal Balloon Endometrial Ablation For Heavy Menstrual Bleeding - A Systematic Review And Economic Modelling (2004)
- Do The Findings Of Case Series Studies Vary Significantly According To Methodological Characteristics?(2005)
- The Effectiveness And Cost-Effectiveness Of Pimecrolimus And Tacrolimus For Atopic Eczema - A Systematic Review And Economic Modelling (2005)
- The Effectiveness And Cost-effectiveness Of Dual Chamber Pacemakers Compared To Single Chamber Pacemakers For Bradycardia Due To Atrioventricular Block Or Sick Sinus Syndrome - Systematic Review And Economic Evaluation (2005)
- The Effectiveness And Cost-Effectiveness Of Surveillance Of Barrett's Oesophagus: Exploring The Uncertainty (2005)
- The Cost-Effectiveness of testing for hepatitis C (HCV) in former injecting drug users. Systematic Review And Economic Evaluation. (2006)
- The Effectiveness And Cost-Effectiveness Of Cinacalcet for Secondary Hyperparathyroidism in end stage renal disease patients on dialysis. Systematic Review And Economic Evaluation (2007)
- The effectiveness and cost-effectiveness of Carmustine Implants and Temozolomide for the treatment of newly-diagnosed High Grade Glioma**.** Systematic Review And Economic Evaluation (2007)
- The Effectiveness And Cost-Effectiveness of Cardiac Resynchronisation Therapy for Heart Failure. Systematic Review And Economic Evaluation (2007)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma in Adults and Children Aged 12 Years and Over: a Systematic Review and Economic Analysis (2007, In Press)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma an Children Under the Age of 12 Years: a Systematic Review and Economic Analysis (2007, In Press)
- The Effectiveness and Cost-Effectiveness of Cochlear Implants for Severe to Profound Deafness in Children and Adults: A Systematic Review and Economic Model (2007, In Press)

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Competing Interests of Expert Advisory Group

Mr Chris Watson is the Principal Investigator of the PPART trial.
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No other competing interests declared in relation to this assessment.

The views expressed in this report are those of the authors and not necessarily those of NICE or the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

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Jacob Akoh	Provided clinical input into the design of the model. Advised on clinical matters. Contributed to the editing of the report.
Rob Anderson	Oversaw the cost-effectiveness aspects of the analysis and report, and obtained costs for the model. Contributed to writing the report. Contributed to the design and development of the model and editing the report. Was overall director of the project and is guarantor of the report
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Martin Hoyle	Provided support in the execution of the economic model and checked calculations within it. Contributed to editing of some parts of the report.
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Martin Pitt	Led the design, development and execution of the economic model. Contributed to writing and editing of the report (cost-effectiveness chapter).

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1. Definition of Terms and List of Abbreviations

List of abbreviations

ATP	Adenosine Triphosphate
BNF	British National Formulary
BSD	Brain Stem Dead [HBD]
CAPD	Continuous Ambulatory Peritoneal Dialysis
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CHEC	Consensus on Health Economics Criteria
CHD	Centre (Hospital) Haemodialysis
CI	Confidence Interval
CIT	Cold Ischaemic Time
CS	Cold Storage
CUA	Cost-Utility Analysis
DCD	Donation After Cardiac Death [NHBD]
DGF	Delayed Graft Function
DGI	Delayed Graft Function – Initial Month*
DM	Difference in Means
DTH	Death*
ECD	Extended Criteria Donors
ERF	Established Renal Failure
ESRD	End Stage Renal Disease
EQ-5D	Euroqol (Quality of Life Instrument)
FDA	United States Food And Drugs Administration

FKD	Failing Kidney After Delayed Graft Function*
FKI	Failing Kidney After Immediate Graft Function*
GFR	Glomerular Filtration Rate
HBD	Heart Beating Donors (i.e. BSD)
HD	Haemodialysis
HHD	Home Haemodialysis
HLA	Human leukocyte antigen
HRG	Healthcare Resource Group
HR-QoL	Health-Related Quality Of Life
HTA	Health Technology Assessment
HTK	Histidine-Tryptophan-Ketoglutarate
ICER	Incremental Cost Effectiveness Ratio
IGF	Immediate Graft Function*
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
ITU	Intensive Treatment Unit
K	Potassium
KDQOL-SF	Kidney Disease Quality of Life – Short Form
Na	Sodium
NA	Not Applicable
NHBD	Non-Heart Beating Donors (i.e. DCD)
NS	Not Significant (statistical test result)
NSRC	National Schedule Of Reference Costs
Mg	Magnesium
MP	Machine Perfusion

PBR	Payment By Results
PD	Peritoneal Dialysis
pH	A measure of acidity or alkalinity
PNF	Primary Non-Function
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life-Year
QLI	Quality of Life Index
QUORUM	Quality of Reporting of Meta-Analyses standards
RCT	Randomised Controlled Trial
RR	Relative Risk
RRT	Renal Replacement Therapy
SD	Standard Deviation
SF-36	Short Form 36 (Quality Of Life Instrument)
SHD	Satellite Haemodialysis
STX	Subsequent Transplant*
TTO	Time Trade-Off
Tx	Transplant
UKT	UK Transplant
UW	University of Wisconsin
UKRR	UK Renal Registry

* These three-letter acronyms abbreviations are mainly (or also) labels for specific Markov states in the decision model

Definition of terms

Anastomosis	The second period of warm ischaemia, following the cold storage time, where the kidney slowly warms up prior to transplant
Chronic kidney disease	Kidney disease which is irreversible and progressive
Established renal failure	Chronic kidney disease that has progressed so far that RRT is needed to maintain life (also known as end-stage renal disease)
Renal replacement therapy	Treatment to replace or augment the function of failing kidneys, by dialysis (peritoneal dialysis or haemodialysis) or transplantation
Delayed graft function	The need for dialysis within seven days of transplant
Graft failure	When a transplant recipient returns to chronic dialysis
Graft survival	When a transplant recipient does not need dialysis
Brain stem dead	Those diagnosed as dead by brain stem tests who are maintained on a ventilator in an ITU
Donation after cardiac death	Those who cannot be diagnosed as BSD but whose death is established by the absence of a heart-beat
Extended criteria donor	A sub-group of BSD donors who are older or who have co-morbidities that would mean they do not meet standard transplant criteria
Primary non-function	A graft that never works after transplantation
Cold ischaemic time	The length of time that a graft is both cold and without oxygen

Utility estimates	The valuation of a health state based on either an individual's preference or community preferences for being in that state, relative to being dead (a utility value of 0) or "in full health" (a utility value of 1)
Time trade-off	A method for determining quality of life based on subjective judgement of the value of a life-span in the current health state compared to a reduced life-span in perfect health.
Quality-adjusted life-year (QALY)	A unit for measuring the effectiveness of health interventions obtained by multiplying the number of life-years lived by a utility weight (a score between 0 and 1) to reflect the health-related quality of life in those years.

2. Summary

2.1. Background

Established renal failure (ERF) or end-stage renal disease is defined as an irreversible decline in a person's kidney function that is severe enough to be fatal in the absence of renal replacement therapy (RRT). Kidney transplantation is the best form of renal replacement therapy for people with end-stage renal disease where it is possible. Unfortunately, the demand for donor organs greatly outstrips supply.

Most kidneys for transplantation are obtained from deceased heart-beating donors; that is, people in whom death has been diagnosed by brain stem tests who are maintained on a ventilator in an intensive care unit. These donors will be referred to as brain stem dead (BSD) donors in the remainder of this report. The availability of organs from this type of donor has declined by about 20% in the UK over the last decade.

One means of expanding the donor pool is to use organs retrieved from non-heart-beating donors. These are people who cannot be diagnosed as brainstem dead but whose death is verified by the absence of a heart beat (cardiac arrest). These donors will be referred to as donation after cardiac death (DCD) donors in the remainder of this report. However, kidneys from these donors are more likely to fail due to the damaging period of warm ischaemia they undergo.

Apart from the increased use of DCD donors, a second means of expanding the pool of kidney donors is through the use of extended criteria donors (ECD). These provide poorer quality kidneys, generally from donors who are either over sixty, or are over fifty and with two or more of the following features (1) a history of hypertension, (2) a history of cerebral vascular accident, (3) terminal creatinine levels greater than 133µmol/L (1.5mg/dl). Kidneys from extended criteria donors have a lower chance of long term success and a higher incidence of delayed graft function (DGF).

It is necessary to preserve all types of kidneys from deceased donors prior to transplantation in order to allow time for, matching the kidney to the recipient, transportation and preparation of the recipient and the kidney, and implantation of the kidney. However, ischaemia, particularly warm ischaemia, causes deterioration of the graft. Therefore it is important to cool the core of the kidney as quickly as possible.

There are two main methods for the cold storage of kidneys; cold static storage or hypothermic machine perfusion.

In cold static storage, the kidney is flushed through with a preservation solution, and kept in bags of solution on ice. Two preservation solutions are widely used in the NHS for cold storage; Marshall's hypertonic citrate (Soltran™) and University of Wisconsin (ViaSpan™). We will also consider Celsior™ (Genzyme) in the clinical effectiveness systematic review.

Hypothermic machine perfusion, maintains core cooling of the kidney by continuously pumping cold preservation solution through it. This solution also provides nutrients, sometimes oxygen, carries away toxic metabolites and provides 'buffering' (reducing the build up of lactic acid). In theory this process should reduce the damage associated with cold ischaemic time. Currently only the LifePort Kidney Transporter (Organ Recovery Systems) is used in the UK, but we will also assess the RM3 (Water's Medical Systems).

2.2. Objectives

This project reviews the evidence for the effectiveness and cost-effectiveness of different ways of storing kidneys from deceased donors prior to transplantation. This was done by answering the following questions:

- What is the most effective way of storing kidneys donated from deceased donors?
- What is the most cost-effective way of storing kidneys donated from deceased donors?

2.3. Methods

2.3.1. Clinical effectiveness systematic review

Electronic databases were searched for systematic reviews and/or meta-analyses, randomised controlled trials (RCT), other study designs and ongoing research in January 2008 and updated in May 2008. The updated search revealed no new studies that met our inclusion criteria. Reference lists of articles were also searched for further relevant studies, and the Food and Drugs Administration (FDA) and European

Regulatory Agency Medical Device Safety Service websites were searched for relevant studies. The search was limited to English language papers only. Manufacturers' submissions were searched for additional evidence.

Relevant studies were identified in two stages. Firstly titles and abstracts returned by the search strategy were examined independently by two researchers (MB and AZ) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Secondly two researchers (MB and AZ) examined these independently for inclusion or exclusion, and disagreements were again resolved by discussion.

2.3.2. PenTAG cost-utility model

A Markov (state transition) model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), to simulate the main post-transplantation and outcomes of kidney graft recipients. The structure of the model was informed by current research literature, data from the Renal Registry and UK Transplant and expert opinion on the process and outcomes of kidney transplantation and renal replacement therapy. The model captures the cost and quality of life (utility) impacts of both short-term kidney function (e.g. delayed graft function, primary non-function) as well as longer term outcomes such as graft survival, patient survival, and possible re-transplantation of returning to dialysis.

The model estimates incremental cost-utility; i.e. the ratio of the difference in both costs (measured in pounds) and benefits (in terms of quality-adjusted life-years (QALYs) between the compared arms). The population examined is those receiving kidney transplants. The treatments compared are kidney transplants using a variety of storage methods as outlined (in particular the use of cold storage of kidneys vs. the use of machine perfusion methods).

The reference case uses costs for 2007 and takes the perspective of the UK's NHS and personal social services. A mixed sex cohort, of 1000 adult patients, is modelled until the whole cohort has died. Five separate age groups (18-34, 35-44, 45-54, 55-64, 65+) are simulated in the model, which are aggregated to represent the real population of kidney transplant recipients. The model uses a cycle length of one month.

2.4. Effectiveness results

2.4.1. Number and quality of effectiveness studies

The systematic search of electronic databases for clinical effectiveness studies produced 2665 titles and abstracts, of which 2529 were judged not to meet our inclusion criteria, and were excluded.

One hundred and thirty six papers were obtained. Thirteen articles were found that met the inclusion criteria, leaving 123 exclusions.

The 13 articles included were: two systematic reviews, three full journal published RCTs, two ongoing RCTs, one cohort study three full journal published retrospective record reviews and two retrospective record reviews published as posters or abstracts only.

However, the two systematic reviews (of which one was an update of the other) did not include any studies that met our inclusion criteria, and so were not examined any further.

The studies were a mixture of good to moderate quality RCTs and registry data studies, a poor quality prospective cohort study and poor quality hospital record reviews. Only seven of the studies had been published in peer-reviewed journals. One of the RCTs was still collecting data (Watson and colleagues, PPART trial in the UK) and another was still analysing their data (Moers and colleagues, the Machine Preservation Trial in Germany, the Netherlands and Belgium). Two of the hospital record reviews had only been published as conference abstracts and posters.

2.4.2. Summary of benefits and risks

2.4.2.1. Machine preservation vs. cold storage

Four studies compared machine perfusion with cold storage; two were RCTs (Watson and colleagues (PPART) and Moers and colleagues (Machine Preservation Trial), one was a prospective cohort study (Plata-Munoz and colleagues) and one was a hospital record review (Moustafellos and colleagues).

LifePort machine vs. ViaSpan solution

The donor populations for the two RCTs were different; with DCD donors in the Watson and colleagues trial (N=90 kidneys) and mostly BSD ( ) (DCD= %) donors in the Moers and colleagues study (N= kidneys). Also, the rate of delayed graft function (DGF) in the Moers and colleagues trial was Watson and colleagues (% and 57% respectively); this may have been due to the difference in DGF between DCD and BSD donated kidneys.

Only three months follow up data were available from Watson and colleagues who found no significant differences on any outcome measure (DGF, primary non-function (PNF), patient survival, graft survival, dialysis requirement within seven days of transplant excluding day one, glomerular filtration rate . However, the data from the PPART trial .

Moers and colleagues found

Moers and colleagues did not analyse their data by intention to treat (ITT).

These two studies' results are in recipients whose grafts had a mean cold ischaemic time CIT of approximately . It is not possible to say from this data what the results would be in kidneys after longer follow-up or greater CIT.

The main study characteristics and findings of these two studies are compared below:

Table 1 Comparison of study characteristics of the PPART trial and the Machine Preservation Trial

Characteristic	PPART trial	Machine Preservation Trial
	(UK:)	(Europe: Netherlands, Belgium Germany)
Population	DCD donors Adults	BSD (%) DCD (%) Adults and children

Characteristic	PPART trial	Machine Preservation Trial
Internal validity	Good to poor: smaller sample (n=45 in each arm) Machine preservation [redacted] ITT analysis	Good: large sample size (n=[redacted] in each arm) No ITT analysis Many randomised but [redacted]
External validity	Good (at UK transplant centres) except, only short-term (3-month) outcomes currently available.	Good except: not in UK, [redacted] (to enhance internal validity),
Short-term outcomes	PNF: LifePort 1 (2.2%) ViaSpan 0 (0%) DGF: LifePort 26 (57.8%) ViaSpan 25 (55.6%)	PNF: LifePort [redacted]%) ViaSpan [redacted]%) DGF: LifePort [redacted]%) ViaSpan [redacted]%)
Long-term outcomes	3-month graft survival: LifePort 43 (95.5%) ViaSpan 45 (100%)	12-month graft survival: LifePort [redacted]%) ViaSpan [redacted]%)
Economic/cost outcomes	None yet reported	None yet reported

The results from the smaller record review (Moustafellos and colleagues, N=36) found significant differences in favour of machine preservation for the outcomes of, immediate graft function (IGF), DGF, length of hospitalisation and creatinine concentrations at discharge. However, as the kidneys were not randomised and the LifePort group had a shorter cold ischaemic time that the ViaSpan group, these results should be treated with caution.

Where post-storage, pre-transplant kidney discard rates were reported, these were [redacted] (PPART: machine preservation = [redacted], cold storage = [redacted]; Machine Preservation Trial: machine preservation = [redacted], cold storage = [redacted]).

LifePort machine vs. Marshall's Soltran solution

Plata-Munoz and colleagues' small (N=60) prospective cohort study showed significant differences for the outcomes of DGF, length of hospital stay, and graft function (serum creatinine) at six and twelve months in favour of LifePort. However, they failed to find significant differences between the groups for patient or graft survival outcomes at one and two years. This study lacked internal validity with the groups having different mean ages and CIT.

2.4.2.2. Machine preservation vs. machine preservation

We only found two studies assessing the comparative effectiveness of the LifePort and RM3 machine perfusion systems (Guarrera and colleagues (N =774) and Kazimi and colleagues (N=89). These were both small retrospective hospital record reviews that had not been through a peer-review process and had only been published as abstracts and presented as posters. Therefore, the evidence they present is unreliable.

With the exception of PNF, all outcomes favoured the RM3 over the LifePort perfusion machine. Guarrera and colleagues found significant benefits for kidneys stored in the RM3 machine for ECD and DCD donated kidneys in terms of, DGF, graft function, patient survival and graft survival, all at one year. Guarrera and colleagues calculations did not find these differences to be significant. However, our analysis indicated that the RR of 1.05 [95%CI 1.01, 1.08] was significant at $p<0.01$ for patient and graft survival at one year. There were a large number of discarded kidneys following perfusion (25%); this may have been due to the high percentage of ECD kidneys in that group (78%).

Kazimi and colleagues' much smaller study, of mostly better quality donor kidneys, found a non-significant gain in graft survival at 30 and 90 days for the RM3. They also found that people whose grafts had been stored in an RM3 had fewer days in hospital (RM3 = 3, LifePort = 15, $p = 0.04$). However, there were no differences in the number of times dialysis was needed post-transplant. Post-storage pre-transplant discard rates were similar (RM3 = 98, LifePort = 91). Further robust research is needed using RCTs to determine the relative effectiveness of these perfusion machines.

2.4.2.3. Cold storage solution vs. cold storage solution

Three RCTs (Montalti and colleagues, Pedotti and colleagues and Faenza and colleagues), one registry study (Opelz and Dohler) and one hospital record review (Marcen and colleagues) were found which compared the cold storage solutions of interest.

ViaSpan vs. Marshall's Soltran

A multi-national registry study compared ViaSpan with Marshall's solution (Opelz and Dohler (N=58,607). Our analysis of their data showed that there were no significant differences between these solutions for a range of cold ischaemic times up to 36 hours.

ViaSpan vs. Celsior

The three RCTs comparing ViaSpan with Celsior (Montalti and colleagues, (N=60); Pedotti and colleagues, (N=441); and Faenza and colleagues, (N=187)) found no significant differences on any outcome measure (DGF, PNF, graft survival, patient survival, graft rejection, kidney function or post-operative dialysis); after pooling these data in meta-analysis we found there were still no significant differences between groups.

The retrospective hospital record review comparing ViaSpan with Celsior (Marcen and colleagues (N=117) only found a significant difference in creatinine concentrations at one and 12 months post-transplantation, with ViaSpan stored kidneys having higher levels. However, these higher levels may have been due to the greater age of the recipients of those kidneys, or other confounding factors not reported.

Post-storage pre-transplant discard rates were similar (ViaSpan = 6, Celsior = 7).

Safety

No adverse events were reported from any of the included studies and our systematic review provided no evidence of safety issues related to mode of kidney storage. Furthermore, advice from our clinical expert suggests that there are no particular safety issues associated with kidney storage methods.

However, the British Transplant Society's submission to NICE has highlighted the issue that care should be taken when using Marshall's Soltran cold storage solution when other organs are being retrieved with the kidneys. This is because this solution

is not safe for extended preservation of the liver, pancreas or intestines and it is not possible to perfuse the kidneys without also perfusing these other organs.

Sub-groups

Moers and Colleagues carried out sub-group analyses of their DGF results. [redacted]

2.5. Cost–utility results

2.5.1. Summary of costs included in the PenTAG model

The following costs have been included in the PenTAG cost-utility model:

- Different storage solutions, and the machines or storage containers used.
- Post-transplantation dialysis while an inpatient (related to DGF rate).
- Any kidney graft explantation operations required (e.g. following primary non-function).
- Ongoing care as a successful kidney graft recipient (including routine check-ups, immunosuppressive drug regimes, and the treatment of acute rejection episodes).
- Ongoing care for patients who return to or never come off dialysis (including regular haemodialysis or peritoneal dialysis, routine check-ups, drug treatment for anaemia).

Machine perfusion

The purchase cost of a single LifePort machine is £10,750 (source: Organ Recovery Systems, budget impact analysis in submission to NICE, February 2008) but each transplant centre using machine perfusion would require two machines (total initial cost £21,500). We have annualised this initial capital cost, assuming that the machine preservation technology (not each machine) would be used for 10 years, have a zero resale value after that time, and assuming interest at 3.5% per year. This gives an annualised cost per LifePort machine of £1219, or £2438 for two machines. Transplant centres purchase two machines (each machine perfuses one kidney). We have also added an annual cost for a maintenance contract (£874 per machine),

which covers the cost of all repairs and machine replacements. The annualised purchase cost and the maintenance cost were then divided by an estimate of the number of machine preserved kidneys per transplant unit in England and Wales (16 if DCD only, 61 if both BSD and DCD kidneys could be machine stored) in order to arrive at a per stored kidney machine cost of £261, to which a perfusion kit with preservation fluid cost of £475 is added. The estimated cost per LifePort machine stored kidney is therefore £737.

We were unable to obtain a cost for the Water's RM3 as this machine is not available to the NHS and the manufacturers did not offer a submission to NICE. The manufacturers of Celsior were not invited to make a submission to NICE. Therefore, these interventions have not been included in the cost-utility analysis.

Cold static storage

Two cold storage solutions are used in the UK, ViaSpan and Marshall's Soltran. The cost (excluding VAT) of a one litre bag of ViaSpan is £116 and Soltran is £9.60. Although clinical practice may vary, information from our experts suggested that typically two litres of solution would be used for the initial flushing and subsequent storage of each kidney.

In addition to the storage solutions, the cold storage of kidneys involves the use of two sterile plastic bags, sterile ice, non-sterile ice and water, and non-sterile insulated boxes for storage and transportation. The boxes are bulk-purchased and supplied to all transplant centres in UK the by UK Transplant, with each box being used an estimated 1 to 3 times (mean, estimated from UK Transplant data, of 1.5 times)

Other costs

Although the model had the capacity to incorporate cost differences due to different length of hospital stay, there was no reliable data (especially from the included RCTs) to suggest that the compared technologies resulted in different lengths of hospital stay (even in the presence of differences in delayed graft function). Therefore, we did not use trial data relating to length of hospital stay in our modelling.

The cost of removing a failed transplanted kidney is on average £4135. Following a successful transplant there are ongoing care costs for outpatient appointments and immunosuppressive drug therapy, which come to approximately £5700 per year. In contrast, if the graft fails, there is a continuing cost for dialysis. We estimated dialysis and associated care costs to be between approximately £24,400 and £25,400 per

year (which varies with age, due to more older dialysis patients being on haemodialysis). In addition, some patients whose kidney grafts fail will have a subsequent transplant, at a cost to the NHS of approximately £16,400.

2.5.2. Summary of cost-utility results

Machine perfusion vs. cold static storage solution

- LifePort vs. ViaSpan
- LifePort vs. Marshall's Soltran

Cold static storage solution vs. cold static storage solution

- ViaSpan vs. Marshall's Soltran

2.5.2.1. Deterministic results

The two RCTs which compare cold storage using ViaSpan and machine preservation using LifePort are based on different populations and have therefore been modelled separately. In the European Machine Preservation Trial, machine preservation was both cheaper and generated more QALYs than cold storage. In contrast, when the UK PPART study data is used to parameterise the model, cold storage is cheaper and generates more QALYs than machine preservation. It should be noted that in the PPART study no outcomes demonstrated statistically significant differences between trial arms, and for the Machine Preservation Trial [redacted]. When this underlying uncertainty is embodied in the model little confidence can be given to any conclusions preferring one storage method over another.

The deterministic outputs, based on the small (N=60) comparative cohort study which compared the use of Marshall's Soltran solution with LifePort machine preservation suggest that LifePort would be both cheaper and generate more QALYs than Marshall's Soltran**,** machine preservation is both cheaper and more effective as a treatment option. However, once again, the uncertainty and risks of bias in the effectiveness data from this small non-randomised study would caution against over-reliance on this modelling result.

The comparison of ViaSpan and Marshall's Soltran cold storage solution show very small differences between the arms which, given both the uncertainty in the source

effectiveness data and doubts about its internal validity (non-RCT data), also give little basis for any confident conclusions. Nevertheless, if this non-randomised evidence of a marginally different graft survival reflects a genuine difference in the effectiveness of the two solutions, then using ViaSpan would probably be both cheaper and generate more QALYs than Marshall's Soltran in the long term, despite its higher per litre cost.

It should be noted that the differential costs of kidney storage associated with the different storage methods are relatively small when compared with the potential gains that result from any small improvements in effectiveness that can be demonstrated, especially any gains in graft survival. However, there is currently no strong evidence that such differences in effectiveness exist.

2.5.2.2. Sensitivity analyses

Deterministic one-way sensitivity analyses

Sensitivity analyses were conducted for the four comparisons in order to explore the key interactions of the model. The following general observations can be made from these model outputs.

- Changes to the differential kidney storage costs between comparators have a very low impact on the overall net benefit estimates when set against the large cost, survival and QALY impacts of small differences in graft survival between comparators.

- Where differences in effectiveness exist between comparators, dialysis costs become an important factor in determining the overall net benefit level.

- Levels of DGF between comparators only become important when differences in graft survival are apparent between those patients experiencing immediate graft function (IGF) versus DGF, and are also used to predict long-term graft survival.

- The relative impact of differential changes to graft survival for patients experiencing IGF as opposed to DGF depends on the relative proportion of patients experiencing each of these two outcomes (IGF vs. DGF). For example, if very few patients in the model experience DGF, then graft survival changes for DGF patients has a small impact on the overall net benefit output.

Probabilistic sensitivity analysis

The PSA also showed that the key model input parameter is differential graft survival. Where differential graft survival between the comparators can be demonstrated the advantages of improved graft survival quickly and greatly outweigh the initial incremental costs associated with different storage methods. These advantages are manifested both in terms of improved survival and quality of life outcomes and also in terms of cost savings due to reduced need for dialysis over patients' remaining lifetimes. As a result, many of the probabilistic simulations resulted in either kidney storage method being both cheaper and generating more estimated QALYs than the other; this produced very flat and largely uninformative cost-effectiveness acceptability curves.

2.6. Discussion

The evidence from the systematic review of effectiveness studies is unable to provide a definitive answer to the question of which is the best way to store kidneys from deceased donors. This is mainly because of the lack of medium to long-term follow up data on graft survival for different types of kidney donor graft, [redacted]. Results from the two RCTs indicate that [redacted] the Machine Preservation Trial indicates that at 12-months [redacted] this is in a largely BSD kidney population ([redacted]%). Kidneys from BSD donors are currently not eligible for machine preservation in the NHS because of the local ownership of machines, and therefore their restricted use for regionally retrieved kidneys (i.e. DCD kidneys).

Comparison between the two types of perfusion machine has been difficult due to the lack of RCTs and only partially published results being available from hospital record review studies. The limited data available suggest that for all outcomes other than PNF the RM3 is better than LifePort. However, there is major uncertainty about this finding.

When the cold storage solutions are compared we found that there was no significant difference between ViaSpan and Marshall's Soltran or between ViaSpan and Celsior.

With regard to the cost-utility results, the relatively large cost savings together with the quality of life and survival gains of having a functioning transplant, compared with

returning to dialysis, mean that even very small gains in kidney graft survival would make either comparator both cheaper and more effective (in terms of estimated life-time QALYs) than the other. Given that the Machine Preservation Trial's results were [redacted], in which case it seems considerably likely that LifePort would represent good value for money for the NHS relative to cold storage with ViaSpan in a mixed population of mostly BSD kidneys.

Given the lower quality, non-randomised effectiveness evidence for comparing LifePort with Marshall's Soltran, and for comparing Marshall's Soltran with ViaSpan, the cost-utility results from both these comparisons should be interpreted with great caution. In relation to these comparisons, therefore, there is no strong effectiveness evidence on which to inform technology adoption recommendations on the basis of the derived cost-utility estimates.

2.6.1. Strengths and limitations

Effectiveness review

The clinical effectiveness systematic review looks at the latest evidence for each comparison in a systematic way, through the eyes of an independent research team. However, the review was limited by the premature timing of the report which meant that one of the key trials only had three month data to report. Furthermore [redacted] meant that we are unable to come to any firm conclusions about the relative benefits of either storage method for this key group of donated kidneys. Additionally, only five of the 11 included studies were RCTs, this includes both of the studies that compared perfusing machines with cold storage. These studies had only reported their findings in a limited way as abstracts and posters, making conclusions about which is the better machine impossible. The effectiveness review may have been further limited by the searches only being conducted for articles in the English language. However, our Expert Advisors inform us that we have included all relevant studies.

Cost-utility analysis

Our cost-utility analysis combines both the best available effectiveness data for each comparison, with relevant parameter estimates from reliable national sources (e.g. the UK Transplant records, UK Renal Registry, and the NHS National Schedule of Reference Costs) within a decision model which maps the key short- and long-term

outcomes for kidney transplant recipients. Despite the comprehensiveness of the model structure, and the availability of good data for many of the parameter estimates, the cost-utility results are mainly driven by small differences in graft survival and how these short-term survival estimates are extrapolated. Although some aspects of our estimation of the NHS cost of living on dialysis, or of living with a functioning transplant, could perhaps be improved, such changes in model inputs would be unlikely to change the direction of the results. Moreover, they would not alter the extreme sensitivity of the results to the underlying estimates of differences in graft survival.

2.6.2. Generalisability

In relation to the generalisability of the results of the RCTs and other comparative studies to the UK NHS, most of the studies included in our systematic review were recent, and conducted in the UK or countries where systems and clinical practices for kidney retrieval and transplantations would be largely similar to the NHS. However, a key issue to consider is the different kidney donor types involved in each trial, and whether they reflect the mix of kidneys currently amenable to machine perfusion in the UK. The Machine Preservation Trial comparing LifePort vs. ViaSpan, [redacted], was conducted with mainly kidneys from BSD donors; but these kidneys are currently not available for machine perfusion in the NHS due to organ sharing arrangements.

The other key generalisability issue in this assessment is whether differences in short-term graft survival (e.g. at one year post-transplant) reflect longer term trends in graft survival. In our cost-utility modelling we have inevitably had to extrapolate from short-term to long-term graft survival, and this might not reflect the real impact of better stored kidneys.

2.7. Conclusions

Machine preservation vs. cold storage

Using effectiveness data from the Machine Preservation Trial, there would probably be

[redacted]. This result, however, pertains to mostly BSD kidneys, which are currently not available for machine perfusion in the NHS because of the current regulations and

logistics of deceased kidney retrieval and transplantation. If the use of machine perfusion in the NHS is to remain restricted to DCD kidneys, then the other, lower quality RCT suggests that there would be no short- or long-term health gains from machine perfusion. However, this trial was much smaller and also [redacted] which may both partly explain this trial's statistically non-significant findings.

With regard to the cost-utility of LifePort compared with Marshall's Soltran, the effectiveness data are so unreliable (based on a very small, non-randomised single centre study) that it would be unwise to trust the results based on them.

Machine preservation with LifePort vs. with the RM3 machine

Without a purchase cost for the RM3 machine, nor its current availability in the NHS, it was not possible to conduct a cost-utility analysis of this comparison.

Cold storage with ViaSpan vs. with Marshall's Soltran

Although the only included effectiveness study for this comparison was a large registry-based analysis, there were no statistically significant differences in outcomes between the two storage methods. Therefore, the cost-utility analysis, by magnifying both the QALY gains and related cost savings driven by these very small differences in effectiveness, should probably not be relied upon for choosing one product over another. If anything, in the absence of good research evidence that one of these preservation solutions is better than the other, there may be an argument for using the considerably cheaper Marshall's Soltran (although care should be taken as it is unsafe to use for the extended preservation of the liver, pancreas or intestines, which would also be perfused with the kidneys in multiple organ retrieval).

Cold storage with ViaSpan vs. Celsior

Since the manufacturers of Celsior cold storage solution were not invited to make a submission to this HTA it has not been possible to conduct a cost-utility analysis. However, the results of our meta-analysis of the RCTs comparing ViaSpan with Celsior indicate that these cold storage solutions are equivalent.

2.7.1. Implications for service organisation

The efficient and more widespread use machine preservation for storing both DCD and BSD donor kidneys is contingent upon the prevailing systems and regulations for organ sharing, and also having the logistical arrangements in place for sharing or swapping machines between regions. In the light of current government intentions to create a national Organ Donation Organisation (2008, Department of Health Organ Donation Taskforce, Recommendation 1), and to establish a UK-wide network of organ retrieval teams (Recommendation 10), it seems probable that the machine preservation of BSD as well as DCD donor kidneys may become more practically and widely feasible in the NHS in the near future. In terms of using different kidney preservation solutions, no issues of service organisation or delivery have come to light during our assessment.

2.7.2. Suggested research priorities

1. If evaluators of kidney preservation technologies are to rely upon delayed graft function as an assumed predictor of long-term graft survival or patient survival, then more high quality research is required to establish the strength and reliability of the presumed causal association (including how it is contingent upon other known factors such as cold ischaemic time, donor type and tissue matching).

2. All studies of the effectiveness of alternative kidney preservation methods should collect data on and report the numbers of stored kidneys which are discarded pre-implantation (e.g. after being judged as non-viable), together with an intention-to-transplant analysis.

3. As graft and patient survival have multi-factorial determinants, there is a need for sufficiently large RCTs of comparators of interest to allow for appropriate analysis of sub-groups, which may in turn better identify those combinations of donor kidney, types of recipient, or storage characteristics (such as length of cold ischaemic time) in which machine preservation appears to be most effective at improving short-term and long-term outcomes.

4. More research is needed into the utility impacts of all forms of RRT; most published studies are cross-sectional, but there is a need to know the long-term trajectories that patients follow (e.g. the quality of life impact of dialysis following graft failure). Many current studies are confounded by younger, fitter people receiving transplants and

older people, with more co-morbidities being on dialysis. New studies should try and use both established disease-specific measures and generic quality of life measures for which social preference weights exist (such as the EQ-5D, SF-36 or HUI-III). Also, because quality of life in renal dialysis patients is clearly associated with the different modes and settings for dialysis, all studies should endeavour to report quality of life in these dialysis subgroups separately.

5. Research is needed to determine what the additional cost, survival and QALY impacts are of decreased or increased non-viable kidneys when discarded pre-transplantation.

6. RCTs are needed to determine whether either of the two machines under consideration produces better patient outcomes

7. RCTs are needed to compare the RM3 with cold static storage solutions

8. Further work is needed to clearly identify a reliable measure for predicting kidney viability from machine perfusion

Other issues:

9. UK Transplant should encourage fuller data collection by transplant centres, as about 58% of data parameters are incomplete. We are advised that electronic methods of inputting the data would make this easier to encourage. This might allow the staggered roll-out of new organ preservation methods to be evaluated by planned natural experiments, as well as RCTs.

3. Background

3.1. Description of the problem

Established renal failure (ERF) or end-stage renal disease is defined as an irreversible decline in a person's kidney function that is severe enough to be fatal in the absence of renal replacement therapy (RRT).[1] Kidney transplantation is the best form of renal replacement therapy for people with end-stage renal disease where it is possible.[2] Unfortunately, the demand for donor organs greatly outstrips supply.

Most kidneys for transplantation are obtained from deceased heart-beating donors; that is, people in whom death has been diagnosed by brain stem tests who are maintained on a ventilator in an intensive care unit. These donors will be referred to as brain stem dead (BSD) donors in the remainder of this report. The availability of organs from this type of donor has declined by about 20% in the UK over the last decade,[3] possibly because of a reduction in fatal road traffic accidents and a decrease in the number of deaths from intracranial haemorrhage.

One means of expanding the donor pool is to use organs retrieved from non-heart-beating donors. These are people who cannot be diagnosed as brainstem dead but whose death is verified by the absence of a heart beat (cardiac arrest). These donors will be referred to as donation after cardiac death (DCD) donors in the remainder of this report. Categories of DCD donors have been devised by the Maastricht Group.[4] In addition, procurement of organs from these donors is referred to as 'controlled' where cardiac arrest was expected, for example in someone being cared for in an intensive care unit, or 'uncontrolled' where death occurs unexpectedly, and donation follows unsuccessful resuscitation or cardiac arrest.

Donation after cardiac death may occur in one of five circumstances, according to the Maastricht criteria:

(i) Death occurring outside of hospital – uncontrolled. In this case the moment of sudden death has not necessarily been witnessed and so the time at which it occurred is not necessarily documented.

(ii) Unsuccessful resuscitation – uncontrolled. These individuals have undergone cardiopulmonary resuscitation following collapse, usually in the

Accident and Emergency department where they are declared dead. The time of collapse is known as it is a witnessed event.

(iii) Awaiting cardiac arrest – controlled. These are a group of people for whom continued treatment is futile, and whose death is inevitable and imminent, but who do not fulfil criteria for brainstem death testing.

(iv) Cardiac arrest in a brainstem dead donor – uncontrolled. A donor falls into this category if death has been certified by brainstem criteria and cardiac arrest occurs before organ retrieval has taken place.

(v) Unexpected cardiac arrest in an ITU or critical care unit – uncontrolled. This category has been added to the other four recently.

The use of kidneys from DCD donors is not new; before the concept of brainstem death was legally defined in the 1970s all deceased donor kidneys came from DCD donors.

The critical difference for viability between organs from DCD and BSD donors is the duration of 'warm ischaemic time'. This is the time when the donor is without a heart beat at normal temperature before the kidney has been flushed and perfused with cold preservation solution. This asystolic warm period does not occur in BSD donors. Another key difference between these types of deceased donors is the chaotic physiology they may have endured in the previous hour or so prior to death, possibly with low blood pressure which can lead to poor organ perfusion and reduced tissue oxygenation.

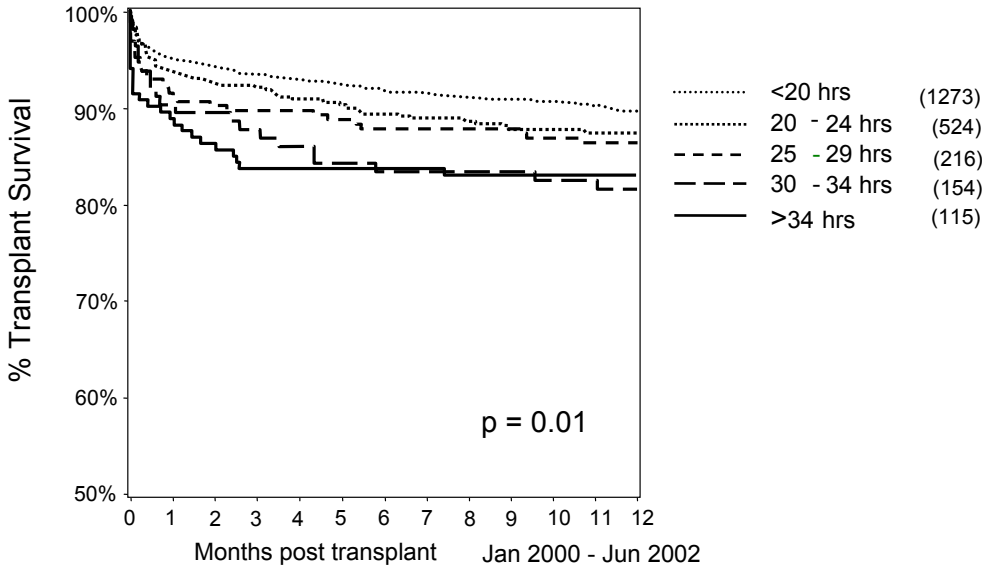
'Cold ischaemic time' is from the start of cold perfusion, through the organ retrieval process and cold storage period until the kidney is removed from the ice or perfusing machine and the anastomois period of re-implanting in the recipient begins. This last anastomois period is also referred to as the secondary warm ischaemic period; the kidney is still cold until it begins to warm up when perfused by the recipient's blood.[5] Both warm ischaemic time and cold ischaemic time are damaging to organs but, after retrieval, cooling the organ suppresses the metabolic rate and so reduces the rate of damage.[6]

Organs used for transplantation undergo a varying degree of damage due to cold ischaemia and reperfusion. Prolonged cold ischaemia is associated with delayed graft function that contributes to inferior graft survival.[7;8] Ischaemia has a number of

physiological effects on the kidney. Primarily the nutrient and oxygen supply cease when the circulation stops. This precipitates energy rich anaerobic metabolism, which causes energy stores to run down. Effects of this are that energy dependent systems fail e.g. Na/K ATPase stops and toxic metabolites of anaerobic metabolism begin to build up e.g. lactic acid. The damage from reperfusion is due to the inflammatory response of damaged tissues. White blood cells carried in the newly restored blood flow to the kidney release many inflammatory factors including interleukins and free radicals thought to cause injury. White blood cells may also build up in small capillaries, obstructing them and causing more ischaemia; the longer the period of cold ischaemia, the more severe the damage.

In DCD donors (particularly uncontrolled DCD donors, in Maastricht categories 1, 2, 4 and 5) the asystolic warm period may be prolonged. As a result, kidneys from DCD donors tend to suffer higher rates of PNF (when the graft never works after implantation), DGF (the need for dialysis in the first week post-transplantation) and poorer long term graft survival than those from BSD donors. [9] Delayed graft function is associated with the need for continuing dialysis and longer hospitalisation. The effects of ischaemic damage on transplant survival can be seen in Figure 1 below, taken from the British Transplantation Society's submission to NICE.

Figure 1 Effects of graft cold ischaemic time on transplant survival



Source: Rachel Johnson, Principal Statistician, UK Transplant

Apart from the increased use of DCD donors, a second means of expanding the pool of kidney donors is through the use of ECD donors. These are kidneys from BSD donors who, in the past (particularly in the USA), would not normally meet the criteria for transplantation. The extended criteria include kidneys from donors who are either over sixty, or are over fifty and with two or more of the following features (1) a history of hypertension, (2) a history of cerebral vascular accident, (3) terminal creatinine levels greater than 133µmol/L (1.5mg/dl).[10] In general kidneys from extended criteria donors have a lower chance of long term success and a higher incidence of DGF than those from BSD donors.[10]

3.1.1. Epidemiology

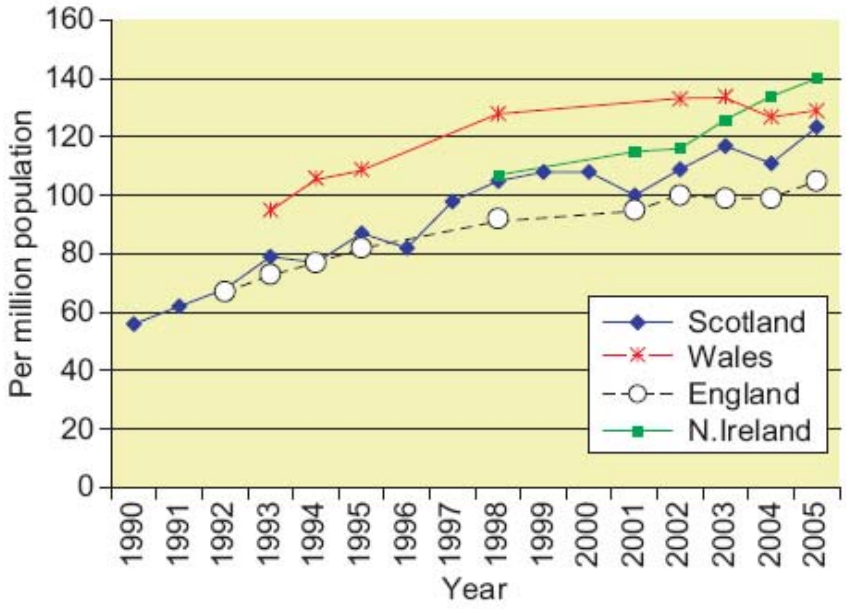
3.1.1.1. Incidence and prevalence

The Renal Registry annual report 2006 shows that there were 41,776 adults on RRT (see section 3.2.1) in the UK in 2005; this gives a prevalence of 694 per million population (pmp). There were also 748 children (<18yrs) on RRT with a prevalence of

12 pmp. These figures show that since the year 2000 there has been a 27.8% percent increase in patient numbers cared for by the 38 renal units which have continuously returned data from 2000 -2005.[11]

Data from the same report show that in 2005 there was an acceptance rate for RRT for adults in the UK of 108pmp and 2pmp for children, showing a total incidence of 110pmp. This reveals a 7.3% increase in incidence from 2001-2005 in 42 renal units in the UK submitting full returns to the Renal Registry. [11] Figure 2 shows the incident rates for the UK from 1990-2005.

Figure 2 Incident rates of adults accepted for renal replacement therapy in the UK 1990-2005



Source: UK Renal Registry Report 2006

In 2005 in the UK 76% of people accepted for RRT began treatment with haemodialysis, 21% started with peritoneal dialysis and 3% with a kidney transplant. Ninety days later 8% had died, 1% had stopped treatment or had been transferred out. Of the remaining 91%, 5% changed from haemodialysis to peritoneal dialysis and 3.2% had a transplant. [11] The median age at which people start RRT has increased in England from 63.8 years in 1998 to 65.2 years in 2005, with people using haemodialysis having a mean age nine years older and having fewer co-morbidities

than those using peritoneal dialysis.[11] Table 2 shows the percentage RRT type for England and Wales in 2005.

Table 2 The percentage of RRT patients using each method of treatment in England and Wales

	Percentage of patients on each modality					
	Haemo-dialysis	**Peritoneal dialysis**	**Transplant**	**Transferred**	**Stopped treatment**	**Died**
England	63.5	24.3	3.1	0.7	0.5	8.0
Wales	63.9	19.1	4.5	0.6	0	12.0

Source: The UK Renal Registry Ninth Annual Report 2006

Survival in the first year following starting RRT for all patients regardless of age is 79%.[11] Five year survival figures including deaths in the first 90 days following beginning RRT are as follows, Table 3.

Table 3 Five year survival following commencement of renal replacement therapy by age

Age group (years)	**18-34**	**35-44**	**45 - 54**	**55 - 64**	**65 - 74**	**75+**
Rates	58%	53%	44%	28%	20%	12%

Source: UK Renal Registry Report 2006

3.1.2. Aetiology

The most common cause of established renal failure is chronic renal damage usually caused by diabetes.[1] Other causes of established renal failure relate to vascular disease, hypertension, glomerulonephritis (inflammation of the kidney's filters) and microscopic vasculitis (inflammation of the small blood vessels). Most causes, with the exception of glomerulonephritis, are associated with getting older. Acute renal failure may follow from traumatic injury or infection and can progress to established renal failure (ERF).[1]

When established renal failure occurs in children it is usually due to innate structural abnormalities, although there may be genetic causes e.g. cystinosis. Established renal failure may also be acquired in childhood through glomerulonephritis.[1]

The risk of ERF increases with age; in 2006 the median age for starting RRT in England was 65 years and 67 years in Wales.[11]

There are also ethnic differences with people from South Asian, African and African Caribbean communities more likely to have higher rates of chronic kidney disease through greater susceptibility to diabetes and hypertension.[12] Evidence also suggests a further link to social deprivation, although the reasons for this are not fully understood.[13-15]

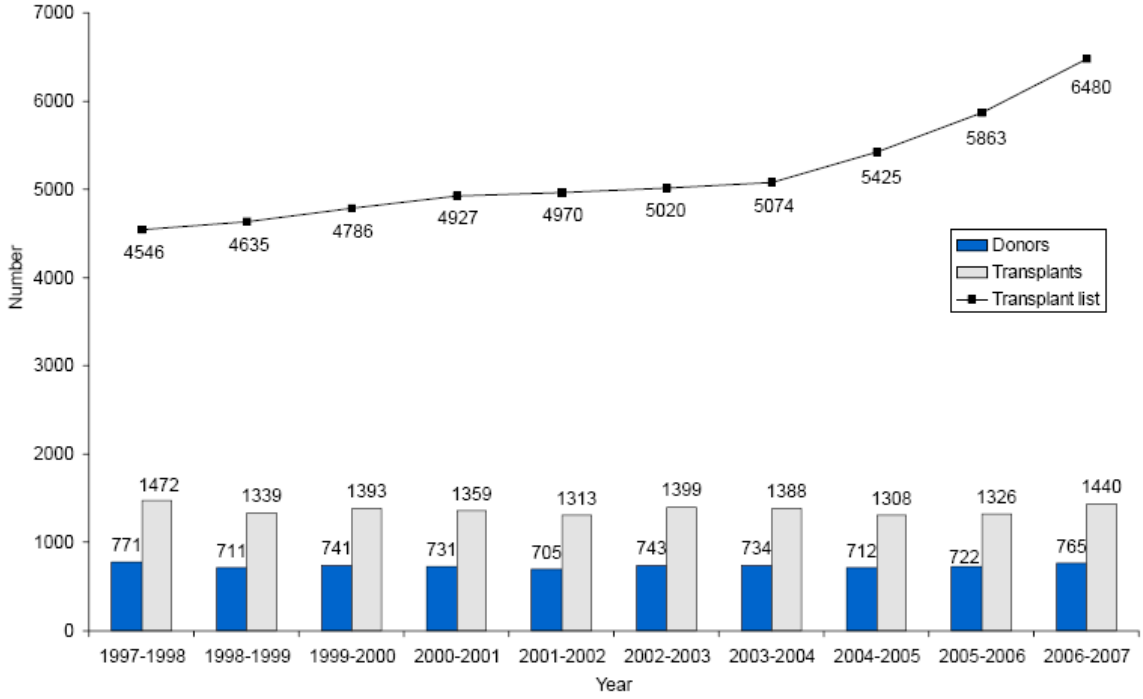
3.1.3. Pathology

When established renal failure is reached people become tired, nauseated, lose their appetite and cope less well both physically and mentally.[1] The signs of ERF include fluid retention (shown as swollen ankles or breathlessness), itching, pallor and raised blood pressure, and poor growth and development in children. These symptoms are accompanied by falling haemoglobin levels and abnormality of biochemical markers e.g. serum urea, serum creatinine and potassium. When someone reaches this point they will need RRT within weeks or months to prevent death; RRT can be provided as dialysis or transplantation. Treatment will continue for the rest of their lives.[1]

3.1.4. Impact of transplant activity

The diagram below, taken from Transplant Activity in the UK 2006-2007,[16] provides an overview of the increasing demand for donated kidneys.

Figure 3 UK deceased donor kidney programme activity, 1997 – 2007



(Source: Transplant Activity in the UK 2006-2007, UK Transplant)

The UK waiting list for kidney or kidney/pancreas transplants has increased by 48% since 1998, although the number of donors rose in 2006-2007 to 765 (BSD = 609, DCD = 156) from 722 (BSD = 599, DCD = 123) the previous year. This represents a 21% increase in DCD donors with a 28% increase in transplants from these donors. BSD donors provided 1208 kidneys of which 1164 (96%) were transplanted in the UK. DCD donors gave 307 kidneys enabling 276 transplants (11 double and one *en bloc*). This gives an overall UK donated kidney rate of 20.1 per million population (pmp). There were 1440 kidney transplants in 2006-2007 in the UK (978 in England and 49 in Wales).[16]

Table 4 Kidney donors, donations and transplants in the UK 2006-2007

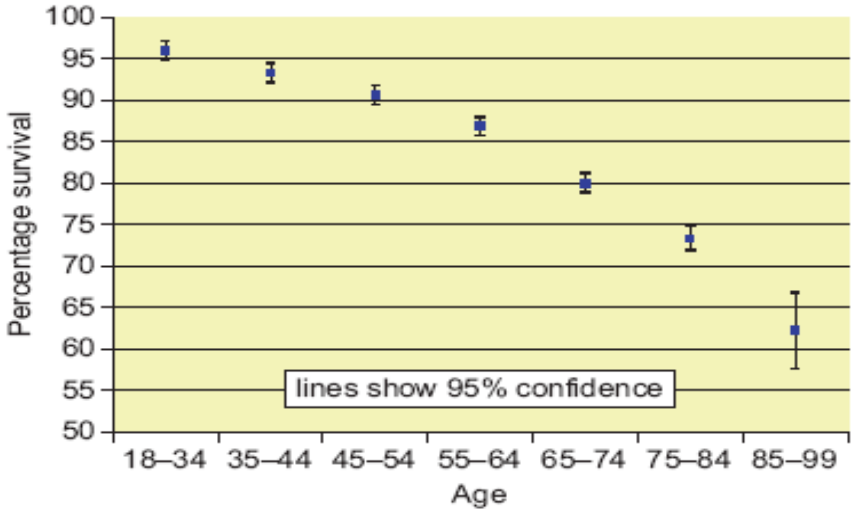
Type of donor	Number of donors	Number of donations	Number of UK transplants
BSD	609	1208	1164
DCD	156	307	276
Total	765	1515	1440

(Source: Transplant Activity in the UK 2006-2007, UK Transplant)

3.1.4.1. Significance for patients

To a person suffering from end-stage renal disease the opportunity to have a kidney transplant is literally a matter of life or death. In the year 2006-2007, in the UK, 231 patients died while on the active and suspended waiting lists for kidney transplantation; an equivalent number were removed from the list because they were no longer fit enough, most of whom would go on to die. In the same year there was an 11% increase in patients actively waiting for a kidney or kidney and pancreas transplant compared with the previous year, with a total of 6480 people waiting for a transplant. Seventeen percent (1101) of those on the 2006 – 2007 waiting list had received a transplant by 31st March 2007.[16] Figure 4 shows the percentage of dialysis patients who survived in 2005.

Figure 4 One year UK survival of prevalent dialysis patients in different age groups - 2005



Source: UK Renal Registry 9th Annual Report 2006[11]

3.1.4.2. Quality of life

Life with dialysis

Established renal failure has a large impact on quality of life. The vast majority of people on RRT will start on dialysis, as opposed to receiving a transplant first (76%).[16] (see section 3.2.1) This time-consuming treatment may affect employment, education, normal family life and require changes in diet and fluid intake, often resulting in malnourishment and the need for nutritional supplements or artificial

feeding.[1] Additionally, medication is required to prevent bone and heart diseases and injections may be necessary to combat iron deficiency or anaemia. Sexual and reproductive problems are common, as are other illnesses, particularly cardiovascular disease.[1] Peritoneal dialysis is often preferred, especially for children, as it can take place over night, at home and has less impact on everyday life.[16]

Rocco and colleagues measured the impact of haemodialysis on adults (n=45) using the SF36.[17] They found that compared to the general population people using haemodialysis had a significantly lower quality of life (HD: 50.08 (SD22.56), control: 91.99 (SD23.41), $p<0.001$).[18]

Kutner and colleagues (USA) compared the quality of life of people using haemodialysis and peritoneal dialysis, with the Kidney Disease Quality of Life-Short Form (KDQOL-SF).[19] They found that after one year on dialysis, the mode of dialysis was a significant predictor of quality of life. This was for the effects of kidney disease on the sub-scales of; daily life ($p=0.002$), burden of kidney disease ($p=0.3$), staff encouragement ($p<0.0001$) and satisfaction with care ($p<0.0001$), with all scores favouring the use of peritoneal dialysis.[20]

Life with a Transplant

Whilst kidney transplantation relieves the person with ERF from lengthy dialysis, it brings a strict regimen of medication in order to prevent rejection of the graft. These immunosuppressant drugs may have unpleasant side effects, including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain.[21] Nevertheless, A large number of studies have similarly documented, using a variety of instruments, the clear quality of life improvements of having a functioning kidney transplant compared with being on dialysis.[22-34] Overbeck and colleagues, for example, compared the quality of life of those who had received a kidney transplant with those dialysing and on the waiting list, they found that, when measured with the SF-36, people who had received a transplant reported better physical functioning, perception of general health, social functioning and overall physical component than those still dialysing, although these scores did not match those of the general population.[34] See Table 5 below.

Table 5 SF-36 mean scores comparing the quality of life of those on dialysis or transplanted with the general population

	Physical functioning	Bodily pain	General health	Social functioning	Physical well-being summary
	(p ≤ 0.001)	(p = 0.062)	(p ≤ 0.01)	(p ≤ 0.01)	(p ≤ 0.001)
Dialysis (n = 65)	62.7	62.8	39.7	71.0	38.9
Transplant (n = 76)	77.0	73.5	51.0	83.9	45.6
General Population	84.8	77.7	68.5	89.0	50.2

Source: Overbeck and colleagues 2005.[34]

3.1.5. Significance for NHS

In 2004 the cost of treating people with ERF was estimated at 1-2% of the NHS budget.[1] Dialysis is frequently associated with the need for surgical procedures for vascular/peritoneal access, or treatment of sepsis. On average a dialysis patient will be admitted to hospital for two to three weeks every year.[1] The number of admissions per year increases with disease progression as interventions increase.[35]

During the first year the costs of transplantation are similar to those of dialysis.[1] Transplantation costs include surgery, immunosuppressive drugs, regular checks and treatment.[1] In subsequent years costs reduce considerably. An economic evaluation of treatments for end stage renal disease by de Wit and colleagues 1998 has shown that transplantation is the most cost-effective form of RRT with increased quality of life and independence for patients.[36]

It is projected that with an increasingly elderly and overweight population the demand for RRT will increase, with consequent pressure on services providing renal units and other healthcare providers dealing with co-morbidities. Increased resources may be needed for; dialysis, surgery, pathology, immunology, tissue typing, histopathology, radiology, pharmacy and hospital beds. Demand is likely to be particularly significant in areas where there are large South Asian, African and African Caribbean

communities and in areas of social deprivation, where people are more susceptible to kidney disease.[1]

3.1.6. Measurement of health

The outcome of kidney transplants can be measured in a variety of ways. These include:

Short-term

Immediate graft function: The graft works immediately following transplantation removing the need for further dialysis.

Delayed graft function: The graft does not work immediately and dialysis is required during the first week post-transplant. Dialysis has to continue until graft function recovers sufficiently to make it unnecessary. This period may last up to twelve weeks in some cases.

Primary non-function: The graft never works after transplantation.

Long-term

Rejection rates: The percentage of grafts that are rejected by the recipients' bodies, these can be acute or chronic.

Graft survival: The length of time that a graft functions in the recipient.

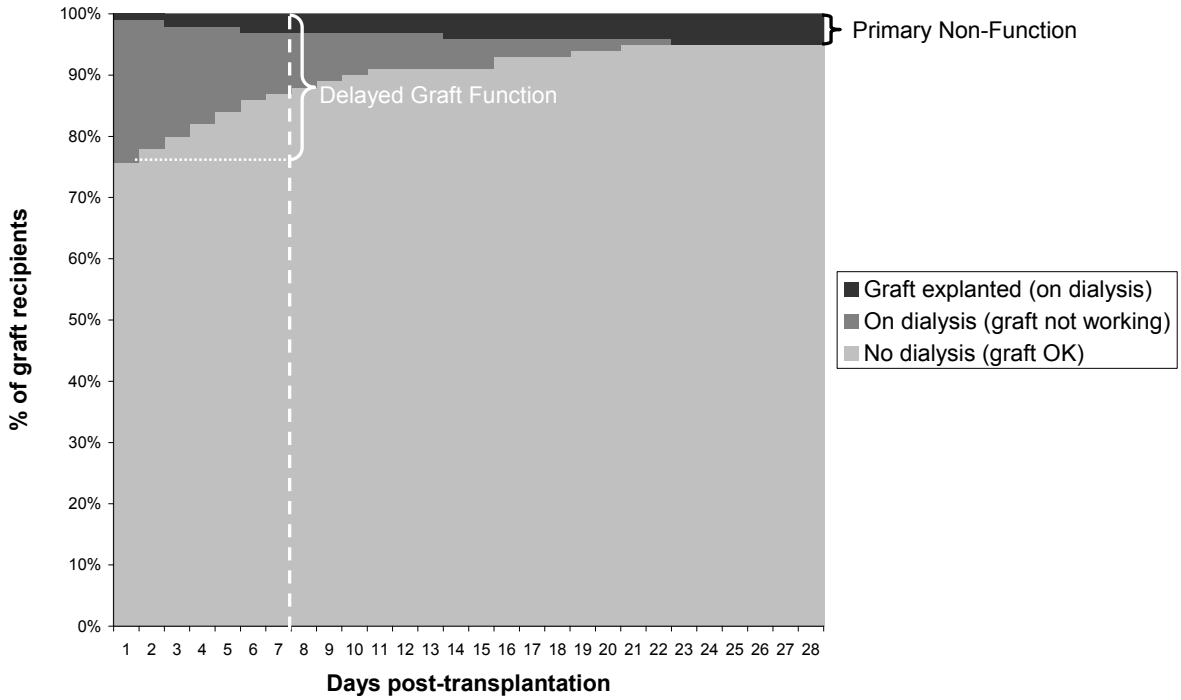
Graft function: A measure of the efficiency of the graft by various markers e.g. glomerular filtration rate and serum creatinine levels.

Patient survival: How long the recipient survives with the transplanted kidney.

Quality of life: How a person's well-being is affected by the transplant.

Figure 5 shows a hypothetical graph to explain the relationship between DGF and PNF. At seven days post-transplant some of the patients who have needed to dialyse and whose grafts are therefore classified as DGF will in fact have grafts that never function. When this has been established these grafts are classified as PNF.

Figure 5 Hypothetical graph to explain the relationship between DGF and PNF

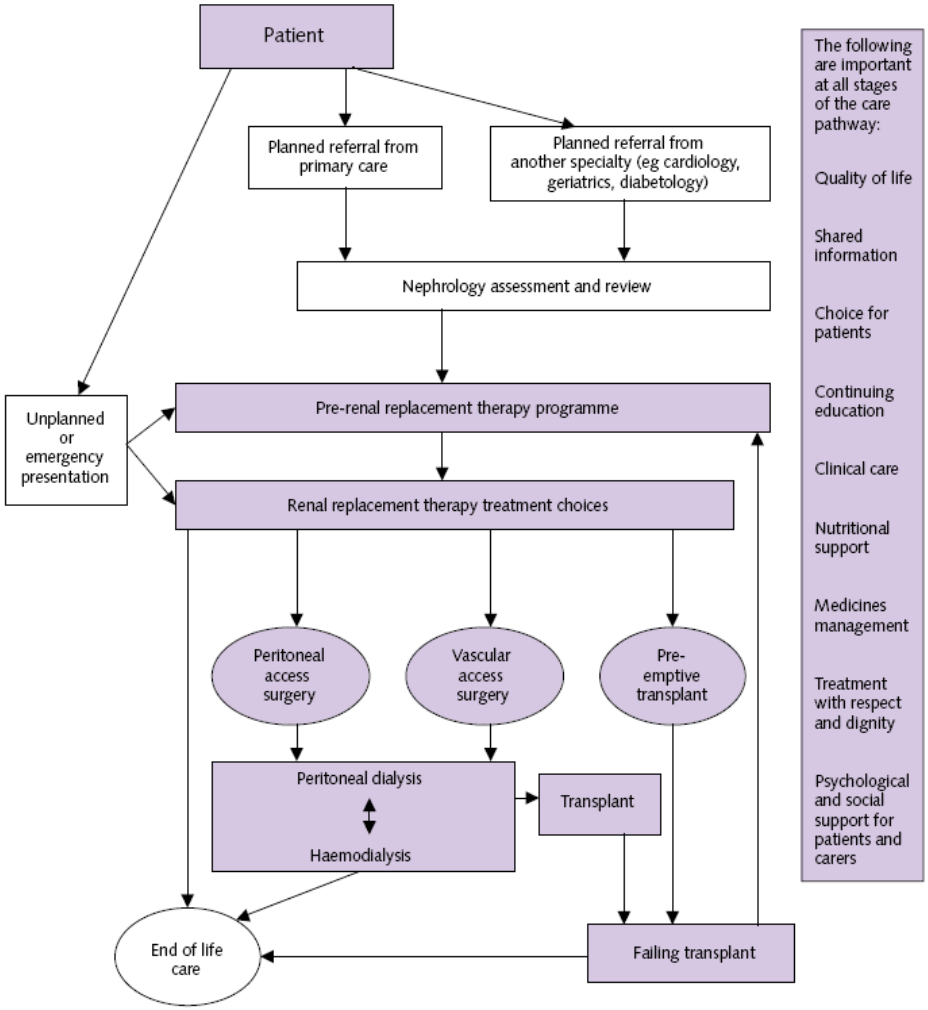


3.2. Current service provision

3.2.1. Management of end-stage kidney disease (established renal failure)

End-stage kidney disease is managed by renal replacement therapy i.e. through dialysis or kidney transplantation. These are effective therapies, allowing some people to live reasonably healthy lives for 30 years or more.[1] The patient pathway for people with ERF can be seen in Figure 6.

Figure 6 The care pathway for renal replacement therapy



Source: The National Service Framework for Renal Services – Part 1: Dialysis and Transplantation

Dialysis, whether peritoneal or haemodialysis, requires access surgery to insert a catheter into the abdomen for the former and the formation of an arteriovenus fistula for haemodialysis to enable easy access to the blood circulation in the later.

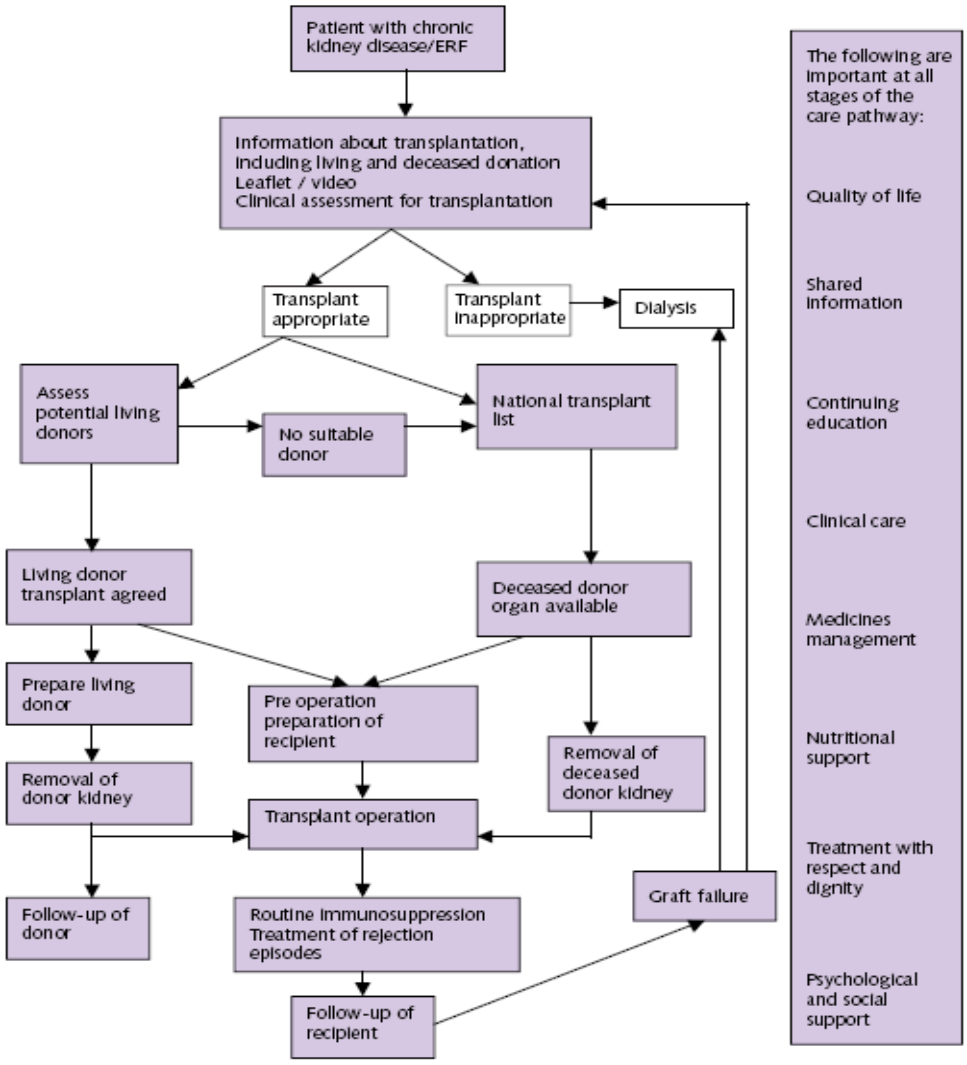
Most people on haemodialysis in the UK attend specialist dialysis centres three times a week for three or four hours each session.[37] Home haemodialysis may occurs more frequently with shorter sessions if this suits the patient better.[1]

For peritoneal dialysis a fluid is introduced into the peritoneal cavity via a catheter and dialysis occurs across the peritoneal membrane. After two or three hours the fluid containing waste products is drained out, and fresh dialysis fluid drained in; such exchanges occur three to five times a day. This is a relatively simple procedure for the individual and can take place at home without medical supervision or specialist

equipment. However, household adaptations may be required such as the installation of showers (as baths are not advisable) and bunkers or sheds to store the considerable quantity of dialysate bags, for which several week supply are often delivered. The greatest risk is from infection of the peritoneal cavity.[37]

Transplantation is the most clinically and cost-effective treatment for many people with ERF.[1] It allows liberation from the invasiveness of dialysis but requires the taking of powerful drugs to prevent rejection for the rest of people's lives. A person being considered for transplantation will progress according to the routes in Figure 7.

Figure 7 Care pathways for potential transplant recipients



Source: The National Service Framework for Renal Services – Part 1: Dialysis and Transplantation

Following surgery, a transplant patient will need long-term follow up to monitor the graft.

3.2.2. Variation in services

Services for people with established renal failure have traditionally centred on dialysis based in hospital renal units or at home. Since the 1990s a 'hub and spoke' organisation of care has become more common, with a central renal unit supporting satellite haemodialysis units to provide clinical care as close to people's homes as possible.

3.2.3. National guidelines

There are a number of national guidelines relating to this technology:

- NHS Transplant list criteria for potential renal transplant patients[38]
- Draft Standards for Renal Transplantation. The Renal Association 2006 [39]
- National Service Framework for Renal Services; Part One: Dialysis and Transplantation. Dept. Health, 2004 [1]
- Guidelines relating to solid organ transplants from non-heartbeating donors. British Transplantation Society, 2004[3]
- Saving Lives, Valuing Donors: a transplant framework for England. Dept. Health, 2003[40]
- Standards for solid organ transplantation in the UK. British Transplantation Society, 2003. [41]

3.3. Description of technology under assessment

3.3.1. Summary of intervention

It is necessary to preserve kidneys prior to transplantation in order to allow time for matching the kidney to the recipient, transportation and preparation of the recipient and the kidney, and implantation of the kidney. However, as noted above in section 3.1. ischaemia, particularly warm ischaemia, causes deterioration of the graft.

Therefore it is important to cool the core of the kidney quickly and flush and perfuse the kidney with solutions which preserve as much of the organ's function as possible. There are two established methods for cold storage of kidneys; cold static storage or hypothermic machine perfusion.

3.3.1.1. Cold storage

In cold static storage, the kidney is flushed through with a preservation solution, and kept on ice. Two preservation solutions are widely used in the NHS for cold storage; Marshall's hypertonic citrate, (Soltran™, Baxter Healthcare) and University of Wisconsin (ViaSpan™,Bristol Myers Squibb). Other cold storage solutions used in other health systems are; Celsior™ (Genzyme), Histidine-tryptophan-ketoglutarate (HTK, Custodiol) and EuroCollins (Fresenius). The characteristics of these solutions can be seen in Table 6. Preservation solutions used in cold static storage are different from those used in machine perfusion.

Three cold storage solutions will be considered in this assessment. These are Viaspan, Soltran and Celsior; the first two have been selected because they are in current NHS use, additionally Celsior will be included because it has been relatively newly developed and may become used in the UK.

The other cold storage solutions will not be considered because they are outside the scope for this assessment.

The benefits of simple cold storage are; that it is not labour intensive, organ exchange is easy and there are no additional risks of damaging the kidney.

Table 6 Composition of cold storage preservation solutions

Solution	Cations[a]	Buffer	Osmotic agents	Other constituents	Osmolality (Osm/l)	pH
ViaSpan	High K^+; low Na^+, Mg^{2+}	Phosphate	actobinate, raffinose	Glutathione,[I] allopurinol,[I] adenosine, insulin dexamethasone	320	7.4
Marshall's (Soltran)	Medium K^+, Na^+, Mg^{2+}	Sulphate, citrate	Mannitol		400	7.1
HTK	Low K^+, Na^+, Mg^{2+}, Ca^{2+}	Histidine	Mannitol	Cl-, tryptophan,[II] ketoglutarate[III]	310	7.2
EuroCollins	High K^+, low Na^+	Bicarbonate	Glucose	Cl-	340	7.3
Celsior	Low K^+, High Na^+, Mg^{2+}, Ca^{2+}	Histidine	Lactobionate, mannitol	Glutathione,[I] glutamate[II]	360	7.3

I antioxidants; II amino acids; III metabolic substrate

[a] Positively charged ions, [b] This maintains the pH balance, [c] To prevent cellular oedema

Source: Saeb-Parsey and colleagues 2007[42]

3.3.1.2. Hypothermic machine perfusion

In hypothermic machine perfusion, core cooling of the kidney is maintained by continuously pumping cold preservation solution through it. This solution also provides nutrients, sometimes oxygen, carries away toxic metabolites and provides 'buffering' (reducing build up of lactic acid). In theory this process should reduce the damage associated with cold ischaemic time. Machine perfusion can be used to preserve grafts from both BSD and DCD donors. However, in the UK they are predominantly used for DCD donors or kidneys with an anticipated long ischaemic time. It is suggested that assessments carried out during machine perfusion may also provide information about the viability of kidneys for transplantation which would aid the selection of grafts.[43] Up to 10% of kidneys from DCD donors never function after transplantation, predominantly those from uncontrolled donors. [9]

The disadvantages of machine perfusion are that it is more labour intensive, less practical in organ exchange and potentially risks damage to the renal artery.

Two commercially available machine perfusion systems have been identified: the LifePort Kidney Transporter (Organ Recovery Systems), a portable system which can perfuse one kidney and can run without being overseen. The other machine is the Waters' RM3 Renal Preservation System (Waters Medical Systems); this non-portable system can perfuse two kidneys simultaneously but needs to have its running supervised. It is not intended to be transportable between hospitals and is not used in the UK. A perfusion solution with a formula developed at the University of Wisconsin is used with machine perfusion (sometimes known as University of Wisconsin machine preservation solution or Belzer MPS; it is sold under the brand name KPS-1 by Organ Recovery Systems for use with their machine).

Two other hypothermic perfusion machines have been identified in development; these are TRANSren (Organ Assist, www.organ-assist.nl) and Airdrive (Indes, www.indes.eu). TRANSren research has only taken place in animals, similarly the Airdrive disposable perfusion system has only had research conducted in animals and in the human liver. Therefore, due to the lack of comparative human kidney studies, these devices will not be included in this assessment.

3.3.2. Current usage in the NHS

Machine perfusion has been used to help preserve donated kidneys since the 1970s in the NHS. However, the practice was overtaken by the successful development of cold static storage which offered a simpler, cheaper, effective alternative for maintaining and transporting kidneys. However, as the numbers of BSD donors decreased and kidneys were increasingly sought from extended criteria donors and DCD donors, interest in machine perfusion returned.

Currently there are 21 kidney transplant centres in England and Wales, eight of which use machine perfusion (all LifePort) as well as cold storage.

At present kidneys from DCD donors are only used for patients in the local transplant region, and are not shared through the national allocation system. However, this situation is likely to change with the implementation of the UK Organ Donation Taskforce's recommendations in their report 'Organs for Transplants'.[44] An effect of their recommendation that a UK wide network of dedicated organ retrieval teams be

set up for all BSD and DCD donors, is that this work will be commissioned by UK Transplant, with the result that perfusion machines (if considered to be cost-effective) would be purchased nationally as part of the retrieval service and hence allow a larger pool for tissue typing with fewer DCD kidneys discarded due to lack of a matched recipient.

3.3.3. Anticipated costs associated with intervention

Table 7 below shows the estimated costs associated with Machine Perfusion using the LifePort Kidney Transporter. The actual cost per stored kidney will further depend on estimates of: the estimated lifetime of the technology (before it is superseded); the number of machines in use at transplant centres, and: the number of donated kidneys stored in the machines during any given period.

In our reference case analysis (see cost-effectiveness section), we assume that each NHS transplant unit would have two machines (one per kidney), use them for storing 16 kidneys per year (the current mean number transplanted for those centres with a DCD donor programme), and that the technology will become superseded in 10 years (i.e. new types of machines would replace the LifePort). Combining the annualised initial purchase cost, the annual maintenance cost, and the per kidney preservation liquid/kit costs with these assumptions therefore gives a per stored kidney estimated cost with LifePort of £737 (see cost-effectiveness section for detailed calculation). It should be noted that this estimate is based upon the current numbers of BSD and DCD donor kidneys that are transplanted at transplant centres in England and Wales, and current regulations and logistics for sharing organs (i.e. only DCD donor kidneys are shared within regions). If both DCD and BSD donor kidneys become shared locally, or, alternatively, if a system is introduced for sharing and exchanging perfusion machines between centres, then the per kidney cost of this storage method may well reduce substantially.

Table 7. Cost components of machine perfusion with LifePort Kidney Transporter

Component	Cost	Source
Purchase cost of machine	£10,750	Source: Industry submission (Table 13 in Budget Impact assessment)
Annual cost of maintenance contract	£874	Personal communication with a transplant unit (US$1750 per machine – converted using March 2008 sterling exchange rate 2.0032, ONS 2008)
Preservation liquid and perfusion kit per kidney stored	£475	Source: Industry submission (Table 13 in Budget Impact assessment)

Table 8 below shows the estimated main costs associated with storing kidneys in cold storage solution. The actual cost per stored kidney will further depend on estimates of: the number of uses (kidneys) of each storage box before disposal or contamination, and the number litres of fluid used in flushing and then storing each kidney.

Data from UK Transplant, which supplies the storage boxes and other accessories to transplant units, suggests that each box gets used on average only 1½ times before becoming too contaminated or damaged to be used again. Different transplant surgeons estimate different quantities of solutions used per stored kidney, although our analysis and another UK study have assumed two litres per stored kidney.[45] Enough solution is required in order to both flush the organ and then to store it.

Table 8. Cost components of cold static storage of kidneys

Component	Cost	Source
Cost of each storage box (with satchel)	£45.80	Cost data supplied by UK Transplant
Cost of each storage box (without satchel, with refill pack)	£20	Cost data supplied by UK Transplant
Cost per litre of Viaspan	£116	Supplied by Bristol Myers Squibb (cost per pack of six 1-litre bags = £696)
Cost per litre of Marshall's Soltran	£9.60	Baxter's web-based catalogue

4. Definition of the decision problem

4.1. Decision problem

4.1.1. Interventions

We are considering two methods of storing deceased donated kidneys; pulsatile, hypothermic machine perfusion and cold static storage solutions. Two perfusion machines have been identified; Organ Recovery Systems' LifePort Kidney Transporter and the Waters Medical Systems' RM3 Renal Preservation System. These are described in the Background section of 3.3. The cold storage solutions under review are University of Wisconsin (Viaspan, Bristol Myers Squibb), Marshall's hypertonic citrate (Soltran, Baxter Healthcare) and Celsior (Genzyme). The characteristics of these solutions are described in the Background section, Table 6.

4.1.2. Populations including sub-groups

The population being assessed are recipients of kidneys from deceased donors (BSD, DCD or ECD). Where the data allows we will consider these types of donors as subgroups.

4.1.3. Relevant comparators

Each intervention is to be compared with the others as data permits.

4.1.4. Outcomes

The outcomes to be included in this report are:

Discard rates of non-viable kidneys

Delayed graft function (incidence and duration): DGF is defined as the need for dialysis in the first seven days following transplantation.[a]

[a] This may also be a measure of the time, post-transplantation, during which dialysis is required until the kidney starts functioning.

Primary non-function (incidence): PNF is defined as the state of a graft that has never functioned post-transplant.

Graft rejection rates: The number of times kidney grafts are rejected by the recipients' body.

Graft function: This will be measured by:

- Glomerular filtration rate (GFR): this is a measure of the kidneys' ability to filter and remove waste products.
- Serum creatinine concentration: Creatinine is a waste product of protein metabolism. Abnormally high concentrations may indicate kidney failure.
- Urinary output: this is normally about 1.5 litres over 24 hours, this rate decreases in the event of kidney failure.

Patient survival

Graft survival

Health-related quality of life

Cost-effectiveness

4.1.5. Key issues

A number of factors may influence the survival and function of a donated kidney and the survival of the recipient.

The viability of the kidney may depend on the type of donor; whether they are BSD, DCD or ECD, the age of the donor, whether they had co-morbidities such as diabetes, whether there was a period of warm ischaemia after death and if so how long it lasted, and the length of cold ischaemia. These issues are discussed in more detail in the background 3.1. Furthermore, the age and health of the recipient may affect the success of transplantation.

4.2. Overall aims and objectives

This project will review the evidence for the effectiveness and cost-effectiveness of different ways of storing kidneys from deceased donors prior to transplantation. This will be done by conducting a systematic review of clinical effectiveness studies and a model based economic evaluation of machine perfusion and cold storage. This will include building a new decision analytic model of kidney transplantation outcomes to investigate which storage method is the most cost-effective option.

5. Assessment of clinical effectiveness

5.1. Methods for reviewing effectiveness

The clinical effectiveness of methods for the storage of donated kidneys was assessed by a systematic review of research evidence. The review was undertaken following the principles published by the NHS Centre for Reviews and Dissemination. [46]

5.1.1. Identification of studies

Electronic databases were searched for systematic reviews and/or meta-analyses, randomised controlled trials (RCT) and other designs (see Section 5.1.2.1), and ongoing research in January 2008 and updated in May 2008. The updated search revealed no new studies that met our inclusion criteria. Appendix 1 shows the databases searched and the strategies in full. These included; Cochrane Library, Medline, EMBASE, CINHAL, ISI Web of Knowledge, DARE, NRR, ReFeR, Current Controlled Trials and (NHS) HTA. Bibliographies of articles were also searched for further relevant studies, and the Food and Drugs Administration (FDA) and European Regulatory Agency Medical Device Safety Service websites were searched for relevant material. Due to resource limitations the search was restricted to English language papers only.

Relevant studies were identified in two stages. Titles and abstracts returned by the search strategy were examined independently by two researchers (MB and TM) and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained. Two researchers (MB and AZ) examined these independently for inclusion or exclusion, and disagreements were again resolved by discussion. The process is illustrated by the flow chart in Appendix 2.

5.1.2. Inclusion and exclusion criteria

5.1.2.1. Study design

Inclusion

For the review of clinical effectiveness, systematic reviews of randomised controlled trials (RCTs), RCTs, quasi-experimental studies (where allocation to intervention or control group is determined by the investigator but without randomisation or allocation concealment), retrospective registry/hospital record designs and unpublished ongoing trials were considered.

Where only the abstract or a poster of a study had been published, it was included if there was sufficient information for quality assessment. Where this was the case these abstract/poster only studies are reported separately as they are unlikely to have undergone a full peer-review process.

Exclusion

Reports published only as abstracts or posters where insufficient details of methods are reported to allow critical appraisal of study quality.

5.1.2.2. Interventions and comparators

Each intervention will be compared with all the others, data permitting.

Two methods of cold storing kidneys are being considered; hypothermic machine perfusion and cold static storage solutions. Both these technologies are being reviewed from the perspective of the UK NHS and so we only consider those specific products that are either in current use or are likely to be available and comparable to those currently used. We will not be looking at studies of kidney storage technologies that predate current technologies and have been shown to be technically inferior or are not available in the UK.

Machine perfusion interventions:

- LifePort Kidney Transporter (Organ Recovery Systems)
- RM3 Kidney Preservation System (Waters Medical Systems).

Cold storage solutions:

- University of Wisconsin (ViaSpan, Bristol Myers Squibb)
- Marshall's (Soltran, Baxter Healthcare)
- Celsior (Genzyme).

For more details of the processes of machine perfusion and cold storage see the Background 3.3.

5.1.2.3. Population

The population being assessed are recipients of transplanted kidneys from deceased donors. These can be either:

Brain stem dead: death is diagnosed by absence of any brain stem activity, although, their hearts are still beating.

Donated after Cardiac death: death is diagnosed by cessation of the heart beat. They can be further sub-divided into those whose cardiac arrest occurred in a controlled or uncontrolled setting.

Extended criteria donors: these are less than optimal BSD donors, either due to their age (>60 years) or over 50 years with serious co-morbidities e.g. diabetes or hypertension.

More details of the characteristics of the population can be found in the background 3.1.1.

5.1.2.4. Outcomes

The outcomes of interest include:

- Discard rates of non-viable kidneys post-storage
- Incidence delayed graft function
- Incidence of primary non-function
- Patient survival

- Graft survival
- Graft rejection rates
- Graft function measured by creatinine concentrations and glomerular filtration rate
- Adverse events

These outcomes are more fully described in Section 4.1.4 of the Decision Problem.

5.1.3. Data extraction strategy

Data were extracted by MB and checked by ZL. Disagreements were resolved by discussion. Data extraction forms of included studies are available in a separate pdf document: All DX forms.pdf.

5.1.4. Critical appraisal strategy

Assessments of study quality were performed using the indicators shown below. Results were tabulated and these aspects described in Table 12 below and the data extraction forms.

5.1.4.1. Internal validity

Consideration of internal validity addressed:

1. Sample size:
(a) Power calculation at design – for RCTs

2. Selection bias:
(a) Explicit eligibility criteria
(b) Proper randomisation and allocation concealment- for RCTs
(c) Similarity of groups at baseline

3. Performance bias:
(a) Similarity of treatment other than the intervention across groups.

4. Attrition bias and intention-to-treat (ITT) analysis:
(a) All kidneys are accounted for

(b) Number of withdrawals specified and reasons described

(c) Analysis undertaken on an ITT basis

5. Detection bias:

(a) Blinding

(b) Objective outcome measures

6. Appropriate data analysis

5.1.4.2. External validity

External validity was judged according to the ability of a reader to consider the applicability of findings to a patient group and service setting. Study findings can only be generalisable if they describe a cohort that is representative of the affected population at large. Studies that appeared representative of the UK kidney transplant population with regard to these considerations were judged to be externally valid.

5.1.5. Methods of data synthesis

Where data permitted, the results of individual trials were pooled using fixed or random effects meta-analysis. The analyses were carried out using StatsDirect software. Heterogeneity was explored through consideration of the study populations, methods and interventions and statistical heterogeneity by X^2 and the I^2 statistics.

5.2. Results

5.2.1. Quantity and quality of research available

The systematic search of electronic databases for clinical effectiveness studies produced 2665 titles and abstracts, of which 2529 were judged not to meet our inclusion criteria and were excluded.

5.2.1.1. Number of studies included

One hundred and thirty six full papers were reviewed to see if they met the inclusion criteria. In addition on-going studies were considered. Thirteen articles were found that met the inclusion criteria, leaving 123 exclusions. A flow chart of papers through the review process including reasons for exclusion, and a table of studies excluded at the paper review stage can be found in Appendix 4.

The 13 articles included were: two systematic reviews,[45;47] three full journal published RCTs,[48-50] two ongoing RCTs,[51;52], one cohort study[53] three full journal published retrospective record reviews[54-56] and two retrospective record reviews published as posters and abstracts only.[57;58]

Further examination of the systematic reviews showed that the review conducted by Wight and colleagues 2003[45] did not include any studies that met the inclusion criteria for this systematic review, as at least one comparator in every study was of an older technology and outside the scope of this report. Therefore this systematic review was excluded.

The other systematic review by Costa and colleagues 2007[47] updated Wight and colleagues 2003. They found 10 new studies, one of which, [59] seemed to meet our inclusion criteria. However, upon further examination it was found that there was not sufficient information for critical appraisal; the authors were contacted but little further information was gleaned. Therefore this study and the systematic review it came from were excluded. See Table 9 for a comparison of study type and publication status.

Table 9 Comparison of study design and publication status of included studies

Design	Full publication	Unpublished studies	Abstract or Poster only
Systematic review	Costa et al.[47] 2007		
RCT	Montalti et al.[48] 2005 Pedotti et al.[49] 2004 Faenza et al.[50] 2001	Moers et al.[60] Watson et al.[51]	
Cohort study	Plata-Munoz et al.[53] 2008		
Retrospective record review	Opelz & Dohler[55] 2007 Moustafellos et al.[54] 2007 Marcen et al.[56] 2005		Guarrera et al.[57] 2007 Kazimi et al.[58] 2007

Upon further examination of the papers it emerged that in one of the trials [52] cold storage using both ViaSpan and HTK cold storage solutions was allowed. However, the data were not disaggregated, making analysis of the ViaSpan results alone impossible. We therefore conducted further searches for studies comparing HTK with our interventions and found 10 studies. One of these was a RCT comparing ViaSpan and HTK [61]. This showed that the solutions were broadly equivalent in terms of kidney graft and patient outcomes with BSD donated kidneys. The other papers found did not fill in any evidence gaps in our study comparisons table, so we decided to exclude them, but allow papers that used a combination of ViaSpan and HTK for cold storage as we considered them to be comparable. Table 10 shows a matrix of the comparisons of interest in this assessment; shaded cells illustrate which comparators were investigated.

Table 10 Matrix of comparisons of interest showing included studies

Study	LifePort	RM3	ViaSpan	Marshall's Soltran	Celsior
Watson et al.					
Moers et al. 2008					
Moustafellos et al. 2007					
Plata-Munoz et al. 2008					
Guarrera et al. 2007					
Kazimi et al. 2007					
Opelz & Dohler 2007					
Montalti et al. 2005					
Pedotti et al. 2004					
Faenza et al. 2001					
Marcen et al. 2005					

5.2.1.2. Summary table of included studies' characteristics

Table 11 below, contains a summary of the key design characteristics of the included studies. Data extraction tables for each study can be found in the separate pdf document: All DX forms.pdf.

A summary of assessment of the quality of our included studies can be found in Table 12.

Table 11 Summary characteristics of included studies

Study	Design (N kidneys)	Participants (inclusion criteria)	Intervention	Comparator	Outcomes (length of follow-up)
Watson et al. 2008 **UK (ongoing)** Funded by: Novartis Pharma and Organ Recovery Systems	RCT ([redacted])	Donors: DCD, [redacted] Recipients: [redacted]	Machine Perfusion: LifePort N = 45	Cold storage: ViaSpan N = 45	DGF, patient survival, graft survival, GFR, PNF, time to last dialysis, total ischaemic time (5 years: only 3 month data available)
Moers et al. 2008 **Netherlands, Belgium, Germany** Funded by: Organ Recovery Systems	RCT ([redacted])	Donors: DCD (Maastricht categories III & IV) and BSD ≥ 16 yrs Recipients: not multiple organ transplant, only one kidney received	Machine Perfusion: LifePort N = [redacted]	Cold storage: ViaSpan N = [redacted]	DGF, patient survival, graft survival, acute rejection, creatinine concentrations, duration of hospital stay, PNF, panel reactive antibodies (1 year)
Plata-Munoz et al. 2008	Cohort (60)	Donors: DCD (Maastricht category III) Recipients: criteria not reported	Machine Perfusion: LifePort N = 30	Cold storage: Marshall's N = 30	DGF, IGF, PNF, acute rejection, duration of hospital stay, graft function, graft survival and patient survival. (I year)
Moustafellos et al. 2007	Hospital record review (36)	Donors: DCD (Maastricht categories III & IV) Recipients: criteria not reported	Machine Perfusion: LifePort N = 18	Cold storage: ViaSpan N = 18	Immediate renal function, DGF, creatinine concentrations, duration of hospital stay, graft rejection Data collected between 2004 -2006 (in-patient stay)
Opelz & Dohler 2007 Europe, N. America, Australia	Registry (58607)	Donors: deceased Recipients: criteria not reported	Cold storage: ViaSpan N = 53560	Cold storage: Marshall's N = 5047	Graft survival, death censored functional survival Data collected between 1990 -2005 (3 years)
Montalti et al. 2005 Italy	RCT (60)	Donors: deceased Recipients: criteria not reported	Cold storage: ViaSpan N = 25	Cold storage: Celsior N = 25	DGF, urinary output, creatinine concentrations (5 years)

Study	Design (N kidneys)	Participants (inclusion criteria)	Intervention	Comparator	Outcomes (length of follow-up)
Marcen et al. 2005 Spain	Hospital record review (177)	Donors: BSD Recipients: criteria not reported	Cold storage: ViaSpan N = 138	Cold storage: Celsior N = 39	DGF, PNF, creatinine concentrations, graft survival, acute rejection, graft rejection. Data collected between Jan 1997 – Oct 2001 (12 months)
Pedotti et al. 2004 Italy	RCT (441)	Donors: deceased multi-organ Recipients: criteria not reported	Cold storage: ViaSpan N = 269	Cold storage: Celsior N = 172	Patient survival, graft survival, creatinine concentrations, urinary output. (12 months)
Faenza et al. 2001 Italy	RCT (187)	Donors: deceased > 15 yrs, Multiple-organ Recipients: > 15 yrs, not previously had a transplant	Cold storage: ViaSpan N = 88	Cold storage: Celsior N = 99	DGF, creatinine concentrations, urinary output, post-transplant dialysis, graft survival, graft rejection, HLA mismatches, ischaemic time. (2 years)
Guarrera et al. 2007 USA	Hospital record review (774)	Donors: ECD: > 60 yrs or 50 – 59 + hypertension, diabetes > 5 yrs DCD: any Other: Prolonged ischaemic time, creatinine concentrations that doubled from admission to final, disseminated intravascular coagulopathy Recipients: criteria not reported	Machine perfusion: RM3 N = 378	Machine perfusion: LifePort N = 396	DGF, patient survival, graft survival, PNF, graft function, creatinine concentrations, ischaemic time, renal resistance, transplanted > 60 yrs Data collected between Dec 2001 – Sep 2006 (1 year)
Kazimi et al. 2007 USA	Hospital record review (89)	Donors: deceased, either kidney, kidney & pancreas or kidney & liver Recipients: criteria not reported	Machine perfusion: RM3 N = 37	Machine perfusion: LifePort N = 52	Graft survival, incidence of post-transplant dialysis, creatinine concentrations, duration of hospital stay Data collected between Feb 2005 – Nov 2006 (90 days)

Studies published as posters or abstracts only are shaded grey – limited data available

Abbreviations: DCD = donated after cardiac death, DGF = delayed graft function, GFR = glomerular filtration rate, PNF = primary non function, BSD = brain stem dead, IGF = immediate graft function, ECD = extended criteria donor.

The Maastricht categories are specified in Section 3.1

Table 12 Summary of key quality indicators of included studies

Quality indicator	Watson et al. 2008	Moers et al. 2008	Plata-Munoz et al. 2008	Moustafellos et al. 2007	Opelz & Dohler 2007	Montalti et al. 2005	Marcen et al. 2005	Pedotti et al. 2004	Faenza et al. 2001	Guarrera et al. 2007	Kazimi et al. 2007
Prospective	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No
Appropriate eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Representative population	DCD	BSD & DCD III & IV	DCD III	DCD III & IV	Yes	ECD	BSD	Yes	Yes	ECD	Yes
Power calculation	Yes	Yes	NA	NA	NA	Not reported	NA	Not reported	Not reported	NA	NA
Randomisation	Yes	Yes	NA	NA	NA	Yes	NA	Yes	Yes	NA	NA
Allocation concealment	Yes	Yes	No	NA	NA	NA	NA	No	Not reported	NA	NA
Groups similar at baseline	Yes	Yes	MP younger than CS	No	Unclear	Yes	No	Yes	Yes	Yes	No
ITT analysis	Yes	No	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Attrition reported	Yes	Yes	NA	NA	NA	No	NA	No	Yes	NA	NA
All participants accounted for	Yes	Yes	Yes	NA	NA	Yes	NA	Yes	Yes	NA	NA
Generalisable	Yes to DCD	Yes	Yes to DCD III	No	Yes	Partial to ECD	Partial to BSD	Yes	Yes	Partial to ECD	No

Studies published as posters or abstracts only are shaded grey – limited data available Abbreviations: DCD = donation after cardiac death, BSD = brain stem dead, III & IV this refers to the Maastricht criteria for DCD donors Background section 3.1, ECD extended criteria donor

5.3. Assessment of effectiveness

The systematic review of clinical effectiveness will report the comparisons of interest in the following order:

- Machine perfusion systems vs. Cold storage solutions
- Machine perfusion systems vs. Machine perfusion systems
- Cold storage solutions vs. Cold storage solutions

Data extraction tables for included studies can be found the separate pdf document: All DX forms.pdf.

5.3.1. Machine perfusion systems vs. Cold storage solutions

Four studies compared machine perfusion with cold storage solutions; three contrasted the LifePort Kidney Transporter (further referred to as LifePort) with the ViaSpan solution and one compared LifePort with Marshall's Soltran.

LifePort vs. ViaSpan

Of the three studies comparing LifePort with ViaSpan one is an ongoing RCT (Watson and colleagues),[51], one RCT has not completed economic data analysis (Moers and colleagues),[52], and the other is a retrospective review of hospital records.[54]

ACADEMIC IN CONFIDENCE

Watson and colleagues (2008)51 UK, N = [redacted] (kidneys), conducted a well designed, UK, [redacted] RCT that is still ongoing (the 'PPART trial'). At the time of the submission of this report only the 3 month outcome data were available, although the trial will be reporting outcomes up to five years post-transplant. Watson and colleagues randomised 45 pairs of kidneys from DCD donors to 90 adult recipients (LifePort = 45, ViaSpan = 45). [redacted] patients did not receive kidneys due to anatomical abnormalities [redacted]. No kidneys were discarded post-storage and prior to transplant. There were [redacted] baseline characteristics of the treatment groups i.e.kidney recipients. However, it should be noted that

[redacted]

[redacted]

The results were analysed by intention-to-treat (ITT). At three months post-transplant there were no significant differences on any of the outcomes measured (DGF, patient survival, graft survival, PNF, dialysis requirement within 7 days excluding day 1, glomerular filtration rate, [redacted], total ischaemic time (ViaSpan =15h12m SD (4h45m), LifePort =14h55m SD (4h27m)) [redacted]. However, as [redacted] any differences in treatment effect between the two trial arms. The authors do not present data on the sub-group of kidneys that were treated [redacted]. However, due to the very small sample size this would be unlikely to show any differences in treatment effect between the two sub-groups. This [redacted] may partly explain the absence of significantly different results between the groups. It is not possible to say whether these results show anything about the comparative effects of mode of storage. See Table 13 for main results.

COMMERCIAL IN CONFIDENCE

Moers and colleagues (2008),[52], Germany, Netherlands and Belgium, N = [redacted] (kidneys), conducted a good quality European multi-centre RCT (The Machine Preservation Trial). This good quality study randomised [redacted] kidneys from DCD and BSD (Maastricht criteria III & IV) donors to LifePort (n = [redacted]) or ViaSpan or HTK (n = [redacted]). Immediately post-randomisation, [redacted] kidneys were excluded. Randomisation allocation was kept for [redacted] kidneys and broken for [redacted]; this was only permitted when the anatomy of the kidney made machine perfusion unsuitable. Subsequently [redacted] kidneys were discarded post-storage and prior to transplant for a variety of reasons (if a kidney was excluded from one arm then it's contralateral pair was excluded from the other arm) (LifePort = [redacted], ViaSpan = [redacted] and [redacted] excluded post-transplant (LifePort =[redacted]), ViaSpan = [redacted]). This left [redacted] kidneys for data analysis (BSD = [redacted], DCD = [redacted]), LifePort N = [redacted], ViaSpan N = [redacted]. In total [redacted] kidneys were excluded post-randomisation. Recipients who died in the first week [redacted]. See Appendix 5 for details of reasons for exclusions.

Recipients were [redacted] who were followed up for one year. There were [redacted] baseline characteristics

including [redacted]. Results were reported at six and 12 months. Analysis was not by ITT.

The results showed that for the primary end point of DGF [redacted].

The secondary end point of duration of DGF showed that [redacted]. Another measure, [redacted] was added post hoc and not specified in the trial protocol; this outcome showed [redacted]. Other secondary outcome measures showed [redacted].

At six months post-transplant there were [redacted]. Similarly at 12 months post-transplant patient survival was [redacted].

Graft survival at six months [redacted] However, the LifePort group [redacted] graft survival at 12 months post-transplant [redacted].

When the results were censored for death at 12 months, Moers and colleagues found that for grafts that had been subject to DGF, [redacted]. There were [redacted] death censored survival of grafts that had not had DGF. Main results can be found in Table 13.

Moers and Colleagues carried out sub-group analyses for DGF. In order to carry this analysis out further DCD participants were enrolled (N=[redacted]). They found [redacted].

Moustafellos and colleagues (2007)[54] UK, N = 36 (kidneys), reviewed the previous three years records of patients receiving a DCD kidney (Maastricht class III or IV) at the

Oxford Transplant Unit. They found that 18 people had received kidneys preserved by a LifePort machine and 18 by ViaSpan in cold storage. The two groups received different induction therapies and the mean age of the ViaSpan transplant recipients was older by 18 years (LifePort = 36 years, ViaSpan = 54.5 years, p< 0.001). The groups also varied in length of cold ischaemia (LifePort = mean 15 hrs, ViaSpan = mean 17 hrs; DM -1.5 hrs, P< 0.001). These differences in group characteristics and the potential for bias introduced by lack of randomisation mean that the results of this study must be interpreted with great caution.

Moustafellos and colleagues found that on their primary outcome measure of immediate renal function, kidneys stored by machine perfusion were more likely to work straight away than those cold stored (LifePort = 13/18, ViaSpan = 2/18; RR 6.5, 95%CI 1.71, 24.77; p< 0.001). Their secondary outcome measures were similarly significant: DGF (LifePort = 5/18, ViaSpan = 16/18; RR 0.31, 95%CI 0.15, 0.67; p< 0.001); length of hospitalisation (LifePort = mean 8 days, ViaSpan = mean 14 days; difference in means (DM) -6, 95%CI -7.66, -4.34; p< 0.001); and creatinine concentrations at discharge (DM -118 µmol/L, p< 0.001), all favouring machine perfusion.

A table of the principal outcomes can be seen below in Table 13.

Table 13 Main results of studies comparing LifePort machine with ViaSpan solution

Outcome	Study (follow up)	Donor Population	LifePort n/N (%)	ViaSpan n/N (%)	Effect	95% CI	p	Comment
DGF	Watson et al. 2008 RCT	DCD	26/45 (58)	25/45 (56)	RR 1.04	0.73, 1.49	ns	McNemar's exact test
	Moers et al. 2008 RCT	BSD & DCD	[redacted]	[redacted]			[redacted]	McNemar's exact test
	Moustafellos et al. 2007 record review	DCD	5/18 (28)	16/18 (89)	RR 0.31	0.15, 0.67	<0.001	
PNF	Watson et al. 2008 RCT	DCD	1/45 (2)	0/45 (0)	RR 3.00	0.13, 71.74	ns	
	Moers et al. 2008 RCT	BSD & DCD	[redacted]	[redacted]			[redacted]	
Acute rejection	Watson et al. 2008 RCT (3 months)	DCD	[redacted]	[redacted]			[redacted]	McNemar's exact test
	Moers et al. 2008 RCT (6 months)	BSD & DCD	[redacted]	[redacted]			[redacted]	
	Moustafellos et al. 2007 record review (till discharge)	DCD	0/18	0/18				
Kidneys rejected post-storage/pre-transplant	Watson et al. 2008 RCT (3 months)	DCD	0/45	0/45				McNemar's exact test
	Moers et al. 2008 RCT (6 months)	BSD & DCD	[redacted]	[redacted]				

Outcome	Study (follow up)	Donor Population	LifePort n/N (%)	ViaSpan n/N (%)	Effect	95% CI	p	Comment
Patient survival	Watson et al. 2008 RCT (3 months)	DCD	44/45 (98)	45/45 (100)	RR 0.98	0.92, 1.04	ns	Log rank
	Moers et al. 2008 RCT (6 months)	BSD & DCD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	(12 months)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Graft survival	Watson et al. 2008 RCT (3 months)	DCD	43/45 (96)	45/45 (100)	RR 0.96	0.89, 1.03	ns	
	Moers et al. 2008[a] RCT (6 months)	BSD & DCD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Log rank
	(12 months)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Log rank
	death censored survival							
	No DGF (12 months)		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Post transplant hospital stay (mean)	Moers et al. 2008 (12 months)	BSD & DCD	[redacted]	[redacted]			[redacted]	McNemar's exact test
Glomerular filtration rate (eGFR)	Watson et al. 2008 RCT (3 months)	DCD	46.0 ml/min/1.73m2 (18.1)	48.9 ml/min/1.73m2 (21.3)			=0.42 ns	Paired t-test

Significance at p >0.05. Abbreviations: DCD = donated after cardiac death, BSD = brain stem dead, RR = relative risk, HR = hazard ratio, ns = not significant

LifePort vs. Marshall's cold storage solution (Soltran)

Plata-Munoz and colleagues (2008) [53] UK, N = 60 (kidneys) conducted a sequential cohort study of DCD Maastricht category III controlled donor kidneys (March 2002 – December 2005). For the first two years of the study all kidneys were cold stored using Marshall's solution (N = 30); subsequently all kidneys were stored using the LifePort machine perfusion system (N = 30).

They found that the baseline characteristics of the groups were similar apart from mean recipient age (LifePort group = 47 years [range 20-69], Marshall's = 54 years [range 34-76], $p < 0.01$). Also, the mean CIT was slightly greater for kidneys stored by LifePort (LifePort group = mean 19 hrs (15-23), Marshall's = mean 18 hrs (14-22). Clinical outcomes showed a lower proportion of DGF in the LifePort group (RR 0.64, 95% CI 0.43, 0.89, $p < 0.05$) as well as length of hospital stay (LifePort = 10 days, Marshall's = 14 days, $p < 0.05$). Graft function (serum creatinine) was better at six and 12 months for kidneys stored in the LifePort machine (6 months, DM -38.00 µmol/L 95% CI -46.32, -29.68, $p<0.001$ and 12 months, DM -39.00 µmol/L 95% CI -48.51, -29.49, $p<0.001$). Rates of acute rejection were low for both interventions (LifePort = 4/30 (13%), Marshall's = 2/30 (7%). However, there were no significant differences between groups in patient or graft survival after one or two years. See Table 14.

Table 14 Results of the study comparing LifePort machine perfusion to Marshall's cold storage solution (Plata-Munoz)

Outcome	LifePort n/N (%)	Marshall's n/N (%)	Effect	95% CI	P	Comment
DGF	16/30 (53)	26/30 (87)	RR 0.64	0.43, 0.93	0.012	PenTAG calculation
Length of hospitalisation (days)	10 days	14 days			= 0.03	Plata-Munoz Fisher exact test
Graft function (6 months) µmol/L	163 ± 10	201 ± 21	DM -38	-46.32, -29.68	0.001	PenTAG calculation
Graft function (12 months) µmol/L	154 ± 9	193 ± 25	DM -39	-48.51, -29.49	0.001	PenTAG calculation
Patient survival (1 year)	30/30 (100)	28/30 (93)	RR 1.07	0.96, 1.20	ns	PenTAG calculation
Patient survival (2 years)	29/30 (97)	27/30 (90)	RR 1.07	0.94, 1.23	ns	PenTAG calculation
Graft survival (1 year)	30/30 (100)	28/30 (93)	RR 1.07	0.96, 1.20	ns	PenTAG calculation
Graft survival (2 years)	29/30 (97)	27/30 (90)	RR 1.07	0.94, 1.23	ns	PenTAG calculation

Abbreviations: RR = relative risk, ns = not significant, DM = difference in means, ± it is not reported what this means

5.3.1.1. Summary of machine perfusion vs. cold storage solutions

Four studies compared machine perfusion with cold storage; two were RCTs, one was a prospective cohort study and one was a hospital record reviews. Although the PPART trial had a strong design it's results were [redacted].

The donor populations for the two RCTs were different; with DCD donors in the Watson and colleagues trial and mostly BSD (with some DCD) donors in the Moers and colleagues study. The overall rate of DGF in the Moers and colleagues trial was [redacted] Watson and colleagues ([redacted]57% respectively); this may have been due to the difference in DGF between DCD and BSD donated kidneys and [redacted]. However, Watson and colleagues found less DGF with ViaSpan (LifePort=58%, ViaSpan=56%) and Moers and colleagues found [redacted].

Overall, there were [redacted] Moers and colleagues found that [redacted] 12 months post-transplant [redacted]. Only three months follow up data were available from Watson and colleagues who found that there was no significant difference in graft survival at this time, perhaps unsurprisingly [redacted]. These two studies' results are in recipients whose grafts had a mean CIT of approximately [redacted]. It is not possible to say from this data what the effects of longer follow-up or greater CIT may have on the results.

Moers and Colleagues carried out sub-group analyses for DGF. They found [redacted].

In contrast, the results from the smaller cohort (Plata-Munoz and colleagues) and record review (Moustafellos and colleagues) studies found significant differences for DGF, length of hospital stay, and graft failure at six and twelve months favouring LifePort over ViaSpan and Marshall's Soltran. Plata-Munoz and colleagues also reported patient graft survival outcomes at one and two years but found no significant differences between groups. As these non-RCT results may have been influenced by selection bias and other

confounding factors, they cannot be considered as internally valid as those from the two RCTs.

Where post-storage, pre-transplant discard rates were reported, these were [redacted]

5.3.2. Machine perfusion systems vs. Machine perfusion systems

Two studies compared the LifePort Kidney Transporter to the RM3 Kidney Preservation System. Both these studies were record reviews and had only reported their findings as abstracts and posters at the time of the submission of this report. See Table 12. Furthermore, these studies were not randomised and their findings have not been subject to a peer review process; therefore, their results should be viewed with caution.

ABSTRACT AND POSTER ONLY

Guarrera and colleagues (2007)[57] USA, N = 774 (kidneys) reviewed their transplant centre's records over approximately 5 years (12/2001 to 9/2006). The RM3 (N=378) was used from the beginning of the study until March 2004 when it was replaced by the LifePort machine (N=396). The same criteria for referring kidneys to machine perfusion were used throughout this time. The donor population were either ECD (78%) (including those > 60 years, > 50 years with hypertension, having diabetes for > 5 years)[a]; or DCD (22%). More DCD donors were used with the LifePort machine than the RM3 (RM3 = 75 (20%), LifePort = 96 (25%), ns). Following machine perfusion 190 kidneys were discarded (RM3 = 98 (28%), LifePort = 91(23%), ns). Cold ischaemic time was similar for both groups (RM3 = mean 23 hrs, LifePort = mean 24 hrs).

Guarrera and colleagues found that the DGF rate was lower when the RM3 was used (RM3 = 90/378 (31%), LifePort = 162/396 (41%), p = 0.025; our calculations gave this a relative risk of RR 0.76, 95% CI 0.62, 0.94, p < 0.01. Guarrera and colleagues also found that graft function at one year was better with the RM3 (RM3 = 347/378 (91%), LifePort = 367/396 (93%), p = 0.05. Our calculations gave a relative risk of RR 1.07, 95% CI 1.02, 1.13, p < 0.01. They found no significant difference for patient survival or graft survival (same results) at one year (RM3 = 366/378 (97%), LifePort = 367/396 (93%)). However, our analysis showed that patients with kidneys stored by the RM3 machine were more likely to survive, and have their grafts survive, their first year post-transplant: RR = 1.05,

[a] This definition of ECD varies from that generally used and given in Section 2.1 of the Background.

95% CI 1.01, 1.08, p < 0.01. There were no significant differences in the rate of PNF (RM3 = 11/378 (3%), LifePort = 8/396 (2%). Guarrera and colleagues used t-tests and Chi squared tests to analyse their data, we used Chi squared tests. It is therefore unclear why in a number of cases we have come to different conclusions about the statistical significance of these results. Thus, Guarrera and colleagues found that kidneys stored with the RM3 machine had less DGF, better graft function at 1 year and better 1 year patient and graft survival than those stored with LifePort. See Table 15.

ABSTRACT AND POSTER ONLY

Kazimi and colleagues (2007)[58] USA, N = 89 (kidneys) retrospectively reviewed the kidney transplant records at their transplant centre over a 22 month period (Feb 2005 – Nov 2006). They included multi-organ as well as kidney alone transplants and compared the use of the RM3 to the LifePort perfusion machine. It is not clear whether the different perfusion machines were used simultaneously at any time although the LifePort was solely used most recently. The baseline characteristics show that there were nearly five times as many kidney/liver transplants from LifePort storage than RM3 which may have confounded the results as these kidneys may have had a longer CIT as the liver is transplanted before the kidney (CIT times were not reported). The donor population were 98% BSD and 2% DCD.

Kazimi and colleagues' results found that people whose grafts had been stored in a LifePort machine stayed in hospital longer (mean days: LifePort = 15, RM3 = 9, p = 0.04). There were no significant differences in: graft survival at 30 days (LifePort = 49/52 (94%), RM3 = 36/37 (97%)) and 90 days (LifePort =37/41 (90%), RM3 = 35/36 (97%)), change in creatinine concentrations at discharge; or the need for post-transplant dialysis. However, as this was a small non-randomised study care should be taken in interpreting the results.

These two studies only have one reported outcome measure in common (graft survival) and although measures were taken at different follow-up times, both studies showed that graft survival was longer with the RM3 (one showing statistical significance). Larger randomised studies comparing these machines are needed to more carefully determine their relative effectiveness.

Outcome	Study (follow up)	Donor Population	RM3 n/N (%)	LifePort n/N (%)	Effect	95% CI	p	Calculation by
DGF	Guarrera et al. 2007 record review	ECD (78%) DCD (22%)	90/378 (24)	125/396 (32)	RR 0.76	0.62, 0.94	0.013 0.025	PenTAG Guarrera et al.
PNF	Guarrera et al. 2007 record review	ECD & DCD	11/378 (3)	8/396 (2)	RR 1.44	0.59, 3.54	ns	PenTAG
Kidneys rejected post-storage/ pre-transplant	Guarrera et al. 2007 record review	ECD & DCD	98/378 (26)	91/396 (23)			ns	Guarrera et al.
Patient survival	Guarrera et al. 2007 record review (1 year)	ECD & DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01, 1.08	0.01 ns	PenTAG Guarrera et al.
Graft Survival	Guarrera et al. 2007 record review (1 year)	ECD & DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01, 1.08	0.01 ns	PenTAG Guarrera et al.
	Kazimi et al. 2007 (30 days)	BSD (98%) DCD (2%)	36/37 (97)	49/52(94)	RR 0.97	0.89, 1.06	ns	PenTAG
	(90 days)		35/36 (97)	37/41(90)	RR 0.93	0.83, 1.04	ns	PenTAG
Graft function 1 year	Guarrera et al. 2007 record review (1 year)	ECD & DCD	347/378 (92)	339/396 (86)	RR 1.07	1.02, 1.13	0.007 0.05	PenTAG Guarrera et al.
Post-transplant Dialysis	Kazimi et al. 2007	BSD (98%)	2/37 (5)	2/52 (4)	RR 0.71	0.11, 4.83	ns	PenTAG
Length of hospitalisation (days)	Kazimi et al. 2007 (90 days)	BSD (98%)	N = 37 mean = 9	N = 52 mean = 15			0.04	Kazimi et al.

Table 15 has a summary of their key results.

Table 15 Results of studies comparing the RM3 Kidney Preservation system to the LifePort Kidney Transporter

Outcome	Study (follow up)	Donor Population	RM3 n/N (%)	LifePort n/N (%)	Effect	95% CI	p	Calculation by
DGF	Guarrera et al. 2007 record review	ECD (78%)	90/378 (24)	125/396 (32)	RR 0.76	0.62, 0.94	0.013	PenTAG
		DCD (22%)					0.025	Guarrera et al.
PNF	Guarrera et al. 2007 record review	ECD & DCD	11/378 (3)	8/396 (2)	RR 1.44	0.59, 3.54	ns	PenTAG
Kidneys rejected post-storage/ pre-transplant	Guarrera et al. 2007 record review	ECD & DCD	98/378 (26)	91/396 (23)			ns	Guarrera et al.
Patient survival	Guarrera et al. 2007 record review (1 year)	ECD & DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01, 1.08	0.01	PenTAG
							ns	Guarrera et al.
Graft Survival	Guarrera et al. 2007 record review (1 year)	ECD & DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01, 1.08	0.01	PenTAG
							ns	Guarrera et al.
	Kazimi et al. 2007 (30 days)	BSD (98%)	36/37 (97)	49/52(94)	RR 0.97	0.89, 1.06	ns	PenTAG
	(90 days)	DCD (2%)	35/36 (97)	37/41(90)	RR 0.93	0.83, 1.04	ns	PenTAG
Graft function 1 year	Guarrera et al. 2007 record review (1 year)	ECD & DCD	347/378 (92)	339/396 (86)	RR 1.07	1.02, 1.13	0.007	PenTAG
							0.05	Guarrera et al.
Post-transplant Dialysis	Kazimi et al. 2007	BSD (98%)	2/37 (5)	2/52 (4)	RR 0.71	0.11, 4.83	ns	PenTAG
Length of hospitalisation (days)	Kazimi et al. 2007 (90 days)	BSD (98%)	N = 37 mean = 9	N = 52 mean = 15			0.04	Kazimi et al.

Abbreviations: ECD = extended criteria donors, DCD = donated after cardiac death, BSD = brain stem dead, RR = relative risk, ns = not significant

Guarrera and colleagues calculations used Chi squared and T-tests, PenTAG calculations used Chi squared tests.

5.3.2.1. Summary of machine perfusion vs. machine perfusion

We only found two studies assessing the comparative effectiveness of the LifePort and RM3 machine perfusion systems (Guarrera and colleagues and Kazimi and colleagues). These were both retrospective hospital record reviews that had not been through a peer-review process and had only been published as abstracts and presented as posters. Therefore, the evidence they present is unproven.

With the exception of PNF, all outcomes favoured the RM3 over the LifePort perfusion machine. Guarrera and colleagues found significant benefits for kidneys stored in the RM3 machine, for ECD and DCD donated kidneys, in terms of DGF, graft function, patient survival and graft survival, all at one year. Guarrera and colleagues calculations did not find these differences to be significant. However, our analysis indicated that the RR 1.05 [95%CI 1.01, 1.08] was significant at $p<0.01$ for patient and graft survival at one year. There were a large number of discarded kidneys following perfusion (25%); this may have been due to the high percentage of ECD (78%).

Kazimi and colleagues' much smaller study, of mostly better quality donor kidneys, found a non-significant gain in graft survival at 30 and 90 days for the RM3. They also found that people whose grafts had been stored in an RM3 had fewer days in hospital (RM3 = 3, LifePort = 15, $p = 0.04$). However, there were no differences in the number of times dialysis was needed post-transplant. Post-storage pre-transplant discard rates were similar (RM3 = 98, LifePort = 91).

Further robust research is needed using RCTs to determine the relative effectiveness of these perfusing machines.

5.3.3. Cold storage solution vs. Cold storage solution

Five studies compared cold storage solutions; one compared ViaSpan with Marshall's solution (a registry data review) and four compared ViaSpan with Celsior (three RCTs and one hospital record review).

ViaSpan vs. Marshall's Soltran

Opelz and Dohler (2007)[55] global, N = 91,674 used the Collaborative Transplant Study database (195 transplant centres in Europe, Australia and North America), to compare different methods of storing kidneys including ViaSpan (n = 53,560) and Marshall's Soltran (n = 5047) on graft survival between 1990 – 2005. We used their data to

compare these solutions at various lengths of cold ischaemia, and found there were no significant differences for graft survival between solutions for different cold ischaemic times. These results can be seen in Table 16.

Oplez and Dohler were more interested in how graft failure rates changed with increasing CIT. They found that graft survival with either solution was similar with a CIT time of < 18 hours (RR =1.02, 95% CI 0.99, 1.04, ns). However, as CIT increased an increasing incidence of graft failure was found for both solutions; with a small increased risk at 19 - 24 hours (ViaSpan: RR1.10, 95%CI 1.05, 1.15, p <0.001, Marshall's: RR1.09, 95% CI 0.95, 1.26, p = 0.23). The rate of graft failure remained the same at 25-36 hours CIT for kidneys stored with ViaSpan but increased for those stored with Marshall's solution, (ViaSpan: RR1.10, 95%CI 1.05, 1.16, p <0.001, Marshall's: RR1.20, 95% CI 1.01, 1.41, p = 0.03). As CIT increased beyond 36 hours, kidneys stored in both solutions had an increased risk of graft failure (ViaSpan: RR1.21, 95%CI 1.09, 1.33, p <0.001, Marshall's: RR1.38, 95% CI 1.07-1.78, p = 0.02).

In summary, the relative risk point estimates favour ViaSpan. However, at all time points ViaSpan does not significantly improve graft survival compared to Marshall's Soltran.

Table 16 Results of Opelz and Dohler's study comparing ViaSpan with Marshall's Soltran cold storage solutions

Outcome	Donor Population	ViaSpan n/N (%)	Marshall's solution n/N (%)	Effect	95% CI	p	Comment
Graft survival 0-18 hrs cold ischaemia (3 years)	Deceased	19,746/24,258 (81)	1782/2225 (80)	RR 1.02	0.10, 1.04	ns	PenTAG calculation
Graft survival 19-24 hrs cold ischaemia (3 years)	Deceased	12756/16147 (79)	1260/1636 (77)	RR 1.03	0.10, 1.05	ns	PenTAG calculation
Graft survival 25-36 hrs cold ischaemia (3 years)	Deceased	8636/11158 (77)	709/944 (75)	RR 1.03	0.99, 1.07	ns	PenTAG calculation
Graft survival > 36 hrs cold ischaemia (3 years)	Deceased	1855/2486 (75)	220/303 (73)	RR 1.03	0.96, 1.11	ns	PenTAG calculation

Abbreviations: RR = relative risk, ns = not significant

ViaSpan vs. Celsior

Of the four studies comparing ViaSpan with Celsior cold storage solution, three were RCTs[48-50] and one a review of hospital records.[56].

Montalti and colleagues (2005)[48] N = 60 (kidneys) conducted a two centre RCT to compare the effectiveness of ViaSpan (N=25) with Celsior (N=25) in kidneys from elderly donors (>60 years). Ten kidneys were discarded following histological examination (ViaSpan = 6, Celsior = 4), it is not clear whether this was before or after storage. There were no significant differences in donor or recipient characteristics including HLA matching and ischaemic time (ViaSpan = 19±6.5 hrs, Celsior = 18±4.5 hrs). Outcome measures included DGF (ViaSpan = 12/25, Celsior = 13/25), graft survival at one and five years, (ViaSpan = 92% and 79%, Celsior = 96% and 87%), the need for post-operative dialysis (ViaSpan: n = 3.1±4.9, Celsior: n = 2.2±3.8) and the number of rejection episodes (ViaSpan = 2/25, Celsior = 2/25), there were no significant differences on any of these measures, indicating that these two solutions are equivalent for kidneys from elderly donors. It was not reported what ± meant.

Pedotti and colleagues (2004)[49] N = 441 (kidneys) carried out a larger multi-centre RCT to compare the effects of storing kidneys from multiple-organ donors with ViaSpan (N=269) or Celsior (N=172) cold storage solutions. The unequal numbers in the groups was not explained. The mean CIT for both groups was 15 hours (ViaSpan = ± 4.8, Celsior =± 4.3). Recipients were followed up for one year. The outcome measures included DGF (ViaSpan = 61/269, Celsior = 40/172), PNF (ViaSpan = 4/269, Celsior = 4/172), patient survival at one month (ViaSpan = 269/269, Celsior = 172/172) and one year (ViaSpan = 263/269, Celsior = 171/172), graft survival at one month (ViaSpan = 245/269, Celsior = 162/172) and one year (ViaSpan = 245/269, Celsior = 162/172), creatinine concentrations (mean range from day 1 to 15: ViaSpan, 671.8 µmol/L to 220.4 µmol/L; Celsior 663.0 µmol/L to 200.8 µmol/L) and urinary output (mean range from day 1 to 15: ViaSpan, 2520 mL/24hrs to 2500 mL/24hrs; Celsior 2180 mL/24hrs to 2600 mL/24hrs). Pedotti and colleagues found no significant differences on any measure. Our analysis showed that day 1 urinary output was significantly greater for people whose kidneys had been stored with ViaSpan. However, this may be unreliable as the standard deviations used were calculated from the ranges given in the paper. It was not reported what ± meant.

Faenza and colleagues (2001)[50] N =187 (kidneys) conducted a multi-centre RCT of adult multiple-organ donor kidneys to assess the effectiveness of Celsior cold storage

solution compared to ViaSpan on DGF and kidney function. Recipients were adults receiving their first transplant. Both groups had a mean CIT of 17 hours (ViaSpan = ± 5.0, Celsior =± 6.6). Thirteen kidneys that had been stored were not transplanted (ViaSpan = 6, Celsior = 7); this was for a variety of histological reasons. Faenza and colleagues found there were no significant differences on any outcome measure: DGF (ViaSpan = 30/80, Celsior = 31/99), Graft survival after 2 years (ViaSpan = 66/80, Celsior = 83/99), graft rejections (ViaSpan = 13/80, Celsior = 12/99) and mean (SD) number of post-operative dialyses (ViaSpan = 1.9 (3.5), Celsior = 1.0 (3.3). Serum creatinine and urinary output were measured in those whose grafts had more than 17 hours of cold ischaemia; measures were taken between day one and discharge. Mean levels on day one and discharge were as follows; creatinine: ViaSpan = 3.9 mg/dL & 2.2 mg/dL, Celsior = 2.9 mg/dL &1.9 mg/dL, urinary output: ViaSpan = 1568 ml & 1754 ml, Celsior = 2265 ml & 1971ml. Faenza and colleagues concluded, like the other RCTs, that these two solutions are equivalent. ± = standard deviation.

We conducted a meta-analysis using a random effects model of some of the outcomes: DGF, graft survival at one year and graft rejection and found that the pooled effects showed no significant differences between the groups on any measure. Tests for heterogeneity were all negative. Forest plots can be seen in Figure 8, Figure 9 and Figure 10.

See **Table** 17 for a comparison of the results from these RCTs.

Table 17 Results of RCTs comparing ViaSpan to Celsior cold storage solution

Outcome	Study (follow up)	Donor Population	ViaSpan	n/N	Celsior	n/N	Effect	95% CI	p	Comment
DGF	Montalti et al. 2005 RCT	BSD & DCD		13/25		12/25	RR 1.08	0.62, 1.89	ns	PenTAG calculation
	Pedotti et al. 2004 RCT	BSD & DCD		61/269		40/172	RR 0.98	0.69, 1.38	ns	PenTAG calculation
	Faenza et al. 2001 RCT	BSD & DCD		30/80		31/99	RR 1.09	0.72, 1.64	ns	PenTAG calculation
PNF	Pedotti et al. 2004 RCT	BSD & DCD		4/269		4/172	RR 0.64	0.16, 2.52	ns	PenTAG calculation
Kidneys rejected post-storage/ pre-transplant	Faenza et al. 2001 RCT	BSD & DCD		6/88		7/99			ns	
Graft survival	Montalti et al. 2005 RCT	BSD & DCD								
	(1 year)			24/25		23/25	RR 1.04	0.91, 1.20	ns	PenTAG calculation
	(5 years)			22/25		20/25	RR 1.10	0.86, 1.40	ns	PenTAG calculation
	Pedotti et al. 2004 RCT	BSD & DCD								
	(1 month)			245/269		162/172	RR 1.00	0.96, 1.01	ns	PenTAG calculation
	(1 year)			245/269		162/172	RR 0.97	0.92, 1.02	ns	PenTAG calculation

Outcome	Study (follow up)	Donor Population	ViaSpan	n/N	Celsior	n/N	Effect	95% CI	p	Comment
	Faenza et al. 2001 RCT	BSD & DCD								
	(2 years)			66/80		83/99	RR 0.90	0.77, 1.04	ns	PenTAG calculation
Patient survival	Pedotti et al. 2004 RCT	BSD & DCD								
	(1 month)			269/269		172/172	RR 1.00	0.99, 1.01	ns	PenTAG calculation
	(1 year)			263/269		171/172	RR 0.98	0.96, 1.01	ns	PenTAG calculation
Graft rejection	Montalti et al. 2005 RCT	BSD & DCD								
	(before discharge)			2/25		2/25	RR 1.00	0.15, 6.55	ns	PenTAG calculation
	Faenza et al. 2001 RCT	BSD & DCD								
	(before discharge)			13/80		12/99	RR 1.22	0.59, 2.53	ns	PenTAG calculation
Creatinine concentrations	Pedotti et al. 2004 RCT	BSD & DCD		Mean		Mean				
	(day 1)		220.4 µmol/L		200.8 µmol/L		DM 19.60	-121.00, 160.20	ns	PenTAG calculation
	(day 15)		671.8 µmol/L		663.0 µmol/L		DM 8.80	-11.78, 29.39	ns	PenTAG calculation

Outcome	Study (follow up)	Donor Population	ViaSpan	n/N	Celsior	n/N	Effect	95% CI	p	Comment
	Faenza et al. 2001 RCT	BSD & DCD	Mean		Mean					
	(day 1)		3.9 mg/dL		2.9 mg/dL		DM 0.88	-0.08, 1.84	ns	PenTAG calculation
	(discharge)		2.2 mg/dL		1.9 mg/dL		DM 0.50	-0.40, 1.40	ns	PenTAG calculation
Urinary output	Pedotti et al. 2004 RCT	BSD & DCD	Mean		Mean					
	(day 1)		2520 mL/24hrs		2180 mL/24hrs		DM 340.0	305.99, 374.01	ns	PenTAG calculation
	(day 15)		2500 mL/24hrs		2600 mL/24hrs		DM -100.0	-266.9, 66.09	ns	PenTAG calculation
	Faenza et al. 2001 RCT	BSD & DCD	Mean		Mean					
	(day 1)		1568 mL/24hrs		2265 mL/24hrs		DM -697.1	-1586.43, 192.23	ns	PenTAG calculation
	(discharge)		1754 mL/24hrs		1971 mL/24hrs		DM -193.1	-691.91, 304,99	ns	PenTAG calculation
Post-operative dialysis events	Montalti et al. 2005 RCT	BSD & DCD	Mean (SD) 3.1 (4.9)		Mean (SD) 2.2 (3.8)		DM 0.90	-1.53, 3.33	ns	PenTAG calculation
	Faenza et al. 2001 RCT	BSD & DCD	1.9 (3.5)		1.0 (3.3)		DM 0.90	-0.08, 1.88	ns	PenTAG calculation

Abbreviations: BSD = brain stem dead, DCD = donation after cardiac death, RR = relative risk, DM = difference in means, ns = not significant

Figure 8 Forest plot of the relative risk of DGF comparing ViaSpan with Celsior

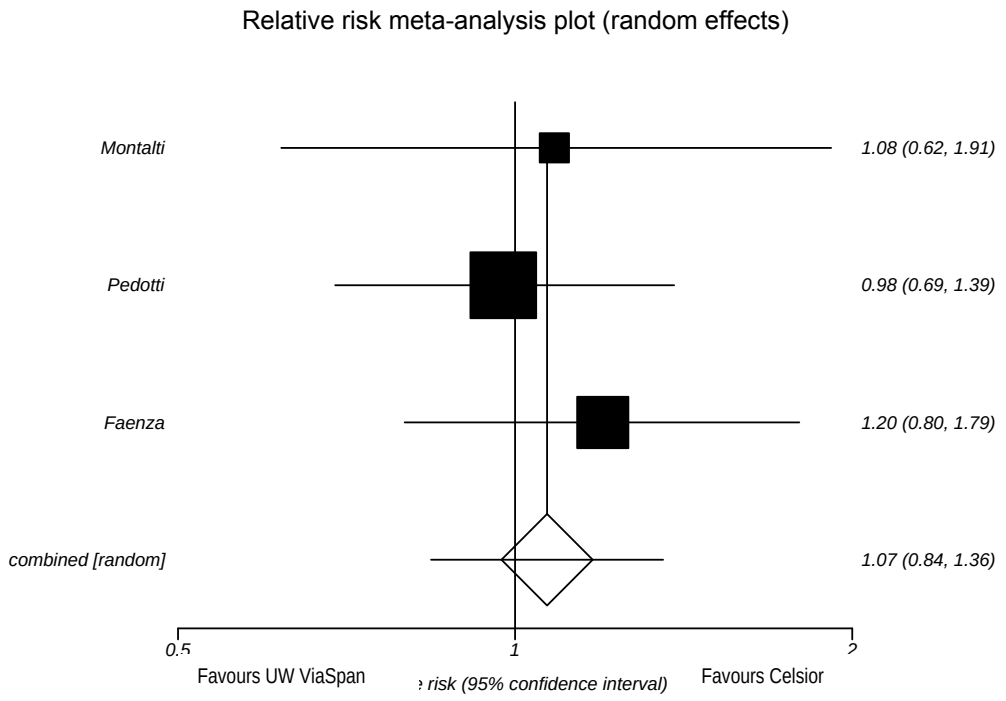


Figure 9 Forest plot of the relative risk of graft survival at 1 year comparing ViaSpan with Celsior

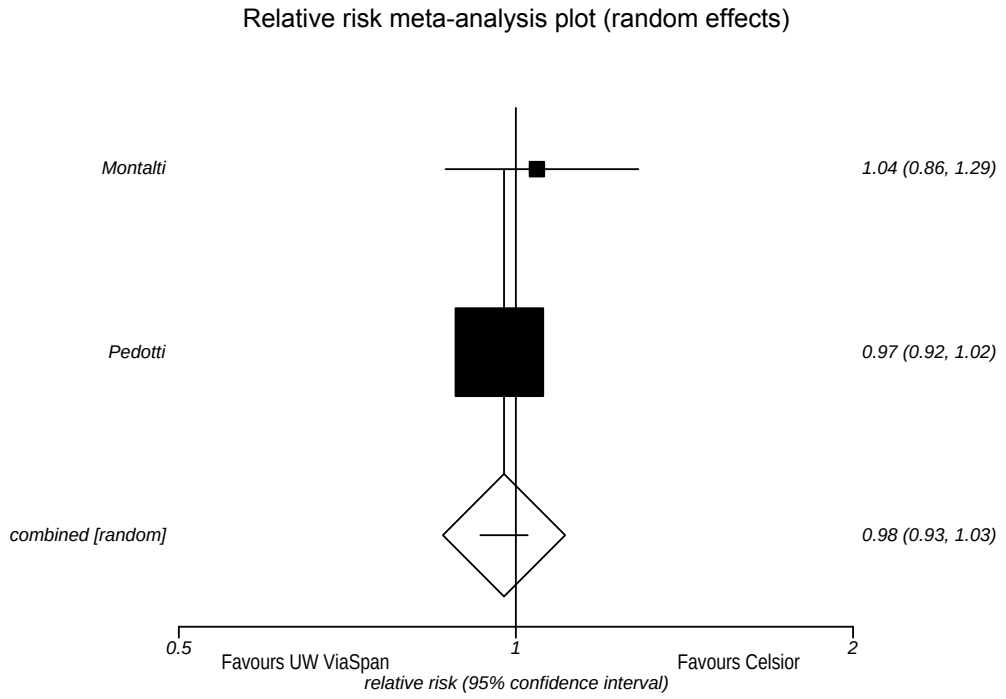
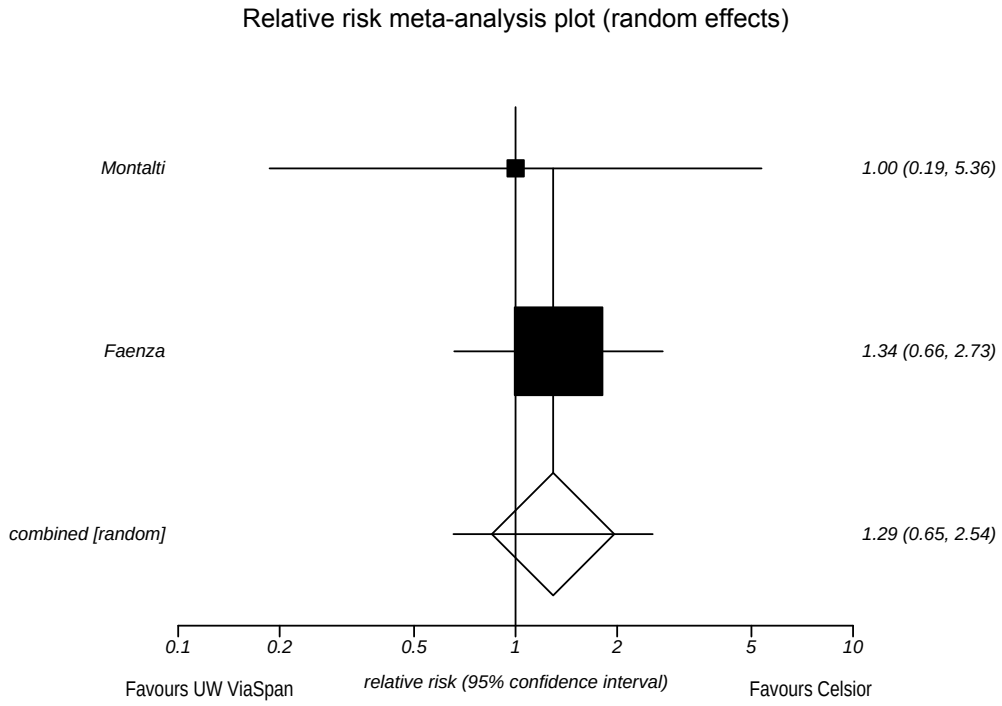


Figure 10 Forest plot of the relative risk of graft rejection before discharge comparing ViaSpan with Celsior



Marcen and colleagues (2005)[56] N = 177 (kidneys) reviewed the hospital records of the recipients of kidneys from BSD donors (ViaSpan =139, Celsior = 39), the method of allocation to solution type was not reported. Data were collected between January 1997 and October 2001. Recipients of kidneys stored with ViaSpan were significantly older than those whose kidneys had been stored with Celsior cold storage solution (mean (SD): ViaSpan = 49.5 (14.4), Celsior = 43.3 (13.0), [95% CI 1.47, 10.93], p <0.01). Other baseline characteristics showed no significant differences; although mean (SD) CIT was longer for kidneys stored in Celsior (ViaSpan = 18 ±4 .3 hrs, Celsior = 17 ± 3.7 hrs, ns).

Marcen and colleagues found no significant differences for DGF (ViaSpan = 54/138 (39%), Celsior = 9/39 (23%)), PNF (ViaSpan = 8/138 (6%), Celsior = 1/39 (3%)), graft survival at 12 months (ViaSpan = 121/138 (88%), Celsior = 38/39 (97%)), or graft rejection (ViaSpan = 23/138 (17%), Celsior = 2/39 (5%)), although all measures favoured Celsior. However, they found that creatinine concentrations at one and 12 months were significantly higher for those people whose grafts had been stored with ViaSpan (1 month mean (SD): ViaSpan = 1.9 (0.9), Celsior = 1.5 (0.5) DM 0.4 [95% CI 0.18, 0.62], p<0.001), (12 months mean (SD): ViaSpan = 1.63 (0.5), Celsior = 1.35

(0.4) DM 0.28 [95% CI 0.13, 0.43] p<0.001). The greater age of recipients of kidneys stored with ViaSpan may have contributed to this result, together with the disproportionate size of the groups and possible selection bias.

5.3.3.1. Summary of cold storage solution vs. cold storage solution

Three RCTs, one registry study and one hospital record review were found which compared the cold storage solutions of interest.

A multi-national registry study compared ViaSpan with Marshall's solution. Our analysis of the data showed that there were no significant differences between solutions for a range of cold ischaemic times.

The three RCTs comparing ViaSpan with Celsior found no significant differences on any outcome measure; pooling these data continued to show no significant differences between groups.

The hospital record review comparing ViaSpan with Celsior only found a significant difference in creatinine concentrations at one and 12 months, with ViaSpan stored kidneys having higher levels; these higher levels may have been due to the greater age of the recipients of those kidneys, or other confounding factors not reported.

Post-storage pre-transplant discard rates were similar (ViaSpan = 6, Celsior = 7).

5.4. Safety

No adverse events were reported from any of the included studies and our systematic review provided no evidence of safety issues related to mode of kidney storage. Furthermore, advice from our clinical expert suggests that there are no particular safety issues associated with kidney storage methods.

However, the British Transplant Society's submission to NICE has highlighted the issue that care should be taken not to use Marshall's Soltran cold storage solution when other organs are being retrieved with the kidneys. This is because this solution is not safe for extended preservation of the liver, pancreas or intestines and it is not possible to perfuse the kidneys without also perfusing these other organs if they are being retrieved.

5.5. Sub-groups

The heterogeneity of the studies included in this systematic review did not allow sub-group analyses.

5.5.1. Summary of clinical effectiveness

1. Eleven papers were found that met our inclusion criteria: five were RCTs, one was a cohort study, one was a registry study and four were hospital record reviews.

2. Seven studies had been published in peer-reviewed journals, two were unpublished ongoing or un-written up trials and two had only been published as conference abstracts and presented as posters.

3. The studies ranged from good quality RCTs to poor quality hospital record reviews, with a wide variation in the comprehensiveness of the description of study methods and results.

4. Results from one RCT (Moers and Colleagues) showed that [redacted]. However, [redacted] machine preservation (LifePort) and cold storage (ViaSpan) for mainly BSD donors with a smaller proportion of DCD donors (with average cold ischaemic time [redacted]) for the outcomes of: [redacted]. Sub-group analyses for DGF found [redacted].

5. The results from the other RCT comparing machine perfusion with cold storage with DCD kidneys (Watson and colleagues), found no significant differences on any outcome measure. However, these results were [redacted].

6. Two hospital record reviews provide the only evidence comparing different perfusion machines; these are unpublished and open to confounding influences. Both studies favoured the RM3 on all outcomes.

7. Data from a multi-national registry study showed that for a range of cold ischaemic times, there was no significant difference in graft survival between ViaSpan and Marshall's Soltran.

8. Three RCTs found no significant differences between ViaSpan and Celsior cold storage solutions on any outcome measure. Pooling their data failed to show any overall significant differences, indicating their equivalence.

6. Assessment of cost-effectiveness

6.1. Some economic aspects of kidney preservation methods

Our reading of a broad range of studies in the field of organ transplantation and renal replacement therapy, suggests that there are a number of ways in which better preserved donated kidneys may provide *theoretical* economic advantages. These are:

- Fewer stored kidneys are non-viable, and therefore discarded, prior to transplantation;
- There is a greater chance that the transplanted kidney will start functioning more quickly (e.g. lower rates of delayed graft function), with corresponding lower hospital stays and in-hospital dialysis requirement;
- There is a lower chance that the transplanted kidney will never work, and the patient will be unable to come off dialysis (i.e. lower rates of primary non-function usually leading to an explant operation, and possibly a subsequent transplant);
- Those transplanted kidneys which start functioning, function better and for longer;

Each of these theoretical benefits has related costs. The economic implications of the first benefit, however, are very hard to estimate. This is because the main impact of differing rates of discarded kidneys after storage, will be on the size of the transplant waiting list. With more discarded kidneys, the waiting list will be larger (as those who would have received a kidney remain on the list) and, all other things being equal, people with ESRD will therefore on average remain on the waiting list for longer. During that time they will cost more and have a lower quality of life than transplanted patients;[25;36;62] they also have a greater risk of death while waiting for a kidney transplant than had they been transplanted earlier.[2]

Few of our included effectiveness studies have reported post-storage kidney discard rates, and those that did [redacted]. Therefore, our main analysis focuses purely on the post-transplantation outcomes of different storage methods.

The last three of the hypothetical benefits directly impact on how many patients will need dialysis again, and how soon they will need it (and also perhaps a subsequent transplant). The lifetime cost-effectiveness of different methods of kidney preservation is likely to depend on the pattern of time ESRD patients spend with a functioning transplant as opposed to needing dialysis; the decision problem therefore has considerable parallels with technology assessments of different immunosuppressive therapy regimes for transplant recipients. It may also usefully be informed by analyses of the cost-effectiveness of transplantation versus dialysis as forms of renal replacement therapy.

6.2. Systematic review of existing cost-effectiveness evidence

6.2.1. Aim

The aim of this systematic review was to identify and critically appraise all published economic evaluations of the relevant intervention and comparator technologies, and all UK-based cost analyses, for the purpose of:

- Justifying the need for an original cost-utility analysis
- Informing the design and analysis of our model-based analysis
- Providing insights into the main cost-benefit trade-offs relevant to our decision problem

6.2.2. Methods

6.2.2.1. Search strategy

The search strategy for economic evaluations and other economic studies is shown in Appendix 1. The range of sources searched are the same as those for clinical effectiveness, plus Econlit and NHSEED.

6.2.2.2. Study selection criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations were identical to those for the systematic review of clinical effectiveness, except:

- Decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies will be included.
- Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost consequence analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data).
- Stand alone cost analyses based in the UK NHS will also be sought and appraised.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer (RA).

6.2.3. Data extraction strategy

Data was extracted by one researcher into two summary tables; one to describe the important study design features of each economic evaluation, and the other to describe the main results.

6.2.3.1. Study quality assessment

The methodological quality of the two included full economic evaluations has been assessed by an experienced health economist, partly by using the CHEC list questions developed by Evers and colleagues.[63]

6.2.4. Results

The search strategy for economic studies yielded 173 citations. On the basis of reviewing their titles and abstracts, only five studies potentially met the review's inclusion criteria. One was the 2003 HTA Monograph by Wight and colleagues on machine perfusion vs. cold storage of donated kidneys.[45] The other four citations reported one study which compared ViaSpan preservation solution with HTK,[64] and two studies which compared ViaSpan with EuroCollins.[65;66] These four papers/abstracts were therefore not relevant to the comparator technologies of interest in this review, and were excluded from further detailed appraisal. However, they were retrieved and studied for any insights about methods or data sources they might provide.

In addition to the 2003 HTA Monograph mentioned, we also found another more recent health technology assessment report (which was not in any of the bibliographic databases searched) on machine perfusion versus cold storage in kidney preservation, produced by a Canadian university hospital research group.[47] Below, we review the cost-effectiveness analyses presented in these two technology assessment reports in more detail.

6.2.5. Summary of existing evidence

6.2.5.1. Summary of studies in our systematic review

Details of the key features and methods and the main results of the two included full economic evaluations are shown in **Table 18** and **Table 19.**

Wight and colleagues (2003) produced a systematic review of economic studies of machine perfusion of kidneys, and also reviewed research on the hypothetical relationship between Delayed Graft Function (DGF) and graft survival.[45] These reviews helped inform an original probabilistic cost-utility analysis of machine perfusion (MP) versus cold storage (CS), which was directly based on a model of the relationship between DGF and graft survival using data from a single transplant centre in the USA (from 1985 to 1990).[67]

Their review of economic studies identified only three relevant studies (four articles), all of which were judged to be of poor quality. Two of the studies were not randomised and also reported that marginal kidneys were targeted to specified preservations systems.[68;69]

In a more recent technology assessment report, for a Canadian university hospital research group, **Costa** and colleagues (2007) also examined the cost-effectiveness of machine perfusion vs. cold storage of donated kidneys.[47] Although in most respects this appears to be a relatively high quality model-based analysis, their cost-effectiveness results were only expressed in terms of the cost per DGF event avoided. Since this can only be regarded as a surrogate outcome measure, the meaningfulness of their findings is somewhat limited. Furthermore, their analysis adopted a time horizon of only one year, and did not include any cost or other impacts of differential graft survival (and therefore any long-term changes in the pattern of life-years with a transplant as opposed to on dialysis).

Both studies predated the availability of effectiveness data from randomised controlled trials of machine perfusion versus cold storage.

Appendix 6 shows the extent to which each study satisfied different items in the CHEC criteria list for assessing the quality of economic evaluations.[63]

Table 18. Summary characteristics and methods of included studies

Author, year published	Analysis type and year	Country, setting	Population	Comparators	Perspective	Sensitivity analyses
Wight et al. 2003	Model-based CUA, 2002	UK, NHS	Not stated – but implicitly initially successful transplant recipients (NHBDs and HBDs)	Machine perfusion (RM3 Waters machine) Cold storage (solution not specified)	Health service (UK NHS)	PSA only (separately for DCD and BSD kidneys)
Costa et al. 2007	Model-based CEA, 2006	Canada, University Hospital	Not stated – but implicitly initially successful transplant recipients	Machine perfusion Cold storage	McGill University Health Centre	PSA

Abbreviations: CUA = cost-utility analysis (generating costs per Quality-Adjusted Life-Year); CEA = cost-effectiveness analysis; NHS = National Health Service; PSA = probabilistic sensitivity analysis.

Table 19 Model characteristics and results of included studies

Author, year published	Time horizon & discounting	Costs included	Effects included	Incremental cost	Incremental effects	Incremental cost-effectiveness ratio
Wight et al. 2003	Lifetime(?), 6% (costs) 1.5% (QALYs)	Initial purchase (machine) Maintenance Solutions/disposables Cost of transplant management Cost of HD Cost of CAPD	QALYs (as driven by graft failure/survival in turn based on DGF %)	DCD: -£1900 BSD: -£600	DCD: 0.05 QALYs BSD: 0.03 QALYs	Net Monetary Benefit per patient (with WTP of £20,000 per QALY): DCD: £1200 BSD: £1200 Machine perfusion dominates cold storage in 80% (DCD) and 50-60% (BSD) of PSA simulations.
Costa et al. 2007	1 year No discounting	Equipment cost per transplant Solutions/disposables	DGF events avoided	-CA$698	0.059 DGF events	Machine perfusion dominates cold storage in 99.1% of PSA simulations

Abbreviations: QALYs = Quality-adjusted life-years; HD = haemodialysis; CAPD = Continuous Ambulatory Peritoneal Dialysis; DGF = Delayed Graft Failure (need for dialysis within 7 days post-transplant); DCD = Died from Cardiac Death; BSD = Brain Stem Dead; WTP = Willingness-to-pay; PSA = Probabilistic sensitivity analysis

6.2.5.2. Other relevant studies found

Two of the main purported benefits of better-stored kidneys are that transplant recipients are less likely to need dialysis in the short-term (i.e. lower rates of DGF), and may also need less dialysis in the longer term (i.e. because better stored kidneys may also have better long-term function and survival). Therefore, apart from the cost of machine perfusion or storage solutions themselves, the main economic (and quality of life) implication of better stored kidneys is reduced health care costs due to reduced patient life-years on dialysis. This happens to be the same main trade-off in economic evaluations which compare different forms of renal replacement therapy, or methods for expanding donor numbers. We examined several economic evaluations of alternative forms of renal replacement therapy,[36;70] methods for enhancing the kidney donor pool,[71;72] alternative post-transplantation immunosuppressive regimes,[73;74] or the economics of transplantation in general,[62] in order to better understand the key trade-offs and how they might be estimated or simulated.

We also examined a number of economic studies which compared alternative methods of kidney storage.[65;66;68;75] Another older study, by Hornberger and colleagues, has also highlighted the potential importance for cost-effectiveness analyses of including re-transplantation as a treatment pathway.[76]

6.3. Assessment of industry submissions to NICE

Two industry submissions were received by NICE; they were from Organ Recovery Systems who manufacture the LifePort® Kidney Transporter and Bristol Myers Squibb who make ViaSpan® cold storage solution. Neither of these submissions contained cost-effectiveness analyses or economic models, making such a critique impossible.

6.3.1. Organ Recovery Systems

The Organ Recovery Systems' submission consisted of a presentation of the six month follow-up results from The Machine Preservation Trial.[60] and a paper in press.[52] This is the same data that was considered in the clinical effectiveness assessment 5.3.1 and will not be further reviewed here. A section of their submission referred to an economic study that is part of The Machine Preservation Trial. However, no details or results of this analysis have been received.

Their submission also contained a review of published economic literature. They found two studies; Wight and colleagues[45] and Costa and colleagues[47]. These studies were both systematic reviews with original economic analyses, and were also found by the PenTAG systematic review (see Section 6.2.5.1 for our assessment of them).

6.3.2. Bristol Myers Squibb

Bristol Myers Squibb conducted a systematic review to identify evidence for the effectiveness of cold storage solutions and machine preservation systems as specified in the NICE scope for this assessment. They included 14 studies in their review. Four of these studies are included in our systematic review of clinical effectiveness[48-50;55]. These studies are critiqued in 5.3.3. The other studies fell outside the inclusion criteria for this assessment because they had comparators that were excluded.

6.4. The PenTAG cost-utility assessment

6.4.1. Decision problem

The aim of this analysis is to determine, using a Markov decision model, the relative cost-utility of the different identified methods of storage of donated kidneys for kidney transplant.

Relevant cost and utility data were only available to permit the following cost-effectiveness comparisons:

- Machine perfusion with LifePort vs. Cold storage with ViaSpan solution, in DCD kidney recipients (based on the PPART study)
- Machine perfusion with LifePort vs. Cold storage with ViaSpan solution, in both DCD and BSD kidney recipients (based on the Machine Preservation Trial)
- Machine perfusion with LifePort vs. Cold storage with Marshall's Soltran solution
- Cold storage with ViaSpan vs. Cold storage with Marshall's Soltran solution

Although specified in the protocol, and reviewed in the clinical effectiveness chapter, we were unable to obtain a cost (for potential NHS purchasers) for the Waters RM3 machine. It is therefore omitted from the following cost-utility analyses.

6.4.2. Methods summary

A Markov (state transition) model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The structure of the model was informed by current research literature and expert clinical opinion on the process and outcomes of kidney transplant surgery and its treatment.

The model estimates incremental cost-utility; that is, the ratio of the difference in costs (measured in pounds) to the difference in benefits (in terms of quality-adjusted life-years (QALYs) between the two comparators. The population examined is those receiving kidney transplants. The treatments compared are kidney transplants following a variety of kidney storage methods as outlined (in particular the use of cold storage of kidneys versus the use of machine perfusion methods).

The reference case uses costs for 2007 and takes the perspective of the UK's NHS and personal social services. A mixed sex cohort, of 1000 adult kidney transplant recipients, is modelled until the virtually all the cohort has died (97%). Five separate age groups (18-34, 35-44, 45-54, 55-64, 65+) are simulated in the model, whose results are aggregated to represent the incident population of adult kidney transplant recipients. The model uses a cycle length of one month.

6.4.3. Sources of effectiveness data

The effectiveness studies whose data are used in the economic model were chosen on the basis of study quality, from those found by the effectiveness systematic review. For the comparison of LifePort and ViaSpan we selected the two RCTs[51;60]. The PPART study provided effectiveness data relating only to DCD donated kidneys, whilst the Machine Preservation Trial gave data that represented both BSD and DCD donated kidneys. As we had RCT data for this comparison, we did not include data from the small hospital record review study that also examined this comparison.[54] We only found one study that compared LifePort with Marshall's Soltran,[53] this was a prospective cohort study that was of moderate to poor quality: the LifePort group had a significantly shorter mean CIT than the Marshall's group (LifePort = 15 hours,

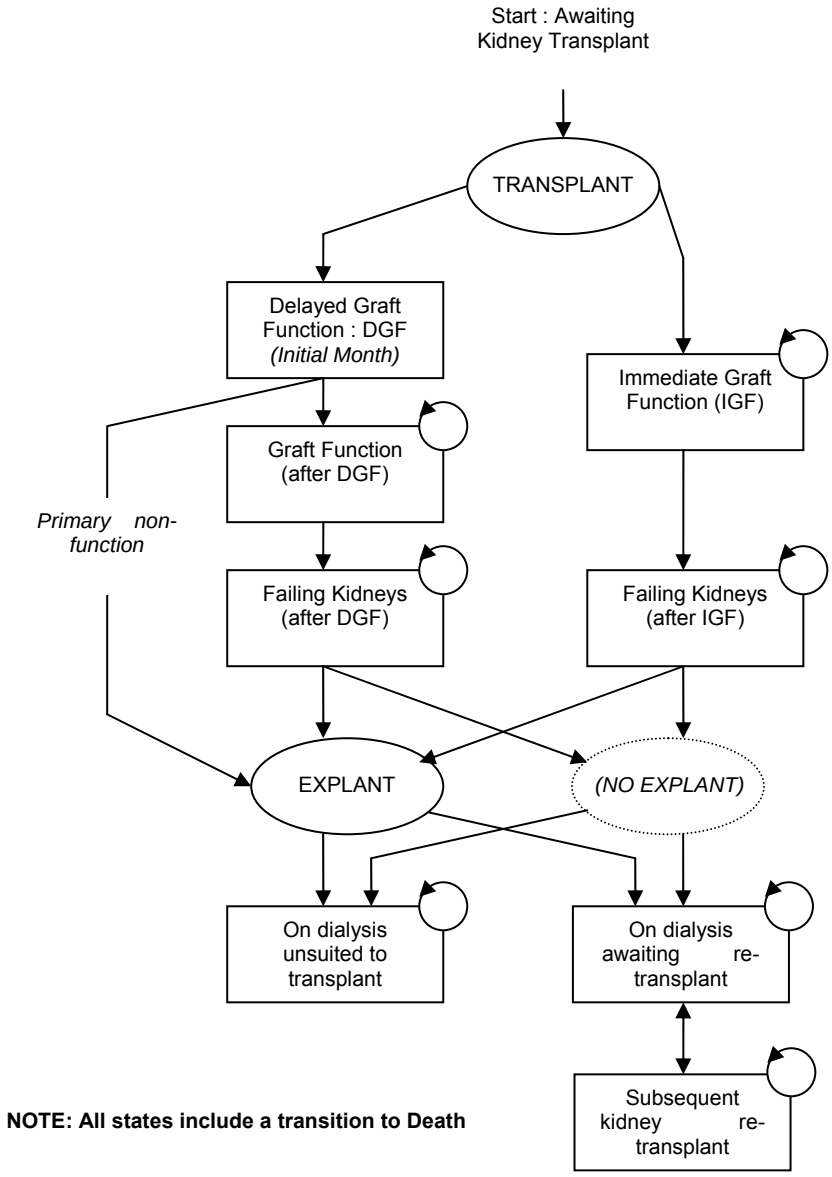
Marshall's Soltran = 17 hours) and the mean age of the LifePort recipient group was seven years younger (LifePort = 47 years [range 20-69], Marshall's Soltran = 54 years [range 34-76]). Only one study was found that compared cold storage solutions, this was a multi-national registry study comparing ViaSpan with Marshall's Soltran.[55]

6.4.4. Model structure

Within a Markov state transition model, patients reside in one of a number of discrete health states. At regular time intervals (the model cycle) patients make at most one transition between states. In this model, a one-month cycle was deemed appropriate to accurately capture the main clinical pathways and events. During each cycle, all patients must be in one of the health states in the model. The probabilities attached to each transition between model cycles are based, where possible, on published data, and where no data were available on expert opinion.

The structure diagram for the model of post-transplantation outcomes is shown below in Figure 11. Health states are depicted as boxes, and transitions between these states are shown as arrows. Circular arrows linked to particular states indicate that patients can remain in that state at the end of each cycle. All states in the model include a transition to death. Ellipses in the diagram represent specific treatment 'events' which have important implications for costs and outcomes. For example, the transplant event is the starting point in the model after which patients have a probability of moving into the following states: Immediate Graft Function (i.e. non-delayed graft function), Delayed Graft Function or Death. A patient who experiences Immediate Graft function will remain in this state (re-cycle arrow in the diagram) or eventually experience kidney failure (move to the Failing Kidneys after IGF state) or alternatively they may die.

Figure 11 : Structure Diagram of the PenTAG Kidney Transplant Model



6.4.5. Model states

Table 20 below describes in more detail each of the states used in the model to capture the key aspects of the outcomes for kidney transplant patients.

Table 20. List of patient states represented in the PenTAG model

STATE TITLE	DESCRIPTION
Immediate Graft Function (IGF)	Immediate Graft Function following transplant. Patients remain in this state until kidney failure or death.
Delayed Graft Function : DGF *(Initial Month)*	Delayed Graft Function - Initial Month. This is a 'tunnel state' where patients whose grafts do not work immediately spend the first month. DGF is defined as the requirement for dialysis in the first week following transplant. This sub-group of patients comprises (a) those whose kidney graft will not have started working by the end of this month (i.e. primary non-function), and (b) those whose graft starts to function before the end of the month. It therefore reflects the costs and QALY impacts of a mixture of being on dialysis and having a functioning kidney graft.
Graft Function (after DGF)	Graft Function after delay. Graft starts to function after DGF. Patients remain in this state until kidney failure or death.
Failing Kidneys (after IGF)	Kidneys start to fail following a period of function after a transplant with immediate graft function. Full failure of the graft follows.
Failing Kidneys (after DGF)	Kidneys start to fail following a period of function after a transplant with delayed graft function. Full failure of the graft follows.
On dialysis awaiting re-transplant	Original graft from transplant fails and patient returns to routine dialysis and is put back on the waiting list to receive another transplant.
On dialysis unsuited to transplant	Original graft from transplant fails and patient returns to routine dialysis. Patient is judged to be unsuitable to receive another transplant.
Subsequent Kidney re-transplant	Patient receives another transplanted kidney after the failure of the original graft. This state aggregates all possibly states of graft function for the re-transplant.
Death	The time horizon of the model (the period for which model is run) is set such that virtually all patients eventually end in this state (97%).

6.4.5.1. Transitions between states

After each cycle of the model, patients are transferred from one state to another (or remain in the same state) according to the permitted transitions within the model. These transitions are represented by the arrows in the structure diagram of the model (See Figure 11 above). The probability of transferring from one state to another state

is dependent on assigned transition probabilities which were derived from various sources and represent aspects of treatment effectiveness or natural disease progression (as described below). The full list of transitions represented in the model is shown in Appendix 7.

6.4.6. Modelled population

The population simulated in the model is a mixed age cohort of patients who receive a kidney transplant at the first cycle of the model. Simulating more realistic cohorts with a mix of different ages, rather than a single birth cohort (with the same starting age in the model), can have a major impact on estimated cost-effectiveness ratios.[77] The age ranges were chosen to be consistent with data presented by UK Transplant and the UK Renal Registry: 18-34, 35-44, 45-54, 55-64, 65+ and the proportion allocated to each age range in the model set to match those receiving kidney transplants in the UK. Apart from life-expectancy, other important factors which vary with age in this patient group include: the likelihood of re-listing for a subsequent transplantation; the proportion of dialysis patients on haemodialysis (HD) versus peritoneal dialysis (PD) and the utility (quality of life) of patients in each group. The outputs from these five age groups are combined in our analyses to create a realistic weighted aggregated output that represents a mixed age cohort of transplant recipients.

Some of the key transition probabilities within the model are time-dependant, which means that the probability varies dependant on the age of patients and duration of graft survival. To determine the probabilities for graft and patient survival, regression analysis was used to fit Weibull curves to the Kaplan-Meier curves represented by the data in the literature.

6.4.7. Model assumptions

A number of simplifying assumptions have been incorporated in the model, which include the following:

- Primary non-function of kidney graft is determined within the first cycle (i.e one month) following kidney transplant.
- All patients who experience primary non-function (or graft failure in the first month following transplant) receive a kidney explantation operation.

- Graft survival is not modelled as a function of patient age (since no data were available to parameterise age groups separately).

- In each age group, patients who received re-transplant (after initial graft failure) are modelled as a homogenous group, using aggregated costs and graft survival. Levels of graft failure and explant for this group are modelled using constant probabilities and all patients with graft failure after re-transplant are assumed to re-join the transplant waiting list (where they can receive subsequent re-transplants).

- The model does not explicitly distinguish between different types of kidney donated for transplant (eg BSD versus DCD) since no data were available to parameterise these aspects. Sensitivity analysis has been used where possible to explore the possible impact of some of these factors.

- Within each age group, patients have been treated as homogeneous, no allowance has been made for the spread of ages within each age group. (For example, age-related increases in dialysis cost, or decreases in health-related utility, are applied simply at year 10, 20, 30 etc.)

- Lack of individual patient data means that no distinctions can be made in the model to account for the effect of recipient characteristics such as sex, race, or co-morbidities (such as diabetes).

- Apart from the storage mode for donated kidneys which was modelled in the compared model arms, it was not possible to model the effects of other factors affecting the quality of donated kidneys (e.g. cold ischaemic time, age of donor).

- The impacts of complications either during or post-transplantation were not included in the model.

6.4.8. Time horizon

The time horizon of the model (the duration of time modelled) is set such that all patients in the modelled cohort eventually die. This ensures that all consequences of compared treatments are modelled.

6.4.9. Discount rates

Both costs and benefits (QALYs) in the model have been discounted at an annual rate of 3.5% according to the NICE guidelines.[78]

6.5. Model parameters – the standard data set

In order to run the model a number of key input parameters are required. These relate primarily to the transition probabilities, costs and utilities required to calculate the model cost-utility outputs. Each model state therefore has an associated utility and cost and, in addition, some of the model transitions ('events') have a cost. Transition probabilities are assigned to each of the transitions (arrows in the model diagram - Figure 11 above). The data values for these parameters have been obtained from a variety of sources which are described in the following sections.

A standard, or "natural history", set of data was used to initially populate the model of post-transplantation costs and outcomes. Key differential data for the compared storage technologies were drawn from our own cost estimates of the different storage methods and outcome data sourced from clinical study data. The standard data set, described in more detail below, was based largely on registry sources such as the UK Renal Registry and UK Transplant.

6.5.1. Sources of model parameters

For each cost-utility comparison an initial *standard dataset* has been input into the Markov model (as described above) to provide a starting point to represent typical treatment outcomes for kidney transplant patients. The standard dataset parameters are set to be equivalent for each of the compared arms. Differences between the arms are then introduced for each cost-utility comparison based on available data (eg. differential costs for kidney storage, differential outcome data supplied in the relevant studies for the modelled comparison). The standard dataset also provides a basis for sensitivity analysis, which is used to explore the relationships between model inputs and outputs.

The standard dataset used to populate the model is shown in sections 6.5.3 to 6.5.5 below. Much of this has been drawn from national registry sources, especially from UK Transplant and the UK Renal Registry.[16;79]

6.5.2. Standard age group weightings

The proportion of deceased donor kidney transplantations in each age group was supplied by UK Transplant statisticians. See Table 21.

Table 21. Proportions of modelled adult transplant recipients in each age group.

Age when transplant was received	18-34	35-44	45-54	55-64	65+
Proportion of transplants in age group	18.18%	24.21%	24.86%	22.62%	10.13%

Source: Data supplied by UK Transplant, for adult recipients between 1 January 2002 and 31 December 2004

These proportions were those used to weight the outputs for each age group in the model, to provide cost and QALY outputs for an aggregated mixed age cohort.

6.5.3. Costs estimates

Our cost comparison of the different methods for storing deceased donated kidneys includes the cost of:

- Different storage solutions, and the machines or storage containers used.
- Post-transplantation dialysis while an inpatient (related to DGF rate).
- Any kidney graft explantation operations required (e.g. following primary non-function).
- Ongoing care as a successful kidney graft recipient (including routine check-ups, immunosuppressive drug regimes, and the treatment of acute rejection episodes).
- Ongoing care for patients who return to or never come off dialysis (including regular haemodialysis or peritoneal dialysis, routine check-ups, drug treatment for anaemia).

6.5.3.1. Pulsatile perfusion machines and solutions (LifePort only)

The cost of Waters RM3 machines to the NHS is not available (there was no industry submission for this machine, and no transplant centres in the UK have bought this machine). A price was requested (via NICE) from the manufacturer, but not supplied.

The purchase cost of a single LifePort machine is £10,750 (source: Organ Recovery Systems, budget impact analysis in submission to NICE, February 2008) but each transplant centre using machine perfusion would require two machines (one for each donated kidney), because kidneys are usually retrieved in pairs and each machine perfuses one kidney (total initial cost £21,500).

We have annualised this initial purchase cost, using the formula recommended by Drummond and colleagues 2005.[80] In this calculation we have initially assumed that the LifePort technology (note, not each particular machine) will be used for 10 years in the NHS (before obsolescence or replacement by newer technologies). This is because, in addition to the initial purchase cost, most centres pay for a maintenance contract which replaces or repairs any broken or faulty machine (at an annual cost of US$1750 per machine). The annualised purchase cost therefore assumes a zero resale value after that time, the annuity factor for 10 years at 3.5% per year, and gives an annualised cost per LifePort machine of £1219, or £2438 for two machines. Transplant centres purchase two machines because usually two kidneys are retrieved from a deceased person. In addition, most UK centres currently using LifePort machines pay for an maintenance contract which costs US$1750 per machine (£874 using March 2008 exchange rates[81]) making the annual cost per machine £2092 (or £4184 for two machines). Finally, each LifePort stored kidney also requires solutions and other consumables that are supplied as a perfusion kit (£475 each; source: Organ Recover Systems, submission to NICE).

However, during any given year, the machines will be used for storing different numbers of kidneys in different transplant centres. Table 22 below shows how the cost per kidney stored was calculated.

Table 22. Costs of machine perfusion for kidney storage

Donor types for which machine perfusion is feasible	Mean number of kidneys transplanted per centre	Annualised machine cost per kidney	Cost per perfusion kit	Machine perfusion cost per kidney stored
From both BSD and DCD donors	61[a]	£69	£475[d]	£544
From DCD donors only[c]	16[b]	£262	£475[d]	£737

[a] 22 transplant centres in the UK (excluding Glasgow and Edinburgh) transplanted 1332 kidneys in the year 2006-7.[16]

[b] 17 transplant centres in the UK with a DCD donor programme (excluding Glasgow and Edinburgh) transplanted 267[80] kidneys in the year 2006-7.[16]

[c] At present in the UK, the transport of LifePort machines to organ retrieval centres, and then back to organ transplant centres, is only compatible with regional organ sharing systems; the machines are therefore only used for kidneys from DCD donors under present organ sharing arrangements.

[d] Source: Organ Recovery Systems, industry submission.

6.5.3.2. Cold storage boxes and solutions

In addition to the storage solutions, cold storage of kidneys involves the use of two sterile plastic bags, sterile ice, non-sterile ice and water, and non-sterile insulated boxes for storage and transportation. The boxes are bulk-purchased and supplied to all transplant centres in the UK by UK Transplant. The vast majority are supplied with a satchel and the required accessories/consumables, costing £45.80 each (information supplied by UK Transplant); we use this figure in our base case anaalyses. However, it should be noted that the current cost of replacement tubs with refill packs (i.e. without the satchel) is only £20.

Data supplied by UK Transplant indicates that 930 kidney boxes were supplied last year to transplant centres in the UK (figures for April 2007 to March 2008). Deducting an estimated 80 DCD kidneys which would have been stored using the LifePort machines (at eight Transplant Units), from the total of 1440 deceased donor transplants conducted in the UK in 2006-7, gives approximately 1360 kidneys which would have been stored using cold storage. This implies that each kidney storage box is used, on average, only 1½ times (i.e. 1360 ÷ 930), assuming all storage boxes are used up during this period.

Table 23 below shows the cost per litre (excluding VAT) of the different storage solutions compared in our analysis.

Table 23. Per litre cost of kidney storage solutions

Type of solution	Cost per litre bag	Source
ViaSpan	£116	Information supplied to NICE by Bristol Myers Squibb (manufacturer) (£696 for a pack of 6 one-litre bags)
Marshall's Soltran	£9.60	Baxter e-catalog (Web pages accessed 19th May 2008; product code FKB4708G at: http://www.ecomm.baxter.com/ecatalog/)

6.5.3.3. Number and cost of kidney graft explantation

UK Transplant supplied data on the proportion of failed grafts which were explanted by time since transplant. Our assumptions regarding the probability of kidney graft explantation following graft failure are shown in section 6.5.5.3.

Each kidney explant operation is given a unit cost of £4135, which is the weighted average of the 2006-07 national average unit costs for Kidney Major Open Procedures (HRG codes LB02B - with intermediate complex co-morbidities, and LB02C - without complex co-morbidities: £3949 and £4424 respectively).

6.5.3.4. Ongoing care costs with a functioning kidney transplant

Table 24 below shows the main resource use assumptions and resultant monthly health care costs we have included for those patients in the model with a functioning transplant.

Two transplant surgeons in our Expert Advisory Group suggested typical frequencies of outpatient appointments, which tend to reduce with time since transplant. The probability of acute rejection was also difficult to estimate, because most studies only report short-term post-operative rates, which would over-estimate long-term rates. We have therefore suggested simple reducing rates of acute reduction, with the initial rate for the first three months based on the rates reported in three of our included effectiveness studies.

For the cost of immunosuppression, in the absence of reliable national data on the exact drug protocols and doses used in all transplant centres, we relied on responses from our expert advisors (transplant surgeons) and NICE Guidance.[82] We assumed that most transplant centres in the NHS use a triple regime involving (i) a calcineurin inhibitor (either Cyclosporin or Tacrolimus) (ii) an anti-proliferative agent (either Azathioprine or Mycophenolate Mofetil, and (iii) a steroid (usually Prednisolone). We have not included the costs of initial "induction" drug therapy (which is assumed to be incurred by all transplant recipients), and also have not specified lower immunosuppression costs for later years (as doses may be lowered over time).

Table 24. Costs associated with a functioning transplant

Cost type	Units used	Source	Unit cost(s)	Source	Monthly cost
Routine outpatient appointments	20 (in months 1-3) 30 (in months 4-12) 6 (per year thereafter)	Approximation of figures suggested by Expert Advisory Group membersa	£258	NSRC 2006-07	£1720, or £860, or £129
Monthly probability of acute rejection (requiring a hospital stay)	0.15 (months 1-3) 0.05 (months 4-12) 0.01 (thereafter)	Informed assumption. See noteb	£1489	NSRC 2006-07	£223, or £74, or £15
Proportion of episodes of acute rejection requiring intravenous treatment with ATG	10%	Estimate by a transplant surgeon	£2960[c]	Renal Pharmacist, Plymouth Hospitals NHS Trust	NA

Cost type	Units used	Source	Unit cost(s)	Source	Monthly cost
Immunosuppressive drug therapy	Various but typically a triple regime involving (i) a calcineurin inhibitor (ii) an anti-proliferative agent, and (iii) steroidsd	Plymouth Hospitals NHS Trust & NICE Guidance[82]	Various	Drug Tariff 2006 and UKd Transplant "Fact Sheet 7"	£417 (= £5000 per year ÷ 12)

NSRC = National Schedule of Reference Costs; ATG = Anti-thymocyte Globulin

[a]The average number of clinic visits at one transplant unit during the first year was estimated to be 34; 5 during year 2 and 4 during subsequent years after transplantation. At another unit, visits were believed to be typically 2-3 times a week during first month, once a week in the second month, and about once every two weeks from the third month onwards.

[b] 0.15 broadly reflects short-term rates reported in three published studies comparing machine perfusion with cold storage.[53;54;60;83] 0.05 and 0.01 represent our assumption that the risk of acute rejection would reduce substantially over time.

[c] Based on average "typical" dose of 125mg ATG given intravenously (centrally given) per day for 3 days.

[d] Based on a regime based either on Cyclosporin or Tacrolimus (as per current NICE Guidance[82]) with either Azathioprine and prednisolone or Mycophenolate Mofetil and Prednisolone (information supplied by renal pharmacist at Plymouth Hospitals NHS Trust, based on NHS Drug Tariff 2006)

With these ingredient costs, the estimated monthly NHS cost of living with a functioning transplant is initially £2464, decreasing to £1386, and then £567 per month from year two onwards.

6.5.3.5. Ongoing care costs when on dialysis

Table 25 below shows the main resource use assumptions and resultant monthly health care costs we have included for those patients in the model who are on dialysis. Since older patients are more likely to be on haemodialysis (rather than peritoneal dialysis), we calculated age-band specific costs of being on dialysis to reflect how the costs of dialysis sessions and anaemia treatment would vary with age (Table 26).

Table 25. Costs associated with being on dialysis

Cost type	Units used	Source	Unit cost	Source	Monthly cost
Haemodialysis treatments (HD)	3 sessions per week	Standard practice throughout NHS	£158	NSRC 2006-07	£2049
Peritoneal dialysis (PD) treatments	per day cost (as in NSRC)a	NSRC 2006-07	£44	NSRC 2006-07	£1338
Routine outpatient appointments	2 per year	Expert advice	£114	NSRC 2006-07	£17
Drug therapy to treat anaemia (in HD patients)	In 93% of patients, mean weekly dose 9223 IU	Chapter 8 of UKRR 10th Annual Report[79]	£0.000754	BNF no. 55,[84] (Epoietin Alfa: Eprex®)b	£281
Drug therapy to treat anaemia (in PD patients)	In 79% of patients, mean weekly dose 5969 IU	Chapter 8 of UKRR 10th Annual Report[79]	£0.000754	BNF no. 55,[84] (Epoietin Alfa: Eprex®)b	£155

NSRC = NHS National Schedule of Reference Costs; UKRR = UK Renal Registry; BNF = British National Formulary; IU = International Units.

[a] Communication with NHS Payment by Results/casemix team confirmed that the National Average Unit cost supplied in the NSRC is a cost per day for the relevant dialysate bags and deliveries.

[b] Unit cost of Epoietin Alfa was used in absence of reliable data on typical mix of alternative EPO drugs that might be used (Epoietin Beta and Delta); however, they all have a similar cost per unit.

Table 26. Data on the proportion of adult patients on different dialysis modalities

Age-band	18-24	25-34	34-44	45-54	55-64	65-74	75-84	85+
% on HD	35%	43%	42%	45%	46%	53%	62%	70%
% on PD	65%	57%	58%	55%	54%	47%	38%	30%

Source: Numbers read off from bar chart (Figure 4.10) in Chapter 4 of UK Renal Registry Tenth Annual Report

Together these cost assumptions result in an average monthly cost of between £2034 and £2117, gradually increasing with patient age.

6.5.3.6. Costs not included

A more comprehensive analysis of the health care cost of living with a transplant or on dialysis might include the following categories of resource use:

- GP visits/consultations and district nurse visits, which may differ between transplant patients and those on dialysis
- Consultations with social care/social work professionals
- Home adaptations (especially for people on home haemodialysis, or on peritoneal dialysis e.g. showers, bunkers or sheds for storing deliveries of dialysate bags)

6.5.3.7. Summary of standard cost parameters

Table 27 below lists the standard values of each of the cost variables used to calibrate the model.

Table 27. Summary listing of standard cost data for Markov states

PARAMETER	Value £	Source
State costs (£s per patient per monthly cycle)		
Patients with functioning graft:		
Months 1-3 post-transplant	£2464	See section 6.5.3.4
Months 4-12 post-transplant	£1386	
Months 13+ post-transplant	567	
Patients on dialysis (by age-group):		
18-34	£2034	See section 6.5.3.5
35-44	£2040	
45-54	£2052	
55-64	£2060	
65+	£2117	

PARAMETER	Value £	Source
FKI : Failing Kidney after Immediate Graft Function or Delayed Graft Function	£1134	Assumed double cost of functioning transplant
DGI : Delayed Graft Function - Initial Month	Differs by comparator	Weighted average of costs of (i) in-hospital dialysis and (ii) successful transplant
FKD : Failing Kidney after Delayed Graft Function	1134	Assumed double cost of functioning transplant
STX : Post-Subsequent Transplant (monthly cost)	976.65	Weighted average of costs post-Tx See section 6.5.3.4
DTH : Death	0.00	
Event costs (£s per patient)		
Transplant costs (not including costs of kidney storage)	£16,413	NSRC 2006-7
Primary Non-function with explant	£4134	NSRC 2006-7
Graft fails with explant	£4134	NSRC 2006-7
Graft fails no explant	0	

6.5.4. Quality of life - utility estimates

Aside from potential improvements in long-term patient survival, it is clear that one of the other potential consequences of more initially successful grafts, and grafts which function for longer, will be the difference in quality of life between having a functioning transplant and being on dialysis.

Our strategy for identifying the best sources for the difference in utility between being on dialysis and having a functioning kidney transplant was threefold. First, we conducted a systematic search and purposive review of comparative empirical quality of life studies in ESRD patients. Second, the first review was supplemented by a review of recent empirical studies of: the economics of kidney transplantation; the cost-effectiveness of different immunosuppressive drug regimes; or any other cost-utility studies in ERF or ESRD patients where a key driver of outcomes is the different time spent with a transplant versus being on dialysis. Lastly, we examined the studies included in a highly relevant and very recently published systematic review (by Dale and colleagues, 2008) of "utility of health states in chronic kidney disease", which was found separately from the first two reviews. Ultimately it was this last more recent review which led to the identification of what we thought was the best published source for our required utility decrement.

6.5.4.1. Systematic search for comparative quality of life studies

Methods

We conducted a bibliographic search for published papers which reported either utility values and/or quality of life assessments of being a kidney transplant recipient or being on dialysis (see Quality of Life search strategy in Appendix 1). In particular, we sought to identify:

- Comparative studies, which measured quality-of-life or utility in both kidney transplant and dialysis patients, or in different types of dialysis patient.
- Such comparative or other studies which have used generic health-related quality of life instruments for which there are UK population social preference weights (i.e. utility values from either EQ-5D or SF-36 health state descriptions), or estimated utility using the time trade-off (TTO) approach.

Also, when assessing full papers, particular attention was given to whether age-specific or age-adjusted values were reported. This is extremely important for estimating the utility decrement associated with going back onto dialysis after transplant failure, because the age-profile of prevalent transplant patients is typically much younger than that of prevalent dialysis patients. Similarly, data from longitudinal studies were sought which might indicate any specific quality of life impacts associated with returning to dialysis following transplant failure. This is because there may be systematic differences in health status or the perception of quality of life between dialysis patients who have never had a transplant, and those who have had a previous transplant.[31;85]

In addition to this main search, a second search of reference lists sought to identify recent published cost-utility analyses to identify potential sources of research-based utility values for kidney transplantation and/or kidney dialysis. This search identified a number of cost-utility analyses of; different methods of storing donated kidneys; different immunosuppressive drug regimes; different modalities of renal replacement therapy; different criteria for kidney donor selection.

Results – systematic review of comparative quality of life studies

The main bibliographic search, of utility and/or quality-of-life studies in kidney transplant patients, dialysis patients or those with end-stage-renal disease, generated 1189 titles and abstracts. Of these, 18 papers were retrieved which either appeared to have measured, or stated that they had measured, quality of life in both kidney transplant patients and those on dialysis.[22;26-28;30-33;86-95] These were in addition to the two studies already found (for researching our Background section) which had used the SF-36 in both dialysis patients and kidney transplant recipients.[23;34] (A further 49 studies appeared to have evaluated quality-of-life in *either* kidney transplant patients *or* those on different modalities of dialysis.)

On reading the 18 retrieved studies, two were found to be narrative reviews (not empirical studies),[90;91] one was in haemodialysis patients only,[87] and one collected quality of life data in different types of dialysis patient and transplant recipients, but provided no comparative analysis across these groups.[86] None of the 18 studies found had used the EQ-5D (or EuroQol) quality of life instrument, and the only two remaining studies which had used the SF-36 were in dialysis and transplant patients with diabetes.[22;32] All of the remaining comparative studies had either used bespoke

subjective or objective indicators of quality of life,[26;30;31;92;94;95] or used generic instruments for which no general population utility weights exist (e.g. General Health Questionnaire, General Well-Being, the "15-D", Sickness Impact Profile). The studies by Girardi and colleagues and by Russell and colleagues both used TTO or standard gamble methods to elicit utility weights from the patients themselves.[89;93] In general, it seems that empirical quality of life studies in groups of patients on dialysis and/or with end-stage renal disease or kidney transplants have more often used disease-specific than generic measures of health-related quality of life. For example, a number of studies had used versions of the KD-QOL, the QLI (Quality of Life Index), or Parfrey's health questionnaire for ESRD.[96-101]

In conclusion, none of the studies found by this review could provide a reliable estimate of the decrease in utility associated with going back onto dialysis following the failure of a kidney transplant. Fortunately, previous cost-utility studies in ESRD patients helped us identify other possible sources of utility values, and the systematic review published in early 2008 by Dale and colleagues identified two studies which had collected EQ-5D quality of life data in both dialysis and kidney transplant patients, and reported the related utility values.[25]

Results – Review of cost-utility studies in ESRD

Seven recent published cost-utility analyses in ESRD and/or kidney transplant patients were identified (Table 28). This was not intended to be an exhaustive systematic review of such studies, but was to give us an indication of the main previous sources of utility estimates in this patient group, and the consistency of these values.

Table 28. Recent economic evaluations using utility values for living on dialysis and living with a working kidney transplant

Author, year	Comparing	Source(s) of utility values	Values used	Notes
Wight et al. 2003[45]	Machine Perfusion vs. Cold Storage of donated kidneys	Hornberger et al 1997[76]	Tx = 0.84 Dialysis after graft failure = 0.65 Difference = 0.19	

Author, year	Comparing	Source(s) of utility values	Values used	Notes
McEwan et al. 2006[73]	Sirolimus vs. Tacrolimus for immunosuppression in Tx patients	3 sources: Laupacis et al. 1996[102] Gudex 1995[103] Kiberd 1994[104]	Differences reported in these sources: 0.3, 0.26, 0.23 Difference used = 0.27	Authors chose Laupacis' figures for hypothetical 'good dialysis' and 'good transplantation'
Woodroffe et al 2005 (4 industry-submitted analyses)[74]	Different renal immunosuppression regimes	Hornberger et al 1997[76] Russell et al. 1992[93] Booth-Clibborn et al 1997[105]	Differences = 0.19 – 0.3	Table 30 of HTA Monograph

Author, year	Comparing	Source(s) of utility values	Values used	Notes
Woodroffe et al 2005 (own analysis)[74]	Different renal immunosuppression regimes	Used modified Novartis model (i.e. values from Hornberger et al. 1997[76])	Tx = 0.84 Dialysis after graft failure = 0.65 Difference = 0.19	
Mendeloff et al. 2004[71]	Different methods of organ procurement	Hornberger et al 1997[76] Russell et al. 1992[93]	With Tx = 0.76 (low 0.74, high 0.84) Without Tx = 0.56 (low 0.41, high 0.68) Difference = 0.2	3 other sources were cited, 2 of which were unpublished reports and one was an abstract.

Yen et al. 2004[106]	Medicare coverage vs. no coverage for immunosuppressive medications	Hornberger et al 1997[76]	Tx = 0.84 Dialysis after graft failure = 0.68 Difference = 0.16	
Rutten et al. 1993[66]	ViaSpan solution vs. EC solution for storing deceased kidneys	De Charro 1998 (PhD thesis)	Functioning graft = 0.8 On dialysis = 0.4 *Difference = 0.4*	Possibly assumed figures
De Wit et al. 1998[36]	2 HD and 2 PD dialysis modalities	Own data (EQ-5D) for dialysis modalities. For transplantation ASSUMED = 0.90	Full care centre HD = 0.66 Limited care HD = 0.81 CAPD = 0.71 Continuous cycling PD = 0.81 *Differences = 0.09 – 0.24*	

Abbreviations: Tx = Transplant; HD = haemodialysis; PD = Peritoneal dialysis;

In these cost-utility analyses, the utility difference between the transplanted state and being on dialysis ranged from 0.09 to 0.4. It generated four potential published original sources of utility values (excluding the De Charro PhD thesis (cited in Rutten 1993), and the De Wit and colleagues study - in which the utility for living with a transplant had been assumed, and the analysis by Hornberger and colleagues, whose utility values were mainly drawn from the 1992 study by Churchill and colleagues).[36;66;76;107]

The only studies reporting utility values for both dialysis and transplant patients had used the Time Trade-Off (TTO) method for eliciting preferences (nb. in all cases these elicited patients' preferences with regard to the patient's own health state, rather than the general public's perception of described ESRD health states).

Table 29. Published utility values for both dialysis and kidney transplant patients/health states (from primary studies)

Study	N	Trans-plant	Haemodialysis			Peritoneal dialysis		Method
			HHD	SHD	CHD	CAPD	Other	

Study	N	Trans-plant	Haemodialysis			Peritoneal dialysis		Method
			HHD	SHD	CHD	CAPD	Other	
Churchill et al. 1987[108] (cited in Hornberger et al. 1997)	171[a]	0.84	0.49		0.43	0.56		TTO
Russell et al. 1992[93]	27[b]	0.74					0.41	TTO
Gudex 1995[103]	501	0.79	0.63			0.53		HMQ & Rosser scores
Laupacis et al. 1996[102]	134	0.77					0.62[c]	TTO

Abbreviations: HHD = Home (or self) haemodialysis; SHD = Satellite haemodialysis; CHD = Centre/Hospital haemodialysis; TTO = Time Trade-Off technique; HMQ = Health Measurement Questionnaire.

[a] n = 73 Transplant, 36 HHD, 38 CHD, 24 CAPD.

[b] Prospective before and after study n = 27 Transplant, 16 HHD, 3 CHD, 8 CAPD.

[c] for those (n=26) who had experienced graft loss 12 months post-transplant

A recently published systematic review of studies reporting utility values in end-stage renal disease, by Dale and Colleagues 2008,[25] also identified two studies which reported utility values derived from EQ-5D questionnaire completion by patients. The first, larger, study by Greiner and colleagues reported EQ-5D based utility values for 150 German transplant recipients, both before (when on dialysis) and up to 2 years post-transplantation.[109]

A smaller cross-sectional study (n=27 in each group) in Swedish kidney transplant recipients also used the EQ-5D.[110] However, despite usefully matching dialysis and transplant recipients on a number of characteristics, it may not be so reliable as the German study because of the lower sample size, and because the values for haemodialysis patients were substantially lower than those for those on peritoneal dialysis; this is contrary to most other high quality studies, which usually show those on haemodialysis (particularly home or satellite unit dialysis) having a better or similar quality of life to those on peritoneal dialysis. In addition, their assessed utility difference between being on haemodialysis and living as a kidney transplant recipient

was 0.42 (0.86 – 0.44) which is very large compared to most other estimates (see Table 29 above).

The main characteristics and results of the Greiner and colleagues study are shown in Table 30 below. Despite the stated weaknesses, we thought this study gave a utility difference for having a working kidney transplant compared with being on dialysis which most closely meets both the NICE Methods Guidance for Health technology Assessment, and the particular needs of our analysis. In addition, a recent validation study by Cleemput and colleagues (2004) has shown the EQ-5D to be a valid instrument for measuring health status is renal transplant patients.[111]

Table 30. Summary of utility elicitation study by Greiner and colleagues, 2001

Study design	Prospective before and after study of 150 kidney transplant waiting list patients on dialysis, self-completing the EQ-5D (postally distributed) both while on the waiting list and at six time-points post-transplantation (at 14 days, and one, three, six, 12 months, and "more than one year" after transplant)		
Study strengths	Uses EQ-5D (a generic health-related quality of life instrument) on the same patients, both when on dialysis and after transplantation Relatively long follow-up (for some transplant patients)		
Study weaknesses	Small sample sizes at longer follow-up (risk of bias) Not clear whether UK population utility weights for EQ-5D were used[a] Ideally, following transplant patients until they go back onto dialysis would have been a more relevant source for the utility estimates for our cost-utility analysis.		
Study results	**Time-point**	**n**	**EQ-5D utility weight**
	Pre-transplantation (dialysis)	150	0.76
	14 days post-transplant	99	0.73
	1 month post-transplant	105	0.78
	3 months post-transplant	98	0.82
	6 months post-transplant	96	0.83
	1 year post-transplant	58	0.86
	More than 1 year post-transplant	26	0.88
	Value used for reduction in utility due to going back on dialysis		-0.12

[a]We contacted the author to clarify this, but received no reply.

6.5.4.2. Utility values used

Table 31 below gives the utility values by age group for dialysis and transplant states in the model. The basis for these values is the age related norms for the UK general population to which a 0.1 decrement has been applied.

Table 31. Summary listing of standard data for utilities in the model

PARAMETER		Utility	Source
Transplant states (by age group)			
	18-34	0.83	Assumed 0.1 decrement subtracted from Health State Index Norms - MVH National Survey Data 1993 - CHE, University of York[112]
	35-44	0.81	
	45-54	0.75	
	55-64	0.70	
	65+	0.66	
Dialysis states (by age group)			
	18-34	0.71	0.12 decrement subtracted from corresponding living with transplant utility above. (Source: Greiner and colleagues, 2001[109])
	35-44	0.69	
	45-54	0.63	
	55-64	0.58	
	65+	0.54	

The first month post-transplant for those who experience DGF includes both time on dialysis and/or with functioning graft. Therefore the utility used for this state is a weighted average of the values for dialysis and transplant states.

6.5.5. Transition probabilities

6.5.5.1. Immediate graft function/delayed graft function

The probabilities for immediate versus delayed graft function following transplant is a key parameter in the model and in general has been taken directly from the individual studies used in the model. The values used for each comparison are described at the beginning of each results section in this chapter.

6.5.5.2. Survival of functioning grafts

Graft survival was estimated using estimated graft survival curves which, in turn, were used to derive time-dependent probabilities for transition to the failing kidney states. In all cases graft survival was modelled using Weibull curves which were fitted to the data using regression analysis. For three of the four comparisons presented here, the study data presented gave a basis for estimating the shape of the graft survival curves in each arm. However, in general, the study data did not provide sufficient length of follow up to provide a high level of confidence around the fitted curves. In this context therefore we chose to use data provided by UK Transplant (see Table 32 below) to extrapolate the curves to provide a more reliable fit. One comparison, ViaSpan versus LifePort based on the PPART trial did not provide graft survival data beyond three months post transplantation and showed no significant differences between arms. In this case therefore we chose to use the UK Transplant graft survival data below to fit the Weibull survival parameters for the model.

Table 32. Five-year graft survival following first kidney transplant in UK

Graft Function (donor type)	No. at risk on day 0	% graft survival (95% confidence intervals)				
		Year 1	Year 2	Year 3	Year 4	Year 5
Immediate (BSD)	863	96 (94-97)	94 (92-95)	92 (90-94)	91 (88-92)	88 (85-90)
Immediate (DCD)	42	88 (74-95)	88 (74-95)	86 (71-93)	86 (71-93)	83 (67-91)
Delayed (BSD)	271	93 (89-96)	91 (87-94)	88 (83-91)	87 (82-90)	84 (78-88)
Delayed (DCD)	48	94 (82-98)	94 (82-98)	94 (82-98)	89 (76-95)	85 (71-92)

Source: Data supplied by UK Transplant, May 2008.

6.5.5.3. Kidney graft failure

Once graft failure occurs in the model, patients enter a failing kidney state where within a very few cycles of the model (average 1.4 months) they are transferred to subsequent treatment by dialysis. The failing kidney model states have been introduced to reflect both the likely reduction in quality of life, and higher associated treatment costs for patients whose kidney transplants are not functioning well, but who have not yet become dialysis dependant.

After graft failure, the model has two dialysis states – i) receiving dialysis and waiting for further transplant and ii) receiving dialysis unsuited to transplant. The relative probability of moving to each of the states is dependant on the age of the patient as outlined below.

Suitability for re-transplant after graft failure

The probabilities of a patient re-joining the waiting list for re-transplant after graft failure for each age were derived from UK Transplant data representing the proportion of dialysis patients in each age group actively waiting for transplant (Table 33 below).

Table 33. Proportion of patients in each age group suitable for re-transplant

Age Group	18-34	35-44	45-54	55-64	65+
Percentage of graft failures suitable for re-transplant	54%	49%	38%	27%	10%

Source: Numbers read from scatter plot chart (Figure 5.5) in Chapter 5 of UK Renal Registry Eighth Annual Report 2005.

In each of these age groups the remaining patients with graft failure are transferred to the *receiving dialysis unsuited to transplant* state, where they will remain until death.

Kidney explantation following graft failure

Patients may or may not receive kidney explantation after kidney graft failure. It is known that the probability of receiving a kidney explant is highly dependant on the duration of graft function prior to failure. Early graft failures are far more likely to result in explantation. Data provided by UK Transplant (Table 34 below) were used in the model to sequentially decrease the probability of an explantation following a graft failure relative to the duration of graft function.

Table 34. Kidney graft explant post graft failure, by months since transplant

Months since transplant	0 to 3	3 to <12	12 to <24	24 to <36	36+
Proportion of graft failures explanted	41%	23%	9%	4%	4%

Source: Data supplied by UK Transplant, May 2008.

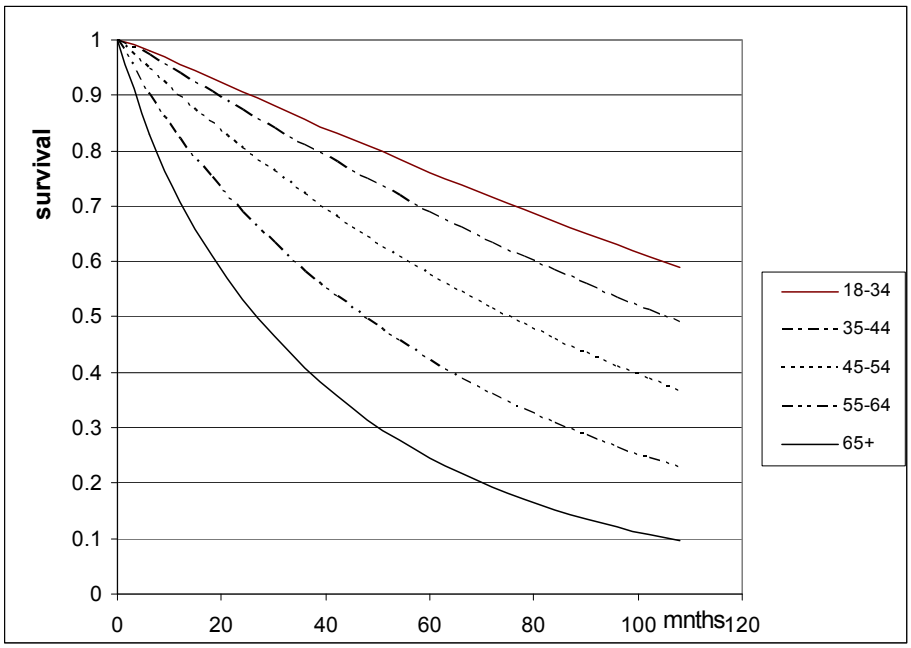
6.5.5.4. Dialysis and re-transplantation following graft failure

Patients deemed suitable for re-transplantation following graft failure can receive subsequent (one or more) transplants in the model. This is represented using a single state which aggregates the costs, utilities and outcomes across all scenarios following re-transplant. The probability and waiting time for a patient receiving a subsequent transplant is known to be age related. Transition probabilities for re-transplant were therefore calculated independently for each age group based on data for the known numbers of re-transplant supplied by UK Transplant.

6.5.5.5. Patient survival

Renal registry data[79] were used to derive patient survival curves by age group and treatment modality (dialysis or transplant) for the standard data set used in the model. For those patients on dialysis, regression analysis was used to fit Weibull curves to Kaplan-Meier survival data for each of the age groups modelled (as shown in Figure 12 below).

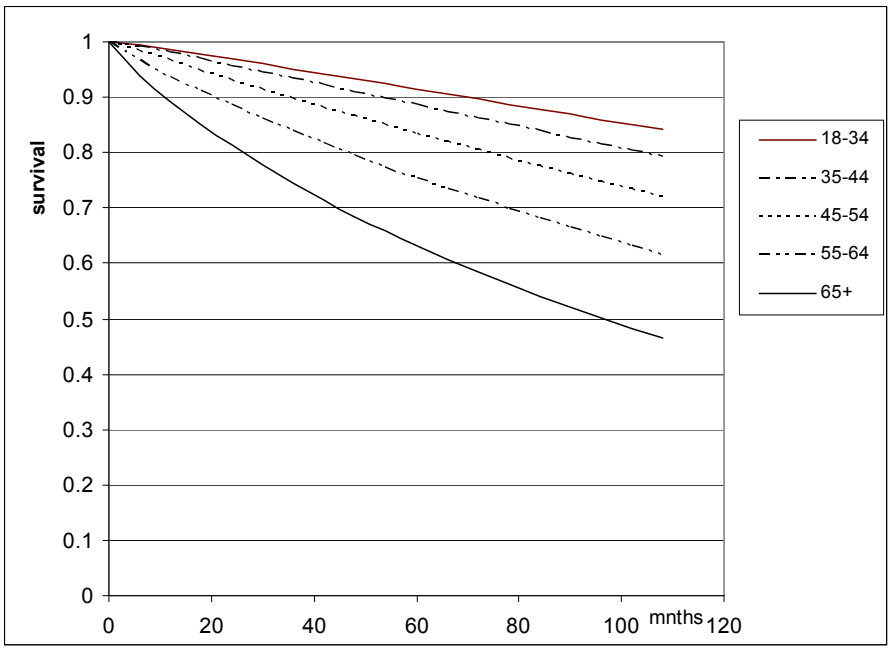
Figure 12. Standard patient survival curves by age group for patients on dialysis



Source: UK Renal Registry 10th Annual Report (Figure 6.3b. p.100)

Survival probability for patients on transplant is recognised to be significantly higher than for those on dialysis. An extensive analysis by Wolfe and colleagues[2] revealed relative risk values of death across four differing age bands of patients ranging from 0.24 to 0.39. These data were confirmed by UK data supplied by UK Transplant for five years patient survival since transplant. To incorporate the improved survival of transplant patients relative to those on dialysis within the model a hazard ratio of 0.327 was calculated as a weighted average based on the data presented by Wolfe and colleagues. This yielded the survival curves are shown in Figure 13 below. Sensitivity analysis was used to explore the effects of changes to this hazard ratio on model outputs.

Figure 13. Standard patient survival curves by age group for patients with transplant



Source: UK Renal Registry 10th Annual Report.

A summary of the parameters used in the PenTAG model is shown in Table 35.

Table 35. Summary of PenTAG model parameters, values and sources

Parameter	Base case value	Source
Time horizon	Lifetime	NICE requirement
Annual discount rate (cost and benefits)	3.5%	UK treasury recommendation REF
Age Group Weights (proportions)		
Ages 18 – 34	18.18%	Data supplied by UK Transplant
Ages 35 – 44	24.21%	Personal communication to Rob Anderson from Alex Hudson - May 08
Ages 45 – 54	24.86%	
Ages 55 – 64	22.62%	
Ages 65 and over	10.13%	
Utilities by Age Group for Transplant		
Ages 18 – 34	0.83	Assumed 0.1 decrement applied to age related health utility norms.
Ages 35 – 44	0.81	
Ages 45 – 54	0.75	

Ages 55 – 64	0.70	
Ages 65 and over	0.66	
Decrement applied to all patients of dialysis	0.12	Greiner et al. 2002 (see section 6.5.4)
Dialysis Costs (per month) by Age Group		
Ages 18 – 34	£2034	Various costing sources - see section 6.5.3.5 (costs increase with age due to increasing proportions on haemodialysis compared with peritoneal dialysis)
Ages 35 – 44	£2040	
Ages 45 – 54	£2052	
Ages 55 – 64	£2060	
Ages 65 and over	£2117	
Transplant operation cost	£16,413	NSRC 2006-7
Explantation operation cost	£4134	NSRC 2006-7
Kidney Storage costs (by Arm)		
ViaSpan (cold storage)	£262.53	See section 6.5.3.2
Marshall's Soltran (cold storage)	£49.73	See section 6.5.3.2
LifePort (machine perfusion)	£736.55	See section 6.5.3.1
Patients with functioning graft (Monthly cost)		
Months 1-3 post-transplant	£2463.60	See section 6.5.3.4
Months 4-12 post-transplant	£1385.83	See section 6.5.3.4
Months 13+ post-transplant	£567.47	See section 6.5.3.4
Transitions		
Proportion of transplants DGF	various	Comparator-specific based on trial data
Proportion of transplant PNF	various	Comparator-specific based on trial data
Graft survival for IGF patients	various	Survival curve based on trial data
Graft survival for DGF patients	various	Survival curve based on trial data
Suitability for re-transplant by Age Group		
Ages 18 – 34	54%	Numbers read from scatterplot chart (Figure 5.5) in Chapter 5 of UK Renal Registry Eighth Annual Report 2005. See section 6.5.5.4 above
Ages 35 – 44	50%	
Ages 45 – 54	38%	

Ages 55 – 64	28%	
Ages 65 and over	10%	
Patient Survival with functioning graft	See above	Estimated survival curves based on Renal Registry and UK Transplant data. See section 6.5.5.5 above
Patient Survival whilst on dialysis	See above	

6.6. Results of PenTAG cost-utility analysis

Due to limitations in the data we were able to obtain, and exclusion (by prior agreement with NICE) of Celsior storage solution from the cost-utility analyses, we were only able to make the following three comparisons:

Machine perfusion vs. cold static storage solution

- LifePort vs. ViaSpan
- LifePort vs. Marshall's Soltran

Cold static storage solution vs. cold static storage solution

- ViaSpan vs. Marshall's Soltran

6.6.1. Machine perfusion vs. cold static storage

6.6.1.1. LifePort vs. ViaSpan

Two studies provide RCT data for the comparison of ViaSpan Cold storage solution with LifePort Machine Perfusion. Since these studies are based on different populations of both donor kidneys and recipients, and different trial conditions each data set was modelled separately.

LifePort vs. ViaSpan - PPART study with DCD kidney transplants in UK

In order to model cost-utility outcomes based on the PPART Trial data, the standard dataset was modified with the following differential data. For each of the arms data were drawn from the reported trial outcomes and differential costs based on the resource analysis (described above).

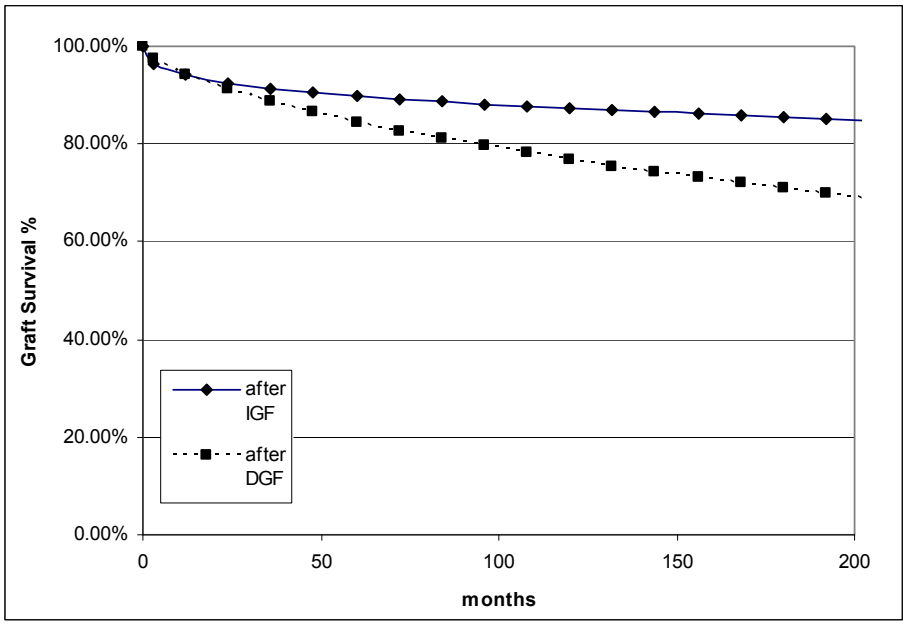
Table 36. Summary of differential input parameters based on PPART Trial Data.

Parameter	ViaSpan	LifePort
Storage cost per kidney	£262.53	£736.55
Percentage of DGF following transplant	55.6%	57.8%
Percentage of Primary Non-function	0%	2.2%

Parameter	ViaSpan	LifePort
Graft Survival at 3 months (all patients)	100%	95.6%

In order to fit graft survival curves for this data in the model it was necessary to use data supplied by UK Transplant for five year graft survival (classified by IGF and DGF) since the single three month data point provided by this trial does not provide a basis for survival curve fitting. The following survival curves were derived using the UK Transplant data.

Figure 14. Weibull Survival estimates of Graft Survival for IGF and DGF patient groups used by the model for comparison of ViaSpan and LifePort based on PPART Trial.



These data yielded the following summary deterministic outputs from the model for cost and benefit differences. See Table 37.

Table 37. Base case deterministic outputs from PenTAG model based on PPART Trial data

	DISCOUNTED COSTS (£s) Per patient	DISCOUNTED BENEFITS (QALYs) Per patient	ICER
ViaSpan Cold Storage	139,205	9.19	
LifePort Machine Perfusion	141,319	9.13	Was dominated
differences	£2,114	-0.066	

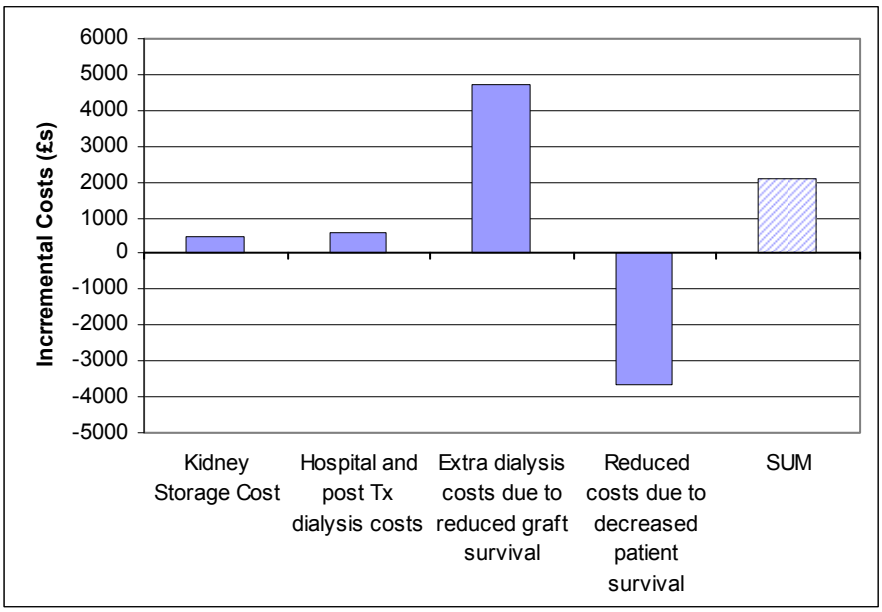
	UNDISCOUNTED COSTS (£s) Per patient	UNDISCOUNTED BENEFITS (QALYs) Per patient	ICER
ViaSpan Cold Storage	228,885	16.51	
LifePort Machine Perfusion	231,387	16.36	Was dominated
differences	£2,502	-0.153	

The outputs from the model show only very small differences between the arms both for costs and benefits. This reflects the fact that there are only very small differences in the rates of DGF and PNF. However, LifePort was dominated by ViaSpan. i.e. ViaSpan was both less costly and produced more benefits than LifePort. Appendix 8 shows the breakdown of these results by age group.

N.B. When uncertainty about the effectiveness estimates is factored into these inputs it is difficult to arrive at any firm conclusion about a preferred storage alternative based on these trial data.

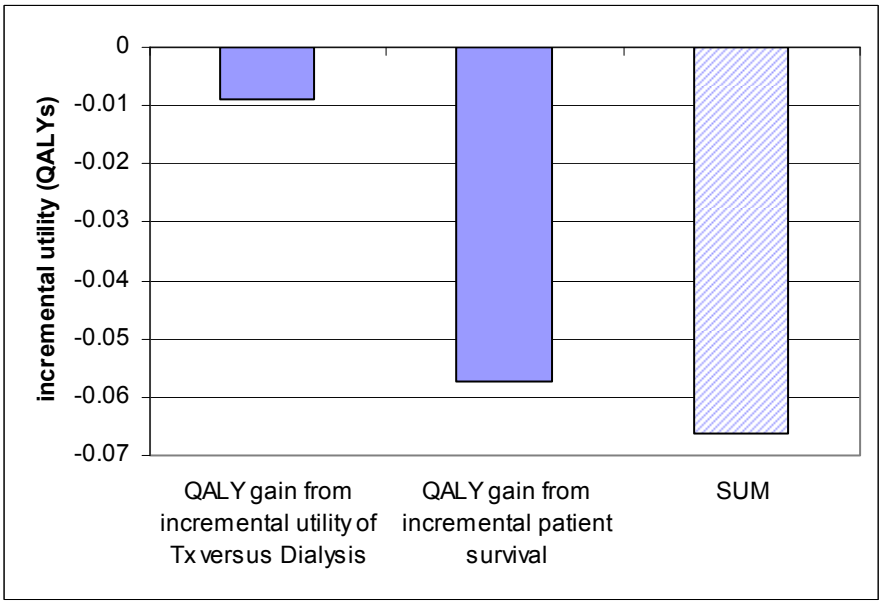
The following component analyses (Figure 15 and Figure 16) show how the incremental costs and benefits between the comparator arms is broken down in terms of their contributory elements. They show that the cost increases from the overall higher life-time dialysis requirements are higher than any savings associated with reduced survival (LifePort confers slightly less patient survival so there is an associated cost saving).

Figure 15. Component analysis of incremental cost of LifePort vs. ViaSpan (PPART data)



The component analysis in Figure 16 shows that most of the estimated reduction in QALYs with LifePort were due to reduced patient survival (in turn due to more life-years on dialysis), and only partly due to the reduced quality of life when on dialysis.

Figure 16. Component analysis of utility gains LifePort vs. ViaSpan



The following event counts were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients. See Table 38

Table 38. Events count output from PenTAG model based on PPART Trial data

DESCRIPTION	ViaSpan	LifePort
Immediate Graft Function	444	422
Delayed Graft Function	556	578
Primary Non-Function	0	22
Graft Failures after IGF	60	57
Deaths in IGF	366	347
Graft Failures after DGF	181	181
Deaths in DGF	362	362
Explants after Graft Failure	18	18
Non-Explant after Graft Failure	219	216
Waiting List after Graft Failure	96	95
Unsuitable for Tx after Graft Failure	141	139
Re-transplants	97	119
Graft failures after re-transplant	66	81
Deaths in subsequent Tx	29	36
Deaths whilst waiting for re-Tx	64	77
Deaths on Dialysis (Tx unsuited)	140	138

LifePort vs. ViaSpan – The Machine Preservation Trial in BSD and DCD patients in Germany, Belgium and the Netherlands.

In order to model cost-utility outcomes based on the Machine Preservation Trial (MPT) data, the standard dataset was modified with the following data drawn from the costing assumptions (described above), and the reported trial outcomes.

Table 39. Summary of differential input parameters based on Machine Preservation Trial Data.

Parameter	ViaSpan	LifePort
Storage cost per kidney	£262.53	£736.55
Percentage of DGF following transplant	[redacted]	[redacted]
Percentage of Primary Non-function	[redacted]	[redacted]
Graft Survival (IGF patients)	[redacted]	[redacted]
Graft Survival (DGF patients)	[redacted]	[redacted]

For the graft survival in the model, regression analysis was used to fit a Weibull curve for the graft survival parameters. In order to provide a representative fit, data supplied by UK Transplant for five year graft survival (classified by IGF and DGF) was used to extrapolate the hazard rate for each population beyond the first year supplied in the trial data. This yielded the following survival curves. See Figure 17. It should be noted here that it was necessary to read survival estimates directly from presented Kaplan-Meier curves, permitting possible error. It would have been useful to have the corresponding numerical data for graft survival from this trial in accordance with best practice for presenting survival data [113].

Figure 17. Weibull Survival estimates of Graft Survival for IGF and DGF patient groups used by the model for comparison of ViaSpan and LifePort based on MPT Trial.

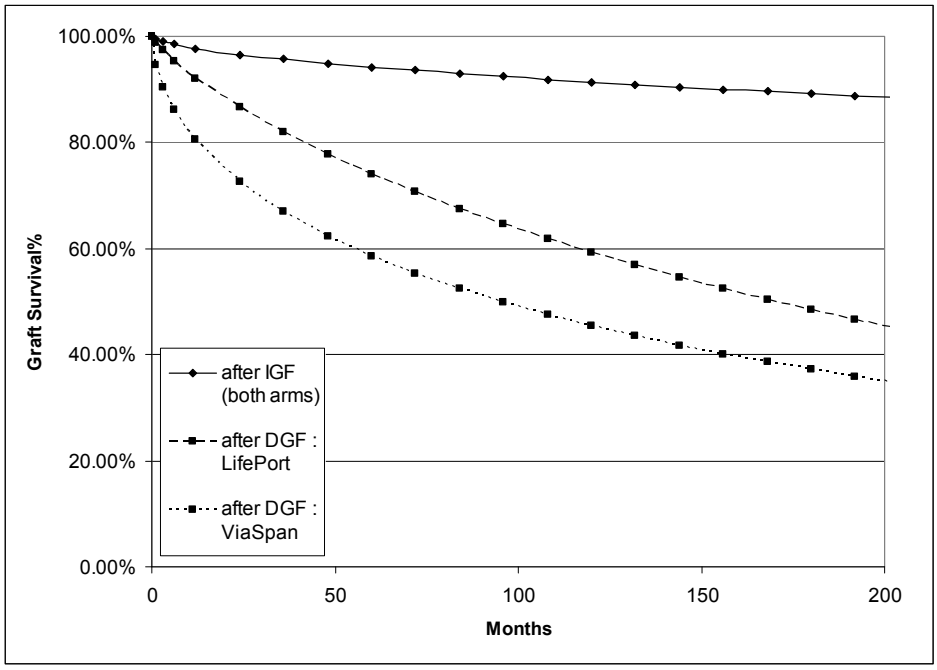


Table 40 below shows the base case outputs from the model for each comparator arm. These are the deterministic model outputs with discounting and show the cost and utilities per patient for each treatment option, as well as the incremental values for costs and QALYs.

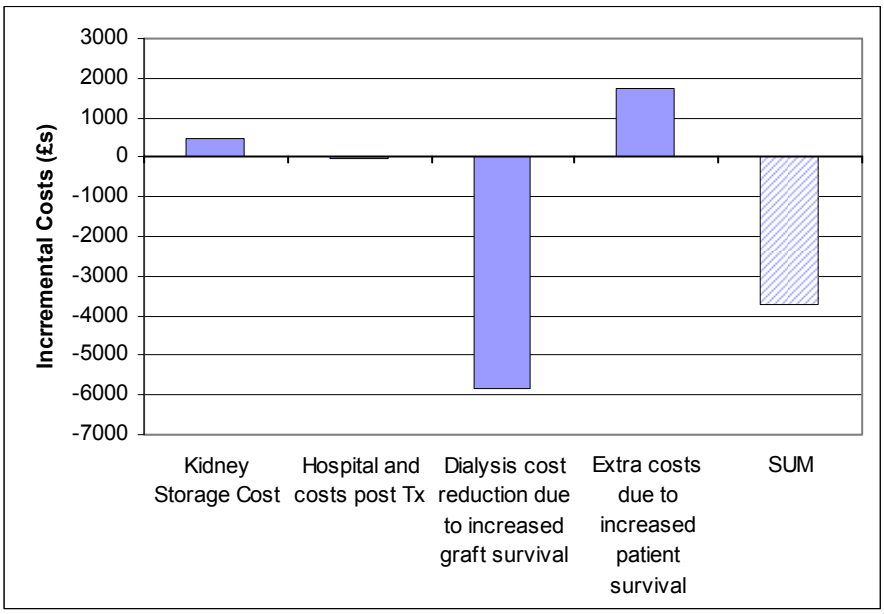
Table 40. Base Case deterministic outputs from PenTAG model based on Machine Preservation Trial data

	DISCOUNTED COSTS (£s) per patient	DISCOUNTED BENEFITS (QALYs) Per patient	ICER
ViaSpan Cold Storage	142,805	9.58	Was dominated
LifePort Machine Perfusion	139,110	9.79	
	-£3,695	0.218	
	UNDISCOUNTED COSTS (£s) per patient	**UNDISCOUNTED BENEFITS (QALYs) Per patient**	**ICER**
ViaSpan Cold Storage	232,301	17.20	Was dominated
LifePort Machine Perfusion	228,540	17.68	
differences	-£3,761	0.485	

The deterministic outputs from the model show that, for the input parameters derived from this study, LifePort Machine Perfusion dominates the cost-utility analysis. That is to say that this method of storage results in both lower overall costs of treatment and greater benefits to patients when compared to cold storage using the ViaSpan solution. Appendix 8 shows the breakdown of these results by age group.

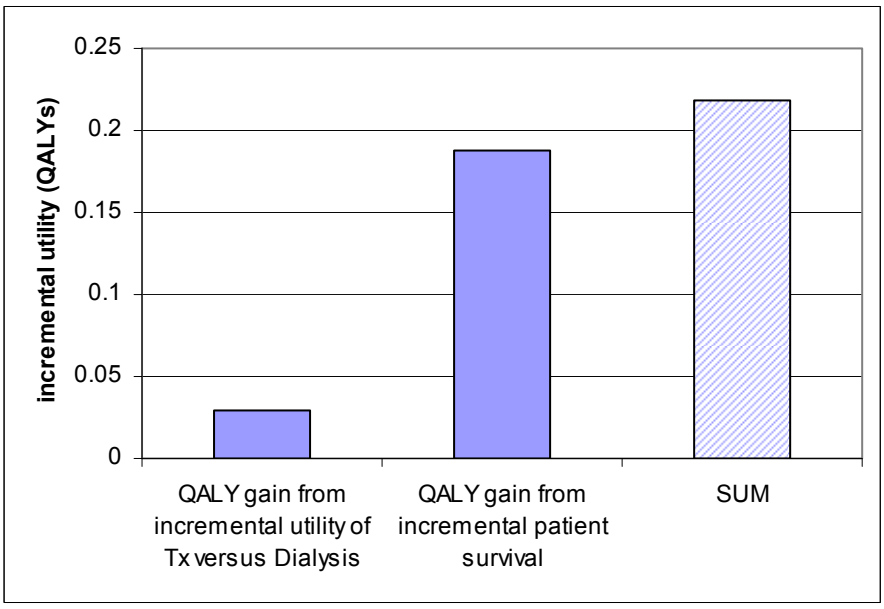
The following component analyses (Figure 18 and Figure 19) show how the difference in costs and benefits between the comparator arms is broken down. Here it can be seen that the cost savings from reducing the dialysis requirement far outweighs the costs associated with kidney storage.

Figure 18. Component analysis of incremental costs of LifePort vs. ViaSpan (MPT Data)



In Figure 19 it can be seen that, compared to ViaSpan, LifePort machine preservation confers additional QALYs mainly through survival gains rather than the utility gains associated with less time back on dialysis.

Figure 19. Component analysis of utility gains LifePort vs. ViaSpan



The following event counts in Table 41 were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

Table 41. Events count output from PenTAG model based on Machine Preservation Trial data

DESCRIPTION	ViaSpan Cold Storage	LifePort Machine Perfusion
Immediate Graft Function	[redacted]	[redacted]
Delayed Graft Function	[redacted]	[redacted]
Primary Non-Function	[redacted]	[redacted]
Graft Failures after IGF	93	100
Deaths in IGF	612	660
Graft Failures after DGF	132	103
Deaths in DGF	84	83
Explants after Graft Failure	18	14
Non-Explant after Graft Failure	203	186
Waiting List after Graft Failure	89	81
Unsuitable for Tx after Graft Failure	132	119
Re-transplants	142	103
Graft failures after re-transplant	97	70
Deaths in subsequent Tx	44	31
Deaths whilst waiting for re-Tx	90	68
Deaths on Dialysis (Tx unsuited)	131	118

6.6.1.2. LifePort vs. Marshall's Soltran cold storage solution

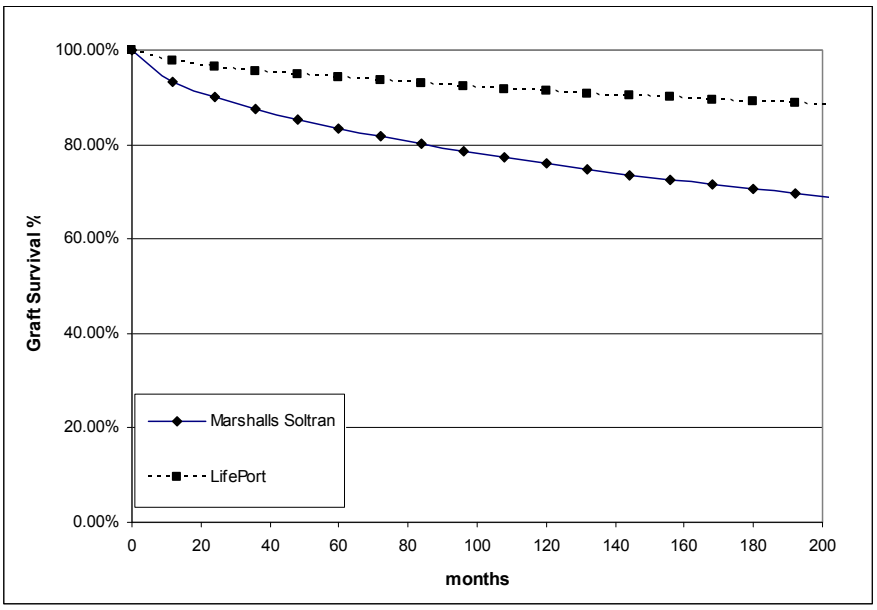
For the cost-utility comparison of Marshall's Soltran solution vs. the LifePort MP, one clinical effectiveness study by Plata-Munoz and colleagues[53] has been used to provide effectiveness data for this cost-utility analysis. The following comparator-specific data were input into the model in addition to the standard dataset described above. See Table 42.

Table 42. Differential input data for compared arms based on Plata-Munoz data

	Marshall's Soltran Solution	LifePort
Storage cost per kidney	£49.73	£736.55
Percentage of DGF following transplant	83%	53%
Percentage of Primary Non-function	0%	0%
Graft Survival (All patients) at 2 years	90.0%	96.7%

Regression analysis was used to fit a Weibull curve for each of the graft survival parameters used for this comparison. In order to provide a representative fit, data supplied by UK Transplant for five year graft survival (classified by IGF and DGF) was used to extrapolate beyond the two year data supplied in the trial data. No data were supplied in the trial to discriminate between graft survival for IGF and DGF patients so both population groups were assumed to experience the same graft survival. The following survival curves for each arm were employed in the model.

Figure 20. Weibull Survival estimates of Graft Survival for each arm of comparison of Marshall's Soltran and LifePort.



These data yielded the following summary base case outputs from the model for cost and benefit differences.

Table 43. Base Case deterministic outputs from PenTAG model based on Plata-Munoz data

	DISCOUNTED COSTS (£s) Per patient	DISCOUNTED BENEFITS (QALYs) Per patient	ICER
Marshall's Soltran Solution	144,332	8.55	Was dominated
LifePort Machine Perfusion	132,953	9.54	
differences	-£11,379	0.993	
	UNDISCOUNTED COSTS (£s) Per patient	**UNDISCOUNTED BENEFITS (QALYs) Per patient**	**ICER**
Marshall's Soltran Solution	235,844	14.99	Was dominated
LifePort Machine Perfusion	220,662	17.54	
differences	-£15,182	2.551	

The deterministic outputs from the model show that, for the input parameters derived from this study, LifePort Machine Perfusion dominates the cost-utility analysis. That is to say that this method of storage results in both lower overall costs of treatment and greater benefits to patients when compared to cold storage using the Marshall's solution. Appendix 8 shows the breakdown of these results by age group.

The following component analyses (Figure 21 and Figure 22) show the breakdown of costs and utility gains between the comparator arms. These figures show that the reduction in dialysis costs is the most important factor in the relatively lower costs of LifePort, and that improved graft survival is the key factor leading to the greater QALY output for LifePort compared to Marshall's Soltran.

Figure 21. Component analysis of incremental costs of LifePort vs. Marshall's Soltran

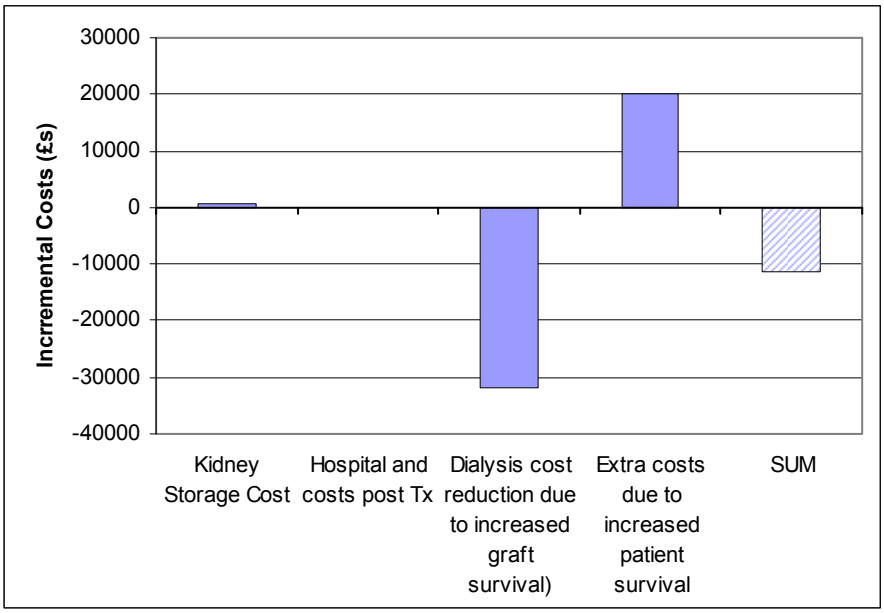
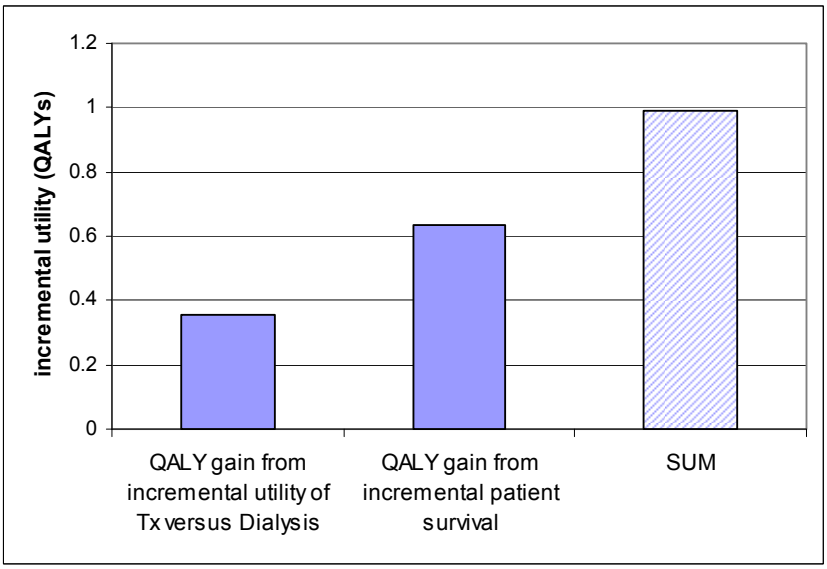


Figure 22. Component Analysis of Incremental utility gains of LifePort vs. Marshall's Soltran



The following event counts in Table 44 were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

Table 44. Events count output from PenTAG model based on Plata-Munoz data

DESCRIPTION	Marshall's Cold Storage Solution	LifePort Machine Perfusion
Immediate Graft Function	167	467
Delayed Graft Function	833	533
Primary Non-Function	0	0
Graft Failures after IGF	54	60
Deaths in IGF	109	388
Graft Failures after DGF	267	67
Deaths in DGF	547	444
Explants after Graft Failure	23	9
Non-Explant after Graft Failure	293	116
Waiting List after Graft Failure	128	51
Unsuitable for Tx after Graft Failure	188	74
Re-transplants	129	49
Graft failures after re-transplant	88	34
Deaths in subsequent Tx	39	15
Deaths whilst waiting for re-Tx	85	34
Deaths on Dialysis (Tx unsuited)	186	73

6.6.2. Cold storage solution vs. cold storage solution

6.6.2.1. ViaSpan vs. Marshall's Soltran solution

For the cost-utility comparison of Marshall's Soltran solution vs. LifePort, one study Opelz and Dohler [55] satisfied our inclusion criteria. This registry data study provided inputs for graft survival at three years. The following between arms data were put into the model in addition to the underlying standard dataset. See Table 45.

Table 45. Differential input data for compared arms based on Opelz and Dohler data

	ViaSpan	Marshall's Soltran
Storage cost per kidney	£262.53	£49.73
Graft Survival (IGF patients) at 3 Years	79.5%	77.7%

Weibull curve fits for each of the graft survival parameters used for this comparison were calculated using regression analysis. Three year graft survival data for each arm

was extracted from the study data and used to calculate representative Weibull parameters for each arm of the trial. Since no data were supplied to distinguish between graft survival for IGF versus DGF patients in this study both patient groups were assumed to have the same graft survival. The following survival curves for each arm were employed in the model. For many data points, it was necessary to read survival estimates directly from presented Kaplan-Meier curves and it would have been useful to have the corresponding numerical data for graft survival from this trial in accordance with best practice for presenting survival data [113].

Figure 23. Weibull Survival estimates of Graft Survival for each arm of comparison of ViaSpan and Marshall's Soltran.

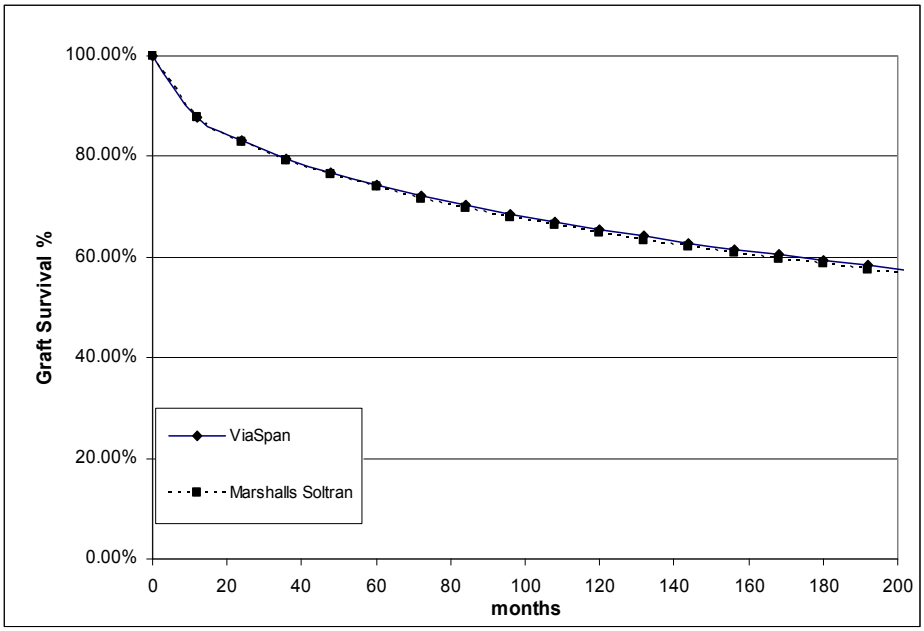


Table 46. Base case deterministic outputs from PenTAG model based on Opelz and Dohler data

	DISCOUNTED COSTS (£s) Per patient	DISCOUNTED BENEFITS (QALYs) Per patient	ICER
ViaSpan Solution	151,001	8.62	
Marshall's Soltran Solution	151,826	8.57	Was dominated
Differences	£825	-0.049	

	UNDISCOUNTED COSTS (£s) Per patient	UNDISCOUNTED BENEFITS (QALYs) Per patient	ICER
ViaSpan Solution	242,714	14.78	
Marshall's Soltran Solution	243,658	14.64	Was dominated
differences	£944	-0.141	

Table 46 shows the summary base case outputs from the model, these indicate that for the specific input parameters derived from this study, ViaSpan results in both lower overall costs of treatment and confers greater benefits to patients when compared to cold storage using the Marshall's Soltran solution. However, these differences are seen to be very small in the context of the overall levels of uncertainty surrounding the input parameters. In practice it is difficult to make conclusions based on these output data with any level of confidence. Appendix 8 shows the breakdown of these results by age group.

The following component analyses (Figure 24 and Figure 25) show the breakdown of costs and benefits between the comparator arms. This again shows that it is the costs of dialysis that are having the major influence on cost outcomes, together with gains in survival from ViaSpan causing it to dominate Marshall's Soltran.

Figure 24. Component analysis of incremental costs of Marshall's Soltran vs. ViaSpan

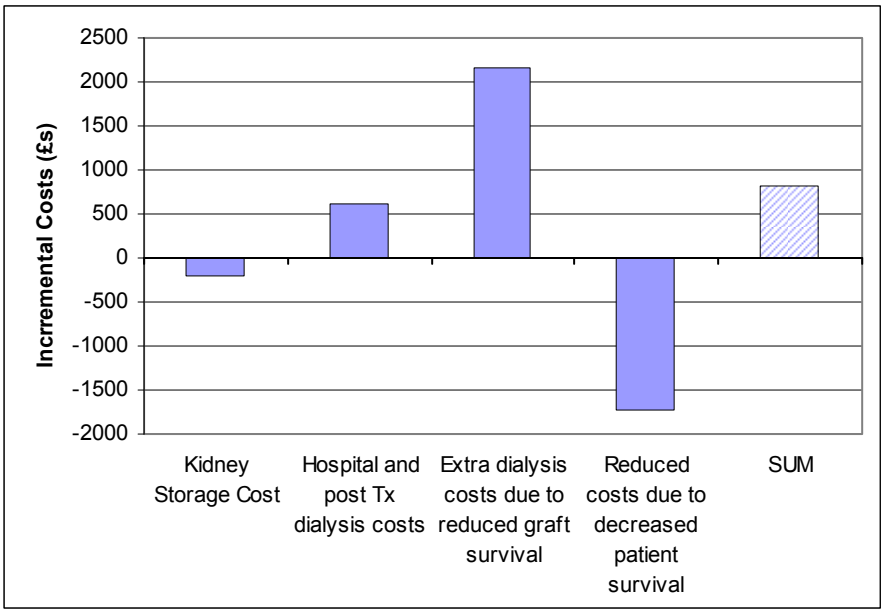
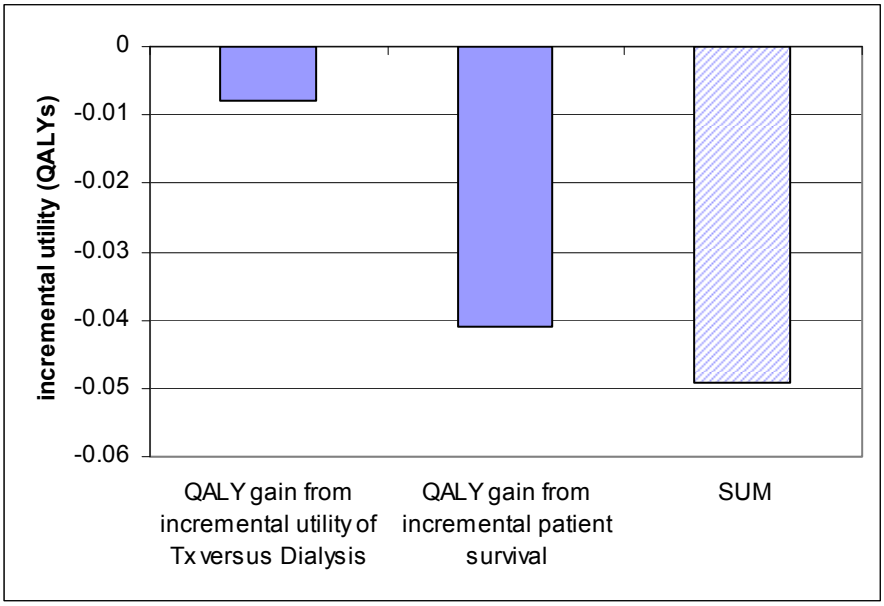


Figure 25. Component analysis of incremental benefits of Marshall's Soltran vs. ViaSpan



The following event counts in Table 47 were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

Table 47. Events count output from PenTAG model based on Opelz and Dohler data

DESCRIPTION	ViaSpan Solution	Marshall Solution
Immediate Graft Function	500	500
Delayed Graft Function	500	500
Primary Non-Function	0	0
Graft Failures after IGF	208	212
Deaths in IGF	284	281
Graft Failures after DGF	204	216
Deaths in DGF	287	276
Explants after Graft Failure	35	36
Non-Explant after Graft Failure	370	383
Waiting List after Graft Failure	163	169
Unsuitable for Tx after Graft Failure	242	251
Re-transplants	170	177
Graft failures after re-transplant	116	121
Deaths in subsequent Tx	51	53
Deaths whilst waiting for re-Tx	107	111
Deaths on Dialysis (Tx unsuited)	240	250

6.6.3. Summary of deterministic results

The two RCTs based on the comparison of cold storage with ViaSpan versus LifePort Machine preservation are based on different populations and have therefore been modelled separately. In the European Machine Preservation Trial, machine preservation dominates cold storage in the cost-utility analysis (i.e. machine preservation is both cheaper and more effective than cold storage). In contrast when the UK PPART study data is used to parameterise the model, cold storage dominates machine preservation. It should be noted that in the PPART study no outcomes demonstrated significant differences between trial arms, and for the Machine Preservation Trial [redacted]. When this underlying uncertainty is embodied in the model little confidence can be given to any conclusions preferring one storage method over another.

The deterministic outputs based on the study which compared the use of Marshall's Soltran solution with LifePort machine preservation showed that LifePort dominated Marshall's Soltran, indicating that machine preservation is both cheaper and more effective as a treatment option. However, once again, the uncertainty associated with the data inputs from this study would caution against any confident conclusions.

The comparison of ViaSpan and Marshall's Soltran cold storage solution show very small differences between the arms which given the uncertainty in the input data also give little basis for any confident conclusions. However, ViaSpan was shown to dominate Marshall's Soltran.

It should be noted that the differential costs of kidney storage associated with the different storage methods are relatively small when compared with the gains that result from any small improvement in effectiveness that can be demonstrated, e.g. through gains in graft survival. However, strong evidence that such differences in effectiveness exist have yet to be found.

6.7. One-way sensitivity analysis

In order to explore the dynamics and key interactions of our decision model an initial series of one-way sensitivity analyses were conducted. For these, individual model parameters of interest are varied between selected minimum and maximum values

and the impact that these specific input changes have on the key model outputs was examined.

One-way sensitivity analyses were performed for each of the four treatment comparisons undertaken and are reported separately below. Observations from the one-way sensitivity analyses are then discussed more generally.

The chosen metric used to summarise the model output in the following analyses below is Net Benefit shown at willingness-to-pay threshold at £30,000 per QALY. Net benefit is calculated by using the following formula:

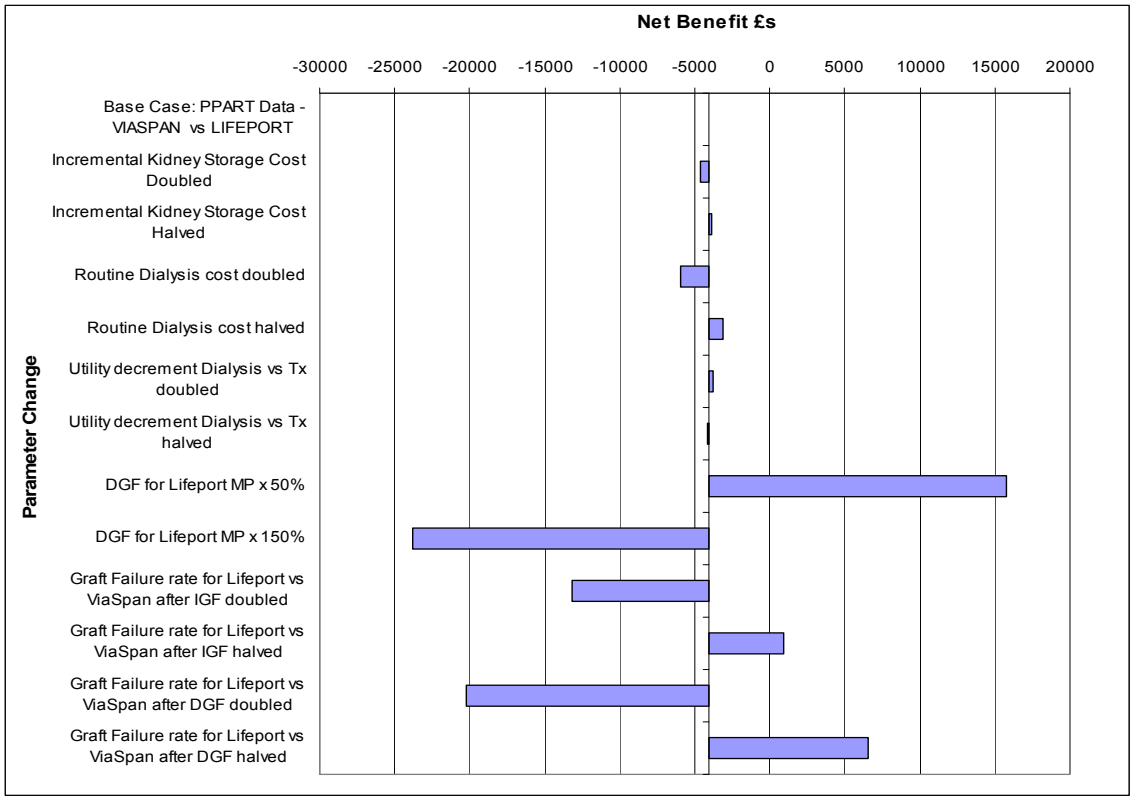
Net Benefit = wQ - C

where *Q*=incremental benefit of comparison, *C*=incremental cost of comparison and *w*=willingness-to-pay for each additional unit of benefit.

6.7.1. One-way sensitivity analysis: LifePort vs. ViaSpan (PPART study with DCD donor kidney transplants)

The tornado chart below (Figure 26) shows the output changes from the base case in the model induced by each of the listed changes in the input parameter when the model is used to compare ViaSpan with LifePort based on the data derived from the PPART trial.

Figure 26. Net Benefit changes to LifePort vs. ViaSpan (measured at a willingness-to-pay of £30K per QALY) caused by specific input parameter changes to model - PPART.

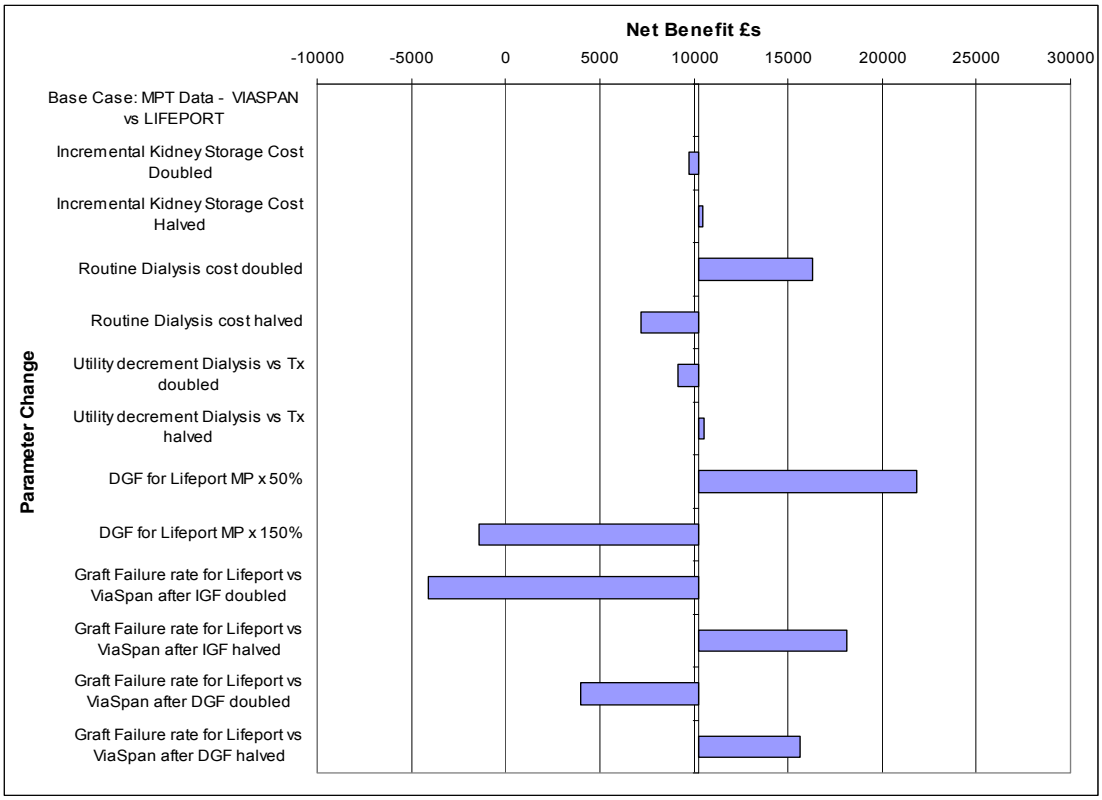


In this comparison the largest impact to net benefit output is seen to arise from changes to the effectiveness parameters. Differential DGF rates between the treatment arms and differential rates of graft failure between arms create the largest changes to net benefit outputs. Costs of dialysis and kidney storage as well as the level of utility decrement applied to dialysis in relation to transplant have relatively little impact on the net benefit output.

6.7.2. LifePort vs. ViaSpan (Machine Preservation Trial in BSD and DCD patients)

Figure 27 shows the one way sensitivity outputs from the model for the LifePort vs. ViaSpan comparison, based on the data derived from the Machine Preservation trial.

Figure 27. Net Benefit changes to LifePort vs ViaSpan (measured at a willingness-to-pay of £30K per QALY) caused by specific input parameter changes to model - MPT.

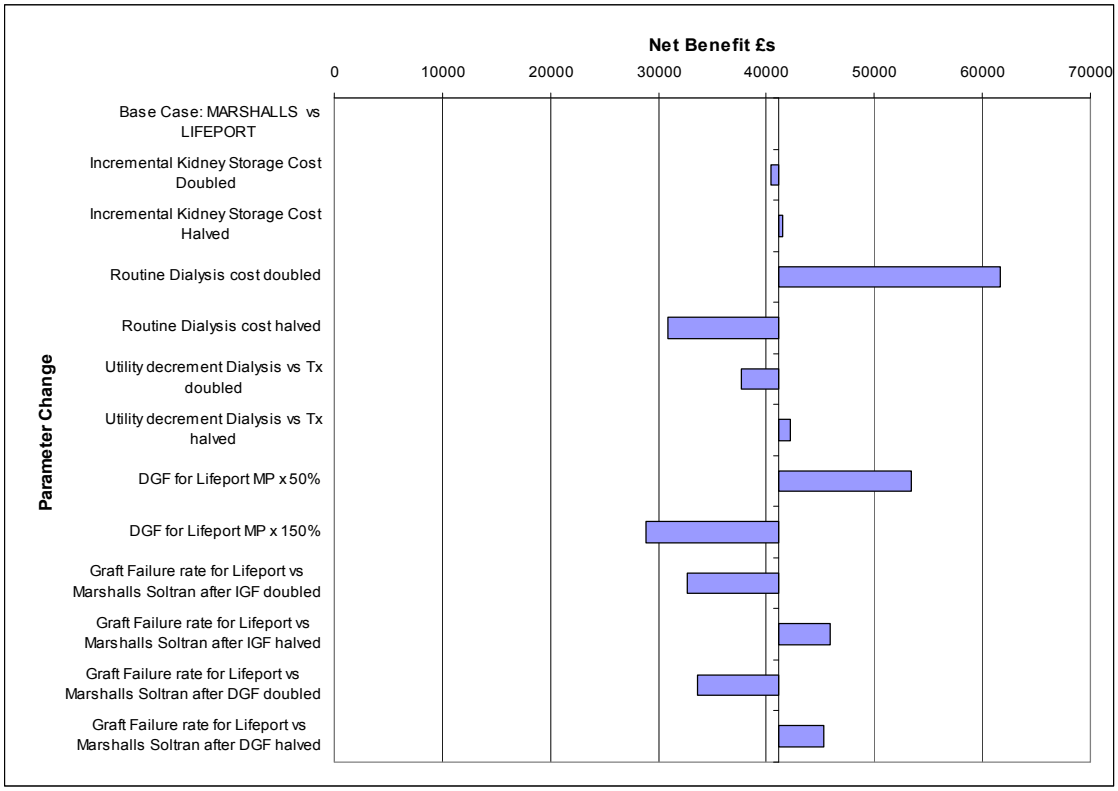


In this comparison the largest impact to net benefit output arises from changes to the effectiveness parameters and changes to dialysis costs. The latter result is explained by the fact that differential effectiveness levels inherent in the input parameters for this comparison mean that dialysis cost savings are a major factor in the incremental cost which in turn affects net benefit. Changes to the cost of kidney storage and the level of utility decrement applied to dialysis in relation to transplant have relatively little impact net benefit output.

6.7.3. Marshall's Soltran vs. LifePort

Figure 28 shows one way sensitivity outputs from the model for the Marshall's Soltran vs. LifePort MP comparison.

Figure 28. Net Benefit changes to LifePort vs Marshall's Soltran (measured at a willingness-to-pay of £30K per QALY) caused by specific input parameter changes to model.

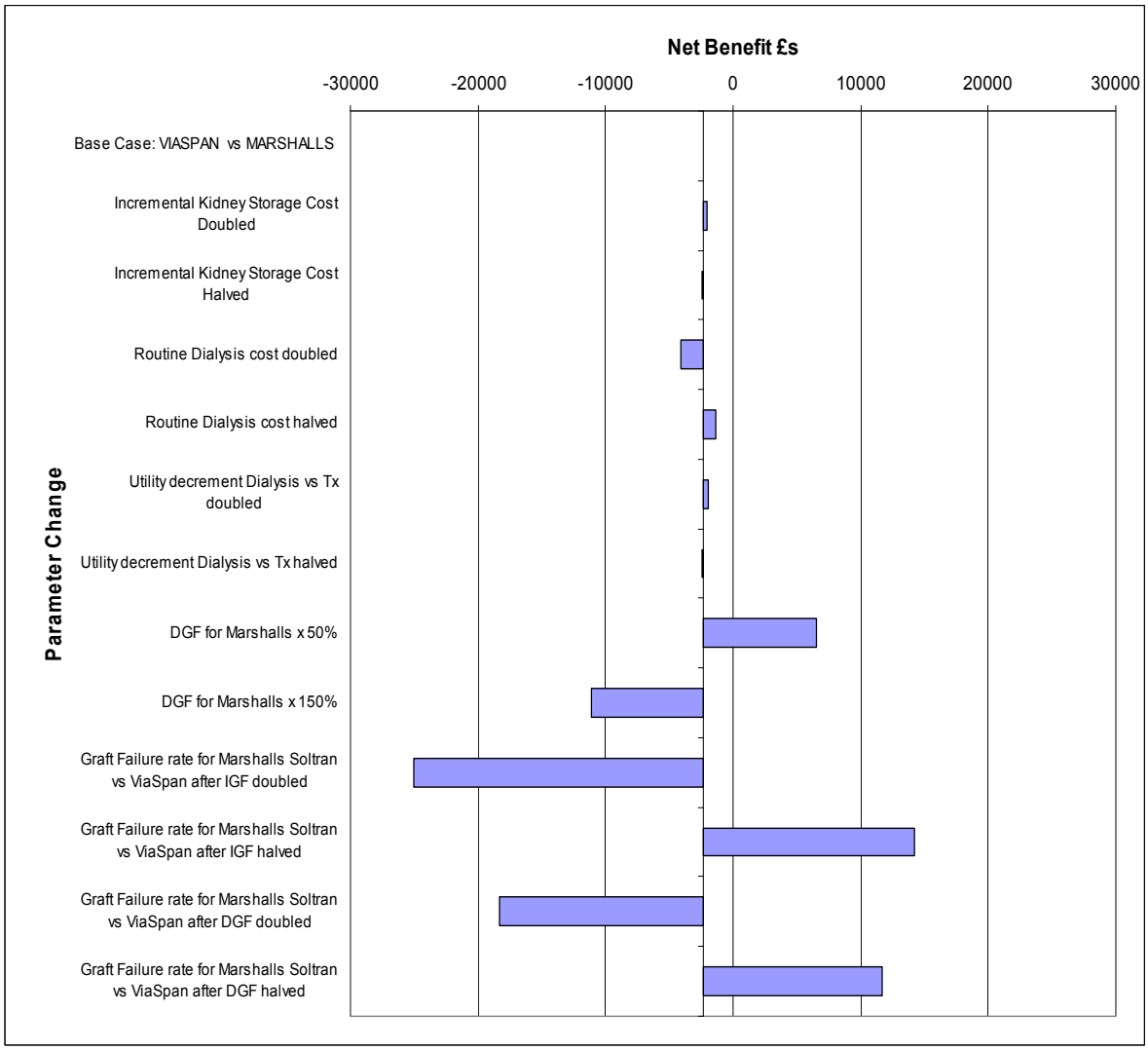


For this comparison the largest impact to net benefit output arises from changes to the effectiveness parameters and changes to dialysis costs. High levels of DGF inherent in this study data mean that differential graft failure after DGF has a particularly strong impact on the net benefit output by the model when these data are used. Changes to the utility decrement in this analysis have had a small but significant effect on the net benefit. Cost of kidney storage has relatively little impact net benefit output.

6.7.4. Marshall's Soltran vs. ViaSpan

The following tornado chart (Figure 29) shows one way sensitivity outputs from the model for the ViaSpan vs. Marshall's Soltran comparison.

Figure 29. Net Benefit changes to Marshall's Soltran vs ViaSpan (measured at a willingness-to-pay of £30K per QALY) caused by specific input parameter changes to model – ViaSpan vs. Marshall's Soltran.



For this comparison the largest impact to net benefit output arises from changes to the effectiveness parameters related to differential graft failure rate for those patients in the model who experienced IGF. This reflects the fact that relatively low levels of DGF are recorded in this study. The lack of any differential impact of DGF on graft survival in the inputs also entails that changes to the hazard ratio of DGF has a relatively small impact on net benefit. Dialysis cost changes do not have a large impact since for the base case data little effectiveness difference is apparent, hence incremental cost caused by dialysis costs in the model are small. Once again, changes to the storage costs for donated kidneys have a very minor impact.

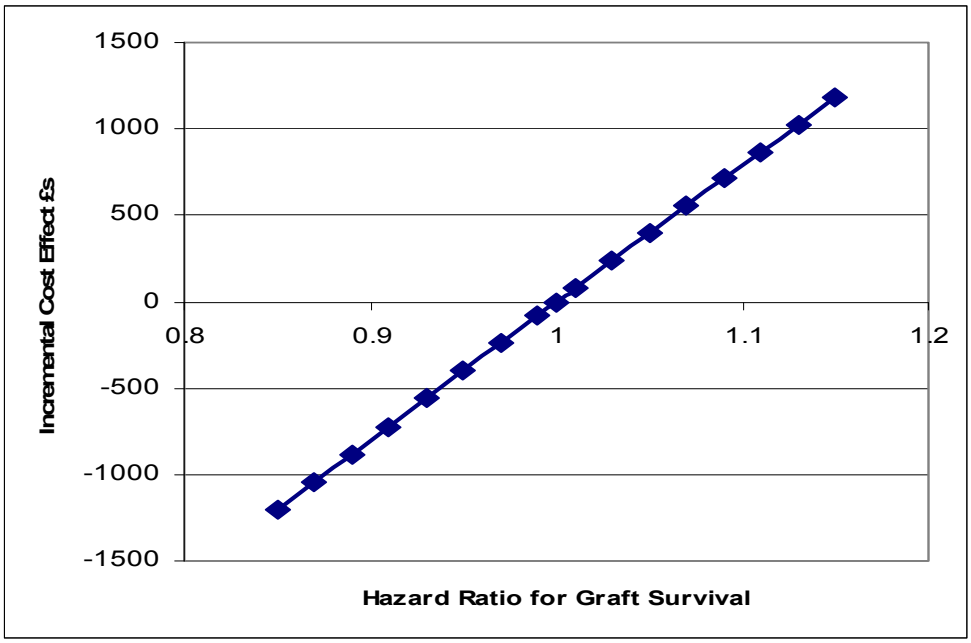
6.7.5. General observations from the one-way sensitivity analyses

Although the one-way analyses described above are for different comparisons the following general observations can be made from these model outputs.

- Changes to the differential kidney storage costs between comparators have a very low impact on the overall net benefit estimates, when set against the impact of changes to differential levels of graft survival between comparators.
- Where differences in graft survival exist between comparators, dialysis costs become an important factor in determining the overall net benefit level.
- Levels of DGF between arms become important where differences in graft survival are apparent between those patients experiencing IGF versus DGF.
- The relative impact of differential changes to graft survival for patients experiencing IGF as opposed to DGF depends on the relative proportion of patients experiencing each of these two outcomes (IGF vs. DGF). For example, if very few patients in the model experience DGF, then graft survival changes for DGF patients has a small impact on the overall net benefit output.

A simple analysis was conducted using the graft survival data from the standard dataset (see Table 32 above) where both comparators were given identical input parameters apart from graft survival, which was varied between the arms according to a hazard ratio. It can be seen from Figure 30, below, that there is a relatively linear relationship between the hazard ratio for graft survival between comparators and cost savings over the range in this analysis. A graft survival hazard ratio of 0.1 between arms (which equates to about a 1% graft survival advantage after five years) will generate a cost saving of around £800 per patient, which is already enough to cover the estimated additional per kidney cost of using LifePort. In addition, utility gains will be associated with any incremental advantage in hazard ratio for graft survival. Graphs showing the effect on incremental QALYs between arms and overall net benefit are included in Appendix 9.

Figure 30. Impact on costs of incremental hazard ratio for graft survival between comparator arms



Although one-way sensitivity analysis provides a useful tool for investigating some of the key relationships in the model, it is limited in that only single input parameters are varied. Possible interaction effects between the input variables in the model are therefore not revealed in such analyses. The probabilistic sensitivity analyses (PSA) presented below partly explore these potential interaction effects.

6.8. Probabilistic sensitivity analysis

In order to explore the underlying parameter uncertainty on cost-effectiveness for the different comparisons, a probabilistic sensitivity analysis (PSA) was undertaken using the PenTAG model. In this randomly determined approach, Monte Carlo simulation is used to sample parameter values from specified probability distributions rather than using fixed input values. The Markov model is run 1000 times using parameter values randomly drawn from probabilistic density functions for each model run. In this simulation, transitions, utility values and costs are all sampled from probability distributions in order to represent the underlying uncertainty associated with these input variables. A full listing of the values used for the probabilistic distributions in the PSA, as well as a description of the methods used to derive these values, is given in Appendix 10.

Outputs for the Monte-Carlo simulation are shown for each of the comparisons below. For each comparison, these illustrate the Incremental Cost-effectiveness Ratio (ICER) values for 1000 simulated trials. A cost-effectiveness acceptability curve (CEAC) has also been calculated showing, at different levels of willingness-to-pay for an additional QALY, the probability that each compared kidney storage method is cost-effective.

6.8.1. PSA for machine perfusion vs. cold static storage

6.8.1.1. LifePort vs. ViaSpan

LifePort vs. ViaSpan - PPART study with DCD donor kidney transplants

Figure 31 below shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation. These demonstrate the levels of uncertainty associated with the cost and effectiveness outputs from both arms of this comparison when the parameter uncertainty is included in the model. The figure shows that the variation due to parameter uncertainty within each arm is much greater than any difference between the arms.

Figure 31. Scatter plot from probabilistic simulation based on PPART data for ViaSpan vs. LifePort

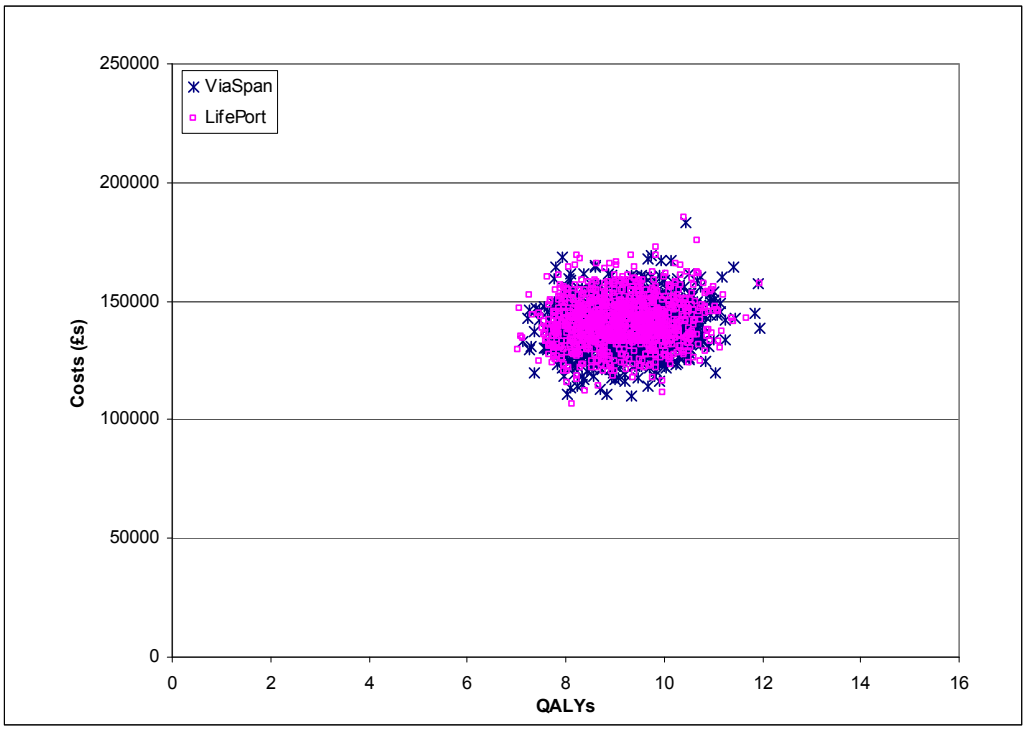


Figure 32 below represents the outputs shown above in terms of the incremental costs and benefits of LifePort vs. ViaSpan. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000 per QALY (solid line) and £30,000 per QALY (dashed line). Once again the inherent uncertainty of the outputs is shown by the distribution of dots across the cost-effectiveness plane. This graph shows that there is no clear conclusion that can be drawn about the relative cost-effectiveness.

Figure 32. Incremental cost-effectiveness ratio of LifePort vs. ViaSpan based on PPART trial data

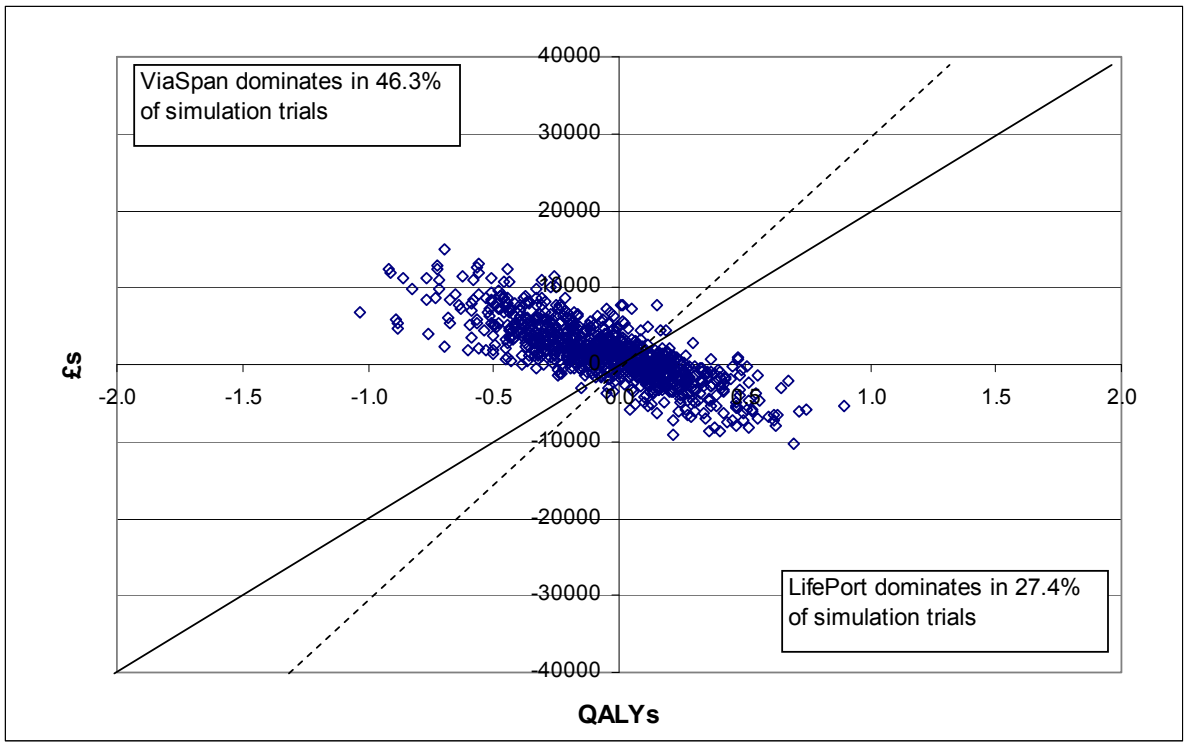
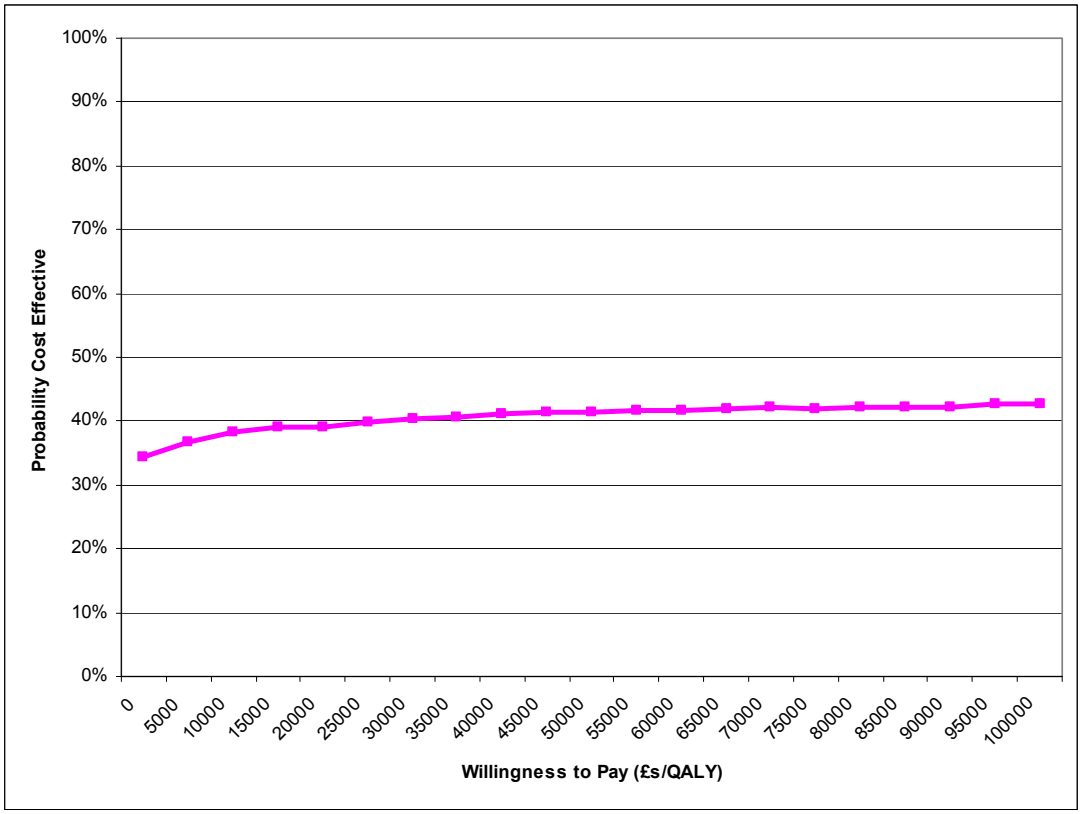


Figure 33 below shows the Cost-effectiveness Acceptability Curve (CEAC) for the comparison of ViaSpan with LifePort based on the PPART data. This shows the probability, based on the probabilistic model outputs that the LifePort storage option is cost-effective over a range of different levels of willingness-to-pay for each extra QALY conferred by adopting this treatment. This shows that over a range of WTP thresholds the model predicts around a 40% likelihood that LifePort will be cost-effective when compared to ViaSpan.

Figure 33. Cost-effectiveness acceptability curve for LifePort vs. ViaSpan: PPART Trial data



LifePort vs. ViaSpan – The Machine Preservation Trial in BSD and DCD patients

Figure 34 below shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation based on the inputs from the MPT trial data. Levels of uncertainty associated with the cost and effectiveness outputs from both arms of this comparison when the parameter uncertainty is included in the model are demonstrated by the distribution of output points. The scatter plot shows that the estimated cost-effectiveness of the comparators is very similar.

Figure 34. Scatter plot from probabilistic simulation based on MPT data for LifePort vs. ViaSpan

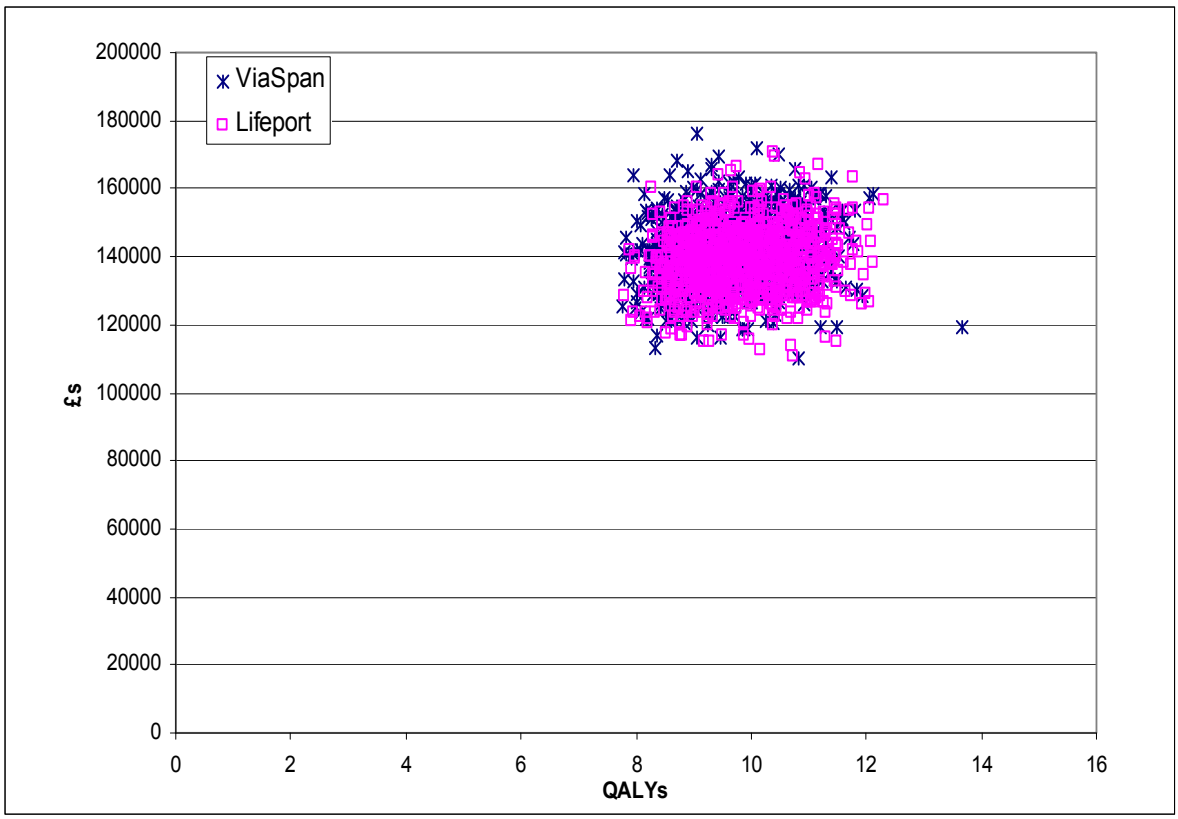


Figure 35 below represents the outputs shown above in terms of the incremental costs and benefits of LifePort vs. ViaSpan. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000 per QALY (solid line) and £30,000 per QALY (dashed line). Once again the inherent uncertainty of the outputs is shown by the distribution of dots across the cost-effectiveness plane. The majority of data points in the lower right hand quadrant indicates that LifePort is more likely to be cost-effective at any level of willingness-to-pay.

Figure 35. Incremental cost-effectiveness ratio of LifePort MP vs. ViaSpan based on MPT data

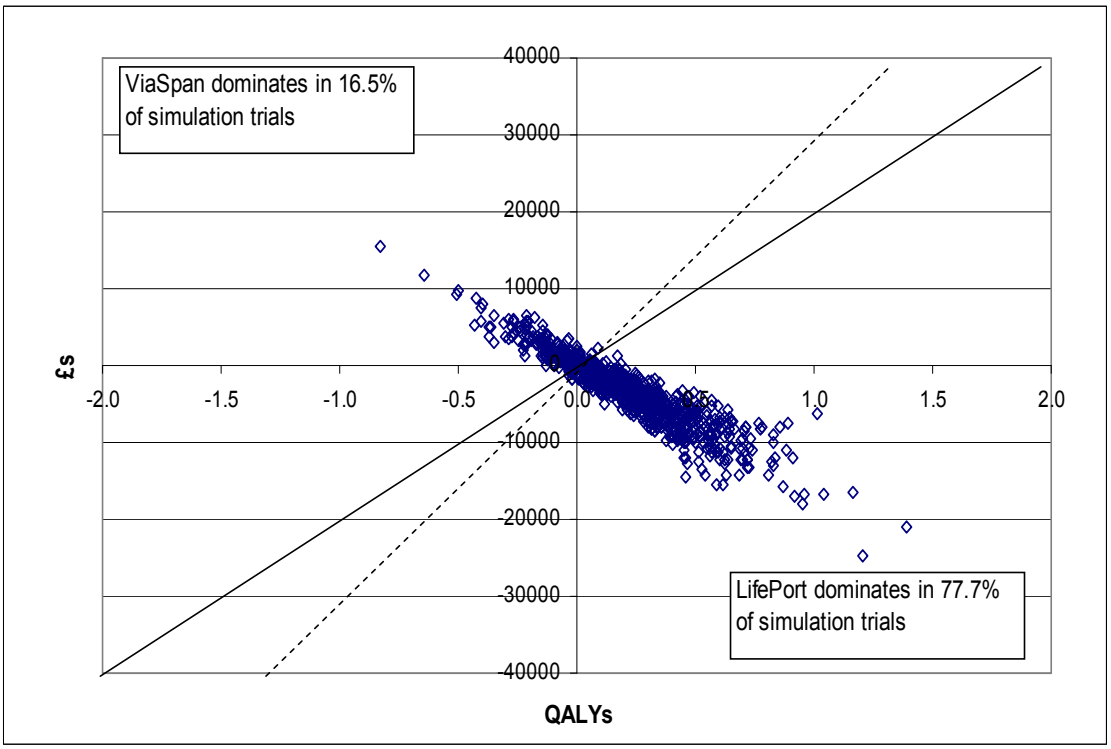
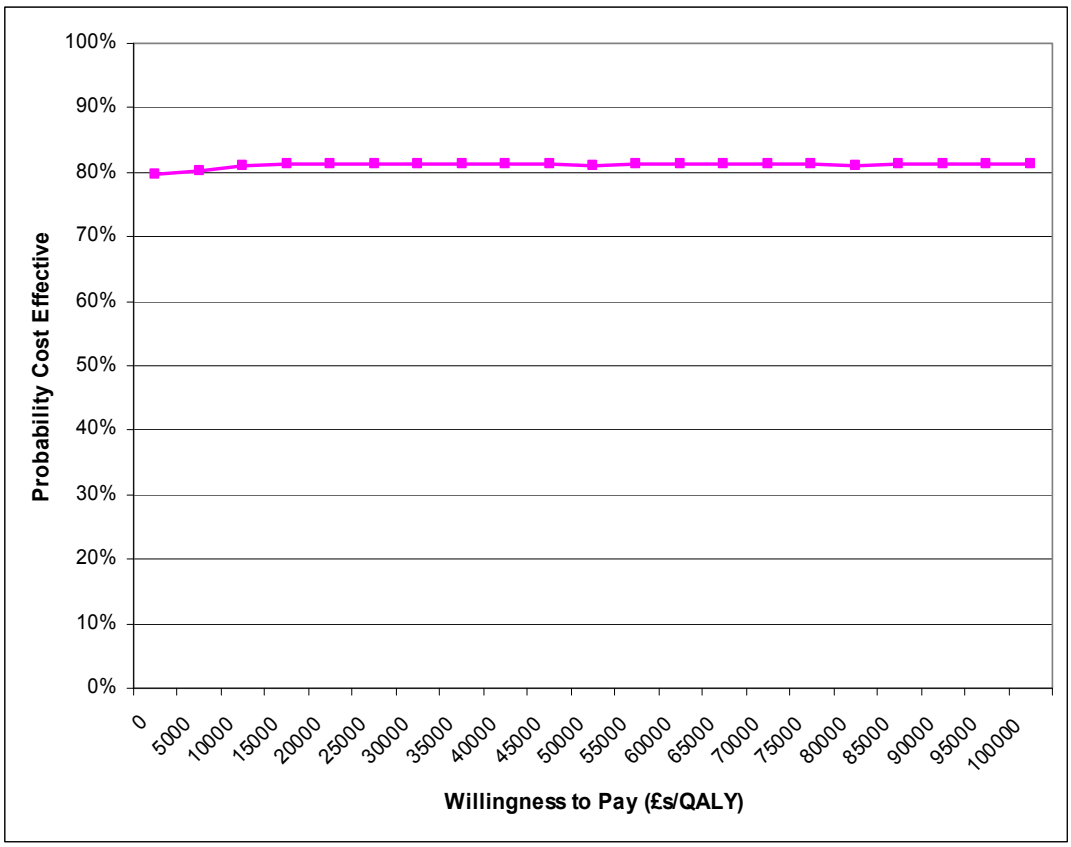


Figure 36 below shows the CEAC for the comparison of LifePort with ViaSpan based on the MPT data. This shows the probability based on the PSA outputs that the LifePort storage option is cost-effective over a range of different levels of willingness-to-pay for each extra QALY conferred by adopting this treatment. It indicates that there is a 80% probability that LifePort is cost-effective across the willingness-to-pay range.

Figure 36. Cost-effectiveness acceptability curve for LifePort vs. ViaSpan based on MPT data



6.8.1.2. LifePort vs. Marshall's Soltran cold storage solution

Figure 37 below shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation based on the trial data for cold storage with Marshall's solution vs. LifePort machine preservation. The distribution of output points illustrates the levels of uncertainty associated with the cost and effectiveness outputs from both arms of this comparison when the parameter uncertainty is taken into account in the model. This illustrates the large level of uncertainty apparent in model outputs when parameter uncertainty is incorporated. Once again there is a strong overlap between the outputs from each arm indicating much more variation within the comparator arms than between them.

Figure 37. Scatter plot from probabilistic simulation for Marshall's Soltran vs. LifePort

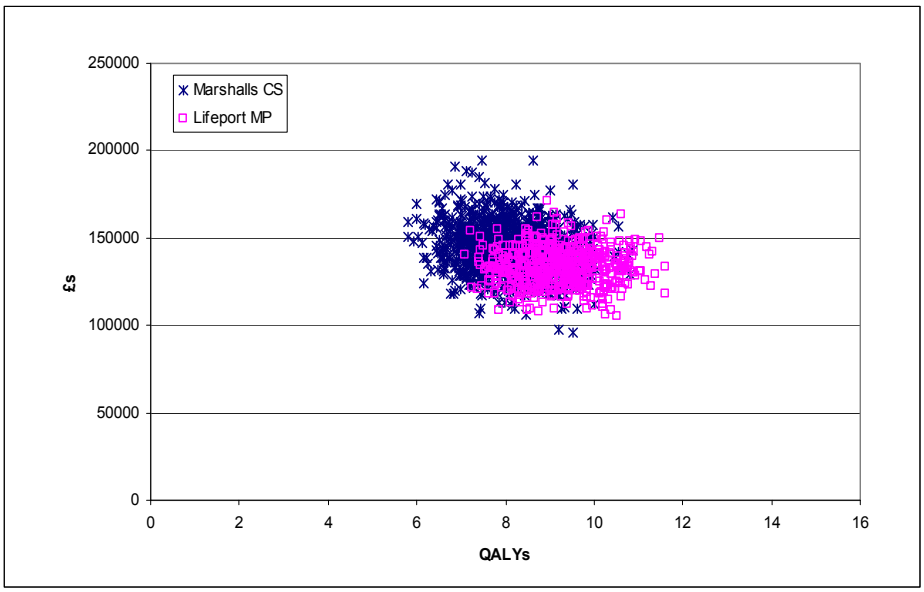


Figure 38 below represents the outputs shown above in terms of the incremental costs and benefits of LifePort vs. Marshall's Soltran. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000 per QALY (solid line) and £30,000 per QALY (dashed line). This shows that for these data there is a high level of uncertainty inherent in the output simulations with LifePort dominating over Marshalls Soltran in a great number of the simulation trials.

Figure 38. Incremental Cost-effectiveness of LifePort vs. Marshall's Soltran

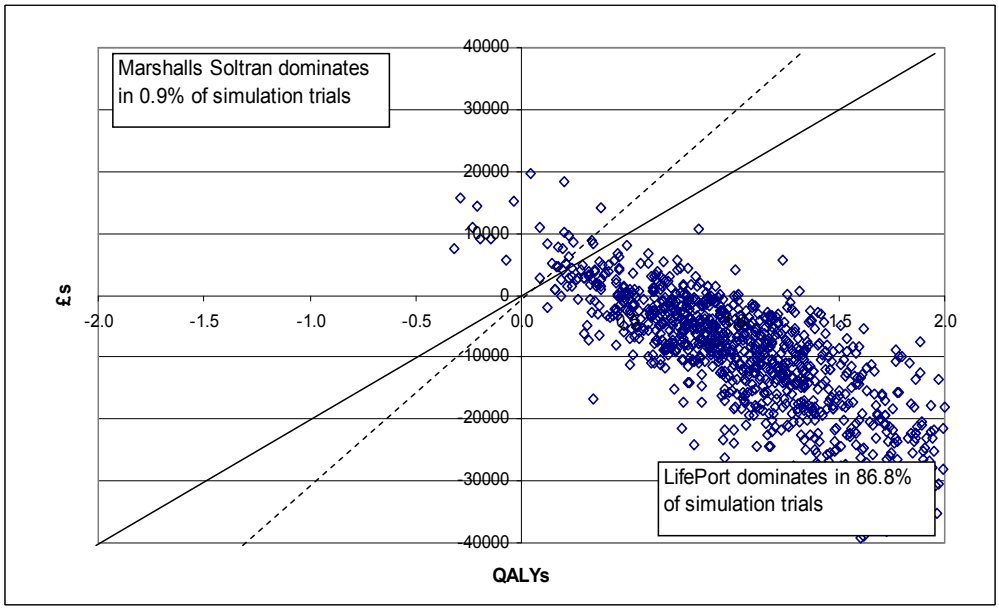
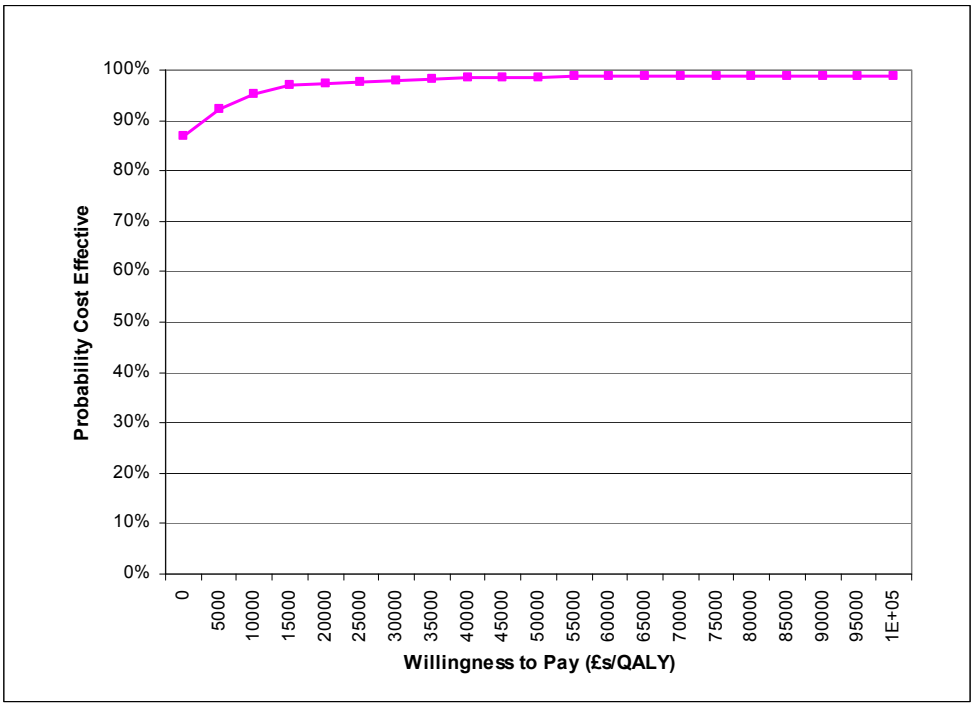


Figure 39 below shows the Cost-effectiveness Acceptability Curve for the comparison of Marshall's Soltran with LifePort. This shows that LifePort is estimated to have a greater than 95% probability of being more cost-effective than Marshall's Soltran for this data set for a large range of willingness-to-pay thresholds. However, this is not RCT data and these outputs should be treated with caution.

Figure 39. Cost-effectiveness Acceptability Curve for LifePort vs. Marshall's Soltran



6.8.2. Cold storage solution vs. cold storage solution

6.8.2.1. ViaSpan versus Marshall's Soltran solution

Figure 40 below shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation based on the trial data for cold storage with Marshalls solution vs. LifePort machine preservation. The distribution of output points illustrates the levels of uncertainty associated with the cost and effectiveness outputs from both arms of this comparison when the parameter uncertainty is taken into account in the model. Once again this distribution shows that the within comparator variation is much greater than the between comparator variation, once parameter uncertainty is incorporated into the model.

Figure 40. Scatter plot from probabilistic simulation for Marshall's Soltran vs. ViaSpan

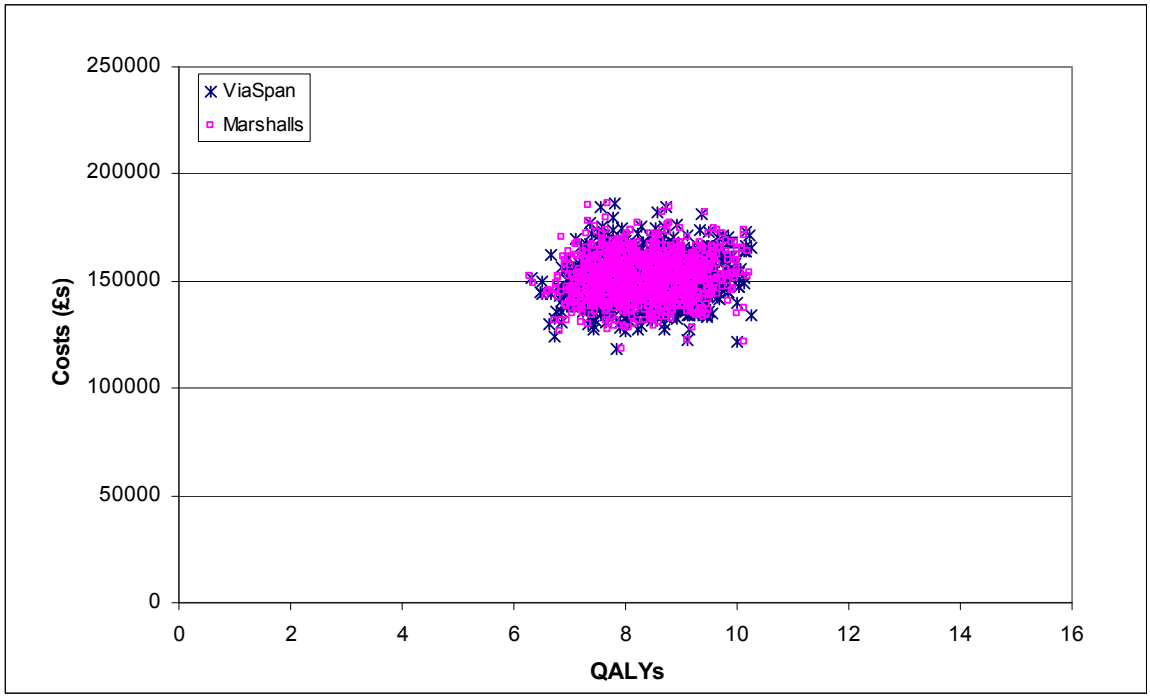


Figure 41 below represents the outputs shown above in terms of the incremental costs and benefits of LifePort vs. Marshall's Soltran. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000 per QALY (solid line) and £30,000 per QALY (dashed line). This graph shows that based on the data from this study there is very little to distinguish between the cost-effectiveness of Marshall's Soltran and ViaSpan. It should be noted that these outputs are based on a single study.

Figure 41. Incremental Cost-effectiveness of Marshall's Soltran vs. ViaSpan

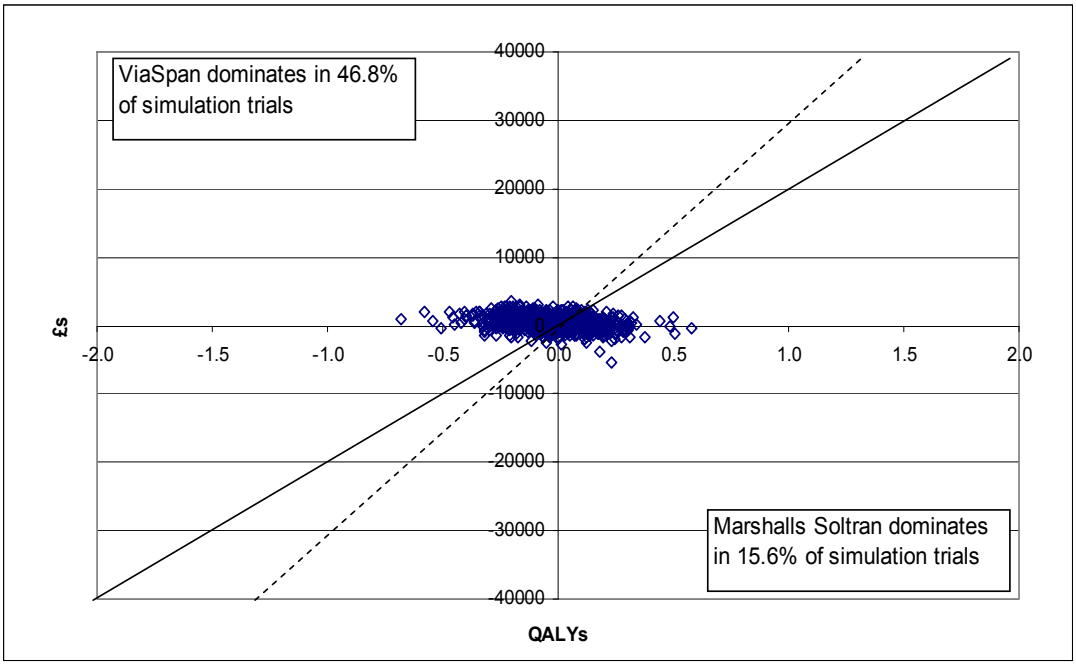
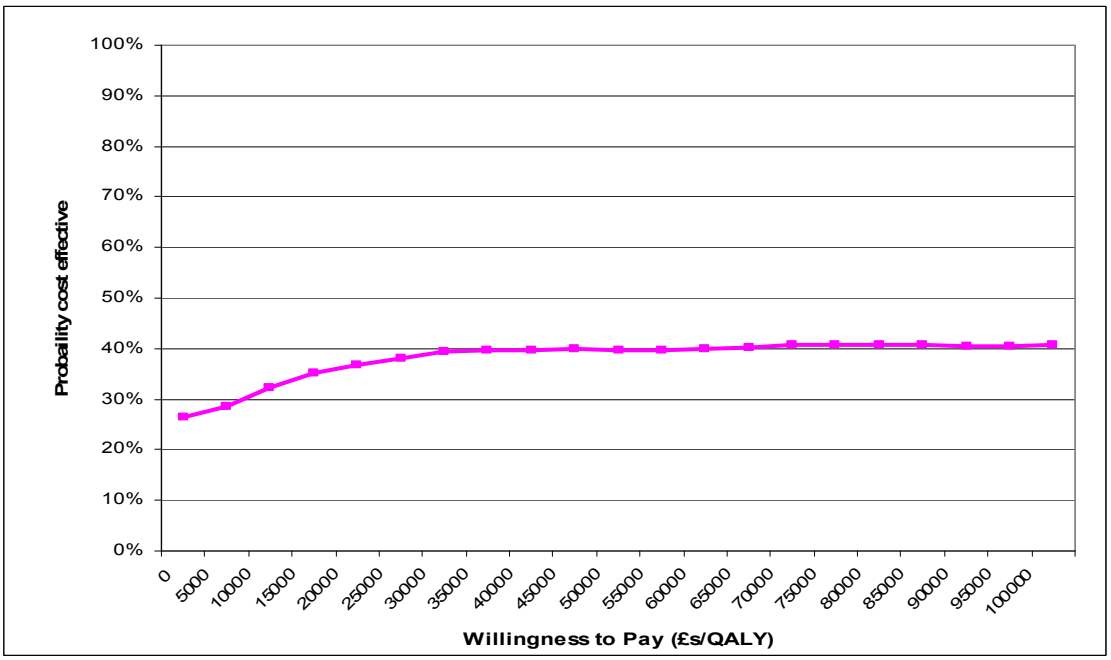


Figure 42 below shows the Cost-effectiveness Acceptability Curve for the comparison of Marshall's Soltran with ViaSpan. This graph shows around a 40% probability that Marshall's Soltran is cost-effective when compared with ViaSpan across a wide range of willingness-to-pay thresholds. Hence there is little in these outputs to help us to determine cost-effectiveness between the two comparators.

Figure 42. Cost-effectiveness Acceptability Curve for Marshall's Soltran vs. ViaSpan



6.8.2.2. Summary of probabilistic sensitivity analysis outputs

In general, because the outputs of the PSA embody the inherent uncertainty associated with model inputs, they provide a more balanced picture of the comparisons undertaken in this cost-effectiveness analysis than the simple deterministic outputs.

Of the four comparisons modelled in this analysis none of the PSA outputs provide very strong indication to prefer one storage solution over another.

When PPART data are used to parameterise the model the model predicts a slightly greater probability (60% versus 40% over a wide range of willingness to pay thresholds) that ViaSpan is a preferred storage solution to LifePort. However this finding is reversed when the MPT data are used in the model. In this comparison, the model predicts an approximately 80% probability that LifePort is a more cost-effective solution than ViaSpan. The model also predicts around a 86% probability that LifePort is a more cost-effective alternative to Marshall's Soltran when data from the selected study are used. For the final comparison of ViaSpan and Marshall's Soltran there is very little to distinguish the comparators in terms of cost-effectiveness.

The probabilistic outputs from the model confirm the findings of the one-way sensitivity analyses and show the importance of graft survival curves in determining model outputs. This is revealed by the PSA outputs which show a large percentage of the simulation trials in which one or other of the two arms of the comparison dominates over the other. This is due to the fact that when survival curve values are sampled from probabilistic distributions any incremental advantage in graft survival is likely to confer both greater utility and cost savings and hence dominance. This also explains the relatively flat cost-effectiveness acceptability curves since with a large proportion of simulation outputs demonstrating dominance, the willingness to pay threshold is not a significant factor in determining the probability of cost-effectiveness.

This finding indicates that, based on our model outputs, definitive data showing a clear graft survival advantage for one storage method over another would most almost certainly provide clear evidence to prefer this method as the more cost-effective option.

6.8.3. Summary for cost-effectiveness section

1. Although, on the whole, good UK registry data exist to describe many of the characteristics of kidney transplant and dialysis patients, few good quality comparative studies can be sourced which compare the effects of different kidney storage methods. This provides a challenge for the cost-utility analysis for the different comparisons undertaken in this report.

2. Two RCT studies were found which compared LifePort (machine perfusion) with ViaSpan (cold storage). These are based on different populations of donated kidneys and have been modelled separately. One low quality study has been found to parameterise the modelled comparison of Marshall's Soltran with LifePort, and one large registry-based study was found which compared ViaSpan with Marshall's Soltran.

3. Given the lack of studies available to populate the economic model, the uncertainty surrounding the important outcomes of DGF and graft survival, and the additional uncertainty introduced by extrapolating form short-term to longer term outcomes, the deterministic model outputs based on single fixed values for input parameters should be interpreted with great caution.

4. The two comparisons of LifePort versus yield contrasting cost-utility results. The comparison based on the PPART study shows that ViaSpan is both cheaper and confers more QALYs for fixed input values and the PSA outputs in this comparison show that there is around a 60% probability for preferring ViaSpan as a storage method over LifePort. The modelled comparison using the Machine Preservation Trial data shows, in contrast, that for the deterministic outputs, LifePort is both cheaper and confers greater QALYs when compared to ViaSpan. The PSA outputs in this comparison indicate around an 80% probability that LifePort provides a cost-effective alternative to ViaSpan across a wide range of willingness to pay thresholds.

5. The comparison of Marshall's Soltran with LifePort indicates in the deterministic model, that LifePort is both cheaper and confers more QALYs than the use of Marshall's Soltran as a storage method. The PSA analysis confirms this finding,

however the nature of the underlying study data indicates that these outputs should be interpreted with caution.

6. The deterministic outputs for the modelled comparison of ViaSpan versus Marshall's Soltran show that ViaSpan is marginally cheaper and confers more QALYs overall than the use of Marshall as a cold-storage method. However, the probabilistic outputs indicate that there is little if any basis for preferring one storage method over another once uncertainty in included in the model.

7. In general, the sensitivity analyses show that the key model parameter is graft survival. Where differential graft survival between the comparators can be demonstrated, the advantages of improved graft survival quickly and greatly outweigh the incremental costs associated with the storage methods. These advantages are manifested both in terms of improved survival and quality of life outcomes and also in terms of cost savings due to reduced need for dialysis over patients' lifetimes.

7. Assessment of factors relevant to the NHS and other parties

7.1. The use of machine perfusion to predict the viability of kidneys

The possible use of measurements taken during machine perfusion to judge kidney viability prior to transplantation has become of renewed interest since increasing numbers of kidneys have come from DCD and ECD donors. This is because DCD and ECD kidneys tend to have higher rates of primary non-function than those from BSD donors, and effective viability tests could allow the identification of such non-viable kidneys prior to transplantation. The traditional methods of viability testing are visual inspection (subjective) and biopsy of the organ to assess the degree of cellular damage (time consuming). Tests for kidney viability have included the monitoring of perfusate pressures and flows or biochemical indicators of cellular damage. The primary aim of predicting kidney viability is to reduce the incidence of PNF.

Wight and colleagues, 2003[45] conducted a literature review of papers examining the effectiveness of kidney viability testing by machine perfusion. They found 18 relevant studies published between 1974 and 1981. However, only one of these studies used PNF as an outcome measure and did not exclude (i.e. discard) kidneys because of poor perfusion.[114] This study found no correlation between perfusion flow rate and PNF. (Those studies in which some kidneys were not implanted on the basis of perfusion rate, or other measurements taken during storage, are much less reliable for assessing the pre-transplant predictability of non-viable kidneys.) Wight and colleagues found a further 11 studies published between 1993 and 2001. However, only one study did not exclude kidneys on the basis of perfusion characteristics but did not report any instances of PNF. Overall, Wight and colleagues concluded that there was 'little evidence' that machine perfusion was able to accurately predict kidney function post-transplant. Although there was some evidence that the measuring of α-glutathione-S-transferase (GST) concentrations may be a means of predicting which kidneys will not work post-transplant.[43;115-117].

We conducted a search for studies published since 2001, and found 13 new papers reporting 10 studies about the ability of machine perfusion measurements to predict

kidney graft function.[43;118-126;126-128]. A number of different methods for testing viability had been evaluated, including perfusion flow rates, bio-markers and weight gain of the graft.

Overall the debate continues. Matsuno and colleagues believe that perfusion flow can predict PNF rates in DCD grafts,[126] but Sonnerday and colleagues doubt the reliability of perfusion parameters to guide kidney selection.[128] Balupuri and colleagues have shown that selecting kidneys on the basis of a combination of measures (GST, intrarenal vascular resistance (IRVR), perfusion flow characteristics) have together improved their graft survival rates from 46% to 88%.[43] The use of multiple measures was also advocated by Kosieradzki and colleagues[118] who developed a set of parameters (tissue flow, vascular resistance, LDH activity and lactate level) which enabled them to predict graft function with 93% reliability, but found that no single item was able to predict viability on its own. This finding agrees with Metcalfe and colleagues who reported that IRVR did not predict PNF, [120] and Mozes and colleagues who found that renal resistance was not a reliable predictor of graft viability. [125] Gok and colleagues looked at alternative bio-markers to GST; they found that in the short-term alanine aminopeptidase and fatty acid binding protein could also predict kidney function, but they could not predict kidney function in the longer term (> 3 months).[121-124] Wilson and colleagues explored whether the varying weight of perfused kidneys could be used to predict viability, but found this was not so.[127] More recently de Vries and colleagues have found that the amount of redox-active iron that is released into the preservation solution by kidney grafts can predict DGF and PNF. The levels were able to independently predict post-transplant graft reliability (odds ratio 1.68, p=0.01), with higher levels being associated with poor outcome.[119]

Further work is required to determine better ways of assessing organ viability after retrieval – particularly kidneys from uncontrolled non-heart beating donors (a sub-group of DCD donors) as this group has the largest discard rate. Also, future studies need to assess the rate of discard of kidneys that would have been viable, as well as improvements in the rates of graft function and survival. This means there is a need for more observational studies which simply measure proposed viability parameters and track key post-transplantation outcomes, as well as modelling studies of the comparative cost and other impacts of discarding viable kidneys versus implanting non-viable ones

7.2. The safety and ease of use of machine perfusion and cold storage

The cold storage system is simpler to use than machine perfusion. With cold static storage the flushed kidney is placed in a sterile bag within another bag and placed in the ice filled cold storage box. In contrast, machine perfusion requires dissection of the artery to attach it to the machine and further dissection of the kidney to make the seal water-tight. Although this takes more time it has the advantage of forcing an early assessment of the kidney for anatomical abnormalities and tumours. This may avoid unnecessary preliminary surgery on the potential recipient, which can occur if assessment and identification of abnormalities of the kidney does not happen until immediately prior to transplant.

A review of the literature for studies reporting safety issues relating to type of kidney storage produced no results. However, as mentioned in the Clinical Effectiveness Section 5.4, Marshall's Soltran should not be used when the liver, pancreas or intestines are also being retrieved, as it is not safe for the extended preservation of these other organs.

7.3. Systems and regulations for organ retrieval and transport

Like any piece of capital equipment, the cost-effectiveness of kidney preservation machines will greatly depend on the intensity with which each machine is used. At present within the NHS, the number of kidneys stored by this method is restricted to kidneys from DCD donors and those centres which have a DCD donor retrieval programme. This is because machines are locally owned (by NHS Trusts), and must be brought back to the transplant centre which owns the machine. Thus, while there is a national system for sharing BSD organs, including nationally organised supply of storage equipment (boxes and related consumables are provided by UK Transplant), there is currently no national system for sharing or exchanging organ storage machines.

Therefore, the cost-effectiveness of the technology is inherently related to the regulations of organ sharing (national or regional), and the logistics of having machines available at or near retrieval centres, and then returned or exchanged (if locally owned) at the originating centre. The recent report from the Department of Health's Organ Donation Taskforce has indicated that organ retrieval and transport

arrangements (including the central employment of transplant coordinators by UK Transplant) may be less regionally based in the near future, so this might also create opportunities for the shared or national ownership of organ preservation/transport machines, and their more widespread and efficient use.[44]

The geographical extent and population coverage of systems for sharing donated organs also has an impact on the potential for optimal tissue matching, which is also known to alter the risk of acute rejection and graft survival.[55;68]

7.4. Impact of dialysis vs. transplantation on employment status

In addition to well documented quality of life and mortality risk differences between patients with a functioning transplant and those on dialysis (which are reflected in our cost-utility modelling), a number of studies have documented the detrimental effect of being on dialysis on patients' employment status, compared with successfully transplanted patients.[24;102] For example, in Canadian patients, Laupacis and colleagues found that the proportion of people in employment increased from 30% before transplantation to 45% after transplantation.[102] Furthermore, of those with functioning grafts two years after transplantation, 51% were in employment, compared with only 21% of those who had experienced failed grafts (and were back on dialysis). However, another study from Germany, showed similar rates of employment and unemployment between dialysis and transplanted patients (although the proportion who were "permanently out of work on disability" was substantially higher amongst dialysis patients, 42% vs. 26%).[34]

In addition, it is inevitable that people on haemodialysis (except home haemodialysis) will in general only be able to work part-time. Satellite unit or hospital haemodialysis is usually provided as three sessions per week, with each session typically lasting between 3 and 4 hours.[129]

8. Discussion

As the demand for kidney transplants increases, and the number of BSD donors declines, the need to find other reliable ways of increasing the initial function and long-term survival of all types of kidney grafts becomes increasingly important. The main question in this assessment of kidney storage methods is whether kidneys stored by machine perfusion are more likely to work, more likely to start working immediately, and more likely to carry on working for longer. In addition, we examine potential differences between types of kidney storage machine, types of cold storage solution, and the resource use and cost implications of the alternative technologies.

8.1. Principal findings

8.1.1. Clinical effectiveness

Machine perfusion vs. cold storage

Unfortunately we are unable to provide a clear answer to the question comparing machine perfusion to cold storage in DCD kidneys. There were two recent RCTs of this comparison, one of which (PPART, n=90) produced a non-significant result slightly in favour of cold storage (for DGF and graft survival at 3 months), while the other (the Machine Preservation Trial, [redacted]) produced [redacted] there are a number of important differences between these two trials, in terms of the kidney donor types, study design and settings, and the integrity of the actual interventions received, which may explain some of the differences in their results.

The PPART RCT solely used DCD donor kidneys (at [redacted] transplant centres in the UK), and so far has only produced three month post-transplantation results. Furthermore, the value of this study [redacted] Therefore, these results should be treated with caution; they indicate that there is no difference between storage methods for any outcome. However, this may possibly be due to [redacted].

In contrast, the Machine Preservation Trial included both BSD and DCD donor kidneys ([redacted] BSD: [redacted]DCD). Although there was [redacted], their 12 month follow-up results indicate [redacted]. A sub-group analysis included additionally recruited DCD participants [redacted]. It would therefore be speculative to extrapolate the full trial findings, using largely BSD donor kidneys, to DCD kidneys and their recipients. From the Machine Preservation Trial, for the key outcome of one-year graft survival [redacted]. Other outcomes [redacted]. This result may not hold with longer cold ischaemic or at post-transplant follow-up times.

The only study we found comparing LifePort to Marshall's Soltran (Plata-Munoz and colleagues) had many potentially confounding factors: it wasn't randomised; for the first two years all kidneys were perfused with Marshall's Soltran subsequently machine preservation with LifePort was used; the size of the study was small (n=60); the mean age of recipients of kidneys that had been cold stored was seven years older that those stored with LifePort and kidneys stored with LifePort had a longer CIT. Taken together these factors mean that very little credence can be given to this studies' results.

Effectiveness of different kidney perfusion machines

The lack of any RCT or fully published evidence makes it very difficult to say whether either of the two machines assessed is better. However, the two record review studies that we found suggest that the RM3 may perform better than LifePort. These results may have been subject to confounding influences; well designed RCTs are needed to establish if either machine is better.

Effectiveness of different cold storage solutions

The results from the RCTs comparing cold storage solutions indicate that, at least for CIT of less than approximately 15 hours, ViaSpan and Celsior are equivalent for kidney preservation. Registry evidence suggests that there is no significant difference between ViaSpan and Marshall's Soltran for graft survival for a range of cold ischaemic times.

The conclusions that this systematic review can come to are uncertain and limited by the lack of RCTs, and the number of studies that have either not finished collecting and analysing their results, and/or have not published them fully.

8.1.2. Cost-effectiveness

8.1.2.1. Summary of previously published economic evaluations

There were only two previously published economic evaluations which met the inclusion criteria of our systematic review. The analysis by Wight and colleagues (2003), while fairly recent and conducted from a UK NHS perspective, was not able to make use of the two most recent RCTs of machine perfusion versus cold storage of donated kidneys. Also, its results were highly dependent on an estimated relationship between delayed graft function and graft survival, which we think is no longer defensible (given both mixed evidence about the existence of this relationship, and recent trials reporting graft and patient survival as pre-specified outcomes).[45] The other economic evaluation, by Costa and colleagues, was conducted from a Canadian university hospital perspective, and had a number of important shortcomings in relation to the quality of the study, and its relevance to the present decision problem.[47]

8.1.2.2. Summary of PenTAG's model-based cost-utility analysis

We were able to model the lifetime cost and QALY impacts of: machine perfusion with LifePort versus cold storage with ViaSpan; machine perfusion with LifePort vs. cold storage with Marshall's Soltran, and; cold storage with ViaSpan vs. cold storage with Marshall's Soltran. In each case, however, the base case deterministic results should be viewed with considerable caution, due both to the uncertainty surrounding the relevant clinical effectiveness study results, and also the uncertainty surrounding whether short-term differences in graft survival (between different storage methods) would be manifested in the longer term.

Machine perfusion vs. cold storage

Deterministic analyses

The base case deterministic results of our two cost-utility analyses which compare LifePort with ViaSpan show opposite results depending on which trial is used to drive the effectiveness estimates. When using data from the PPART trial (of DCD kidneys),

cold storage is both cheaper and generates more QALYs than machine preservation. In contrast, using outcome data from the larger Machine Preservation Trial, of mixed BSD and DCD kidneys, machine preservation is both cheaper and generates more QALYs than cold storage. As discussed under clinical effectiveness, whether the difference between these two trials' findings is related to differences in study design, kidney donor type, or other reasons to do with the effectiveness of the technologies, is very difficult to disentangle.

The deterministic cost-utility comparison of LifePort with Marshall's Soltran (which is much the cheapest of the two cold preservation solutions), also suggests that machine perfusion might generate both more quality-adjusted life-years and lower lifetime costs than machine perfusion. However, the effectiveness data used for this comparison is from a relatively small non-randomised study, so this cost-utility result should be treated with considerable caution.

Our component analysis shows that a large proportion of the incremental model outputs are due to the differential cost, utility and patient survival related to differing proportions of time spent with a transplant versus on dialysis. Patient time spent in successfully transplanted states versus on dialysis in the model is largely a function of graft survival.

One-way sensitivity analysis further revealed that the model is particularly sensitive to differential levels of graft survival between comparators. Inevitably, where graft survival is linked to DGF (as in our simulation of the MPT study findings), the model is also sensitive to levels of DGF. Kidney storage costs have little impact, but dialysis costs become important where differences in effectiveness are evident.

Probabilistic sensitivity analysis

The probabilistic sensitivity analyses strongly reflect how the cost differences between machine perfusion and cold storage are almost totally driven by the estimated differences in graft survival. The CEACs are generally flat (especially above £20,000 per QALY), because in so many of the simulations either machine perfusion dominates cold storage, or vice versa. Nevertheless, if the MPT study results are relied upon (which used mostly BSD ([redacted]) and some DCD kidneys), and our methods of extrapolating graft and patient survival are realistic, then there is a greater than 75% estimated chance that machine preservation with LifePort would be judged as good value for money compared with cold storage with ViaSpan (i.e. it would either generate more QALYs and be cheaper, or generate extra QALYs at an acceptable

cost to the NHS). In contrast, the probabilistic analysis based upon the PPART study of the same technologies still arrives at the opposite overall finding (with a less than 42% chance that LifePort is good value for money). Finally, when comparing LifePort with Marshall's Soltran, based on the small, poor quality, Plata-Munoz cohort study, machine preservation would under most combinations of assumptions be judged to generate new QALYs at an acceptable cost (or be both more effective and less costly).

Therefore, the probabilistic sensitivity analyses do not really alter the mixed implications of the deterministic analysis, but rather point us back to the problem of deciding which of the two RCTs of LifePort versus ViaSpan is more internally valid, and most generalisable to the current UK NHS context.

Cold storage vs. cold storage

Deterministic analysis

When Marshall's Soltran cold storage solution is compared to ViaSpan, Soltran is both the more expensive and the less effective option (in terms of the estimated QALYs generated).

Probabilistic sensitivity analysis

When cold storage solutions were compared using PSA we found that at a £30,000 per QALY willingness-to-pay threshold, there is only a 40% probability that Marshall's Soltran is the most cost-effective option making ViaSpan the more cost-effective choice.

8.2. Strengths and limitations of the systematic review of clinical effectiveness

8.2.1. Strengths

- The strengths of this assessment are that it is comprehensive, systematic, up-to-date and conducted by an independent research team.

8.2.2. Limitations

- The search strategy was limited to English language publications due to resource limitations. This may have led to the omission of studies. However, our advice from our Expert Advisory Group is that we have included all relevant studies.

Timing of assessment:

- We have not had the 12-month follow-up data from the PPART trial, which, although weakened by the conduct of the study (see above), is the only RCT that has compared hypothermic machine perfusion with cold storage in DCD donors. Although the Machine Preservation Trial included DCD donors (n=[redacted]), this trial was predominantly of BSD donors (n=[redacted]). Sub-group analysis only examined DGF.

- Additionally, the only studies found that compared the two preservation machines, have not yet been published as peer-reviewed articles. This has the effect of limiting the information that can be gleaned about the conduct and outcomes of this research.

- The effects of this limitation are that we cannot be sure of the long term effects on graft and patient survival of mode of kidney storage, especially as no significant differences were found in DGF or PNF. We also have little insight into the relative merits of the two preservation machines.

Quality of effectiveness studies:

- Only five of the 11 included studies were RCTs; this meant that some of the comparisons (LifePort vs. RM3, LifePort vs. Marshall's Soltran and Marshall's vs. ViaSpan) were dependent on data from studies where, due to less robust design, there may have been selection and other biases, possibly confounding the results.

- The PPART trial data [redacted]. We do not know what effect this may have had on the results.

8.3. Strengths and limitations of the cost-utility analysis

8.3.1. Strengths of the cost-utility analysis

- The structure of the decision model was based upon a review of the key cost-generating and potential quality of life and mortality impacts of different methods of storing donated kidneys. Post-transplantation patient pathways are stratified by the main three short-term outcomes of immediate graft function, delayed graft function and primary non-function, which are the most commonly reported effectiveness outcomes in clinical studies.

- It is a lifetime model that incorporates both the short-term cost and quality of life impacts of delayed graft function (e.g. more days of in-hospital dialysis) and primary non-function (e.g. explantation costs), as well as longer term outcomes associated with graft and patient survival (e.g. need for lifelong dialysis or re-transplant). Previous cost-utility analyses have shown the potential importance of including the possibility of re-transplant, as it generally leads to further cost savings and quality of life and survival gains compared with assuming a life-long return to dialysis.

- The analyses make best use of recently available effectiveness data from two RCTs of machine perfusion with LifePort compared to cold storage with UW ViaSpan. Our four cost-utility analyses have, wherever possible, not relied upon any assumed negative correlation between the short-term outcome of DGF and the more important longer term outcome of graft survival.

- Where outcome and other key data were not available from effectiveness studies, we were able in some cases to draw upon relevant data from large national registries of renal replacement therapy patients (the UK Renal Registry) or kidney transplant recipients (annual activity reports or specific data supplied by UK Transplant statisticians).

- We have comprehensively costed the important resource impacts associated with the use of each storage technology (machines, solutions, storage boxes, consumables), as well as the main potentially differential resource implications of delayed graft function, primary non-function and graft survival.

8.3.2. Limitations of the cost-utility analyses

■ The main limitation of our analysis is the validity and generalisability of the effectiveness data and related assumptions. This has two key elements. First, the randomised trials and other comparative studies each have particular limitations and differences with current UK clinical practice or kidney donor availability. Second, we have necessarily had to extrapolate from short-term estimates of graft survival, to estimate the longer-term relative pattern of time with a functioning graft compared with being back on dialysis. Additionally, survival data from the Machine Preservation Trial had to be read from a graph as this information was not available in the text; this may have lead to an under or over estimate of their results.

■ Given the importance of the cost and utility differences between having a functioning transplant and going back onto dialysis, there are some limitations in the data sources that contribute to these estimates. The main ones are:

■ Utility decrement for going back on dialysis following kidney graft failure: Ideally, to reflect NICE methods guidance, an estimate of the utility reduction associated with returning to dialysis following transplant failure would come from a longitudinal study which had used either the SF-36 or the EQ-5D, in a cohort of kidney transplant patients followed until after graft failure. Such a study would provide generic health state descriptions for which UK general population social preference weights exist, and perhaps also reflect any specific quality of life impacts of going back onto dialysis following graft failure (which may be worse than with living on dialysis more generally).[24;31;85] The Greiner and colleagues study, from which we derived our utility decrement value of 0.12, compared EQ-5D-measured quality of life when on pre-transplant dialysis (n = 150) with post-transplantation quality of life up to two years post-transplant (although with smaller respondent numbers at one and two years follow-up, which may have introduced some bias).[109] The Swedish study, which we could have alternatively used, was also based on EQ-5D health status assessment in both transplant recipients and those on dialysis.[110] It would have provided a substantially larger estimated utility decrement for dialysis versus a functioning transplant (of 0.21 with peritoneal dialysis, and 0.44 with haemodialysis). However, this was in three smaller (n=27) but matched samples of transplant, haemodialysis and peritoneal dialysis patients. Also, the difference between haemodialysis and living with a kidney transplant is very high relative to other values in the literature and,

contrary to most other studies,[20;130;131] also assesses quality of life on peritoneal dialysis to be much better than on haemodialysis.

- Cost of being on dialysis: Although, in general, we have been able to use good data in the UK on the mix of renal replacement therapy patients on different forms of dialysis, and the NHS National Schedule of Reference Costs (NSRC) now provides specific per session (or per day) costs for renal dialysis, there may be uncertainty surrounding these substantial costs. The NSRC is, for example, less transparent about variation in the costs between different forms of haemodialysis or different forms peritoneal dialysis, and the exact extent of inclusion of related costs. Also, these national average unit costs are unlikely to include the cost of such things as household adaptations (e.g. showers, sheds for storage) or treating episodes of line infection, which would be part of the total cost of dialysis treatment from an NHS/PSS perspective.

- Cost of living with a functioning transplant: Although, in common with some other studies, we have quite comprehensively costed the various different NHS resources involved in following up and treating someone with a functioning transplant, some of these costs could have been more accurately derived. In particular, with more time we could have obtained more representative data from UK Transplant on the specific immunosuppressive drug regimes being used with kidney transplant recipients, and hopefully obtained more accurate estimates of acute rejection rates in relation to time since transplant.

- Another potential limitation is that we have not modelled the economic impact of stored kidneys that are discarded prior to transplantation. Since none of the included studies which reported these rates showed significant differences between storage methods, we think this is a negligible omission.

- Finally, our estimates of the short-term cost impacts machine perfusion, or of DGF, PNF, and acute rejection rates, would have benefited from resource use data from the two recent RCTs of machine perfusion versus cold storage (the PPART and MPT studies). Despite both trials including parallel economic data collection and plans (mentioned in their protocols) to analyse such data, it was not available at the time of this report.

Scope:

- As the manufacturers of Celsior (Genzyme) were not invited to make a submission for this assessment, it has not been possible to include Celsior in the cost-effectiveness analysis. This is a shame as the pooled results of the three RCTs comparing Celsior to ViaSpan indicate their equivalence.

8.3.3. Uncertainties

The primary area of uncertainty in this assessment is whether machine perfusion generates improvements in short- and long-term in graft survival compared with cold storage. Despite a six-fold difference in the estimated per kidney cost of storage between LifePort and ViaSpan, the absolute difference (of less than £500) is small relative to the very large differences in the cost of being on dialysis compared with living with a functioning kidney transplant. Although there are uncertainties associated with our cost parameters and assumptions (as discussed in the previous section), they would not alter the broad scale of ongoing cost differences between being on dialysis and having a functioning transplant. Therefore, for example, even with more accurate national level data on the pattern of prescribing or time-related dose reductions in immunosuppression drugs, the sensitivity of the cost-utility results to the basic graft survival results would remain.

Two other uncertainties already noted in relation to machine perfusion, are that (a) the number of kidneys stored per year per machine has been based on historical (possibly low) estimates, and in the context of locally owned machines used for intra-regionally retrieved organs, and (b) that the initial cost of machine perfusion has been annualised over an assumed 10 years, as the likely useful life of the technology in the NHS (before replacement by newer machine models or different technologies). While these assumptions, again, are unlikely to substantially alter our main conclusions (see component analyses and one-way sensitivity analyses) they are nevertheless quite uncertain estimates which directly drive the per kidney cost of the technology.

With regard to the comparison of different cold storage solutions, the difference in price between the two solutions is known with certainty, and there was no suggestion from our experts that different quantities of preservation solutions would be used with different products. Again, therefore, the main uncertainty in the cost-utility analysis pertains to the validity and reliability of the effectiveness data, and how estimates of short-term graft survival are projected into the future.

In general, while the short-term outcome of delayed graft function rate is widely used in clinical research into the effectiveness of kidney storage methods (and was the designated primary outcome measure in both the PPART and MPT RCTs of machine perfusion), there is still considerable uncertainty regarding its usefulness as a marker of long-term graft survival, and to what extent such an association is also related to cold ischaemic time, deceased donor type, or other factors. Although, for one of our cost-utility analyses (PPART trial of LifePort vs. UW ViaSpan, where only 3 month outcome data was available) we used historical (UK Transplant-supplied) data on the relationship between DGF and 5-year graft survival to predict long-term graft survival, for the other three comparisons we relied directly on the 1-year or 2-year graft survival data reported in the relevant trials/studies.

8.4. Other relevant factors

Determinants of graft survival

As reported earlier Opelz and Dohler analysed data from the multi-national Collaborative Transplant Study database to investigate the effects of different kinds of kidney preservation, their relationship with ischaemic time and HLA matching: they reviewed records between 1990 – 2005 (N = 91,674). [55] They found that increasing levels of cold ischaemia up to 18 hrs did not appreciably affect graft survival. However, at 19-24 hrs there was a relative risk incurred of 1.09, 25-36 hrs RR 1.16, and >36 hours RR 1.30 ($p<0.001$). However, this gradual decrease in graft survival with cold ischaemic time >18hrs was not paralleled by an increase graft rejection; indicating that worsening rates of graft survival associated with increasing ischaemic time were not related to increased kidney immunogenicity. There was an increase in rejections only when kidneys were preserved for more than 36 hours (RR 1.20, 95% CI 1.04 -1.39, $p=0.011$).[55]

The quality of HLA matching has a greater effect on graft survival than length of cold ischaemia. Short ischaemic time did not overcome the effects of poor HLA matching nor did even shorter ischaemic time of 0-3 hours bring rates of graft survival close to those of living donors. [132]

9. Conclusions

With regard to either the relative effectiveness or the cost-utility of machine perfusion (with LifePort) versus cold storage (with ViaSpan), any conclusion is dependent on which of the two main trial's results is relied upon. The two RCTs for this comparison [redacted]. Also, the extreme sensitivity of the cost-utility model to better kidney graft survival - which directly and substantially lowers costs, and increases QALYs (through both reducing and deferring years on dialysis) – means that even very small differences in estimated graft survival cause one of the technologies to be both cheaper and more effective than the other. This uncertainty about the measured difference in graft survival in these two trials is further compounded by the modelling uncertainty introduced by having to extrapolate graft survival from such short follow-up times to peoples' lifetimes.

The effectiveness data used in the model for the comparison of LifePort to Marshall's Soltran are so unreliable that no conclusions can be drawn about which is the most cost-effective option.

For the comparison of ViaSpan with Marshall's Soltran the model results are again unreliable due to the lack of RCT data. With this degree of uncertainty the cheapest option (Soltran) may be the wisest choice; with the caveat that it should not be used in multiple organ retrieval.

The results of our meta-analysis of the three RCTs comparing ViaSpan with Celsior indicate that these cold storage solutions are probably equivalent in both short term (DGF) and longer term outcomes (one-year graft survival).

9.1. Implications for service provision

There are service implications if the NHS chooses to implement machine perfusion nationally. Currently machine perfusion systems are owned by the hospital Trusts and have to be returned to their hospital following transportation to the recipient site. A national machine perfusion system that allowed kidneys to be transported around England and Wales could pose logistical problems in returning the systems to their source. A possible solution may be for UK Transplant to own the preserving machines. This is a possible outcome of the Department of Health's recent report 'Organs for Transplants', which recommends the creation of a national organ retrieval

network for all deceased kidney donations.[44] UK Transplant could co-ordinate a process for ensuring that transplant centres were not without machine preservation capacity because their preserving machines had been sent to another part of the country.

Another potential advantage of a nationwide system for all types of kidney graft allocation is the larger pool of potential recipients and hence the greater chance for higher quality tissue matching with concomitant positive effects for graft and patient survival.

9.2. Suggested research priorities

A number of research priorities have emerged from this assessment:

- If evaluators of kidney preservation technologies are to rely upon delayed graft function as an assumed predictor of long-term graft survival or patient survival, then more high quality research is required to establish the strength and reliability of the presumed causal association (including how it is contingent upon other known factors such as cold ischaemic time, donor type and tissue matching).

- All studies of the effectiveness of alternative kidney preservation methods should collect data on and report the numbers of stored kidneys which are discarded pre-implantation (e.g. after being judged as non-viable), together with an intention-to-transplant analysis.

- As graft and patient survival have multi-factorial determinants, there is a need for sufficiently large RCTs of comparators of interest to allow for appropriate analysis of sub-groups, which may in turn better identify those combinations of donor kidney, types of recipient, or storage characteristics (such as length of cold ischaemic time) in which machine preservation appears to be most effective at improving short-term and long-term outcomes.

- More research is needed into the utility impacts of all forms of RRT; most published studies are cross-sectional, but there is a need to know the long-term trajectories that patients follow (e.g. the quality of life impact of dialysis following graft failure). Many current studies are confounded by younger, fitter people receiving transplants and older people, with more co-morbidities being on

dialysis. New studies should try and use both established disease-specific measures and generic quality of life measures for which social preference weights exist (such as the EQ-5D, SF-36 or HUI-III). Also, because quality of life in renal dialysis patients is clearly associated with the different modes and settings for dialysis, all studies should endeavour to report quality of life in these dialysis subgroups separately.

- Research is needed to determine what the additional cost, survival and QALY impacts are of decreased or increased non-viable kidneys when discarded pre-transplantation.

- RCTs are needed to determine whether either of the two machines under consideration produces better patient outcomes

- RCTs are needed to compare the RM3 with cold static storage solutions

- Further work is needed to clearly identify a reliable measure for predicting kidney viability from machine perfusion

Other issues:

- UK Transplant should encourage fuller data collection by transplant centres, as about 58% of data parameters are incomplete. We are advised that electronic methods of inputting the data would make this easier to encourage. This might allow the staggered roll-out of new organ preservation methods to be evaluated by planned natural experiments, as well as RCTs.

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(131) Manns B, Johnson JA, Taub K, Mortis G, Ghali W, Donaldson C. Quality of life in patients treated with haemodialysis or peritoneal dialysis: what are the important determinants? Clin Nephrol 2003; 60:341-351.

(132) Opelz G, Wujciak T. Comparative analysis of kidney preservation methods. Transplant Proc 1996; 28(1):87-90.

APPENDIX 1. Literature searching strategies

A wide range of databases and other information resources were searched to locate details of both published and unpublished studies and other information on the clinical effectiveness and cost-effectiveness different methods of storing donated kidneys. Databases searched for the clinical effectiveness sections of the review are listed below with the search strategy used.

A. Searches for the systematic review of effectiveness studies

Cochrane Library (CDSR and CENTRAL)Wiley Online Version 2007 Issue 4. Search Date: 29 November 2007.

#1 MeSH descriptor Kidney Transplantation, this term only
#2 MeSH descriptor Tissue Donors, this term only
#3 MeSH descriptor Organ Preservation Solutions, this term only
#4 MeSH descriptor Organ Preservation, this term only
#5 MeSH descriptor Tissue Preservation, this term only
#6 kidney* OR renal*
#7 MeSH descriptor Kidney explode all trees
#8 (#6 OR #7)
#9 (#2 OR #3 OR #4 OR #5)
#10 (#8 AND #9)
#11 (#1 OR #10)
#12 MeSH descriptor Pulsatile Flow, this term only
#13 MeSH descriptor Perfusion, this term only
#14 (machine or pulsat*)
#15 (#13 AND #14)
#16 lifeport
#17 (machine or pulsat*) NEAR (Perfusion)
#18 RM3
#19 (machine or pulsat*) NEAR (perfus* or preserv* or system)
#20 ((cold or ice or static) AND (storag* or preserv*)):ti,ab
#21 eurocollins
#22 HTK
#23 histidine and tryptophan
#24 celsior
#25 viaspan
#26 soltran
#27 (university NEAR wisconsin):ti,ab
#28 belzer*
#29 (#12 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #27 OR #28)
#30 (#29 AND #11)

Medline 1950 –to date

Dialog DataStar: Online Version

Search date: 29 November, 2007

1. KIDNEY-TRANSPLANTATION#.DE.
2. (RENAL OR KIDNEY$3) NEAR (TRANSPLANT$6 OR PRESERV$ OR REPLACE$ OR DONOR$ OR DONOUR$ OR DONATE$ OR RECIEVE$)

3. TISSUE-DONORS#.DE. OR ORGAN-PRESERVATION-SOLUTIONS.DE. OR ORGAN-PRESERVATION.DE. OR TISSUE-PRESERVATION#.DE.
4. KIDNEY.W..MJ.
5. KIDNEY$3 OR RENAL
6. 4 OR 5
7. 6 AND 3
8. 1 OR 2 OR 7
9. (SOLID ADJ ORGAN ADJ TRANSPLANT$6).TW.
10. (NON-HEART-BEATING OR NON ADJ HEART ADJ BEATING OR NHBD OR HEART ADJ BEATING OR HEART-BEATING OR CADAV$4 OR BRAIN ADJ DEAD).TW.
11. (DONOR$2 OR DONOUR$2) NEAR (MARGINAL OR EXPANDED OR EXTENDED OR HIGH-RISK)
12. 9 OR 10 OR 11
13. 12 AND 6
14. 13 OR 8
15. PULSATILE-FLOW#.DE.
16. MACHINE$2.TW. AND PULSAT$4.TW.
17. LIFEPORT.TW.
18. RM3.TI,AB.
19. (MACHINE$2 OR PULSAT$4).TW. AND (PERFUS$4 OR PRESERV$4 OR SYSTEM).TW.
20. WATER$2 ADJ RM3
21. KIDNEY.W..MJ.OR RENAL OR KIDNEY$3
22. WATER$2 NEAR PRESERVATION AND 21
23. WATER$2 ADJ MEDICAL ADJ SYSTEM$2
24. WATER$2 NEXT RENAL$2
25. 24 AND 21
26. KIDNEY$2 NEXT TRANSPORT$4 AND 22
27. UNIVERSITY ADJ OF ADJ WISCONSIN OR UW ADJ SOLUTION$2
28. CELSIOR
29. MARSHALL'S NEAR SOLUTION
30. VIASPAN
31. SOLTRAN
32. BELZER$
33. PERFUSION#.W..DE. AND (machine OR pulsat$4).TW.
34. (cold OR ice OR static OR hypo OR thermic).TI,AB. AND (storage OR preserv$5).TI,AB
35. (histidine AND tryptophan) OR HTK
36. 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35
37. 36 AND 14
38. LG=EN
39. 37 AND 38
40. PT=EDITORIAL OR PT=LETTER
41. ANIMAL=YES NOT HUMAN ADJ =YES
42. NOT (40 OR 41)

EMBASE 1974 to date

Dialog DataStar: Online Version

Search Date: 29 November, 2007

1. KIDNEY-TRANSPLANTATION#.DE.
2. ((KIDNEY$3 OR RENAL) NEAR (TRANSPLANT$6 OR PRESERV$5 OR REPLACE$6 OR DONOR$2 OR DONOURS$2 OR DONAT$3 OR RECEIVE$4)).TI,AB.
3. ORGAN-DONOR.MJ.
4. KIDNEY-DONOR.MJ.
5. KIDNEY-PRESERVATION.MJ.
6. ORGAN-PRESERVATION.MJ.
7. PRESERVATION-SOLUTION#.DE.
8. TISSUE-PRESERVATION#.DE.

9. ((DONOR$2 OR DONOUR$2) NEAR (MARGINAL OR EXPANDED OR EXTENDED OR HIGH-RISK)).TI,AB.
10. (NON-HEART-BEATING OR NON ADJ HEART ADJ BEATING OR HEART-BEATING OR HEART ADJ BEATING).TI,AB.
11. (SOLID ADJ ORGAN ADJ 12. TRANSPLANT$6).TI,AB.
12. KIDNEY#.W..DE.
13. KIDNEY$3 OR RENAL
14. 12 OR 13
15. 1 OR 2 OR 4 OR 5
16. 3 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
17. 16 AND 14
18. 15 OR 17
19. PULSATILE-FLOW#.DE.
20. KIDNEY-PERFUSION.MJ.
21. PERFUSION#.W..DE.
22. 21 AND (MACHINE OR PULSAT$4)
23. LIFEPORT.TW.
24. RM3.TI,AB.
25 (12 OR 13) AND (MACHINE$2 OR PULSAT$4) AND (PERFUS$4 OR PRESERV$4 OR SYSTEM)
26. (12 OR 13) AND (UNIVERSITY ADJ OF ADJ WISCONSIN OR UW ADJ SOLUTION)
27. CELSIOR
28. MARSHALL'S NEAR SOLUTION
29. VIASPAN
30. SOLTRAN
31. BELZER$
32. HISTIDINE AND TRYPTOPHAN OR HTK
33. (COLD OR ICE OR STATIC OR HYPO OR THERMIC).TI,AB. AND (STORAGE OR PRESERV$5).TI,AB.
34. MACHINE$2 AND PULSAT$4
35. 19 OR 20 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34
36. 35 AND 18
37. LG=EN
38. AT=EDITORIAL OR AT=LETTER
39. ANIMAL=YES NOT HUMAN=YES
40. 38 OR 39
41. 36 AND 37
42. 41 NOT 40

CINAHL 1982-current

Dialog DataStar: Web Version

Search Date: 29 November, 2007

1. (RENAL OR KIDNEY$3) NEAR (TRANSPLANT$6 OR PRESERV$6 OR REPLACE$ OR DONOR$5 OR DONOUR$5 OR DONATE$ OR RECEIVE$).TI,AB.
2. KIDNEY-TRANSPLANTATION#.DE.
3. ORGAN-PRESERVATION#.DE.
4. TRANSPLANT-DONORS#.DE.
5. (SOLID ADJ ORGAN NEAR TRANSPLANT).TI,AB.
6. (NON-HEART-BEATING OR NON-HEART OR HEART-BEATING OR NHBD OR HEART ADJ BEATING OR CADAV$4 OR BRAIN ADJ DEAD).TI,AB.
7. (DONOR$4 OR DONOUR$4) NEAR (MARGINAL OR EXPANDED OR EXTENDED OR HIGH-RISK)
8. KIDNEY#.W..DE.
9. (KIDNEY$3 OR RENAL).TI,AB.
10. 8 OR 9
11. 3 OR4 OR 5 OR 6 OR 7
12. 10 AND 11
13. 12 OR 1 OR 2
14. (MACHINE$2 OR PULSAT$4).TI,AB. AND (PERFUS$4 OR PRESER$4 OR SYSTEM).TI,AB.
15. UNIVERSITY ADJ OF ADJ WISCONSIN OR UW ADJ SOLUTION$

16. LIFEPORT OR RM3
17. CELSIOR OR VIASPAN OR SOLTRAN OR BELZER$
18. MARSHALL$ NEAR SOLUTION$
19. MACHINE AND PULSATILE
20. (10 OR 2) AND KIDNEY$3 NEXT TRANSPORT$4
21. WATER$2 NEXT RENAL$2 OR WATER$2 NEAR PRESERVATION
22. (21 OR 19) AND (2 OR 10)
23. 13 AND (14 OR 15 OR 16 OR 17 OR 18 OR 20 OR 22)
24. 23 AND LG=EN
25. PT=BIBLIOGRAPHY OR PT=CEU OR PT=COMMENTARY OR PT=EDITORIAL OR PT=EXAM-QUESTIONS OR PT=GLOSSARY OR PT=LETTER OR PT=OBITUARY
26. 24 NOT 25

ISI Web of Knowledge (SCI-EXPANDED)--1970-present

Search date: 28 November, 2007

#1 TS=((university SAME wisconsin) OR (UW SAME solution)))
#2 TS=((histidine SAME tryptophan) OR (marshall* SAME solution))
#3 TS=(HTK or celsior or viaspan or soltran or belzer*)
#4 TS=((machine or pulsat* or perfus*) AND (preserv* or system or storage*))
#5 TS=((machine) AND (pulsat* or perfus*))
#6 TS=((cold or ice or static or therm*) AND (storage or preserv*))
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8 TS=((kidney* or renal*) AND (preserv* or replace* or donor* or donour* or receive* or transplant* or procurement))
#9 #8 AND #7
#10 #9 AND Language=(English)
#11 TI=(rat* or porcin* or canin*) AND Language=(English)
#12 #10 not #11 AND Language=(English)

ISI Web of Knowledge. ISI Proceedings. Edition: Science & Technology (1990-present)

Years searched: 2003-present

Date searched: 27 November, 2007

#1 TS=((university same wisconsin) OR (UW same solution) or (histidine SAME tryptophan) OR (marshall* SAME solution))
#2 TS=((eurocollins or HTK or celsior or viaspan or soltran or belzer*))
#3 TS=((machine or pulsat* or perfus*) AND (preserv* or system or storage*))
#4 TS=((machine) AND (pulsat* or preserv*))
#5 TS=((kidney* or renal*) AND (preserv* or replace* or donour* or donor* or receive* or transplant* or procurement))
#6 #4 OR #3 OR #2 OR #1
#7 #6 AND #5
#8 #7 AND Language=(English)
#9 TI=(rat* or porcin* or canin*)
#10 #8 not #9
#11 #10 (*Databases=STP Timespan=2003-2007)*

Database of Abstracts of Reviews of Effects (DARE) on the CRD Website

Search Date: 29 November 2007

#1 MeSH Kidney Transplantation
#2 MeSH Tissue Donors

#3 MeSH Organ Preservation Solutions
#4 MeSH Organ Preservation
#5 MeSH Tissue Preservation EXPLODE 3
#6 kidney* OR renal
#7 MeSH Kidney
#8 #6 OR #7
#9 #2 OR #3 OR #4 OR #5
#10 #8 AND #9
#11 MeSH Pulsatile Flow
#12 MeSH Perfusion
#13 machine*
#14 pulsat*
#15 lifeport
#16 RM3
#17 preserv* OR stor*
#18 static
#19 university AND of AND wisconsin
#20 UW AND solution
#21 Marshall's Soltran*
#22 Eurocollins
#23 HTK
#24 histidine AND tryptophan
#25 celsior
#26 viaspan
#27 soltran
#28 Belzer
#29 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 #1 OR #10
#31 #29 AND #30

Health Technology Assessment Database (HTA) on the CRD Website

Search Date: 29 November 2007

Search Strategy same as DARE

Additionally the following databases of ongoing and recently completed trials were searched:

NRR (National Research Register)

Issue 2007 4

Source: http://www.nrr.nhs.uk/

Search Date: 21 November 2007

NB: Includes information added until September 2007

ReFeR: The Research Findings Register (now withdrawn)

Source: www.refer.nhs.uk/

Search Date: 21 November 2007

Current Controlled Trials including MRC Trials dB

Source: http://controlled-trials.com/

Search Date: 20 November 2007

US Food and Drug Administration (FDA)

Source: http://www.fda.gov/

Search Date: 05 May 2008

a) Center for Drug evaluation and Research: Adverse Events reporting system.

b) Center for Devices & Radiological Health

Medical Healthcare & Regulatory Authority

Source: http://www.mhra.gov.uk/

Search Date: 05 May 2008

B. Databases and their search terms for the systematic review of economic evaluations.

Medline 1950 –to date

Dialog DataStar: Web Version

Search date: 08 February,2008

ECONOMICS#.W..DE.
HEALTH-CARE-ECONOMICS-AND-ORGANIZATIONS#.DE.
ECONOMICS-PHARMACEUTICAL#.DE.
ECONOMICS-NURSING#.DE.
ECONOMICS-MEDICAL#.DE.
ECONOMICS-HOSPITAL#.DE.
DIRECT-SERVICE-COSTS#.DE.
COST-OF-ILLNESS#.DE.
COSTS-AND-COST-ANALYSIS.DE.
COST-ALLOCATION.DE.
COST-BENEFIT-ANALYSIS.DE.
COST-CONTROL#.DE.
COST-OF-ILLNESS.DE.
COST-SHARING#.DE.
HEALTH-CARE-COSTS#.DE.
HEALTH-EXPENDITURES#.DE.
MODELS-ECONOMIC#.DE.
COST-SAVINGS.DE.
FEES-AND-CHARGES#.DE.
BUDGETS#.W..DE.
VALUE-OF-LIFE#.DE.
COST$3.TI,AB.

(ECONOMIC$2 OR PRICE$2 OR PRICING).TI,AB.
PHARMACOECONOMICS$ OR PHARMA$3 ADJ ECONOMIC$
EXPENDITURE$2 NOT ENERGY
(EQ OR EUROQOL) ADJ (5D OR '5' ADJ DIMENSIONS OR FIVE ADJ DIMENSIONS)
VALUE NEAR (MONEY OR MONETARY)
FISCAL OR FUNDING OR FINANCIAL OR FINANCE
(RESOURCE ADJ USE).TI,AB.
BUDGET.TI,AB.

EMBASE 1974 to date

Dialog DataStar: Web Version

Search Date: 8 February, 2008

COST-EFFECTIVENESS-ANALYSIS#.DE.
COST-BENEFIT-ANALYSIS#.DE.
COST#.W..DE.
COST-CONTROL#.DE.
HOSPITAL-COST#.DE.
COST-MINIMIZATION-ANALYSIS#.DE.
COST-OF-ILLNESS#.DE.
COST-UTILITY-ANALYSIS#.DE.
DRUG-COST#.DE.
HEALTH-CARE-COST#.DE.
HEALTH-ECONOMICS#.DE.
ECONOMIC-EVALUATION#.DE.
PHARMACOECONOMICS#.W..DE.
ECONOMICS#.W..DE.
BUDGET.TI,AB.
BUDGET#.W..DE.
ECONOMIC-ASPECT#.DE.
FINANCIAL-MANAGEMENT#.DE.
HEALTH-CARE-FINANCING#.DE.
(PRICE$2 OR PRICING).TI,AB.
(FINANCIAL OR FINANC$3 OR FUNDING).TI,AB.
(FEE OR FEES).TI,AB.
(ECONOMIC$2 OR PHARMACOECONOMIC$2 OR PHARMACO ADJ ECONOMIC$2).TI,AB.
ECONOMIC$2.TI,AB.
COST$4.TI,AB.

NHS Economic Evaluation Database (NHS-EED) on the CRD Website

Search Date: 8 February 2007

Same strategy as DARE databases (clinical effectiveness section).

ISI Web of Knowledge (SCI-EXPANDED)--1970-present

Search date: 8 February, 2008

TS=(economic* or price* or pricing or pharmacoeconomic* or pharma economic*)
TS=(cost* or budget)
TS=(value SAME (money or monetary))
The above were put together (OR) and combined (AND) with line #10 of the clinical effectiveness search

C. Databases and search terms for the review of quality of life and utility studies.

Medline 1950 –to date

Dialog DataStar: Web Version

Search date: 08 February,2007

```
QUALITY-OF-LIFE#.DE.
QUALITY-ADJUSTED-LIFE-YEARS#.DE.
VALUE-OF-LIFE#.DE.
(QUALITY ADJ ADJUSTED ADJ LIFE).TI,AB.
(QUALITY ADJ OF ADJ LIFE).TI,AB.
(QALY$2 OR QALD$2 OR QALE$2 OR QTIME$2).TI,AB.
(DISABILITY ADJ ADJUSTED ADJ LIFE ADJ YEARS).TI,AB. OR DALY$2.TI,AB.
HEALTH-STATUS-INDICATORS#.DE.
COST ADJ UTILITY
(SF36 OR SF ADJ '36' OR SHORT ADJ FORM ADJ '36' OR SHORTFORM ADJ '36' OR SF ADJ THIRTYSIX
      OR SF ADJ THIRTY ADJ SIX OR SHORTFORM ADJ THIRTYSIX OR SHORTFORM ADJ THIRTY
      ADJ SIX OR SHORT ADJ FORM ADJ THIRTY ADJ SIX OR SHORT ADJ FORM ADJ THIRTYSIX
      OR SHORT ADJ FORM ADJ THIRTY ADJ SIX).TI,AB.
(SF6 OR SF ADJ '6' OR SHORT ADJ FORM ADJ '6' OR SHORTFORM ADJ '6' OR SF ADJ SIX OR SFSIX OR
      SHORTFORM ADJ SIX OR SHORT ADJ FORM ADJ SIX).TI,AB.
(SF12 OR SF ADJ '12' OR SHORT ADJ FORM ADJ '12' OR SHORTFORM ADJ '12' OR SF ADJ TWELVE OR
      SFTWELVE OR SHORTFORM ADJ TWELVE OR SHORT ADJ FORM ADJ TWELVE).TI,AB.
(SF16 OR SF ADJ '16' OR SHORT ADJ FORM ADJ '16' OR SHORTFORM ADJ '16' OR SF ADJ SIXTEEN OR
      SFSIXTEEN OR SHORTFORM ADJ SIXTEEN OR SHORT ADJ FORM ADJ SIXTEEN).TI,AB.
(SF20 OR SF ADJ '20' OR SHORT ADJ FORM ADJ '20' OR SHORTFORM ADJ '20' OR SF ADJ TWENTY OR
      SFTWENTY OR SHORTFORM ADJ TWENTY OR SHORT ADJ FORM ADJ TWENTY).TI,AB.
(EUROQOL OR EURO ADJ QOL OR EQ5D OR EQ ADJ 5D).TI,AB.
(HQL OR HQOL OR H ADJ QOL OR HRQOL OR HR ADJ QOL OR QOLY OR QOL).TI,AB.
(HYE OR HYES).TI,AB.
(HEALTH$2 ADJ YEAR$2 ADJ EQUIVALENT$2).TI,AB.
(HEALTH ADJ UTILIT$4 OR HUI OR HUI1 OR HUI2 OR HUI3 OR DISUTIL$6).TI,AB.
ROSSER.TI,AB.
(QUALITY ADJ OF ADJ WELL ADJ BEING).TI,AB. OR (QUALITY ADJ OF ADJ WELLBEING).TI,AB.
QWB.TI,AB.
(WILLINGNESS ADJ TO ADJ PAY).TI,AB.
(STANDARD ADJ GAMBLE$2).TI,AB.
(TIME ADJ TRADE ADJ OFF).TI,AB. OR (TIME ADJ TRADEOFF).TI,AB.
TTO.TI,AB. OR VAS.TI,AB.
(VISUAL ADJ (ANALOG OR ANALOGUE)).TI,AB.
(PATIENT ADJ PREFERENC$2).TI,AB
```

The above terms were put together with “OR” and combined (“AND”) with line 39 from the clinical effectiveness searches.

EMBASE 1974 to date

Dialog DataStar: Online Version

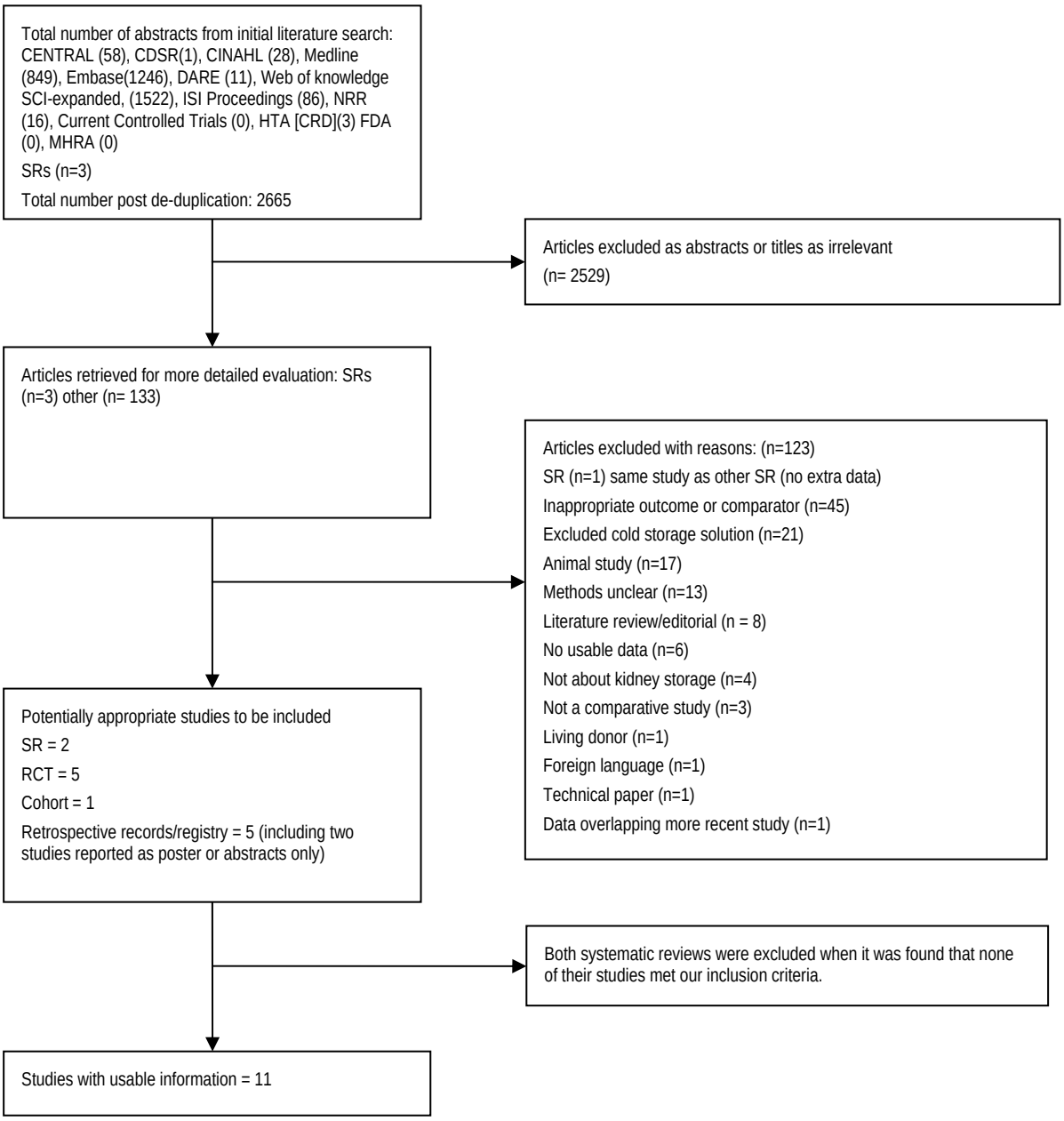
Search Date: 8 February, 2008

```
QUALITY-OF-LIFE#.DE.
(QUALITY ADJ ADJUSTED ADJ LIFE).TI,AB.
SOCIOECONOMICS.W..DE.
(QALY$2 OR QALD$2 OR QALE$2 OR QTIME$2).TI,AB.
```

(DISABILITY ADJ ADJUSTED ADJ LIFE ADJ YEARS).TI,AB. OR DALY$2.TI,AB.
(SF36 OR SF ADJ '36' OR SHORT ADJ FORM ADJ '36' OR SHORTFORM ADJ '36' OR SF ADJ THIRTYSIX OR SF ADJ THIRTY ADJ SIX OR SHORTFORM ADJ THIRTYSIX OR SHORTFORM ADJ THIRTY ADJ SIX OR SHORT ADJ FORM ADJ THIRTY ADJ SIX OR SHORT ADJ FORM ADJ THIRTYSIX OR SHORT ADJ FORM ADJ THIRTY ADJ SIX).TI,AB.
(SF6 OR SF ADJ '6' OR SHORT ADJ FORM ADJ '6' OR SHORTFORM ADJ '6' OR SF ADJ SIX OR SFSIX OR SHORTFORM ADJ SIX OR SHORT ADJ FORM ADJ SIX).TI,AB.
(SF12 OR SF ADJ '12' OR SHORT ADJ FORM ADJ '12' OR SHORTFORM ADJ '12' OR SF ADJ TWELVE OR SFTWELVE OR SHORTFORM ADJ TWELVE OR SHORT ADJ FORM ADJ TWELVE).TI,AB.
(SF16 OR SF ADJ '16' OR SHORT ADJ FORM ADJ '16' OR SHORTFORM ADJ '16' OR SF ADJ SIXTEEN OR SFSIXTEEN OR SHORTFORM ADJ SIXTEEN OR SHORT ADJ FORM ADJ SIXTEEN).TI,AB.
(SF20 OR SF ADJ '20' OR SHORT ADJ FORM ADJ '20' OR SHORTFORM ADJ '20' OR SF ADJ TWENTY OR SFTWENTY OR SHORTFORM ADJ TWENTY OR SHORT ADJ FORM ADJ TWENTY).TI,AB.
(EUROQOL OR EURO ADJ QOL OR EQ5D OR EQ ADJ 5D).TI,AB.
(HQL OR HQOL OR H ADJ QOL OR HRQOL OR HR ADJ QOL OR QOLY OR QOL).TI,AB.
(HYE OR HYES).TI,AB. OR (HEALTH$2 ADJ YEAR$2 ADJ EQUIVALENT$2).TI,AB.
(HEALTH ADJ UTILIT$4 OR HUI OR HUI1 OR HUI2 OR HUI3 OR DISUTIL$6).TI,AB.
ROSSER.TI,AB.
(QUALITY ADJ OF ADJ WELL ADJ BEING).TI,AB. OR (QUALITY ADJ OF ADJ WELLBEING).TI,AB. OR QWB.TI,AB.
(WILLINGNESS ADJ TO ADJ PAY).TI,AB.
(STANDARD ADJ GAMBLE$2).TI,AB.
(TIME ADJ TRADE ADJ OFF).TI,AB. OR (TIME ADJ TRADEOFF).TI,AB.
TTO.TI,AB. OR VAS.TI,AB.
(VISUAL ADJ (ANALOG OR ANALOGUE)).TI,AB.
(PATIENT ADJ PREFERENC$2).TI,AB.
`1

APPENDIX 2. Quality assessment

QUOROM flow diagram for the quality of studies in this TAR



APPENDIX 3. Data extraction tables

Data extraction tables can be found in the separately attached pdf file: All DX forms.pdf

APPENDIX 4. Excluded studies

Stored Kidneys - Excluded Studies	Reason for exclusion
Pulsatile perfusion is beneficial in expanded criteria donor kidney transplantation. NAT CLIN PRACT NEPHROL 2006; 2(9):470-471.	literature review or editorial
Albrecht K, Zuhlke M, Kruschke A, Eigler FW. Impact of preservation solution on early function and graft survival in cadaveric renal transplantation. TRANSPLANT PROC 1993; 25(4):2561-2562.	Inappropriate outcome or comparator
Alijani MR, Cutler JA, Delvalle CJ, Morres DN, Fawzy A, Pechan BW and colleagues. Single-Donor Cold-Storage Versus Machine Perfusion in Cadaver Kidney-Preservation. Transplantation 1985; 40(6):659-661.	Wrong cold storage solution
Baatard R, Pradier F, Dantal J, Karam G, Cantarovich D, Hourmant M and colleagues. Prospective Randomized Comparison of University-Of-Wisconsin and Uw-Modified, Lacking Hydroxyethyl-Starch, Cold-Storage Solutions in Kidney-Transplantation. Transplantation 1993; 55(1):31-35.	Inappropriate outcome or comparator
Bagul A, Sarah HA, Monika K, Mark K, Hellen W, Nicholson ML. A comparison of normothermic resuscitation perfusion using autologous blood and traditional hypothermic methods for renal preservation. AM J TRANSPLANT 2007; 7(1109 Supp2 May 2007):432.	Inappropriate outcome or comparator
Baldan N, Rigotti P, Furian L, Sarzo G, Cadrobbi R, Valente ML and colleagues. Celsior (R), a new organ preservation solution, in kidney and pancreas experimental transplantation. Transplantation 2000; 69(8):S200.	Animal study
Balupuri S, Buckley PE, Mantle D, Manas DM, Talbot D. Outcomes of pulsatile preservation and viability assessment of NHBD kidneys. Transplantation 2000; 69(8):S334-S335.	Not a comparative study
Barber WH, Deierhoi MH, Phillips MG, Diethelm AG. Preservation by Pulsatile Perfusion Improves Early Renal-Allograft Function. TRANSPLANT PROC 1988; 20(5):865-868.	Inappropriate outcome or comparator
Barber WH, Laskow DA, Deierhoi MH, Poplawski SC, Diethelm AG. Comparison of Simple Hypothermic Storage, Pulsatile Perfusion with Belzer Gluconate-Albumin Solution, and Pulsatile Perfusion with Uw Solution for Renal-Allograft Preservation. TRANSPLANT PROC 1991; 23(5):2394-2395.	Wrong cold storage solution
Barry JM, Farnsworth MA, Metcalfe JB, Bennett WM. Human Kidney-Preservation - Comparison of Simple Cold Storage to Machine Perfusion. KIDNEY INT 1978; 14(6):787.	Wrong cold storage solution
Beck TA. Machine versus cold storage preservation and TAN versus the energy charge as a predictor of graft function posttransplantation. TRANSPLANT PROC 1979; 11(1):459-464.	Wrong cold storage solution
Belzer FO. Perfusion preservation versus cold storage. TRANSPLANT PROC 1985; 17(1II):1515-1517.	Literature review or editorial
Belzer FO, Hoffman RM, Stratta RJ, Dalessandro A, Pirsch J, Kalayoglu M and colleagues. Combined Cold-Storage Perfusion Preservation of the Kidney with A New Synthetic Perfusate. TRANSPLANT PROC 1989; 21(1):1240-1241.	Wrong cold storage solution

Benoit G, Jaber N, Moukarzel M, Bensadoun H, Blanchet P, Charpentier B and colleagues. Incidence of Arterial and Venous Complications in Kidney-Transplantation - Role of the Kidney-Preservation Solution. TRANSPLANT PROC 1994; 26(1):295-296.	Inappropriate outcome or comparator
Berenguer I, Pedemonte G, Rodriguez-Martinez D, Alvarado A, Martinez C, Del Canizo JF and colleagues. Comparative study of the hypothermic preservation and pulsatile perfusion effects in autotransplanted ischemic kidneys. INT J ARTIF ORGANS 2005; 28(9):888abstract #79-888.	Animal study
Booster MH, Wijnen RMH, Yin M, Tiebosch ATM, Heineman E, Maessen JG and colleagues. Enhanced Resistance to the Effects of Normothermic Ischemia in Kidneys Using Pulsatile Machine Perfusion. TRANSPLANT PROC 1993; 25(6):3006-3011.	Animal study
Buchanan P, Schnitzler M, Takemoto S, Lentine K, Salvalaggio P. Routine utilization of pulsatile machine preservation reduces the rate of delayed graft function in cadaveric kidney transplantation. AM J TRANSPLANT 2007; 7:286, abstract #532.	Methods unclear
Burdick JF, Rosendale JD, McBride MA, Kauffman HM, Bennett LE. National impact of pulsatile perfusion on cadaveric kidney transplantation. Transplantation 1997; 64(12):1730-1733.	Methods unclear
Cerra FB, Raza S, Andres GA, Siegel JH. Structural Injury Produced by Pulsatile Perfusion Vs Cold Storage Renal Preservation. SURG FORUM 1975; 26:313-315.	Animal study
Cho SI, Bradley JW, Nabseth DC. Graft survival of perfused vs nonperfused cadaver kidneys. SURG FORUM 1975;(-):351-352.	Wrong cold storage solution
Cho YW, Aswad S, Cicciarelli JC, Mendez R, Selby RR. Machine perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation: Analysis of unos database. AM J TRANSPLANT 2005; 5(537 S May):293.	Methods unclear
Clark EA, Terasaki PI, Opelz G, Mickey MR. Cadaver kidney transplant failures at one month. NEW ENGL J MED 1974; 291(21):1099-1102.	Inappropriate outcome or comparator
Cooper J, Kimmelstiel F, Lin J, Mccabe R. Improved Kidney-Preservation by Post Cold-Storage Machine Perfusion. Cryobiology 1988; 25(6):513-514.	Animal study
Corry RJ. A critical comparison of cold storage and dynamic perfusion of cadaver renal allografts. DIAL TRANSPLANT 1979; 8(3):207-210.	Inappropriate outcome or comparator
Daemen JH, Heineman E, Kootstra G. Viability assessment of non-heart-beating donor kidneys during machine preservation. TRANSPLANT PROC 1995; 27(5):2906-2907.	Inappropriate outcome or comparator
Daemen JHC, De W, Bronkhorst MWG, Marcar ML, Yin M, Heineman E and colleagues. Short-term outcome of kidney transplants from non-heart-beating donors after preservation by machine perfusion. TRANSPLANT INT 1996; 9(SUPPL.1):S76-S80.	Inappropriate outcome or comparator
Daemen JHC, deVries B, Oomen APA, DeMeester J, Kootstra G. Effect of machine perfusion preservation on delayed graft function in non-heart-beating donor kidneys early results. TRANSPLANT INT 1997; 10(4):317-322.	Inappropriate outcome or comparator
Daemen JHC, de VB, Kootstra G. The effect of machine perfusion preservation on early function of non-heart-beating donor kidneys. TRANSPLANT PROC 1997; 29(8):3489.	Methods unclear

Degawa H, Matsuno N, Iwamoto H, Hama K, Nakamura Y, Narumi Y and colleagues. Primary nonfunctioning grafts in cadaveric kidney transplantation. TRANSPLANT PROC 2000; 32(7):1903-1904.	Methods unclear
Fabre E, Paradis V, Conti M, Eschwege P, Benoit G. Is renal preservation with pulsatile perfusion a model for reperfusion? TRANSPLANT PROC 2000; 32(8):2742-2743.	Animal study
Florence LS, Christensen LL, Wolfe RA, Galloway J, Distant D, Hull D and colleagues. Machine preservation (NIP) by locale on the risk for delayed graft function (DGF) and graft failure (GF): An analysis of transplanted deceased donor (DD) kidneys in the United States over a two year period. AM J TRANSPLANT 2007; 7(1346 Supp 2 May 2007):493.	Methods unclear
Fuller BJ, Pegg DE. Assessment of Renal Preservation by Normothermic Bloodless Perfusion. Cryobiology 1976; 13(2):177-184.	Inappropriate outcome or comparator
Gage F, Ali M, Alijani MR, Aquino AO, Barhyte DY, Callender CO and colleagues. Comparison of static versus pulsatile preservation of matched-paired kidneys. TRANSPLANT PROC 1997; 29(8):3644-3645.	Inappropriate outcome or comparator
Garcia JA, Holm A, Lagunas J, Camarena A. Static cold storage vs hypothermic pulsatile preservation in cadaveric kidney transplatation in a single institution (Mexico City). Transplantation 1999; 67(7):S91.	Wrong cold storage solution
Goldstein MJ; Guarrera JV, Abreu-Goris M, Kapur S. Pulsatile-machine preservation versus colds storage in mate renal allografts. Am J Transplantation 2006; 6:90.	Methods unclear
Grundmann R, Strumper R, Eichmann J, Pichlmaier H. Immediate Function of Kidney After 24-Hr to 72-Hr Preservation - Hypothermic Storage Versus Mechanical Perfusion. Transplantation 1977; 23(5):437-443.	Animal study
Grundmann R, Kurten K. Mechanical Perfusion Vs Hypothermic Storage for the Preservation of Hypotensively Damaged Kidneys. Cryobiology 1983; 20(6):732-733.	Animal study
Guarrera J, Polyak M, Mar A, Kapur S, Stubenbord W, Kinkhabwala M. Pulsatile machine perfusion with Vasosol solution improves early graft function after cadaveric renal transplantation. Transplantation 2004; 77(8):1264-1268.	Inappropriate outcome or comparator
Guarrera JV, Polyak MMR, and colleagues. Pushing the envelope in renal preservation: Improved results with novel perfusate modifications for pulsatile machine perfusion of cadaver kidneys. TRANSPLANT PROC 2004; 36(5):1257-1260.	Inappropriate outcome or comparator
Halloran P, Aprile M. A Randomized Prospective Trial of Cold-Storage Versus Pulsatile Perfusion for Cadaver Kidney-Preservation. Transplantation 1987; 43(6):827-832.	Wrong cold storage solution
Healthcare Insurance Board/. Preservation of non-heart-beating kidney donors - primary research. 1998.	Foreign language
Heil JE, Canafax DM, Sutherland DER, Simmons RL, Dunning M, Najarian JS. A Controlled Comparison of Kidney-Preservation by 2 Methods - Machine Perfusion and Cold-Storage. TRANSPLANT PROC 1987; 19(1):2046.	Wrong cold storage solution
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Henry ML, Tso P, Elkhammas EA, Davies EA, Pelletier RP, Bumgardner GL and colleagues. Immediate renal allograft function following pulsatile preservation. Transplantation 2000; 69(8):S335.	Inappropriate outcome or comparator
Hermsen JL, Nath DS, Lindsey JD, Wigfield CH, Edwards NM. Outcomes in simultaneous heart and kidney transplantation: The university of Wisconsin experience. Journal of Heart and Lung Transplantation 2007; 26(2):S216.	Not about kidney storage
Hoffmann RM, Stratta RJ, Sollinger HW, Kalayoglu M, Pirsch JD, Belzer FO. Efficacy of Clinical Cadaver Kidney-Preservation by Continuous Perfusion. TRANSPLANT PROC 1988; 20(5):882-884.	Not a comparative study
Jacobbi LM, Gage F, Kravitz D. Machine preservation is an effective evaluation measure for kidneys from asystolic donors. AM J KIDNEY DIS 2003; 41(4):A23.	No usable data
Jacobsson J, Tufveson G, Odlind B, Wahlberg J. Improved Post-Transplant Renal-Function by Recipient Hemodilution and Cold-Storage in A Modified Uw-Preservation Solution. TRANSPLANT PROC 1989; 21(1):1254-1255.	Animal study
Johnson CP, Roza AM, Adams MB. Local procurement with pulsatile perfusion gives excellent results and minimizes initial cost associated with renal transplantation. TRANSPLANT PROC 1990; 22(2):385-387.	Not a comparative study
Kievit JK, Oomen APA, deVries B, Heineman E, Kootstra G. Update on the results of non-heart-beating donor kidney transplants. TRANSPLANT PROC 1997; 29(7):2989-2991.	Inappropriate outcome or comparator
Koning OH, van B, van d, Persijn GG, Hermans J, Ploeg RJ. Risk factors for delayed graft function in University of Wisconsin solution preserved kidneys from multiorgan donors European Multicenter Study Group on Organ Preservation. TRANSPLANT PROC 1995; 27(1):752-753.	Inappropriate outcome or comparator
Koyama H, Cecka JM, Terasaki PI. A Comparison of Cadaver Donor Kidney Storage Methods - Pump Perfusion and Cold-Storage Solutions. CLIN TRANSPLANT 1993; 7(2):199-205.	Inappropriate outcome or comparator
Kozaki K, Sakurai E, Tamaki I, Matsuno N, Saito A, Furuhashi K and colleagues. Usefulness of Continuous Hypothermic Perfusion Preservation for Cadaveric Renal Crafts in Poor Condition. TRANSPLANT PROC 1995; 27(1):757-758.	Wrong cold storage solution
Kozaki K, Sakurai E, Uchiyama M, Matsuno N, Kozaki M, Nagao T. Usefulness of continuous hypotermic perfusion preservation for cadaveric renal high risk grafts. Transplantation 1999; 67(9):S582.	Wrong cold storage solution
Kozaki K, Sakurai E, Uchiyama M, Matsuno N, Kozaki M, Nagao T. Development of hypothermic continuous perfusion preservation machine equipped with nonpulsatile pump and its clinical application. TRANSPLANT PROC 2000; 32(1):5-9.	Animal study
Kozaki K, Sakurai E, Nagao T, Kozaki M. Usefulness of continuous hypothermic perfusion preservation in renal transplantation from non-heart-beating donors. TRANSPLANT PROC 2002; 34(7):2592-2597.	Inappropriate outcome or comparator
Kozaki M, Miyamoto K, Tamaki I, Sakurai E, Tokuchi M, Sugie S and colleagues. Comparative-Study of Hypothermic Pulsatile and Nonpulsatile Perfusion for Kidney-Preservation. Artif-Organs 1984; 8(2):245.	No usable data

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Kumar MSA, Stephan R, Chui J, Brezin J, Lyons P, Katz SM and colleagues. Comparative-Study of Cadaver Donor Kidneys Preserved in University-Of-Wisconsin Solution for Less-Than Or Longer Than 30 Hours. TRANSPLANT PROC 1993; 25(3):2265-2266.	Inappropriate outcome or comparator
Kusaka M, Kubota Y, Sasaki H, Maruyama T, Hayakawa K, Shiroki R and colleagues. Is pulsatile perfusion necessary for renal transplantation engrafting kidneys from cardiac death donors? TRANSPLANT PROC 2006; 38(10):3388-3389.	Methods unclear
Kwiatkowski A, Danielewicz R, Polak W, Michalak G, Paczek L, Walaszewski J and colleagues. Storage by continuous hypothermic perfusion for kidney harvested from hemodynamically unstable donors. TRANSPLANT PROC 1996; 28(1):306-307.	Inappropriate outcome or comparator
Kwiatkowski A, Wszola M, Kosieradzki M, Danielewicz R, Ostrowski K, Domagala P and colleagues. Machine perfusion preservation improves renal allograft survival. AM J TRANSPLANT 2007; 7(8):1942-1947.	Inappropriate outcome or comparator
Kyllonen LEJ, Salmela KT, Eklund BH, Halme LEH, Hockerstedt KA, Isoniemi HM and colleagues. Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection. TRANSPLANT INT 2000; 13(2):122-128.	Not about kidney storage
Laskowski IA, Pratschke J, Wilhelm MJ, Paz D, Tilney NL. Non-heartbeating kidney donors. CLIN TRANSPLANT 1999; 13(4):281-286.	literature review or editorial
Light JA, Annable CA, Spees EK, Oakes DD, Flye MW, Reinmuth B. Comparison of Long-Term Kidney Survival Following Cold Storage Or Pulsatile Preservation. TRANSPLANT PROC 1977; 9(3):1517-1519.	Wrong cold storage solution
Light JA, Kowalski AE, Gage F, Callender CO, Sasaki TM. Immediate Function and Cost Comparison Between Ice Storage and Pulsatile Preservation in Kidney Recipients at One Hospital. TRANSPLANT PROC 1995; 27(5):2962-2964.	Inappropriate outcome or comparator
Light JA, Gage F, Kowalski AE, Sasaki TM, Callender CO. Immediate function and cost comparison between static and pulsatile preservation in kidney recipients. CLIN TRANSPLANT 1996; 10(3):233-236.	Inappropriate outcome or comparator
Light JA, Sasaki TM, Aquino AO, Barhyte DY, Gage F. Excellent long-term graft survival with kidneys from the uncontrolled non-heart-beating donor. TRANSPLANT PROC 2000; 32(1):186-187.	Not about kidney storage
Marshall's Soltran V, Ross H, Scott D. Cadaveric Renal-Allografts - Comparison of Preservation by Ice Storage and Continuous Perfusion. AUST NEW ZEALAND J SURG 1977; 47(1):111.	No usable data
Marshall's Soltran VC, Biguzas M, Jablonski P, Scott DF, Howden BO, Thomas AC and colleagues. Uw Solution for Kidney-Preservation. TRANSPLANT PROC 1990; 22(2):496-497.	Animal study
Matsuno N, Sakurai E, Uchiyama M, Kozaki K, Tamaki I, Kozaki M. Use of in situ cooling and machine perfusion preservation for non- heart- beating donors. TRANSPLANT PROC 1993; 25(6):3095-3096.	Inappropriate outcome or comparator

Matsuno N, Kozaki M, Sakurai E, Uchiyama M, Iwahori T, Kozaki K and colleagues. Effect of Combination Insitu Cooling and Machine Perfusion Preservation on Non-Heart-Beating Donor Kidney Procurement. TRANSPLANT PROC 1993; 25(1):1516-1517.	Inappropriate outcome or comparator
Matsuno N, Sakurai E, Tamaki I, Uchiyama M, Kozaki K, Kozaki M. The Effect of Machine Perfusion Preservation Versus Cold-Storage on the Function of Kidneys from Non-Heart-Beating Donors. Transplantation 1994; 57(2):293-294.	No usable data
Matsuno N, Sakurai E, Uchiyama M, Kozaki K, Miyamoto K, Kozaki M. Usefulness of machine perfusion preservation for non-heart-beating donors in kidney transplantation. TRANSPLANT PROC 1996; 28(3):1551-1552.	Inappropriate outcome or comparator
Matsuno N, Kozaki K, Degawa H, Narumi Y, Suzuki N, Kikuchi K and colleagues. Importance of machine perfusion flow in kidney preservation. TRANSPLANT PROC 1999; 31(5):2004-2005.	Inappropriate outcome or comparator
Matsuoka L, Shah T, Aswad S, Bunnapradist S, Cho Y, Mendez RG and colleagues. Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. AM J TRANSPLANT 2006; 6(6):1473-1478.	Methods unclear
Merion RM, Oh HK, Port FK, Toledopereyra LH, Turcotte JG. A Prospective Controlled Trial of Cold-Storage Versus Machine-Perfusion Preservation in Cadaveric Renal-Transplantation. Transplantation 1990; 50(2):230-233.	Wrong cold storage solution
Merkel FK, Geroulis N, Thornton B, Jensik SC. Perfusion Preservation of Human Cadaver Kidneys - An 8-Year Experience. TRANSPLANT PROC 1982; 14(1):86-87.	Inappropriate outcome or comparator
Mittal VK, Kaplan MP, Rosenberg JC, et a. Pulsatile perfusion: Better than hypothermic storage with cyclosporine as an immunosuppressant. DIAL TRANSPLANT 1985; 14(3):136-140.	Wrong cold storage solution
Mittal VK, Toledo P, Kaplan MP, et a. Effect of preservation method on function in the cyclosporine era. TRANSPLANT PROC 1985; 17(6):2815-2817.	Inappropriate outcome or comparator
Mohacsi PJ, Herbertt KL, Thompson JF. Human Kidney-Preservation with University-Of-Wisconsin Solution - An Initial Report of the Australian Experience. TRANSPLANT PROC 1992; 24(1):256-257.	Inappropriate outcome or comparator
Mozes MF, Finch WT, Reckard CR, Merkel FK, Cohen C. Comparison of Cold-Storage and Machine Perfusion in the Preservation of Cadaver Kidneys - A Prospective, Randomized Study. TRANSPLANT PROC 1985; 17(1):1474-1477.	Inappropriate outcome or comparator
Muhlbacher F, Langer F, Mittermayer C. Preservation solutions for transplantation. TRANSPLANT PROC 1999; 31(5):2069-2070.	literature review or editorial
Net M, Lara EE, Peri L, Saval N, Calsamiglia J, Agusti E and colleagues. Pulsatile renal perfusion machine: Viability prediction and improved preservation of marginal kidneys. AM J TRANSPLANT 2007; 7(194 Supp 2 May 2007):197.	No usable data
Nghiem DD, Schulak JA, Corry RJ. Cadaver Kidney-Preservation Beyond 40 Hours - Superiority of Machine Preservation Over Cold-Storage. TRANSPLANT PROC 1986; 18(3):564-565.	Inappropriate outcome or comparator
Nicholson M. Kidney transplantation from asystolic donors. Br-J-Hosp-Med 1996; 55(1-2):51-56.	literature review or editorial

Nunes P, Mota A, Figueiredo A, Mac¯rio F, Rolo F, Dias V and colleagues. Efficacy of renal preservation: comparative study of Celsior and University of Wisconsin solutions. TRANSPLANT PROC 2007; 39(8):2478-2479.	Included living donors
Opelz G, Terasaki PI. Advantage of Cold-Storage Over Machine Perfusion for Preservation of Cadaver Kidneys. Transplantation 1982; 33(1):64-68.	Wrong cold storage solution
Opelz G, Wujciak T. Comparative analysis of kidney preservation methods. TRANSPLANT PROC 1996; 28(1):87-90.	Data overlap with more recent study
Orlic P, Zelic M, Petrosic N, Maricic A, Zambelli M, Bacic I and colleagues. Use of non-heart-beating donors: Preliminary experience with perfusion in situ. TRANSPLANT PROC 1999; 31(5):2097-2098.	Not about kidney storage
Peri L, Net M, Saval N, Lara E, Agud A, Ruiz A and colleagues. Pulsatile perfusion kidney preservation improves kidney preservation and provides information about organ viability. European Urology Supplements 2007; 6(2):93.	Methods unclear
Pirsch JD, DAlessandro AM, Knechtle SJ, Kalayoglu M, Belzer FO, Sollinger HW. Simultaneous Kidney-Pancreas Transplantation at the University-Of-Wisconsin. TRANSPLANT PROC 1993; 25(4):33-34.	Inappropriate outcome or comparator
Plata-Munoz JJ, Contractor H, Muthusamy A, Shina S, Roy D, Darby C and colleagues. Central role of pulsatile perfusion on preservation of kidneys from controlled non-heart-beating donors. AM J TRANSPLANT 2007; 7(#188 Supp 2 May 2007):195.	Methods unclear
Ploeg RJ, Goossens D, Camesi D, McAnulty JF, Southard JH, Belzer FO. Kidney-Preservation with Belzers New Pancreas Preservation Solution. Cryobiology 1987; 24(6):578.	Animal study
Ploeg RJ, Goossens D, Vreugdenhil P, McAnulty JF, Southard JH, Belzer FO. Successful 72-Hour Cold-Storage Kidney-Preservation with Uw Solution. TRANSPLANT PROC 1988; 20(1):935-938.	Animal study
Polyak M, Arrington B, Stubenbord WT, Kapur S, Kinkhabwala M. Maximizing early renal allograft function in the era of donor scarcity: Introduction of a novel machine perfusate and results utilizing pulsatile preservaton. Transplantation 2000; 69(8):S262.	Technical paper
Polyak MM, Arrington B, Hardy MA, Stubenbord WT, Kinkhabwala M. The state of renal preservation for transplantation in New York. TRANSPLANT PROC 1999; 31(5):2091-2093.	Inappropriate outcome or comparator
Polyak MMR, Arrington B, Stubenbord WT, Kapur S, Kinkhabwala M. Pulsatile machine preservation improves long-term function in the renal allograft. Transplantation 1999; 67(9):S562.	Methods unclear
Polyak MMR, Arrington BO, Stubenbord WT, Boykin J, Brown T, Jean-Jacques MA and colleagues. The influence of pulsatile preservation on renal transplantation in the 1990s. Transplantation 2000; 69(2):249-258.	Inappropriate outcome or comparator
Rice MJ, Southard JH, Hoffmann RM, Belzer FO. Comparison of the Effects of Short-Term Renal Preservation on Renal-Function Determined by 2 Isolated-Perfusion Systems. Cryobiology 1984; 21(6):701-702.	Animal study
Rice MJ, Southard JH, Hoffmann RM, Belzer FO. Effects of Hypothermic Kidney-Preservation on the Isolated Perfused Kidney - A Comparison of Reperfusion Methods. Cryobiology 1985; 22(2):161-167.	Animal study

Rosenthal JT, Herman JB, Taylor RJ, Broznick B, Hakala TR. Comparison of Pulsatile Machine Perfusion with Cold-Storage for Cadaver Kidney-Preservation. Transplantation 1984; 37(4):425-426.	Wrong cold storage solution
Santiago EA, Mason RV, Campos RA, Moberg AW, Najarian JS, Mozes MF. Comparative Analysis of Perfusion and Nonperfusion Methods for Renal Preservation. Surgery 1972; 72(5):793-803.	Animal study
Schold J, Kaplan B, Howard R, Reed A, Foley D, Meier K. Are we frozen in time? Analysis of the utilization and efficacy of pulsatile perfusion in renal transplantation. American journal of transplantation : official journal of the AmericanSociety of Transplantation and the American Society of TransplantSurgeons 2005; 5(7):1681-1688.	Methods unclear
Scott DF, Atkins RC. Results of Ice Storage and Perfusion Storage of Kidneys Prior to Transplantation. AUST NEW ZEALAND J MED 1974; 4(4):436.	Wrong cold storage solution
Scott DF, Whitesid D, Redhead J, Atkins RC. Ice Storage Versus Perfusion for Preservation of Kidneys Before Transplantation. BR MED J 1974; 4(5936):76-77.	Wrong cold storage solution
Sellers MT, Gallichio MH, Hudson SL, Young CJ, Bynon JS, Eckhoff DE and colleagues. Improved outcomes in cadaveric renal allografts with pulsatile preservation. CLIN TRANSPLANT 2000; 14(6):543-549.	Inappropriate outcome or comparator
Sheil AG, Drummond JM, Rogers JH, Boulas J, May J, Storey BG. A controlled clinical trial of machine perfusion of cadaveric donor renal allografts. Lancet 1975; 2(7929):287-290.	Inappropriate outcome or comparator
Sheil AGR, Boulas J, Drummond JM, May J, Rogers JH, Storey BG. Controlled Clinical-Trial of Machine Perfusion of Cadaveric Donor Renal-Allografts. AUST NEW ZEALAND J MED 1976; 6(1):94.	No usable data
Slooff MJH, Vanderwijk J, Rijkmans BG, Kootstra G. Machine Perfusion Versus Cold Storage for Preservation of Kidneys Before Transplantation. ARCH CHIR NEERL 1978; 30(2):83-90.	Wrong cold storage solution
Small A, Feduska NJ, Leapman SB. Function of Autotransplanted Kidneys After 24-Hour Preservation by Hypothermic Pulsatile Perfusion Or Simple Cold Storage. Transplantation 1978; 26(4):228-232.	Animal study
Stratta RJ, Moore PS, Farney AC, Rogers J, Hartmann EL, Reeves-Daniel A and colleagues. Influence of pulsatile perfusion preservation on outcomes in kidney transplantation from expanded criteria donors. J AM COLL SURG 2007; 204(5):873-882.	Inappropriate outcome or comparator
Suarez JF, Riera L, Franco E, Ruiz R, Roig M, Torras J and colleagues. Preservation of kidneys from marginal donors with pulsatile perfusion machine. TRANSPLANT PROC 1999; 31(6):2292-2293.	Inappropriate outcome or comparator
Szust J, Olson L, Cravero L. A comparison of OPO pulsatile machine preservation practices and results. Journal of transplant coordination : official publication of the NorthAmerican Transplant Coordinators Organization (NATCO) 1999; 9(2):97-100.	literature review or editorial
Tisone G, Orlando G, Pisani F, Iaria G, Negrini S, Pollicita S and colleagues. Gravity perfusion versus high-pressure perfusion in kidney transplantation: results from a prospective randomized study. TRANSPLANT PROC 1999; 31(8):3386-3387.	Inappropriate outcome or comparator

Toledo P, Whitten JI, Baskin S, McNichol LJ. Extending the limits of renal preservation (greater than or equal40 hours) - Effect of preservation method and immunosuppressive regimen. TRANSPLANT PROC 1988; 20(5):938-939.	Inappropriate outcome or comparator
van d, V, Kievit JK, Hene RJ, Hilbrands LB, Kootstra G. Preservation of non-heart-beating donor kidneys: A clinical prospective randomised case-control study of machine perfusion versus cold storage. TRANSPLANT PROC 2001; 33(1-2):847.	Inappropriate outcome or comparator
Vaughn WK, Mendezpicon G, Humphries AL. Cold-Storage Versus Perfusion for Cadaver Kidneys Transplanted by Seopf Institutions. Cryobiology 1979; 16(6):619.	Methods unclear
Veller MG, Botha JR, Britz RS, Gecelter GR, Beale PG, Margolius LP and colleagues. Renal-Allograft Preservation - A Comparison of University-Of-Wisconsin Solution and of Hypothermic Continuous Pulsatile Perfusion. CLIN TRANSPLANT 1994; 8(2):97-100.	Inappropriate outcome or comparator
Weinerth JL, Hendrix PC, Anderson EE. Preservation of the cadaveric kidney for transplantation. SOUTH MED J 1974; 67(12):1457-1458.	literature review or editorial
Wight J, Chilcott J, Holmes M, Brewer N. The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. Health Technology Assessment 2003; 7(25):1-81.	No usable data
Xenos ES. Perfusion storage versus static storage in kidney transplantation: Is one method superior to the other? NEPHROL DIAL TRANSPLANT 1997; 12(2):253-254.	literature review or editorial
Yland MJ, Anaise D, Ishimaru M, Rapaport FT. New Pulsatile Perfusion Method for Nonheartbeating Cadaveric Donor Organs - A Preliminary-Report. TRANSPLANT PROC 1993; 25(6):3087-3090.	Inappropriate outcome or comparator
Yland MJ, Nakayama Y, Abe Y, Rapaport FT. Organ Preservation by A New Pulsatile Perfusion Method and Apparatus. TRANSPLANT PROC 1995; 27(2):1879-1882.	Inappropriate outcome or comparator
Zongli H, Zhilian M, Jingqin L, Haikuan Z. Preservation of Cadaveric Kidney Allografts. TRANSPLANT PROC 1992; 24(4):1351-1352.	Wrong cold storage solution

APPENDIX 5. Flow of kidneys in the Machine Preservation Trial

Figure 43 Flow chart of recruited kidneys in the Machine Preservation Trial CiC

CIC diagram removed

APPENDIX 6. CHEC-list assessment of economic evaluations

Table 48. Quality assessment of economic evaluations (using the CHEC criteria list)

Criteria	Wight et al. 2003	Costa et al. 2007
	UK NHS Waters RM3 vs cold storage solution	Canadian hospital Machine (type not specified) vs solution (type not specified)
Is the study population clearly described?	No	No
Are competing alternatives clearly described?	Yes	Yes
Is a well-defined research question posed in answerable form?	No	Yes
Is the economic study design appropriate to the stated objective?	Yes – decision model	Yes – decision model
Is the chosen time horizon appropriate to include relevant costs and consequences?	10-years - Not lifetime	No – only 1 year
Is the actual perspective chosen appropriate?	Yes – health service	Yes - hospital
Are all important and relevant costs for each alternative identified?	Yes – machine perfusion No – no costs for cold storage	No – only initial storage costs (none for dialysis vs transplanted)
Are all resources measured appropriately in physical units?	Yes	Of those measured - yes
Are resources valued appropriately?	Yes	Yes
Are all important and relevant outcomes for each alternative identified?	Yes – DGF and graft survival	Not really – DGF events avoided

Are all outcomes measured appropriately in physical units?	Yes – but the extrapolation of graft survival from DGF rates using a single centre US study is questionable	Yes
Are outcomes valued appropriately?	Yes (QALYs)	NA
Is an incremental analysis of costs and outcomes performed?	Yes (but MP dominates CS)	Yes (but MP dominates CS)
Are all future costs and outcomes discounted appropriately?	Yes	NA
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes – mainly PSA	Yes – mainly PSA, but uncertainty in costs looks too low
Do the conclusions follow from the data reported?	Yes	Yes
Does the study discuss the generalisability of the results to other settings and patient/client groups?	Yes	Not much
Does the article indicate that there is not potential conflict of interest of study researcher(s) and funder(s)?	Yes – no conflicts	Not indicated
Are ethical and distributional issues discussed appropriately?	No	No

Nb. The CHEC list for assessing quality of economic evaluations (Evers et al. 2005) incorporates all but one of the widely used critical appraisal questions recommended by Drummond et al (2005).

APPENDIX 7. PenTAG model transitions

Table 49. Transitions represented in the PenTAG kidney transplant model

Index	Costs	Description
SRT_n_IGF	Yes	Immediate Graft Function following Transplant no complications
SRT_n_DGI	Yes	Delayed Graft Function following Transplant no complications
IGF_IGF	No	Stays (re-circulation) in immediate graft function following transplant
IGF_FKI	No	Graft starts to fail (after IGF) – patient moves to Kidney Failing state (FKI)
IGF_DTH	No	Death whilst in IGF state
DGI_DGF	No	Graft starts to function after Delayed Graft function following transplant
DGI_x_DYW	Yes	Graft failure in first month following DGF patient returns to waiting list
DGI_x_DYU	Yes	Graft failure in first month following DGF patient unsuitable for re-transplant
DGI_DTH	No	Death whilst in DGI state
DGF_DGF	No	Stays (recirculation) in Delayed Graft function following transplant
DGF_FKD	No	Graft starts to fail (after DGF) - patient moves to Kidney Failing state (FKD)
DGF_DTH	No	Death whilst in DGF State
FKI_FKI	No	Stays (recirculation) in Graft Failing state (following IGF)
FKI_u_DYW	No	Graft Fails, no explant, patient returns to waiting list
FKI_x_DYW	Yes	Graft Fails, kidney explanted, patient returns to waiting list
FKI_u_DYU	No	Graft Fails, no explant, patient unsuited for re-transplant
FKI_x_DYU	Yes	Graft Fails, kidney explanted, patient unsuited for re-transplant
FKI _DTH	No	Death whilst in FKI State
FKD_FKD	No	Stays (recirculation) in Graft Failing state (following DGF)
FKD_u_DYW	No	Graft Fails, no explant, patient returns to waiting list
FKD_x_DYW	Yes	Graft Fails, kidney explanted, patient returns to waiting list
FKD_u_DYU	No	Graft Fails, no explant, patient unsuited for re-transplant
FKD_x_DYU	Yes	Graft Fails, kidney explanted, patient unsuited for re-transplant
FKD_ DTH	No	Death whilst in FKD State
DYW_DYW	No	Stays (recirculation) in waiting for re-transplant
DYW_STX	Yes	Re-transplant – patient moves to post subsequent transplant state (STX)
DYW_DTH	No	Death whilst in DYW State
DYU_DYU	No	Stays (recirculation) in unsuitable for re-transplant state (maintains dialysis)
DYU_ DTH	No	Death whilst in DYU State
STX_STX	No	Stays (recirculation) in post subsequent transplant state

STX_DYW	Yes	Graft Fails (from subsequent transplant) patient returns to waiting list
STX_DTH	No	Death whilst in STX State
DTH_DTH	No	Recirculation of dead population (included for completeness)

APPENDIX 8. Base case outputs from the PenTAG model by age group

Summary Age Related outputs for each comparison

Table 50 LifePort versus ViaSpan PPART trial – Summary Model Outputs by Age Group

BY AGE GROUP		Incremental Costs	Incremental QALYs	ICER
Viaspan Age 18-34		173086	12.69	
Lifeport Age 18-34		176034	12.63	is dominated
	diffs	*2948*	*-0.06*	
Viaspan Age 35-44		154771	10.97	
Lifeport Age 35-44		157324	10.91	is dominated
	diffs	*2553*	*-0.06*	
Viaspan Age 45-54		137699	8.84	
Lifeport Age 45-54		139793	8.77	is dominated
	diffs	*2094*	*-0.07*	
Viaspan Age 55-64		117754	6.84	
Lifeport Age 55-64		119277	6.77	is dominated
	diffs	*1522*	*-0.07*	
Viaspan Age 65+		92794	4.78	
Lifeport Age 65+		93728	4.71	is dominated
	diffs	*934*	*-0.07*	

Note: All incremental Costs and QALYs shown are summary totals discounted at 3.5%

Table 51. LifePort versus ViaSpan MPT trial – Summary Model Outputs by Age Group

BY AGE GROUP		Incremental Costs	Incremental QALYs	ICER
Viaspan Age 18-34		178347	13.23	is dominated
Lifeport Age 18-34		172446	13.45	
	diffs	*-5902*	*0.22*	
Viaspan Age 35-44		159370	11.44	is dominated
Lifeport Age 35-44		154557	11.66	
	diffs	*-4813*	*0.22*	

Viaspan Age 45-54		141320	9.22	is dominated
Lifeport Age 45-54		137741	9.45	
	diffs	*-3579*	*0.23*	
Viaspan Age 55-64		120075	7.12	is dominated
Lifeport Age 55-64		117933	7.34	
	diffs	*-2142*	*0.22*	
Viaspan Age 65+		93828	4.94	is dominated
Lifeport Age 65+		93018	5.13	
	diffs	*-811*	*0.19*	

Note: All incremental Costs and QALYs shown are summary totals discounted at 3.5%

Table 52. LifePort versus Marshall's Soltran– Summary Model Outputs by Age Group

BY AGE GROUP		Incremental Costs	Incremental QALYs	ICER
Marshalls CS Age 18-34		181279	11.90	is dominated
Lifeport MP Age 18-34		162191	13.06	
	diffs	*-19088*	*1.16*	
Marshalls CS Age 35-44		161068	10.25	is dominated
Lifeport MP Age 35-44		146627	11.35	
	diffs	*-14441*	*1.10*	
Marshalls CS Age 45-54		142460	8.18	is dominated
Lifeport MP Age 45-54		131941	9.20	
	diffs	*-10519*	*1.02*	
Marshalls CS Age 55-64		121016	6.29	is dominated
Lifeport MP Age 55-64		114412	7.16	
	diffs	*-6604*	*0.87*	
Marshalls CS Age 65+		94691	4.38	is dominated
Lifeport MP Age 65+		91691	5.02	
	diffs	*-3000*	*0.63*	

Note: All incremental Costs and QALYs shown are summary totals discounted at 3.5%

Table 53. ViaSpan versus Marshall's Soltran– Summary Model Outputs by Age Group

BY AGE GROUP		Incremental Costs	Incremental QALYs	ICER
UW Viaspan CS Age 18-34		192205.02	12.06	
Marshall CS Solution Age 18-34		193674.59	12.01	is dominated
	diffs	1469.57	-0.05	
UW Viaspan CS Age 35-44		169670.89	10.35	
Marshall CS Solution Age 35-44		170771.92	10.29	is dominated
	diffs	1101.02	-0.05	
UW Viaspan CS Age 45-54		148749.04	8.24	
Marshall CS Solution Age 45-54		149511.03	8.19	is dominated
	diffs	761.99	-0.05	
UW Viaspan CS Age 55-64		124848.70	6.31	
Marshall CS Solution Age 55-64		125257.38	6.26	is dominated
	diffs	408.68	-0.05	
UW Viaspan CS Age 65+		96360.90	4.39	
Marshall CS Solution Age 65+		96450.31	4.36	is dominated
	diffs	89.41	-0.04	

Note: All incremental Costs and QALYs shown are summary totals discounted at 3.5%

APPENDIX 9. Probabilistic sensitivity analyses

In Probabilistic Sensitivity Analysis (PSA) parameter uncertainty is incorporated into the model. To implement this, model parameters are not given fixed values but are sampled from probability density functions which are chosen to characterise the variability around key parameters. By using Monte Carlo simulation to run the model many times and repeat the process of parameter sampling it is possible to build up a picture of the uncertainty that can be associated with the model outputs based on the uncertainty inherent in the inputs.

In the PenTAG model a wide range of the cost, utility and transition variables of the model were sampled from probabilistic distributions for the PSA. Table 54 below lists the standard data set parameters and distributions used in model for the PSA. The variance attached to each parameter has been assessed from the available evidence (e.g. confidence intervals). Where such data have not been available estimates of the variance have been used to characterise the distribution.

Table 54 Sampled distributions for fixed values of Standard Dataset used in PSA

STANDARD DATASET PARAMETER			
Age Group weightings	**Mean Value**	**Std. Err.**	**Distribution**
Age Group 18-34	18.18%	1.8%	Normal
Age Group 35-44	24.21%	2.4%	Normal
Age Group 45-54	24.86%	2.5%	Normal
Age Group 55-64	22.62%	2.3%	Normal
Age Group 65+	10.13%	1.0%	Normal
Utilities	**Mean Value**	**Range**	**Distribution**
Decrement for Transplant vs. Age Norms	0.1	0-0.2	Uniform

Decrement for Dialysis vs. Transplant	0.12	0.07-0.17	Uniform

Costs

Storage Costs (£s)	**Mean Value**	**Std. Err.**	**Distribution**
Marshall's Soltran	49.73	5.84	Normal
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
Functioning Graft Cost (£s)			
Months 1-3	2464	295.68	Normal
Months 4-12	1386	166.32	Normal
Months 13+	567	68.04	Normal
Failing Kidney States	1135		Normal
Transplant Operation Cost (£s)	16413	3059	Normal
Explant Operation Cost (£s)	4134	656	Normal
Dialysis Costs (£s)			
Peritoneal Dialysis per month	1793.6	35.8	Normal
Haemodialysis per month	2330.03	46.6	Normal
Outpatient Reviews per month	19.12	8.14	Normal
% Peritoneal Dialysis by Age Group			
Age Group 18-34	58.8%	1.8%	Normal
Age Group 35-44	57.7%	0.4%	Normal
Age Group 45-54	55.4%	1.0%	Normal
Age Group 55-64	53.9%	2.0%	Normal
Age Group 65+	43.2%	3.2%	Normal

Transitions

% graft failures suitable for re-transplant			
Age Group 18-34	0.27	0.023	Normal
Age Group 35-44	0.25	0.031	Normal
Age Group 45-54	0.19	0.026	Normal
Age Group 55-64	0.14	0.026	Normal
Age Group 65+	0.05	0.016	Normal
Probability of re-transplant from wait list			
Age Group 18-34	0.0224	0.022	Normal
Age Group 35-44	0.0222	0.022	Normal
Age Group 45-54	0.0191	0.019	Normal
Age Group 55-64	0.0143	0.014	Normal
Age Group 65+	0.0051	0.005	Normal
Re-transplant failure Prob./month	0.0058	0.0006	Normal

PSA sampling for Survival Curves

All survival curves within the model were fitted using Weibull distributions. These include the values for each of the following:

- Patient survival for patients with functioning graft (for each age group)
- Patient survival for patients undergoing dialysis (for each age group)
- Graft Survival for patients who experienced Immediate Graft Function (IGF)
- Graft survival for patients who experience graft function after Delayed Graft Function (DGF)

Standard regression methods were used to calculate the lambda and gamma co-efficients needed to parameterise the survival curves based on the available data.

For each of the five modelled age groups, patient survival data for the populations (bullet points 1 and 2 above) formed part of the standard dataset used in the model and did not vary between the arms or comparisons.

Graft survival curves (bullet points 3 and 4 above) for each of the arms of the modelled comparisons were fitted separately to each arm of the model using regression analysis. Lambda and gamma values for these curves are shown in table below.

For the Probabilistic Sensitivity Analysis (PSA) presented here, all survival curves for graft survival and the patient survival curves for patients with functioning grafts were varied by sampling lambda and gamma co-efficients drawn from a bi-variate normal distribution based on the 95% confidence interval estimates around the mean value. Since it is the relative levels of survival between dialysis and functioning graft patients which is important, it was not deemed necessary to sample for patient survival for patients on dialysis. The method used to derive values for sampling the lambda and gamma co-efficients in the model is described below.

Method for estimation of standard error and correlation co-efficient values for Lambda and Gamma used in the PSA

Standard error values for the survival curves were calculated using estimates of the 95% confidence intervals around the mean values at each point on the survival curve. For this, the distribution of uncertainty around the mean values was assumed to be normal. A method of maximum likelihood was then used to calculate the two dimensional probability matrix for the different combinations of lambda and gamma parameters for different Weibull curve fits against the data.

A bi-variate normal parameterization of this matrix was then conducted using regression techniques to calculate the respective lambda and gamma means, standard errors and the correlation co-efficient between lambda and gamma.

A Cholesky matrix decomposition was then used to sample values for both lambda and gamma for each run of the simulation which incorporated the

calculated co-variance of the survival curve and the estimated correlation between the lambda and gamma co-efficients.

The standard error values and correlation co-efficient for each of the sample lambda and gamma distributions for both the patient survival curves and for the graft survival curves for each comparator arm are shown in Table 55 to Table 59 below.

Table 55. Weibull Co-efficients used for patient survival curves in PSA

Parameter : Patient Survival (patients with functioning graft)			
Age Group 18-34	**Mean Value**	**Range**	**Distribution**
Lambda Co-Eff.	0.0009	0.0002	Normal
Gamma Co-Eff	1.1230	0.0200	Normal
Correlation Co-eff.	-0.9961		
Age Group 35-44			
Lambda Co-Eff.	0.0013	0.0001	Normal
Gamma Co-Eff	1.1062	0.0400	Normal
Correlation Co-eff.	-0.9961		
Age Group 45-54			
Lambda Co-Eff.	0.0028	0.0005	Normal
Gamma Co-Eff	1.0183	0.0500	Normal
Correlation Co-eff.	-0.9947		
Age Group 55-64			
Lambda Co-Eff.	0.0066	0.0002	Normal
Gamma Co-Eff	0.9180	0.0200	Normal
Correlation Co-eff.	-0.9947		

Age Group 65+			
Lambda Co-Eff.	0.0013	0.0009	Normal
Gamma Co-Eff	0.8713	0.0243	Normal
Correlation Co-eff.	-0.8995		

Table 56. Weibull Co-efficients used for graft survival curves in PSA for PPART data comparison of LifePort versus ViaSpan

LIFEPORT VS VIASPAN PPART TRIAL DATA			
Storage Costs(£s)	**Mean Value**	**Std. Err.**	**Distribution**
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
DGF% post transplant	*Mean Value*	*Alpha, Beta*	*Distribution*
ViaSpan	55.6%	(25,20)	Beta
LifePort	57.8%	(26,19)	Beta
Primary Non-Function %			
ViaSpan	2.2%	(1,24)	Beta
LifePort	0%	(1,49)	Beta
Graft Survival post IGF			
ViaSpan & LifePort– Weibull Co-Effs.			
Lambda	0.0256	0.0055	Normal
Gamma	0.3499	0.1065	Normal
Correlation Co-eff.	-0.8967		
Graft Survival post DGF			
ViaSpan & LifePort– Weibull Co-Effs.			

Lambda	0.0118	0.0033	Normal
Gamma	0.6494	0.0580	Normal
Correlation Co-eff.	-0.8599		

Table 57. Weibull Co-efficients used for graft survival curves in PSA for MPT data comparison of LifePort versus ViaSpan

LIFEPORT VS VIASPAN MPT TRIAL DATA			
Storage Costs(£s)	**Mean Value**	**Std. Err.**	**Distribution**
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
DGF% post transplant		Alpha, Beta	
ViaSpan	[redacted]	[redacted]	Beta
LifePort	[redacted]	[redacted]	Beta
Primary Non-Function %			
ViaSpan	[redacted]	[redacted]	Beta
LifePort	[redacted]	[redacted]	Beta
Graft Survival post IGF			
ViaSpan & LifePort– Weibull Fit		Standard Err.	
Lambda Co-Eff.	0.0052	0.0021	Normal
Gamma Co-Eff	0.5923	0.1445	Normal
Correlation Co-eff.	-0.9101		
Graft Survival post DGF			
ViaSpan – Weibull Fit			
Lambda Co-Eff.	0.0542	0.0201	Normal
Gamma Co-Eff	0.5592	0.0974	Normal

Correlation Co-eff.	-0.7000		
LifePort– Weibull Fit			
Lambda Co-Eff.	0.0111	0.0025	Normal
Gamma Co-Eff	0.8057	0.1024	Normal
Correlation Co-eff.	-0.9214		

Table 58. Weibull Co-efficients used for graft survival curves in PSA for comparison of LifePort versus Marshall's Soltran

LIFEPORT VS MARSHALL SOLTRAN			
Storage Costs(£s)	**Mean Value**	**Std. Err.**	**Distribution**
Marshall's Soltran	49.73	5.84	Normal
LifePort	736.55	100.08	Normal
DGF% post transplant		Alpha, Beta	
Marshall's Soltran	83.3%	(25, 5)	Beta
LifePort	53.3%	(16 ,14)	Beta
Graft Survival (all patients)			
Marshall's Soltran – Weibull Co-Effs.		Standard Err.	
Lambda.	0.0157	0.00527	Normal
Gamma	0.5975	0.19	Normal
Correlation Co-eff.	-0.823		
Graft Survival (all patients)			
LifePort – Weibull Co-Effs.			
Lambda	0.0052	0.0012	Normal
Gamma	0.5975	0.162	Normal

Correlation Co-eff.	-0.8782		

Table 59. Weibull Co-efficients used for graft survival curves in PSA for comparison of ViaSpan versus Marshall's Soltran

MARSHALL SOLTRAN VS VIASPAN			
Graft Survival (all patients)	**Mean Value**	**Std. Err.**	**Distribution**
ViaSpan – Weibull Co-Effs			
Lambda	0.0358	0	N/A
Gamma	0.5158	0	N/A
Correlation Co-eff.	N/A		
Graft Survival (all patients)			
Marshall's Soltran – Weibull Co-Effs.			
Lambda.	0.0390	0.006129	Normal
Gamma	0.5158	0.04089	Normal
Correlation Co-eff.	-0.99586		

APPENDIX 10. Hazard ratios for graft survival

Graphs showing the effect of changes to the hazard ratio for graft survival between arms

Figure 44. Cost effect of incremental hazard ratio for graft survival between comparator arms

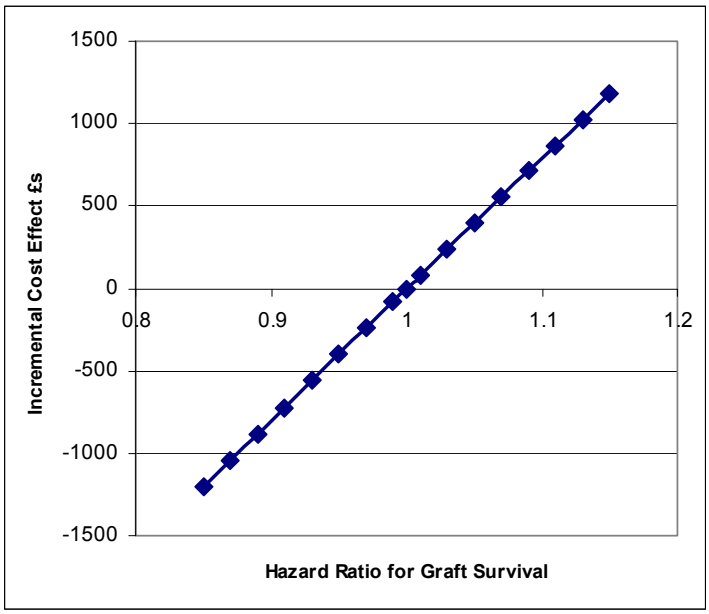

Figure 45. QALY effect of incremental hazard ratio for graft survival between comparator arms

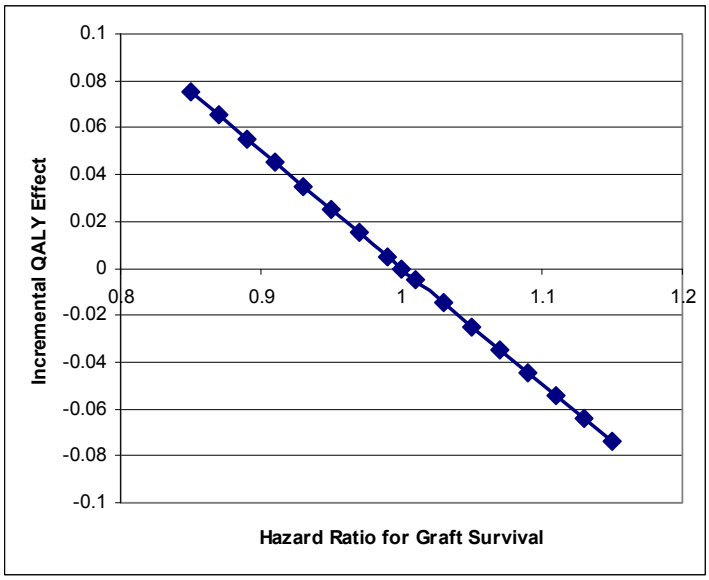

Figure 46. Net Benefit effect of incremental hazard ratio for graft survival between comparator arms