

## **The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model**

M Bond, M Pitt, J Akoh, T Moxham,  
M Hoyle and R Anderson



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# The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model

M Bond,<sup>1\*</sup> M Pitt,<sup>1</sup> J Akoh,<sup>2</sup> T Moxham,<sup>1</sup>  
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## Abstract

### The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: a systematic review and economic model

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**Objective:** To review the evidence for the effectiveness and cost-effectiveness of storing kidneys from deceased donors prior to transplantation, using cold static storage solutions or pulsatile hypothermic machine perfusion.

**Data sources:** Electronic databases were searched in January 2008 and updated in May 2008 for systematic reviews and/or meta-analyses, randomised controlled trials (RCTs), other study designs and ongoing research. Sources included: Cochrane Library, MEDLINE, EMBASE, CINAHL, ISI Web of Knowledge, DARE, NRR, ReFeR, Current Controlled Trials, and (NHS) HTA. Bibliographies of articles were searched for further relevant studies, and the Food and Drugs Administration (FDA) and European Regulatory Agency Medical Device Safety Service websites were searched. Only English language papers were sought.

**Review methods:** The perfusion machines identified were the LifePort Kidney Transporter<sup>®</sup> (Organ Recovery Systems) and the RM3 Renal Preservation System<sup>®</sup> (Waters Medical Systems). The cold storage solutions reviewed were: University of Wisconsin, ViaSpan<sup>™</sup>; Marshall's hypertonic citrate, Soltran<sup>™</sup>; and Genzyme, Celsior<sup>™</sup>. Each intervention was compared with the others as data permitted. The population was recipients of kidneys from deceased donors. The main outcomes were measures of graft survival, patient survival, delayed graft function (DGF), primary non-function (PNF), discard rates of non-viable kidneys, health-related quality of life and cost-effectiveness. Where data permitted the results of studies were pooled using meta-analysis. A Markov (state transition) model was developed to simulate the main post-transplantation outcomes of kidney graft recipients.

**Results:** Eleven studies were included: three full journal published RCTs, two ongoing RCTs [European Machine Preservation Trial (MPT) and UK Pulsatile Perfusion

in Asystolic donor Renal Transplantation (PPART) study], one cohort study, three full journal published retrospective record reviews and two retrospective record reviews published as posters or abstracts only. For LifePort versus ViaSpan, no significant differences were found for DGF, PNF, acute rejection, duration of DGF, creatinine clearance or toxicity, patient survival or graft survival at 6 months, but graft survival was better at 12 months post transplant with machine perfusion (LifePort = 98%, ViaSpan = 94%,  $p < 0.03$ ). For LifePort versus RM3, all outcomes favoured RM3, although the results may be unreliable. For ViaSpan versus Soltran, there were no significant differences in graft survival for cold ischaemic times up to 36 hours. For ViaSpan versus Celsior, no significant differences were found on any outcome measure. In terms of cost-effectiveness, data from the MPT suggested that machine preservation was cheaper and generated more quality-adjusted life-years (QALYs), while the PPART study data suggested that cold storage was preferable on both counts. The less reliable deterministic outputs of the cohort study suggested that LifePort would be cheaper and would generate more QALYs than Soltran. Sensitivity analyses found that changes to the differential kidney storage costs between comparators have a very low impact on overall net benefit estimates; where differences in effectiveness exist, dialysis costs are important in determining overall net benefit; DGF levels become important only when differences in graft survival are apparent between patients experiencing immediate graft function (IGF) versus DGF; 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.

**Conclusions:** The conclusions drawn for the comparison of machine perfusion with cold storage depend on which trial data are used in the model. Owing to the lack of good research evidence that either ViaSpan or Soltran is better than the other, the cheaper, Soltran, may be preferable. In the absence of a cost–utility analysis, the results of our meta-analysis of the RCTs comparing ViaSpan with Celsior indicate that these cold storage solutions are equivalent. Further RCTs of comparators of interest to allow for appropriate analysis of subgroups and to determine whether either

of the two machines under consideration produces better outcomes may be useful. In addition, research is required to: establish the strength and reliability of the presumed causal association between DGF and graft, and patient survival; investigate the utility impacts of renal replacement therapy; determine what the additional cost, survival and QALY impacts are of decreased or increased non-viable kidneys when discarded pre transplantation; and identify a reliable measure for predicting kidney viability from machine perfusion.



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## Glossary and list of abbreviations

### Glossary

**Anastomosis period** The second period of warm ischaemia, following the cold storage time, where the kidney slowly warms up prior to transplant.

**Brain stem dead** Those diagnosed as dead by brain stem tests who are maintained on a ventilator in an intensive treatment unit.

**Chronic kidney disease** Kidney disease which is irreversible and may be progressive.

**Cold ischaemic time** That part of the preservation period when the kidney has been cooled down and is not perfused by blood.

**Delayed graft function** The need for dialysis within 7 days of transplant.

**Donation after cardiac death** Those who cannot be diagnosed as brain stem dead, but whose death is established by the absence of a heart beat.

**Established renal failure** Chronic kidney disease that has progressed so far that renal replacement therapy is needed to maintain life (also known as end-stage renal disease).

**Expanded criteria donor** Donors who are either over 60 or are over 50 and have at least two of the following features: a history of hypertension, death by a cerebral vascular accident or terminal creatinine levels > 1.5mg/dl.

**Graft failure** When a transplant recipient returns to chronic dialysis.

**Graft survival** When a transplant recipient does not need dialysis, i.e. the proportion of transplant recipients with a functioning kidney after a given time period.

**Primary non-function** A graft that never works after transplantation.

**Quality-adjusted life-year** 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.

**Renal replacement therapy** Treatment to replace or augment the function of failing kidneys, by dialysis (peritoneal dialysis or haemodialysis) or transplantation.

**Time trade-off** A method for determining quality of life based on subjective judgement of the value of a lifespan in the current health state compared with a reduced lifespan in perfect health.

**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).

## List of abbreviations

BNF	<i>British National Formulary</i>	GFR	glomerular filtration rate
BSD	brain stem dead	GST	glutathione S-transferase
CAPD	continuous ambulatory peritoneal dialysis	HBD	heart-beating donor
CEA	cost-effectiveness analysis	HD	haemodialysis
CEAC	cost-effectiveness acceptability curve	HHD	home haemodialysis
CHD	centre/hospital haemodialysis	HLA	human leucocyte antigen
CHEC	Consensus on Health Economics Criteria	HR	hazard ratio
CI(s)	confidence interval(s)	HTA	Health Technology Assessment
CIT(s)	cold ischaemic time(s)	HTK	histidine–tryptophan–ketoglutarate
CNI	calcineurin inhibitor	ICER	incremental cost-effectiveness ratio
DCD	donation after cardiac death	IGF*	immediate graft function
DGF*	delayed graft function	IRVR	intrarenal vascular resistance
DGI	delayed graft function – initial month	ITT	intention to treat
DM	difference in means	ITU	intensive treatment unit
DTH*	death	K	potassium
ECD(s)	expanded criteria donor(s)	KDQOL-SF	Kidney Disease Quality of Life – Short Form
EQ-5D	EuroQol – 5 dimensions (quality of life instrument)	Mg	magnesium
ERF	established renal failure	MPT	Machine Preservation Trial
ESRD	end-stage renal disease	Na	sodium
FDA	United States Food and Drugs Administration	NA	not applicable
FKD*	failing kidney after delayed graft function	NHBD	non-heart-beating donor
FKI*	failing kidney after immediate graft function	NHSBT	Organ Donation and Transplantation Directorate of NHS Blood and Transplant
		NICE	National Institute for Health and Clinical Excellence

NS	not significant (statistical test result)	QUOROM	Quality of Reporting of Meta-Analyses standards
NSRC	National Schedule of Reference Costs	RCT(s)	randomised controlled trial(s)
PD	peritoneal dialysis	RR	relative risk
pH	a measure of acidity or alkalinity	RRT	renal replacement therapy
pmp	per million population	SD	standard deviation
PNF	primary non-function	SF-36	Short Form 36 (quality of life instrument)
PPART	Pulsatile Perfusion in Asystolic donor Renal Transplantation	STX*	post-subsequent transplant
PSA(s)	probabilistic sensitivity analysis(es)	TTO	time trade-off
PSS	Personal Social Services	Tx	transplant
QALY(s)	quality-adjusted life-year(s)	UKRR	UK Renal Registry
QLI	Quality of Life Index	UW	University of Wisconsin

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

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

## Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable amount of data that was deemed academic-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of academic-in-confidence information removed and replaced by the statement 'academic-in-confidence information removed' is available on the NICE website: [www.nice.org.uk](http://www.nice.org.uk).

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences and data in tables have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.





## Executive summary

### 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). Where possible, kidney transplantation is the best form of renal replacement therapy for people with end-stage renal disease. Unfortunately, the demand for donor organs greatly outstrips supply.

There are two main methods for the cold storage of kidneys from deceased donors. 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 National Health Service (NHS) for cold storage: Marshall's hypertonic citrate (Soltran™) and University of Wisconsin (ViaSpan™). We also considered Celsior™ (Genzyme), a 'newcomer', 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 also assessed the RM3® (Waters Medical Systems).

### Objectives

This project reviewed the evidence for the effectiveness and cost-effectiveness of storing kidneys from deceased donors prior to transplantation, using either cold static storage solutions or pulsatile hypothermic machine perfusion.

### Methods

#### Interventions

The interventions considered were pulsatile hypothermic machine perfusion and cold static

storage solutions. Two perfusion machines in particular were identified: the LifePort Kidney Transporter and the RM3 Renal Preservation System. The cold storage solutions reviewed were: University of Wisconsin, ViaSpan; Marshall's hypertonic citrate, Soltran; and Genzyme, Celsior.

#### Comparators

Each intervention was compared with the others as data permitted.

#### Population

The population assessed were recipients of kidneys from deceased donors [brain stem dead (BSD), donated after cardiac death (DCD) or expanded criteria donors (ECDs)].

#### Main outcome measures

The main outcomes of this assessment were measures of graft survival, patient survival, delayed graft function (DGF), primary non-function (PNF), discard rates of non-viable kidneys, health-related quality of life and cost-effectiveness.

#### Clinical effectiveness and cost-effectiveness systematic reviews

Electronic databases were searched in January 2008 and updated in May 2008 for relevant published and unpublished literature on the clinical effectiveness and cost-effectiveness of machine perfusion and cold storage for kidneys from deceased donors. Systematic reviews and/or meta-analyses, randomised controlled trials (RCTs), other study designs and ongoing research were included. Appendix 1 shows the databases searched and the strategies in full. These included (with start date): Cochrane Library (no start date), MEDLINE (1950 to date), EMBASE (1974 to date), CINAHL (1982 to date), ISI Web of Knowledge (1970 to date), DARE (no start date), NRR (no start date), ReFeR (no start date), Current Controlled Trials (no start date) and (NHS) HTA (no start date). Bibliographies of articles were also searched for further relevant studies, and the US Food and Drugs Administration (FDA) and European Regulatory Agency Medical Device Safety Service

websites were searched for relevant material. Owing to resource limitations the search was restricted to English language papers only.

## Analysis

Where data permitted the results of studies were pooled using meta-analysis.

### PenTAG cost–utility model

A Markov (state transition) model was developed to simulate the main post-transplantation outcomes of kidney graft recipients. The structure of the model was informed by current research literature, data from the UK Renal Registry of the Renal Association and the Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT), 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. DGF, PNF) as well as longer-term outcomes such as graft survival, patient survival and possible re-transplantation or returning to dialysis. The treatments compared are kidney transplants using LifePort versus ViaSpan (separately from DCD, and BSD with some DCD donors), LifePort versus Soltran and ViaSpan versus Soltran.

The reference case used costs for 2007 and took the perspective of the UK's NHS and Personal Social Services. A mixed-sex cohort, of 1000 adult patients, was modelled until the whole cohort had died. Five separate age groups (18–34, 35–44, 45–54, 55–64, 65+) were simulated in the model, and were aggregated to represent the real population of kidney transplant recipients. The model used a cycle length of 1 month.

## Results

### Number and quality of effectiveness studies

The search 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. Eleven articles were found that met the inclusion criteria, leaving 125 exclusions.

The 11 studies included were: 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.

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, Pulsatile Perfusion in Asystolic donor Renal Transplantation (PPART) trial in the UK] and another was still analysing their data [Moers and colleagues, European Machine Preservation Trial (MPT)].

### Summary of benefits and risks

#### *LifePort versus ViaSpan*

The donor populations for the two RCTs were different; with DCD donors in the PPART trial ( $n = 90$  kidneys) and mostly BSD (88%) (DCD = 12%) donors in the MPT ( $n = 672$  kidneys). These studies were academic-in-confidence at the time of writing.

Also, the rate of DGF in the Moers and colleagues trial was a lot less than in Watson and colleagues [24% and (academic-in-confidence information removed) respectively]; this may have been due to the difference in DGF between DCD and BSD donated kidneys.

Only 3 months' follow-up data were available from Watson and colleagues (academic-in-confidence information removed).

Moers and colleagues found no significant differences between machine perfusion and cold storage solutions for the outcomes of: DGF, PNF, acute rejection, duration of DGF, creatinine clearance or toxicity, patient survival or graft survival at 6 months. However, they found that graft survival was better at 12 months post transplant with machine perfusion (LifePort = 98%, ViaSpan = 94%,  $p < 0.03$ ). Moers and colleagues did not analyse their data by intention to treat.

#### *LifePort versus RM3*

Two studies assessed the comparative effectiveness of the LifePort and RM3 machine perfusion systems. However, the results may well be unreliable as they were both retrospective hospital record reviews and had only been published as abstracts and posters. With the exception of PNF, post-transplant dialysis and kidney rejection post storage (which were not significant), all outcomes

favoured the RM3 over the LifePort perfusion machine (DGF, graft function, patient survival, graft survival and length of hospitalisation).

### **ViaSpan versus Soltran**

A multinational registry study compared ViaSpan with Marshall's solution. Our analysis of their data showed that there were no significant differences in graft survival between these solutions for a range of cold ischaemic times up to 36 hours.

### **ViaSpan versus Celsior**

The three RCTs comparing ViaSpan with Celsior found no significant differences on any outcome measure; after pooling these data in meta-analysis we found there were still no significant differences between groups.

### **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. However, the British Transplantation Society's submission to the National Institute for Health and Clinical Excellence has highlighted the issue that care should be taken when using Soltran cold storage solution when other organs are being retrieved with the kidneys, as 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.

### **Summary of cost-effectiveness**

The two RCTs that compare cold storage using ViaSpan and machine preservation using LifePort are based on different populations and were therefore modelled separately.

When data from the MPT were used in the model, machine preservation both was found to be cheaper and generated more quality-adjusted life-years (QALYs) than cold storage. In contrast, when the UK PPART study data were used to parameterise the model, cold storage was cheaper and generated more QALYs than machine preservation. It should be noted that in the PPART study (academic-in-confidence information removed) outcomes demonstrated statistically significant differences between trial arms, and for the MPT only two did so ('functional DGF' and 12-month graft survival). When this underlying uncertainty is embodied in the model, little confidence can be had in any conclusions preferring one storage method over another.

The much less reliable deterministic outputs of the cohort study suggest that LifePort would be cheaper and would generate more QALYs than Soltran, so that machine preservation would be both cheaper and more effective as a treatment option.

The comparison of ViaSpan and Soltran cold storage solution shows 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 gives little basis for any confident conclusions.

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.

### **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 versus DGF). For example, if very few patients in the model experience DGF, then graft survival changes for DGF patients have a small impact on the overall net benefit output.



The probabilistic sensitivity analysis also showed that the key model input parameter is differential graft survival. Where this 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 both being cheaper and generating more estimated QALYs than the other; this produced very flat and largely uninformative cost-effectiveness acceptability curves.

## Conclusions

### Implications for health care

The conclusions drawn for the comparison of machine perfusion with cold storage depend on which trial data are used in the model. For kidneys from DCD donors, the UK trial data indicate that it is probably more cost-effective to use cold storage. However, data from the European trial suggest the opposite may be the case for their mainly BSD population. There is a large amount of uncertainty surrounding these conclusions.

With regard to the cost–utility of LifePort compared with Soltran, the effectiveness data are so unreliable that it would be unwise to trust the results based on them. Without a purchase cost for the RM3 machine, or its current availability in the NHS, it was not possible to conduct a cost–utility analysis of this comparison.

The only effectiveness study found that compared ViaSpan with Soltran 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 Soltran.

Since the manufacturers of Celsior cold storage solution were not invited to make a submission to this health technology assessment 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.

## Suggested research priorities

1. There is a need for sufficiently large RCTs of comparators of interest to allow for appropriate analysis of subgroups.
2. More research is required to establish the strength and reliability of the presumed causal association between DGF and graft and patient survival.
3. 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.
4. More research is needed into the utility impacts of all forms of RRT. This should try and use both established disease-specific measures and generic quality of life measures for which social preference weights exist. All studies should 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. Further work is needed to clearly identify a reliable measure for predicting kidney viability from machine perfusion.
7. RCTs are needed to determine whether either of the two machines under consideration produces better patient outcomes.
8. The NHSBT should encourage more complete data collection by transplant centres.



# Chapter I

## Background

### Description of the problem

Established renal failure (ERF) or end-stage renal disease (ESRD) 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).<sup>1</sup> Kidney transplantation is the best form of RRT for people with ESRD where it is possible.<sup>2</sup> 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.<sup>3</sup>

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 BSD 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.<sup>4</sup> 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:

1. 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.
2. 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.

3. 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 brain stem death testing.
4. Cardiac arrest in a BSD donor – uncontrolled. A donor falls into this category if death has been certified by brain stem criteria and cardiac arrest occurs before organ retrieval has taken place.
5. Unexpected cardiac arrest in an intensive treatment unit (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 brain stem 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 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' (CIT) 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 anastomosis period of re-implanting in the recipient begins. This last anastomosis 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.<sup>5</sup> Both warm ischaemic time and CIT are damaging to organs but, after retrieval, cooling the organ

suppresses the metabolic rate and so reduces the rate of damage.<sup>6</sup>

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.<sup>7,8</sup> 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, e.g. lactic acid, begin to build up. 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, which are 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 primary non-function (PNF) (when the graft never works after implantation), delayed graft function (DGF) (the need for dialysis in the

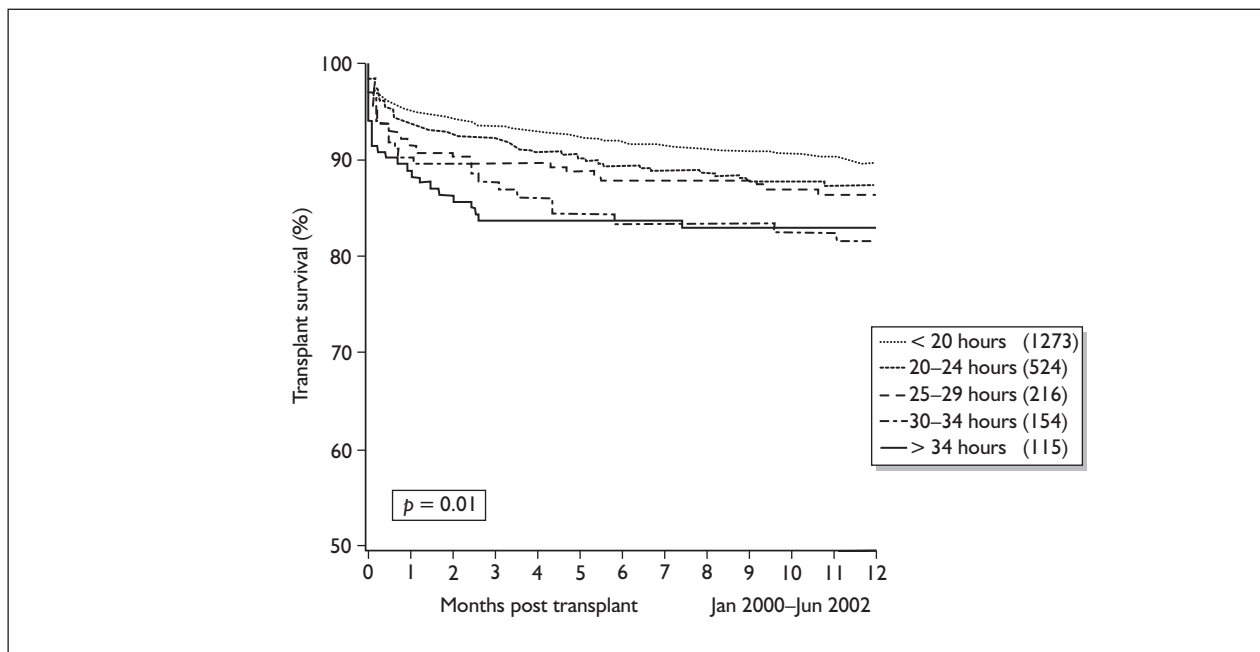
first week post transplantation) and poorer long-term graft survival than those from BSD donors.<sup>9</sup> Delayed graft function is associated with the need for continuing dialysis and longer hospitalisation. The effects of ischaemic damage on transplant survival can be seen in *Figure 1*, taken from the British Transplantation Society's submission to the National Institute for Health and Clinical Excellence (NICE).

Apart from the increased use of DCD donors, a second means of expanding the pool of kidney donors is through the use of expanded criteria donors (ECDs). These are kidneys from BSD donors who, in the past (particularly in the US), would not normally meet the criteria for transplantation. The extended criteria include kidneys from donors who are either over 60, or are over 50 and with at least two of the following features: (1) a history of hypertension; (2) death from a cerebral vascular accident; and (3) terminal creatinine levels greater than 133  $\mu\text{mol/l}$  (1.5 mg/dl).<sup>10</sup> In general, kidneys from expanded criteria donors have a lower chance of long-term success and a higher incidence of DGF than those from BSD donors.<sup>11</sup>

## Epidemiology

### Incidence and prevalence

The Renal Registry annual report 2006 shows that there were 41,776 adults on RRT (see Management of end-stage kidney disease, later in this chapter)



**FIGURE 1** Effects of graft cold ischaemic time on transplant survival. [Source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland.]

in the UK in 2005; this gives a prevalence of 694 per million population (pmp). There were also 748 children (< 18 years) on RRT with a prevalence of 12 pmp. These figures show that since the year 2000 there has been a 27.8% increase in patient numbers cared for by the 38 renal units which have continuously returned data from 2000 to 2005.<sup>12</sup>

Data from the same report show that in 2005 there was an acceptance rate for RRT in the UK of 108 pmp for adults and 2 pmp for children, showing a total incidence of 110 pmp. This reveals a 7.3% increase in incidence from 2001 to 2005 in 42 renal units in the UK submitting full returns to the Renal Registry.<sup>12</sup> Figure 2 shows the incident rates for the UK from 1990 to 2005.

In 2005 in the UK, 76% of people accepted for RRT began treatment with haemodialysis (HD), 21% started with peritoneal dialysis (PD) and 3% with a kidney transplant. Ninety days later 8% had died and 1% had stopped treatment or had been transferred out. Of the remaining 91%, 5% changed from HD to PD and 3.2% had a transplant.<sup>12</sup> 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 HD having a mean age of 9 years older and having fewer co-morbidities than those using PD.<sup>12</sup> Table 1 shows the percentage RRT type for new patients in England and Wales in 2005.

Survival in the first year following commencement of RRT for all patients regardless of age is 79%.<sup>12</sup> Five-year survival figures including deaths in the

first 90 days following commencement of RRT are shown in Table 2.

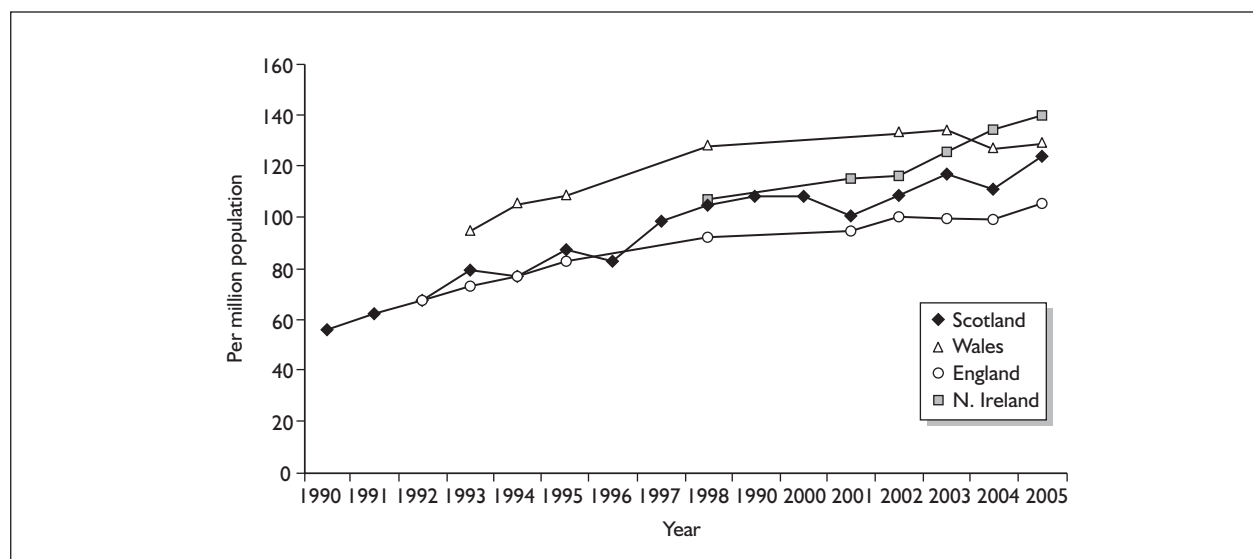
## Aetiology

The most common cause of ERF is chronic renal damage usually caused by diabetes.<sup>1</sup> Other causes of ERF 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 increasing age. Acute renal failure may follow from traumatic injury or infection and can progress to ERF.<sup>1</sup>

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.<sup>1</sup>

The risk of ERF increases with age; in 2006 the median age for commencement of RRT was 65 years in England and 67 years in Wales.<sup>12</sup>

There are also ethnic differences, with people from South Asian, African and African-Caribbean communities more likely to have higher rates of RRT through greater susceptibility to diabetes and hypertension.<sup>13,14</sup> Evidence also suggests a further link to social deprivation, although the reasons for this are not fully understood.<sup>15-17</sup>



**FIGURE 2** Incident rates of adults accepted for renal replacement therapy in the UK 1990–2005. (Source: The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.)

**TABLE 1** Percentage of new renal replacement therapy patients using each method of treatment in England and Wales (extracted from UK Renal Registry Report 2006)

	Percentage of patients on each modality					
	Haemodialysis	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

**TABLE 2** Five-year survival following commencement of renal replacement therapy by age (extracted from UK Renal Registry Report 2006)

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

## Pathology

When ERF is reached, people become tired, nauseated, lose their appetite and cope less well both physically and mentally.<sup>1</sup> 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 life.<sup>1</sup>

## Impact of transplant activity

Figure 3 provides an overview of the increasing demand for donated kidneys.<sup>18</sup>

The UK waiting list for kidney or kidney/pancreas transplants has increased by 48% since 1998, although the number of donors rose in 2006–7 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. Donation after cardiac death donors gave 307 kidneys, enabling 276 transplants (11 double and one en bloc). This gives an overall UK donated kidney rate of 20.1 pmp. There were 1440 kidney transplants in 2006–7 in the UK (978 in England and 49 in Wales).<sup>18</sup> This information is represented in Table 3.

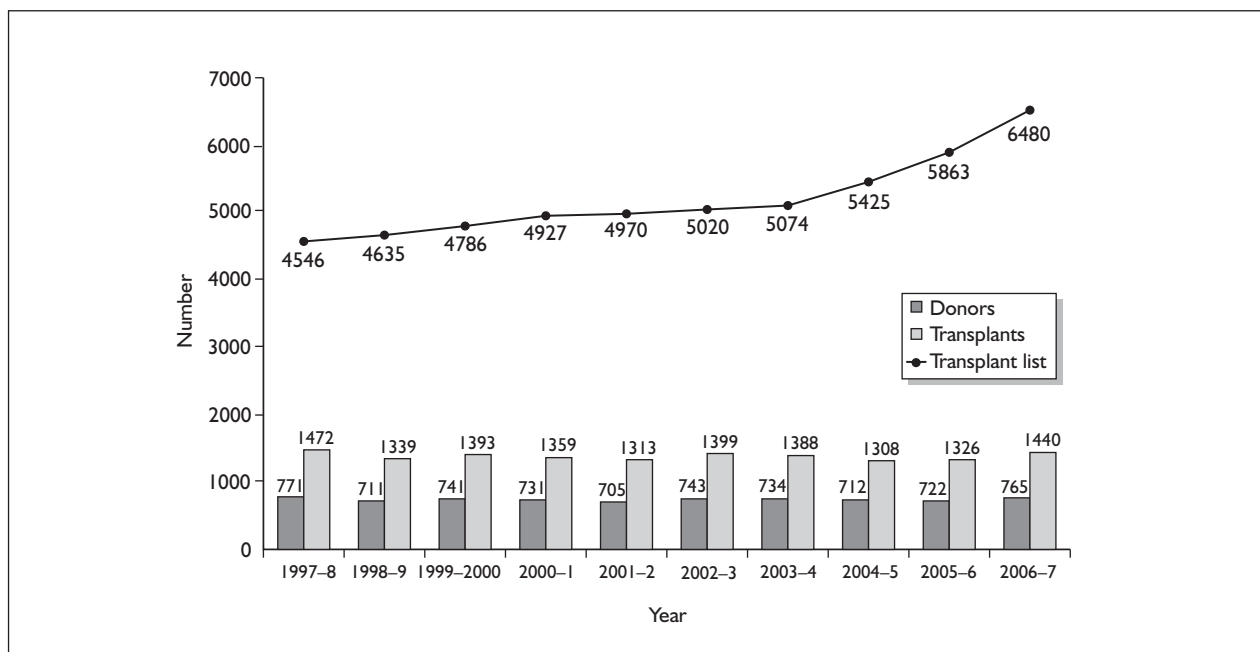
## Significance for patients

To a person suffering from ESRD, the opportunity to have a kidney transplant is literally a matter of life or death. In the year 2006–7, 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 went 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 per cent (1101) of those on the 2006–7 waiting list had received a transplant by 31 March 2007.<sup>18</sup> Figure 4 shows the percentage of dialysis patients who survived in 2005.

## 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%)<sup>18</sup> (see Management of end-stage kidney disease, below) This time-consuming treatment may affect employment, education, normal family life and may require changes in diet and fluid intake, often resulting in malnourishment and the need for nutritional supplements or artificial feeding.<sup>1</sup> 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.<sup>1</sup> Peritoneal dialysis is often preferred, especially for children,



**FIGURE 3** UK deceased donor kidney programme activity 1997–2007. [Source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland.]

**TABLE 3** Kidney donors, donations and transplants in the UK 2006–7 (source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland)

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

BSD, brain stem dead; DCD, donation after cardiac death.

as it can take place overnight, at home, and has less impact on everyday life.<sup>18</sup>

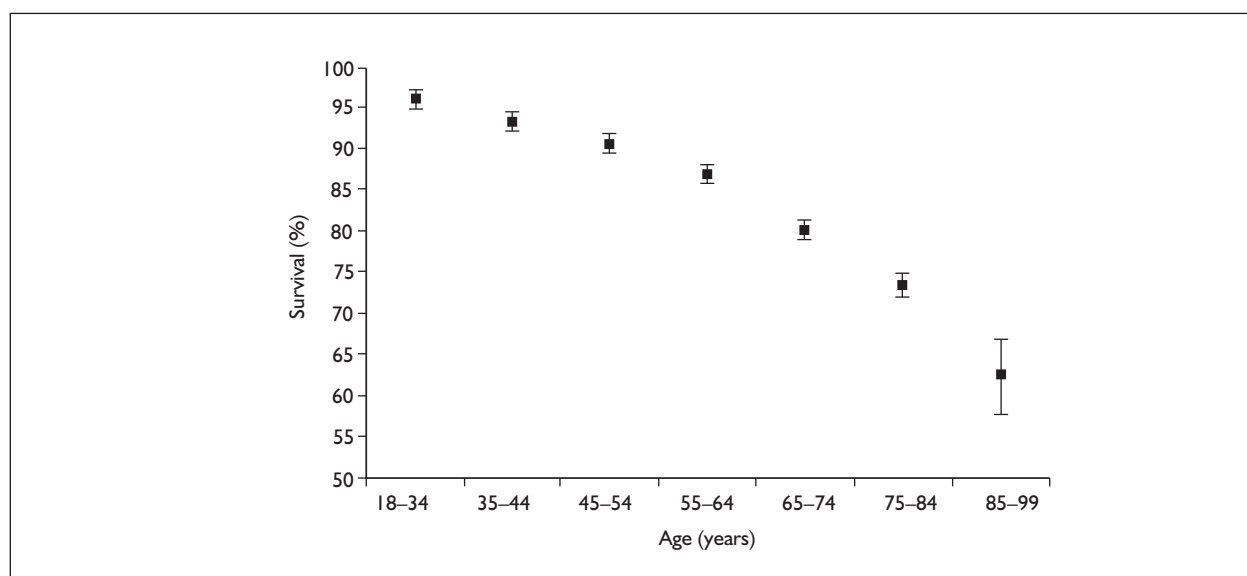
Rocco and colleagues measured the impact of HD on adults ( $n = 45$ ), using the Short Form 36 (SF-36).<sup>19</sup> They found that compared with the general population, people using HD had a significantly lower quality of life [HD: 50.08 (standard deviation, SD 22.56), control: 91.99 (SD 23.41),  $p < 0.001$ ].<sup>20</sup>

Kutner and colleagues (US) compared the quality of life of people using HD and PD, using the Kidney Disease Quality of Life – Short Form (KDQOL-SF).<sup>21</sup> They found that after 1 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 subscales 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 PD, although selection effects may have contributed to this finding.<sup>22</sup>

### Life with a transplant

While 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.<sup>23</sup> 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.<sup>24–36</sup> Overbeck and



**FIGURE 4** One-year UK survival of prevalent dialysis patients in different age groups 2005. Lines show 95% confidence intervals. (Source: The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.)

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<sup>36</sup> (Table 4).

### Significance for NHS

In 2004 the cost of treating people with ERF was estimated at 1–2% of the NHS budget.<sup>1</sup> 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 2–3 weeks every year.<sup>1</sup> The number of admissions per year increases with disease progression as interventions increase.<sup>37</sup>

During the first year the costs of transplantation are similar to those of dialysis.<sup>1</sup> Transplantation costs include surgery, immunosuppressive drugs, regular checks and treatment.<sup>1</sup> In subsequent years costs reduce considerably. An economic evaluation of treatments for ESRD by de Wit and colleagues<sup>38</sup> has shown that transplantation is the most cost-effective form of RRT with increased quality of life and independence for patients.

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

**TABLE 4** Short Form 36 mean scores comparing the quality of life of those on dialysis or transplanted with the general population (extracted from Overbeck et al. 2005<sup>36</sup>)

	Physical functioning ( $p \leq 0.001$ )	Bodily pain ( $p = 0.062$ )	General health ( $p \leq 0.01$ )	Social functioning ( $p \leq 0.01$ )	Physical well-being summary ( $p \leq 0.001$ )
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



of social deprivation, where people are more susceptible to kidney disease.<sup>1</sup>

## Measurement of health

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

- Short-term
  - Immediate graft function (IGF): the graft works immediately following transplantation removing the need for further dialysis.
  - DGF: 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 12 weeks in some cases.
  - PNF: 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 7 days post transplant some patients will have needed to dialyse and these patients will be defined as experiencing DGF. Some of those with DGF will have grafts that never function, and when this has been established these grafts are classified as PNF (and these early-failing grafts will generally be explanted).

## Current service provision

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

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

Dialysis, whether PD or HD, requires access surgery, to insert a catheter into the abdomen for the former and the formation of an arteriovenous fistula for HD to enable easy access to the blood circulation in the latter.

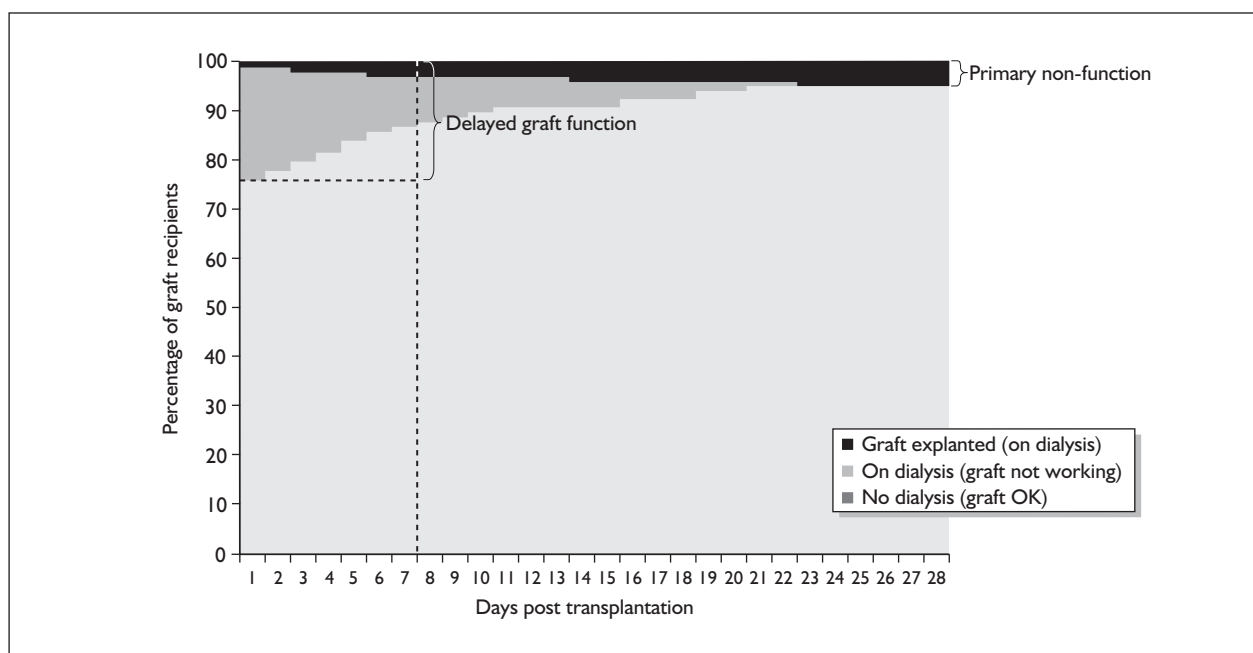
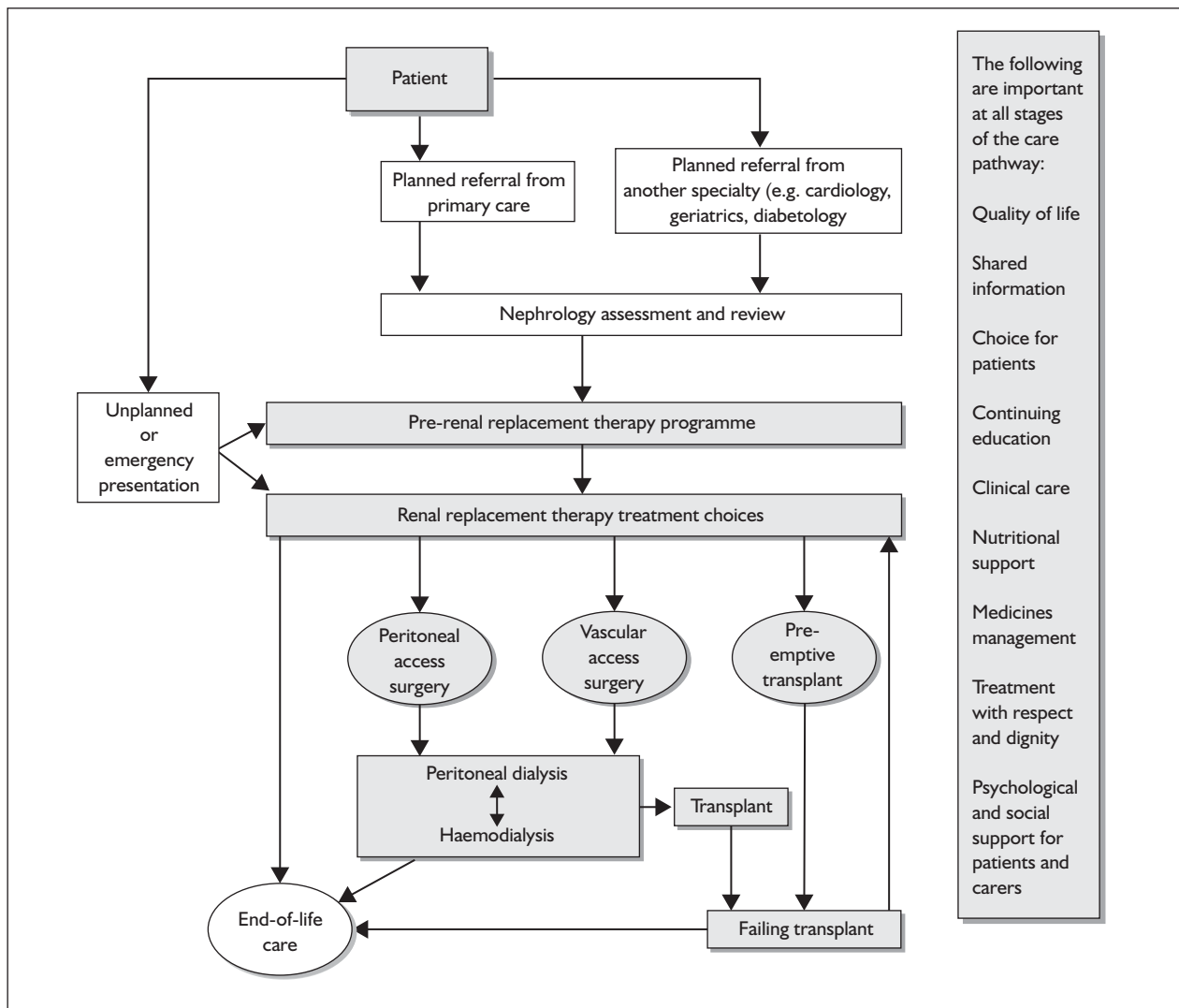


FIGURE 5 Hypothetical graph to explain the relationship between DGF and PNF.



**FIGURE 6** The care pathway for renal replacement therapy. (Source: the National Service Framework for Renal Services: Part One – Dialysis and transplantation.)

Most people on HD in the UK attend specialist dialysis centres three times a week for 3 or 4 hours each session.<sup>39</sup> Home haemodialysis (HHD) may occur more frequently with shorter sessions if this suits the patient better.<sup>1</sup>

For PD, a fluid is introduced into the peritoneal cavity via a catheter and dialysis occurs across the peritoneal membrane. After 2 or 3 hours the fluid containing waste products is drained out, and fresh dialysis fluid is drained in; such exchanges occur 3–5 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, of which several weeks' supply is often delivered.

The greatest risk is from infection of the peritoneal cavity.<sup>39</sup>

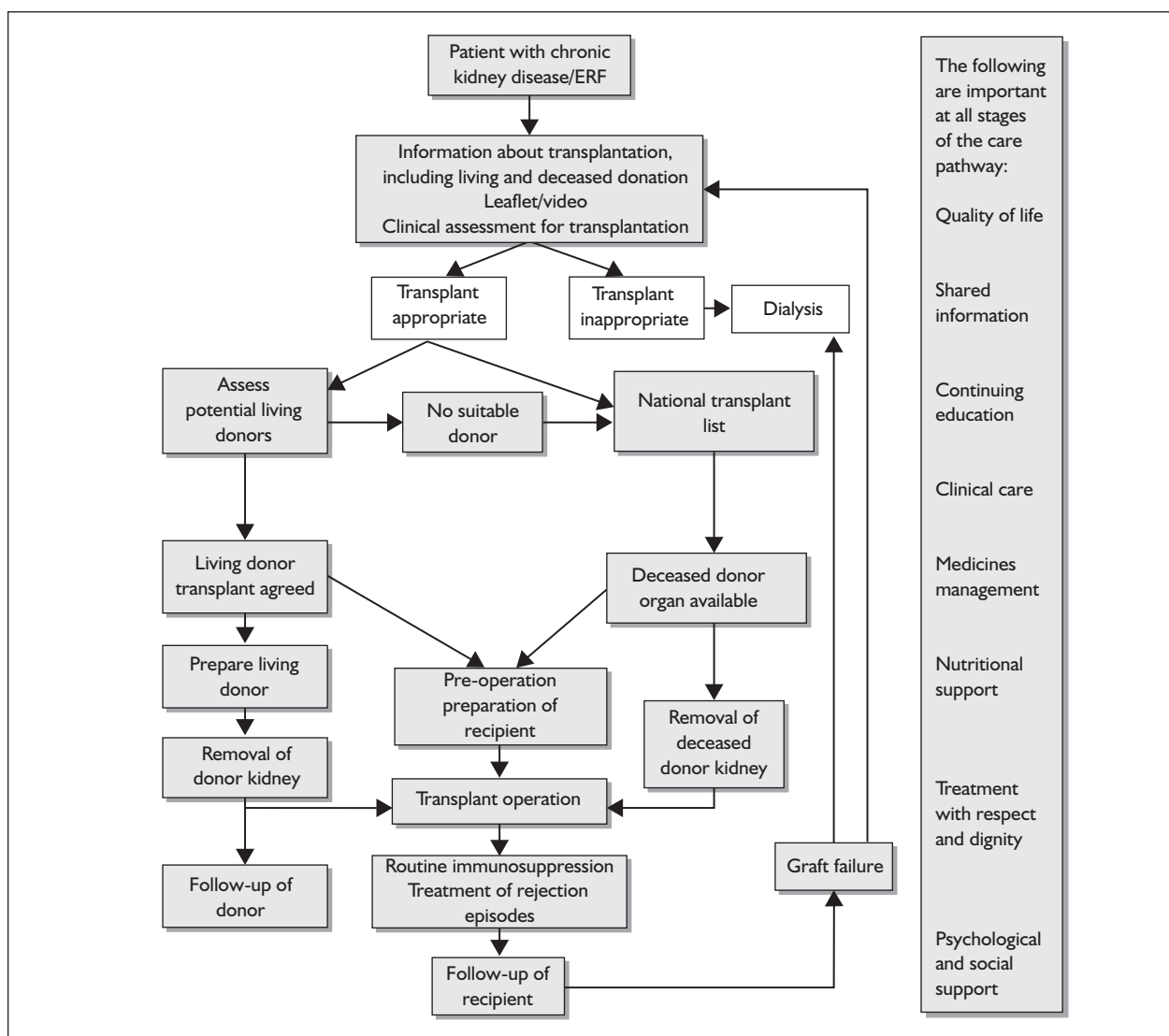
Transplantation is the most clinically and cost-effective treatment for many people with ERF.<sup>1</sup> It allows liberation from the invasiveness of dialysis, but requires the taking of powerful drugs to prevent rejection for the rest of people's lives. A person being considered for transplantation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

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

### Variation in services

Services for people with ERF have traditionally centred on dialysis based in hospital renal units or at home. Since the 1990s a 'hub and spoke'





**FIGURE 7** Care pathways for potential transplant recipients. (Source: the National Service Framework for Renal Services: Part One – Dialysis and transplantation.)

organisation of care has become more common, with a central renal unit supporting satellite HD units to provide clinical care as close to people's homes as possible.

## National guidelines

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

- NHS *Transplant list criteria for potential renal transplant patients*<sup>40</sup>
- *Clinical practice guidelines for the care of transplant patients* (UK Renal Association 2006)<sup>41</sup>
- The *National Service Framework for Renal Services: Part One – Dialysis and transplantation* (Department of Health 2004)<sup>1</sup>

- *Guidelines relating to solid organ transplants from non-heart beating donors* (British Transplantation Society 2004)<sup>3</sup>
- *Saving lives, valuing donors. A transplant framework for England – one year on* (Department of Health 2004)<sup>42</sup>
- *Standards for solid organ transplantation in the United Kingdom* (British Transplantation Society 2003).<sup>43</sup>

## Description of technology under assessment

### Summary of intervention

It is necessary to preserve kidneys prior to transplantation in order to allow time for matching

**TABLE 5** Composition of cold storage preservation solutions (extracted from Saeb-Parsey et al. 2007<sup>44</sup>)

Solution	Cations <sup>a</sup>	Buffer <sup>b</sup>	Osmotic agents <sup>c</sup>	Other constituents	Osmolality (Osm/l)	pH
ViaSpan	High K <sup>+</sup> ; low Na <sup>+</sup> , Mg <sup>2+</sup>	Phosphate	Actobionate, raffinose	Glutathione, <sup>d</sup> allopurinol, <sup>d</sup> adenosine, insulin dexamethasone	320	7.4
Marshall's (Soltran)	Medium K <sup>+</sup> , Na <sup>+</sup> , Mg <sup>2+</sup>	Sulphate, citrate	Mannitol		400	7.1
HTK	Low K <sup>+</sup> , Na <sup>+</sup> , Mg <sup>2+</sup> , Ca <sup>2+</sup>	Histidine	Mannitol	Cl <sup>-</sup> , tryptophan, <sup>e</sup> ketoglutarate <sup>f</sup>	310	7.2
Euro Collins	High K <sup>+</sup> , low Na <sup>+</sup>	Bicarbonate	Glucose	Cl <sup>-</sup>	340	7.3
Celsior	Low K <sup>+</sup> , High Na <sup>+</sup> , Mg <sup>2+</sup> , Ca <sup>2+</sup>	Histidine	Lactobionate, mannitol	Glutathione, <sup>d</sup> glutamate <sup>e</sup>	360	7.3

HTK, histidine–tryptophan–ketoglutarate.  
a Positively charged ions.  
b This maintains the pH balance.  
c To prevent cellular oedema.  
d Antioxidant.  
e Amino acid.  
f Metabolic substrate.

the kidney to the recipient, transportation and preparation of the recipient and the kidney, and implantation of the kidney. However, as noted in Description of the problem, above, ischaemia, particularly warm ischaemia, causes deterioration of the graft. Therefore, it is important to cool the entire 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 and hypothermic machine perfusion.

### 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). Cold storage solutions used in other health systems are: Celsior™ (Genzyme), Histidine–tryptophan–ketoglutarate (HTK, Custodiol) and Euro Collins (Fresenius). The characteristics of these solutions can be seen in Table 5. 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 of 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.

### 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 CIT. 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.<sup>45</sup> Up to 10% of kidneys from

DCD donors never function after transplantation, predominantly those from uncontrolled donors.<sup>9</sup>

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

Two commercially available machine perfusion systems have been identified. One is the LifePort Kidney Transporter<sup>®</sup> (Organ Recovery Systems), a portable system which can perfuse one kidney and can run without being overseen. The other machine is the RM3 Renal Preservation System<sup>®</sup> (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<sup>™</sup> (Organ Assist, www.organ-assist.nl) and Airdrive<sup>™</sup> (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, owing to the lack of comparative human kidney studies, these devices will not be included in this assessment.

### Current usage in the NHS

Machine perfusion has been used in the NHS to help preserve donated kidneys since the 1970s. 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 ECDs 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 used only 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*.<sup>46</sup> 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 the Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT), 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.

### Anticipated costs associated with intervention

*Table 6* 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 be 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 be substantially reduced.

*Table 7* 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,

**TABLE 6** Cost components of machine perfusion with LifePort Kidney Transporter

Component	Cost	Source
Purchase cost of machine	£10,750	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	Industry submission (Table 13 in Budget Impact assessment)

**TABLE 7** Cost components of cold static storage of kidneys

Component	Cost	Source
Cost of each storage box (with satchel)	£45.80	Cost data supplied by Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT)
Cost of each storage box (without satchel, with refill pack)	£20	Cost data supplied by NHSBT
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

and the number litres of fluid used in flushing and then storing each kidney.

Data from the NHSBT, 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 2 litres per stored kidney.<sup>47</sup> Enough solution is required both to flush the organ and then to store it.

## Chapter 2

# Definition of the decision problem

### Decision problem

#### 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 Description of technology under assessment, Chapter 1. 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 *Table 5*, Chapter 1.

#### Populations including subgroups

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

#### Relevant comparators

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

#### 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 7 days following transplantation. 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: this can be either the number of patients who suffer graft rejection or the number of rejection episodes, depending on the definition used in the particular trial under consideration.
- 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.

#### 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 the donor is BSD, DCD or ECD, the age of the donor, whether the donor had co-morbidities such as diabetes, whether there was a period of warm ischaemia after death and if so how long it lasted, the length of cold ischaemia and the quality of the tissue matching. These issues are discussed in more detail in Description of the problem, Chapter 1. Furthermore, the age and health of the recipient may affect the success of transplantation.

#### 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.



## Chapter 3

# Assessment of clinical effectiveness

### 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.<sup>48</sup>

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

### Identification of studies

Electronic databases were searched for systematic reviews and/or meta-analyses, randomised controlled trials (RCTs) and other designs (see Number of studies included, below), 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 (with start date): Cochrane Library (no start date), MEDLINE (1950 to date), EMBASE (1974 to date), CINAHL (1982 to date), ISI Web of Knowledge (1970 to date), DARE (no start date), NRR (no start date), ReFeR (no start date), Current Controlled Trials (no start date) and (NHS) HTA (no start date). Bibliographies of articles were also searched for further relevant studies, and the US Food and Drugs Administration (FDA) and European Regulatory Agency Medical Device Safety Service websites were searched for relevant material. Owing 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 *Figure 43* in Appendix 2.

### Inclusion and exclusion criteria

#### Study design

##### Inclusion

For the review of clinical effectiveness, systematic reviews of 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 were excluded.

##### Interventions and comparators

Each intervention was compared with all the others, data permitting.

Two methods of cold storing kidneys were considered: hypothermic machine perfusion and cold static storage solutions. Both these technologies were reviewed from the perspective of the UK NHS and so we only considered those specific products that are either in current use or are likely to be available and comparable with those currently used. We did not look 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 considered were:

- LifePort Kidney Transporter (Organ Recovery Systems)



- RM3 Kidney Preservation System (Waters Medical Systems).

Cold storage solutions considered were:

- 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 Description of technology under assessment, Chapter 1.

### Population

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

- BSD: death is diagnosed by absence of any brain stem activity, although the heart is still beating.
- DCD: death is diagnosed by cessation of the heart beat. These can be further subdivided into those whose cardiac arrest occurred in a controlled or in an uncontrolled setting.
- ECDs: donors who are either over 60, or are over 50 and with at least two of the following features: a history of hypertension, death by a cerebral vascular accident or terminal creatinine levels > 1.5 mg/dl.

More details of the characteristics of the population can be found in Epidemiology, Chapter 1.

### Outcomes

The outcomes of interest include:

- discard rates of non-viable kidneys post storage
- incidence DGF
- incidence of PNF
- 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 Chapter 2.

### 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 Appendix 3.

### Critical appraisal strategy

Assessments of study quality were performed using the indicators shown below by MB. Results were tabulated and are described in *Table 11* and Appendix 3.

#### Internal validity

Consideration of internal validity addressed:

1. Sample size
  - i. power calculation at design – for RCTs
2. Selection bias
  - i. explicit eligibility criteria
  - ii. proper randomisation and allocation concealment – for RCTs
  - iii. similarity of groups at baseline
3. Performance bias
  - i. similarity of treatment other than the intervention across groups
4. Attrition bias and intention-to-treat (ITT) analysis:
  - i. all kidneys are accounted for
  - ii. number of withdrawals specified and reasons described
  - iii. analysis undertaken on an ITT basis
5. Detection bias
  - i. blinding
  - ii. objective outcome measures
6. Appropriate data analysis.

#### 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.

### Methods of data synthesis

Where data permitted, the results of individual trials were pooled using random-effects meta-analysis. The analyses were carried out using STATEDIRECT software. Heterogeneity was explored through consideration of the study populations, methods and interventions and statistical heterogeneity by  $\chi^2$  and the  $I^2$  statistics. The outcome measures pooled were DGF, graft survival at 1 year and graft rejection. No assumptions were made about missing data and no requests for missing data were made. Subgroup analyses were not conducted and publication bias was not assessed.



## Results

### 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.

#### Number of studies included

One hundred and thirty-six full papers were reviewed to see if they met the inclusion criteria. In addition, ongoing studies were considered. Thirteen articles were found that met the inclusion criteria, leaving 123 exclusions. A flow chart of papers through the review process (*Figure 43*) including reasons for exclusion can be found in Appendix 2, and a list of studies excluded at the paper review stage is given in Appendix 4.

The 13 articles included were: two systematic reviews,<sup>47,49</sup> three full journal published RCTs,<sup>50-52</sup> two RCTs,<sup>53,54</sup> one cohort study,<sup>55</sup> three full journal published retrospective record reviews<sup>56-58</sup> and two retrospective record reviews published as posters and abstracts only.<sup>59,60</sup>

Further examination of the systematic reviews showed that the review conducted by Wight and colleagues (2003)<sup>47</sup> 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),<sup>49</sup> updated Wight and colleagues. They found 10 new studies, one of which,<sup>61</sup> 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 8* for a comparison of study type and publication status.

Upon further examination of the papers it emerged that in one of the trials<sup>54</sup> 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 an RCT comparing ViaSpan and HTK.<sup>63</sup> 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 to allow papers that used a combination of ViaSpan and HTK for cold storage, as we considered these to be comparable. *Table 9*

**TABLE 8** Comparison of study design and publication status of included studies

Design	Full publication	Unpublished studies	Abstract or poster only
RCT	Montalti <i>et al.</i> 2005 <sup>50</sup>	Moers <i>et al.</i> 2008 <sup>62</sup>	
	Pedotti <i>et al.</i> 2004 <sup>51</sup>	Watson <i>et al.</i> 2006 <sup>53</sup>	
	Faenza <i>et al.</i> 2001 <sup>52</sup>		
Cohort study	Plata-Munoz <i>et al.</i> 2008 <sup>55</sup>		
Retrospective record review	Opelz and Dohler 2007 <sup>57</sup>		Guarrera <i>et al.</i> 2007 <sup>59</sup>
	Moustafellos <i>et al.</i> 2007 <sup>56</sup>		Kazimi <i>et al.</i> 2007 <sup>60</sup>
	Marcen <i>et al.</i> 2005 <sup>58</sup>		
RCT, randomised controlled trial.			

**TABLE 9** Matrix of comparisons of interest showing included studies

Study	LifePort	RM3	ViaSpan	Marshall's Soltran	Celsior
Watson et al. 2006 <sup>53</sup>	Shaded		Shaded		
Moers et al. 2008 <sup>62</sup>	Shaded		Shaded		
Moustafellos et al. 2007 <sup>56</sup>	Shaded		Shaded		
Plata-Munoz et al. 2008 <sup>55</sup>	Shaded			Shaded	
Guarrera et al. 2007 <sup>59</sup>	Shaded	Shaded			
Kazimi et al. 2007 <sup>60</sup>	Shaded				
Opelz and Dohler 2007 <sup>57</sup>			Shaded	Shaded	
Montalti et al. 2005 <sup>50</sup>					Shaded
Pedotti et al. 2004 <sup>51</sup>					Shaded
Faenza et al. 2001 <sup>52</sup>					Shaded
Marcen et al. 2005 <sup>58</sup>					Shaded

shows a matrix of the comparisons of interest in this assessment; shaded cells illustrate which comparators were investigated.

No calculations were made to assess the level of agreement on selection or validity decisions.

**Summary of included studies' characteristics**

Table 10 contains a summary of the key design characteristics of the included studies. Data extraction tables for each study can be found in Appendix 3.

A summary of assessment of the quality of our included studies can be found in Table 11.

**Assessment of effectiveness**

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

1. Machine perfusion systems versus cold storage solutions.
2. Machine perfusion systems versus machine perfusion systems.
3. Cold storage solutions versus cold storage solutions.

Data extraction tables for included studies can be found in Appendix 3.

**Machine perfusion systems versus 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 versus ViaSpan**

Of the three studies comparing LifePort with ViaSpan, one is an ongoing RCT (Watson and colleagues),<sup>53</sup> one RCT has not completed economic data analysis (Moers and colleagues)<sup>54</sup> and the other is a retrospective review of hospital records.<sup>56</sup>

Watson and colleagues<sup>53</sup> (academic-in-confidence information removed). Moers and colleagues<sup>54</sup> [Germany, the Netherlands and Belgium, *n* = 1086 (kidneys)] conducted a good quality European multicentre RCT [the Machine Preservation Trial (MPT)]. This study randomised 1086 kidneys from DCD and BSD (Maastricht criteria III and IV) donors to LifePort (*n* = 543) or ViaSpan or HTK (*n* = 543). Immediately post randomisation, 368 kidneys were excluded. Randomisation allocation was kept for 1036 kidneys and broken for 50; this was permitted only when the anatomy of the kidney made machine perfusion unsuitable. Subsequently, 42 kidneys were discarded post storage and prior to transplant for a variety of reasons (if a kidney was excluded from one arm then its contralateral pair was excluded from the other

TABLE 10 Summary characteristics of included studies

Study	Design (kidneys, n)	Participants (inclusion criteria)	Intervention	Comparator	Outcomes (length of follow-up)
Watson et al. 2006 <sup>53</sup> UK (ongoing) Funded by: Novartis Pharma and Organ Recovery Systems	RCT (93)	Donors: DCD > 17 years Recipients: no positive cross-match, no previous non-renal transplant	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. 2009 <sup>54</sup> Netherlands, Belgium, Germany Funded by: Organ Recovery Systems	RCT (1086)	Donors: DCD (Maastricht categories III and IV) and BSD ≥ 16 years Recipients: not multiple organ transplant; only one kidney received	Machine perfusion: LifePort, n = 336	Cold storage: ViaSpan, n = 336	DGF, patient survival, graft survival, acute rejection, creatinine concentrations, duration of hospital stay, PNF, panel reactive antibodies (1 year)
Plata-Munoz et al. 2008 <sup>55</sup>	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, patient survival (1 year)
Moustafellos et al. 2007 <sup>56</sup>	Hospital record review (36)	Donors: DCD (Maastricht categories III and 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 and 2006 (Inpatient stay)
Opelz and Dohler 2007 <sup>57</sup> Europe, N. America, Australia	Registry (58,607)	Donors: deceased Recipients: criteria not reported	Cold storage: ViaSpan, n = 53,560	Cold storage: Marshall's, n = 5047	Graft survival, death-censored functional survival Data collected between 1990 and 2005 (3 years)
Montalti et al. 2005 <sup>50</sup> 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)
Marcen et al. 2005 <sup>58</sup> 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 January 1997 and October 2001 (12 months)
Pedotti et al. 2004 <sup>51</sup> Italy	RCT (441)	Donors: deceased multiorgan Recipients: criteria not reported	Cold storage: ViaSpan, n = 269	Cold storage: Celsior, n = 172	Patient survival, graft survival, creatinine concentrations, urinary output (12 months)

continued

TABLE 10 Summary characteristics of included studies (continued)

Study	Design (kidneys, n)	Participants (inclusion criteria)	Intervention	Comparator	Outcomes (length of follow-up)
Faenza et al. 2001 <sup>52</sup> Italy	RCT (187)	Donors: deceased > 15 years, multiple organ Recipients: > 15 years, 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 <sup>59</sup> US	Hospital record review (774)	Donors: ECD: > 60 years or 50–59 + hypertension, diabetes > 5 years; 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 years Data collected between December 2001 and September 2006 (1 year)
Kazimi et al. 2007 <sup>60</sup> US	Hospital record review (89)	Donors: deceased – kidney, kidney and pancreas or kidney and 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 February 2005 and November 2006 (90 days)

BSD, brain stem dead; DCD, donated after cardiac death; DGF, delayed graft function; ECD, expanded criteria donor; GFR, glomerular filtration rate; HLA, human leucocyte antigen; IGF, immediate graft function; PNF, primary non-function; RCT, randomised controlled trial.  
Studies published as posters or abstracts only are shaded grey – limited data available.  
The Maastricht categories are specified in Description of the problem, Chapter 1.

TABLE 11 Summary of key quality indicators of included studies

Quality indicator	Watson et al. 2006 <sup>53</sup>	Moers et al. 2008 <sup>62</sup>	Plata-Munoz et al. 2008 <sup>35</sup>	Moustafellos et al. 2007 <sup>56</sup>	Opelz and Dohler 2007 <sup>57</sup>	Montalti et al. 2005 <sup>50</sup>	Marcen et al. 2005 <sup>58</sup>	Pedotti et al. 2004 <sup>51</sup>	Faenza et al. 2001 <sup>52</sup>	<sup>a</sup> Guarrera et al. 2007 <sup>59</sup>	<sup>a</sup> Kazimi et al. 2007 <sup>60</sup>
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 and DCD III and IV <sup>b</sup>	DCD III <sup>b</sup>	DCD III and IV <sup>b</sup>	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

BSD, brain stem dead; CS, cold storage; DCD, donation after cardiac death; ECD, expanded criteria donor; ITT, intention to treat; MP, machine perfusion; NA, not applicable.

a Studies published as posters or abstracts only – limited data available.

b III and IV refer to the Maastricht criteria for DCD donors (see Description of the problem, Chapter 1).

arm) [LifePort = 11 (+10), ViaSpan = 10 (+11)] and four were excluded post transplant [LifePort = 0 (+2), ViaSpan = 2]. This left 672 kidneys for data analysis (BSD = 588, DCD = 84): LifePort,  $n = 336$ ; ViaSpan,  $n = 336$ . In total, 414 kidneys were excluded post randomisation. Recipients who died in the first week post transplant were excluded from the analysis. See Appendix 5 for details of reasons for exclusions.

Recipients were children and adults, mean age 52.5 years (range 2–79 years) who were followed up for 1 year. There were no significant differences in baseline characteristics, including CIT (mean 15 hours) (ViaSpan = 2.5–29.7, LifePort = 3.5–29.7). Results were reported at 6 and 12 months. Analysis was not by ITT. However, in the context of a trial with matched kidneys, the lack of ITT analysis might be considered less of a threat to internal validity.

The results showed that for the primary end point of DGF there were no significant differences between the storage methods (LifePort = 70, ViaSpan = 89,  $p = 0.05$ ).

The secondary end point of duration of DGF showed that machine perfusion significantly reduced this parameter [LifePort = 10 (1–48), ViaSpan = 13 (1–41),  $p = 0.04$ ]. Another measure, functional DGF [an absence of a decrease in serum creatinine of at least 10% per day for at least 3 consecutive days in the first week after transplant, not including patients who developed acute rejection and/or calcineurin inhibitor (CNI) toxicity in the first week] was added post hoc and not specified in the trial protocol; this outcome showed a reduced incidence for machine perfusion (LifePort = 77, ViaSpan = 101,  $p = 0.03$ ). Other secondary outcome measures showed no significant differences between the two groups (PNF, acute rejection, creatinine clearance at day 14, CNI toxicity within 14 days and post-transplant hospital stay).

At 6 months post transplant, there were no differences in patient survival between the groups; both were 98% [relative risk (RR) 1.00, 95% confidence interval (CI) 0.98 to 1.00]. Similarly, at 12 months post-transplant, patient survival was 97% for both groups (RR 1.00, 95% CI 0.97 to 1.03).

Graft survival at 6 months failed to show a significant difference between the groups. However, the LifePort group had significantly better graft

survival at 12 months post transplant [LifePort = 329/336, ViaSpan = 316/336: hazard ratio (HR) 0.39, 95% CI 0.17 to 0.89,  $p = 0.03$ ].

When the results were censored for death at 12 months, Moers and colleagues found that for grafts that had been subject to DGF, those that had been machine perfused were more likely to survive (LifePort = 61/65, ViaSpan = 65/79: RR 1.14, 95% CI 1.01 to 1.29,  $p = 0.04$ ). There were no significant differences for the death-censored survival of grafts that had not had DGF. Main results can be found in *Table 12*.

Moers and colleagues carried out subgroup analyses for DGF. In order to carry out this analysis, further DCD participants were enrolled ( $n = 80$  or  $82$  donors – both numbers are given). They found no significant differences between standard criteria donors versus ECD, BSD versus DCD (main data set) or BSD versus DCD (extended data set).

Moustafellos and colleagues<sup>56</sup> [UK,  $n = 36$  (kidneys)] reviewed the previous 3 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 hours, ViaSpan = mean 17 hours; difference in means (DM) –1.5 hours,  $p < 0.001$ ]. 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 straightaway than those cold stored (LifePort = 13/18, ViaSpan = 2/18; RR 6.5, 95% CI 1.71 to 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 to 0.67,  $p < 0.001$ ); length of hospitalisation (LifePort = mean 8 days, ViaSpan = mean 14 days; DM –6, 95% CI –7.66 to –4.34,  $p < 0.001$ ); and creatinine concentrations at discharge (DM –118  $\mu\text{mol/l}$ ,  $p < 0.001$ ), all favouring machine perfusion.

Principal outcomes can be seen in *Table 12*.

TABLE 12 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-value	Comment
DGF	Watson et al. 2006, <sup>53</sup> RCT	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)	RR 1.04	0.73 to 1.49	(Academic-in-confidence information removed)	McNemar's exact test
	Moers et al. 2008, <sup>62</sup> RCT	BSD and DCD	70/336 (21)	89/336 (26)			0.05 (NS)	McNemar's exact test
PNF	Moustafellos et al. 2007, <sup>56</sup> record review	DCD	5/18 (28)	16/18 (89)	RR 0.31	0.15 to 0.67	< 0.001	
	Watson et al. 2006, <sup>53</sup> RCT	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)	RR 3.00	0.13 to 71.74	(Academic-in-confidence information removed)	
Acute rejection	Moers et al., 2008, <sup>62</sup> RCT	BSD and DCD	7/336 (2)	16/336 (5)			0.08 (NS)	
	Watson et al. 2006, <sup>53</sup> RCT (3 months)	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)			(Academic-in-confidence information removed)	McNemar's exact test
Kidneys rejected post storage/pre transplant	Moers et al. 2008, <sup>62</sup> RCT (6 months)	BSD and DCD	44/336	46/336			0.91 (NS)	
	Moustafellos et al. 2007, <sup>56</sup> record review (till discharge)	DCD	0/18	0/18				
	Watson et al. 2006, <sup>53</sup> RCT (3 months)	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)				McNemar's exact test
	Moers et al. 2008, <sup>62</sup> RCT (6 months)	BSD and DCD	11/336	10/336				

continued



TABLE 12 Main results of studies comparing LifePort machine with ViaSpan solution (continued)

Outcome	Study (follow-up)	Donor population	LifePort, n/N (%)	ViaSpan, n/N (%)	Effect	95% CI	p-value	Comment
Patient survival	Watson et al. 2006, <sup>53</sup> RCT (3 months)	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)	RR 0.98	0.92 to 1.04	(Academic-in-confidence information removed)	Log rank
	Moers et al. 2008, <sup>62</sup> RCT (6 months)	BSD and DCD	329/336 (98)	329/336 (98)	RR 1.00	0.98 to 1.00	NS	
Graft survival	Moers et al. 2008, <sup>62</sup> RCT (12 months)	BSD and DCD	326/336 (97)	326/336 (97)	RR 1.00	0.97 to 1.03	NS	
	Watson et al. 2006, <sup>53</sup> RCT (3 months)	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)	RR 0.96	0.89 to 1.03	(Academic-in-confidence information removed)	Log rank
	Moers et al. 2008, <sup>62</sup> RCT (6 months)	BSD and DCD	329/336 (98)	319/336 (95)	HR 0.46	0.22 to 0.99	0.05 (NS)	Log rank
	Moers et al. 2008, <sup>62</sup> RCT (12 months)	BSD and DCD	329/336 (98)	316/336 (94)	HR 0.39	0.17 to 0.89	0.03	Log rank
Post-transplant hospital stay [mean(range)]	Death-censored survival							
	No DGF (12 months)		61/65 (94)	65/79 (82)	RR 1.14	1.01 to 1.29	0.04	
Glomerular filtration rate (eGFR)	Moers et al. 2009, <sup>54</sup> RCT (12 months)	BSD and DCD	19 (4–392)	18 (6–382)			0.78 (NS)	McNemar's exact test
	Watson et al. 2006, <sup>53</sup> RCT (3 months)	DCD	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)			(Academic-in-confidence information removed)	Paired t-test

BSD, brain stem dead; CI, confidence interval; DCD, donated after cardiac death; DGF, delayed graft function; HR, hazard ratio; NS, not significant; PNF, primary non-function; RCT, randomised controlled trial; RR, relative risk. Significance at  $p > 0.05$ .



### **LifePort versus Marshall's cold storage solution (Soltran)**

Plata-Munoz and colleagues<sup>55</sup> [UK,  $n = 60$  (kidneys)] conducted a sequential cohort study of DCD Maastricht category III controlled donor kidneys (March 2002–December 2005). For the first 2 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 hours (range 15–23), Marshall's = mean 18 hours (range 14–22)]. Clinical outcomes showed a lower proportion of DGF in the LifePort group (RR 0.64, 95% CI 0.43 to 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 6 and 12 months for kidneys stored in the LifePort machine (6 months: DM  $-38.00 \mu\text{mol/l}$ , 95% CI  $-46.32$  to  $-29.68$ ,  $p < 0.001$ ; and 12 months: DM  $-39.00 \mu\text{mol/l}$ , 95% CI  $-48.51$  to  $-29.49$ ,  $p < 0.001$ ). 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 1 or 2 years. Results are presented in *Table 13*.

### **Summary of machine perfusion versus 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 review.

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 a lot less than in Watson and colleagues [24% and (academic-in-confidence information removed) respectively]; this may have been due to the difference in DGF between DCD- and BSD-donated kidneys and the large numbers of kidneys that were excluded from Moers and colleagues post storage and prior to analysis ( $n = 42$ ). However, Watson and colleagues found (academic-in-confidence information removed) and Moers and colleagues found less with LifePort (LifePort = 21%, ViaSpan = 26%).

Overall (academic-in-confidence information removed). However, Moers and colleagues found that graft survival was better at 12 months post transplant with machine perfusion (LifePort = 98%, ViaSpan = 94%,  $p = 0.03$ ). Only 3 months' follow-up data were available from Watson and colleagues, who found (academic-in-confidence information removed). These two studies' results are in recipients whose grafts had a mean CIT of approximately 15 hours. It is not possible to say from these data what the effects of longer follow-up or greater CIT may have on the results.

Moers and colleagues carried out subgroup analyses for DGF. They found no significant differences between standard criteria donors (undefined) versus ECD, BSD versus DCD (main data set) or BSD versus DCD (extended data set).

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 6 and 12 months favouring LifePort over ViaSpan and Marshall's Soltran. Plata-Munoz and colleagues also reported patient graft survival outcomes at 1 and 2 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 similar between the two groups (academic-in-confidence information removed); MPT: machine perfusion = 11, cold storage = 10).

### **Machine perfusion systems versus machine perfusion systems**

Two studies compared the LifePort Kidney Transporter with 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 11*). 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.

### **Abstracts and posters only Guarrera and colleagues**

Guarrera and colleagues<sup>59</sup> [US,  $n = 774$  (kidneys)] reviewed their transplant centre's records over

**TABLE 13** Results of the study comparing LifePort machine perfusion to Marshall's cold storage solution (Plata-Munoz et al.<sup>55</sup>)

Outcome	LifePort, n/N (%)	Marshall's, n/N (%)	Effect	95% CI	p-value	Comment
DGF	16/30 (53)	26/30 (87)	RR 0.64	0.43, 0.93	0.012	PenTAG calculation
Length of hospitalisation (days)	10	14			0.03	Fisher's exact test
Graft function (6 months), $\mu\text{mol/l}$	163 $\pm$ 10 <sup>a</sup>	201 $\pm$ 21 <sup>a</sup>	DM -38	-46.32 to -29.68	0.001	PenTAG calculation
Graft function (12 months), $\mu\text{mol/l}$	154 $\pm$ 9 <sup>a</sup>	193 $\pm$ 25 <sup>a</sup>	DM -39	-48.51 to -29.49	0.001	PenTAG calculation
Patient survival (1 year)	30/30 (100)	28/30 (93)	RR 1.07	0.96 to 1.20	NS	PenTAG calculation
Patient survival (2 years)	29/30 (97)	27/30 (90)	RR 1.07	0.94 to 1.23	NS	PenTAG calculation
Graft survival (1 year)	30/30 (100)	28/30 (93)	RR 1.07	0.96 to 1.20	NS	PenTAG calculation
Graft survival (2 years)	29/30 (97)	27/30 (90)	RR 1.07	0.94 to 1.23	NS	PenTAG calculation

CI, confidence interval; DGF, delayed graft function; DM, difference in means; NS, not significant; RR, relative risk.  
<sup>a</sup> It is not reported what  $\pm$  means.

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; note that this definition of ECD varies from that generally used and given in Description of the problem, Chapter 1.); or DCD (22%). More DCD donors were used with the LifePort machine than with the RM3 [RM3 = 75 (20%), LifePort = 96 (25%), not significant (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 hours, LifePort = mean 24 hours).

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 RR of 0.76, 95% CI 0.62 to 0.94,  $p < 0.01$ . Guarrera and colleagues also found that graft function at 1 year was better with the RM3 [RM3 = 347/378 (91%), LifePort = 367/396 (93%),  $p = 0.05$ ]. Our calculations gave an RR of 1.07, 95% CI 1.02 to 1.13,  $p < 0.01$ . They found no significant difference for patient survival or graft

survival (same results) at 1 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, 95% CI 1.01 to 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. Results are presented in Table 14.

#### Kazimi and colleagues

Kazimi and colleagues<sup>60</sup> [US,  $n = 89$  (kidneys)] retrospectively reviewed the kidney transplant records at their transplant centre over a 22-month period (February 2005–November 2006). They included multiorgan as well as kidney alone transplants and compared the use of the RM3 with the LifePort perfusion machine. It is not clear whether the different perfusion machines were used simultaneously at any time although

TABLE 14 Results of studies comparing the RM3 Kidney Preservation system with the LifePort Kidney Transporter

Outcome	Study (follow-up)	Donor population	RM3, n/N (%)	LifePort, n/N (%)	Effect	95% CI	p-value	Calculation by <sup>a</sup>
DGF	Guarrera et al. 2007, <sup>59</sup> record review	ECD (78%) DCD (22%)	90/378 (24)	125/396 (32)	RR 0.76	0.62 to 0.94	0.013	PenTAG
PNF	Guarrera et al. 2007, <sup>59</sup> record review	ECD and DCD	11/378 (3)	8/396 (2)	RR 1.44	0.59 to 3.54	NS	PenTAG
Kidneys rejected post storage/pre transplant	Guarrera et al. 2007, <sup>59</sup> record review	ECD and DCD	98/378 (26)	91/396 (23)			NS	Guarrera et al. <sup>59</sup>
Patient survival	Guarrera et al. 2007, <sup>59</sup> record review (1 year)	ECD and DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01 to 1.08	0.01	PenTAG
Graft survival	Guarrera et al. 2007, <sup>59</sup> record review (1 year)	ECD and DCD	366/378 (97)	367/396 (93)	RR 1.05	1.01 to 1.08	0.01	Guarrera et al. <sup>59</sup> PenTAG
	Kazimi et al. 2007 <sup>60</sup> (30 days)	BSD (98%)	36/37 (97)	49/52(94)	RR 0.97	0.89 to 1.06	NS	Guarrera et al. <sup>59</sup> PenTAG
	Kazimi et al. 2007 <sup>60</sup> (90 days)	DCD (2%)	35/36 (97)	37/41(90)	RR 0.93	0.83 to 1.04	NS	PenTAG
Graft function (1 year)	Guarrera et al. 2007, <sup>59</sup> record review (1 year)	ECD and DCD	347/378 (92)	339/396 (86)	RR 1.07	1.02 to 1.13	0.007	PenTAG
Post-transplant dialysis	Kazimi et al. 2007 <sup>60</sup>	BSD (98%)	2/37 (5)	2/52 (4)	RR 0.71	0.11 to 4.83	NS	PenTAG
Length of hospitalisation (days)	Kazimi et al. 2007 <sup>60</sup> (90 days)	BSD (98%)	n = 37, mean = 9	n = 52, mean = 15			0.04	Kazimi et al. <sup>60</sup>

BSD, brain stem dead; CI, confidence interval; DCD, donated after cardiac death; DGF, delayed graft function; ECD, expanded criteria donors; NS, not significant; PNF, primary non-function; RR, relative risk.

<sup>a</sup> Guarrera and colleagues' calculations used chi-squared and t-tests; PenTAG calculations used chi-squared tests.

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 from RM3, which may have confounded the results as these kidneys may have had a longer CIT because the liver is transplanted before the kidney (CIT times were not reported). The donor population were 98% BSD and 2% DCD.

Kazimi and colleagues 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 have only 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.

Table 14 gives a summary of their key results.

### Summary of machine perfusion versus machine perfusion

We found only 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 1 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 to 1.08) was significant at  $p < 0.01$  for patient and graft survival at 1 year. There were

a large number of discarded kidneys following perfusion (25%); this may have been due to the high percentage of ECDs (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.

### Cold storage solution versus 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 versus Marshall's Soltran

Opelz and Dohler<sup>57</sup> (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 and 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 CITs. These results can be seen in Table 15.

Opelz and Dohler were more interested in how graft failure rates changed with increasing CIT. As CIT increased, an increasing incidence of graft failure was found for both solutions, with a small increased risk at 19–24 hours, compared with a CIT of  $\leq 18$  hours (ViaSpan: RR 1.10, 95% CI 1.05 to 1.15,  $p < 0.001$ ; Marshall's: RR 1.09, 95% CI 0.95 to 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: RR 1.10, 95% CI 1.05, 1.16,  $p < 0.001$ ; Marshall's: RR 1.20, 95% CI 1.01 to 1.41,  $p = 0.03$ ). As CIT increased beyond 36 hours, kidneys stored in both solutions had an

**TABLE 15** Results of Opelz and Dohler's study comparing ViaSpan with Marshall's Soltran cold storage solutions<sup>57</sup>

Outcome	Donor population	ViaSpan, n/N (%)	Marshall's solution, n/N (%)	Effect	95% CI
Graft survival, 0–18 hours' cold ischaemia (3 years)	Deceased	19,746/24,258 (81)	1782/2225 (80)	RR 1.02	0.99 to 1.04
Graft survival, 19–24 hours' cold ischaemia (3 years)	Deceased	12,756/16,147 (79)	1260/1636 (77)	RR 1.03	0.99 to 1.05
Graft survival, 25–36 hours' cold ischaemia (3 years)	Deceased	8636/11,158 (77)	709/944 (75)	RR 1.03	0.99 to 1.07
Graft survival, > 36 hours' cold ischaemia (3 years)	Deceased	1855/2486 (75)	220/303 (73)	RR 1.03	0.96 to 1.11

CI, confidence interval; NS, not significant; RR, relative risk.

increased risk of graft failure (ViaSpan: RR 1.21, 95% CI 1.09 to 1.33,  $p < 0.001$ , Marshall's: RR 1.38, 95% CI 1.07 to 1.78,  $p = 0.02$ ).

However, using an analysis which compared the storage solutions at different lengths of CIT, there is evidence that, at all time points, ViaSpan does not significantly improve graft survival compared with Marshall's Soltran.

### ViaSpan versus Celsior

Of the four studies comparing ViaSpan with Celsior cold storage solution, three were RCTs<sup>50–52</sup> and one was a review of hospital records.<sup>58</sup>

Montalti and colleagues<sup>50</sup> [ $n = 60$  (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 =  $19 \pm 6.5$  hours, Celsior =  $18 \pm 4.5$  hours). Outcome measures included DGF (ViaSpan = 12/25, Celsior = 13/25), graft survival at 1 and 5 years (ViaSpan = 92% and 79%, Celsior = 96% and 87%), the need for postoperative dialysis (ViaSpan:  $n = 3.1 \pm 4.9$ , Celsior:  $n = 2.2 \pm 3.8$ ) 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  $\pm$  meant.

Pedotti and colleagues<sup>51</sup> [ $n = 441$  (kidneys)] carried out a larger multicentre 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 were not explained. The mean CIT for both groups was 15 hours (ViaSpan =  $\pm 4.8$ , Celsior =  $\pm 4.3$ ). Recipients were followed up for 1 year. The outcome measures included DGF (ViaSpan = 61/269, Celsior = 40/172), PNF (ViaSpan = 4/269, Celsior = 4/172), patient survival at 1 month (ViaSpan = 269/269, Celsior = 172/172) and 1 year (ViaSpan = 263/269, Celsior = 171/172), graft survival at 1 month (ViaSpan = 245/269, Celsior = 162/172) and 1 year (ViaSpan = 245/269, Celsior = 162/172), creatinine concentrations (mean range from day 1 to day 15: ViaSpan = 671.8  $\mu\text{mol/l}$  to 220.4  $\mu\text{mol/l}$ , Celsior = 663.0  $\mu\text{mol/l}$  to 200.8  $\mu\text{mol/l}$ ) and urinary output (mean range from day 1 to day 15: ViaSpan = 2520 ml/24 hours to 2500 ml/24 hours, Celsior = 2180 ml/24 hours to 2600 ml/24 hours). 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 SDs used were calculated from the ranges given in the paper. It was not reported what  $\pm$  meant.

Faenza and colleagues<sup>52</sup> [ $n = 187$  (kidneys)] conducted a multicentre RCT of adult multiple-organ donor kidneys to assess the effectiveness of Celsior cold storage solution compared with ViaSpan on DGF and kidney function. Recipients were adults receiving their first transplant. Both groups had a mean CIT of 17 hours (ViaSpan =  $\pm 5.0$ , Celsior =  $\pm 6.6$ ). 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 postoperative 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 1 and discharge. Mean levels on day 1 and discharge were as follows: creatinine: ViaSpan = 3.9 mg/dl and 2.2 mg/dl, Celsior = 2.9 mg/dl and 1.9 mg/dl; urinary output: ViaSpan = 1568 ml and 1754 ml, Celsior = 2265 ml and 1971 ml. Faenza and colleagues concluded, as did the other RCTs, that these two solutions are equivalent.  $\pm$  = SD.

We conducted a meta-analysis using a random-effects model of some of the outcomes – DGF, graft survival at 1 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 *Figures 8–10*.

A comparison of the results from these RCTs is shown in *Table 16*.

Marcen and colleagues<sup>58</sup> [ $n = 177$  (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 to 10.93,  $p < 0.01$ ]. Other baseline characteristics showed no significant differences, although mean (SD) CIT was longer for kidneys stored in Celsior (ViaSpan =  $18 \pm 4.3$  hours, Celsior =  $17 \pm 3.7$  hours, 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 1 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 to 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.

### Summary of cold storage solution versus cold storage solution

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

A multinational 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 CITs.

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.

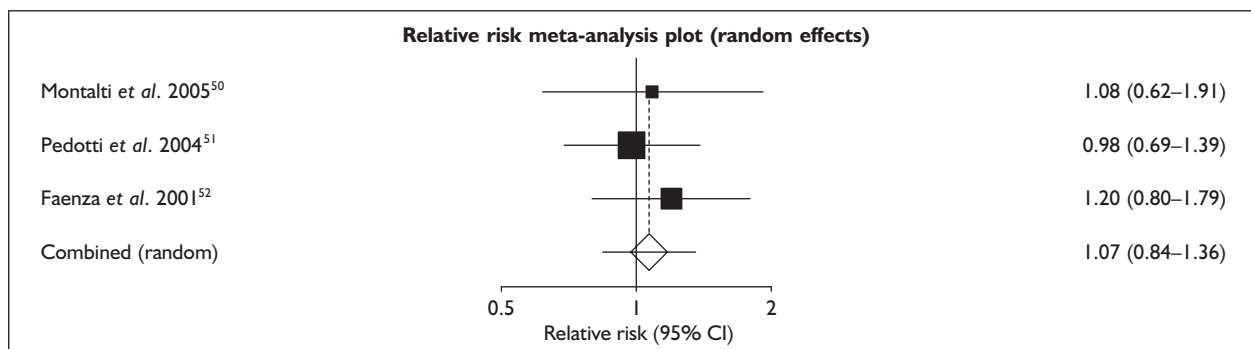
The hospital record review, comparing ViaSpan with Celsior, only found a significant difference in creatinine concentrations at 1 and 12 months, with ViaSpan-stored kidneys having higher levels; these higher levels may have been due to the greater age of the recipients of those kidneys or other confounding factors not reported.

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

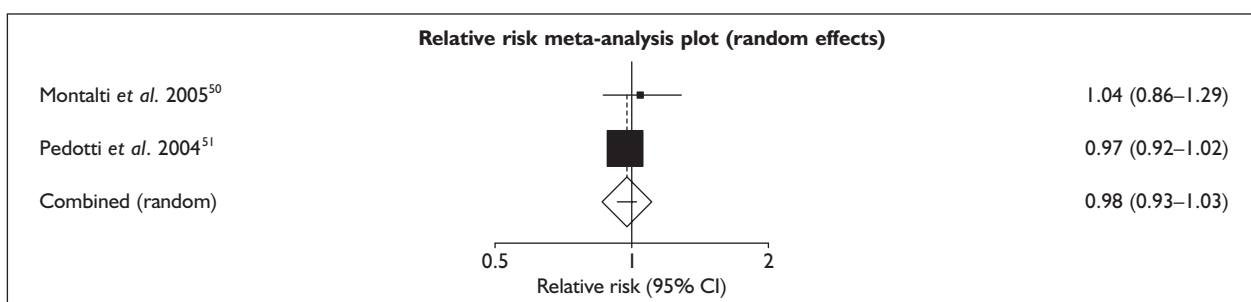
## Safety

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.

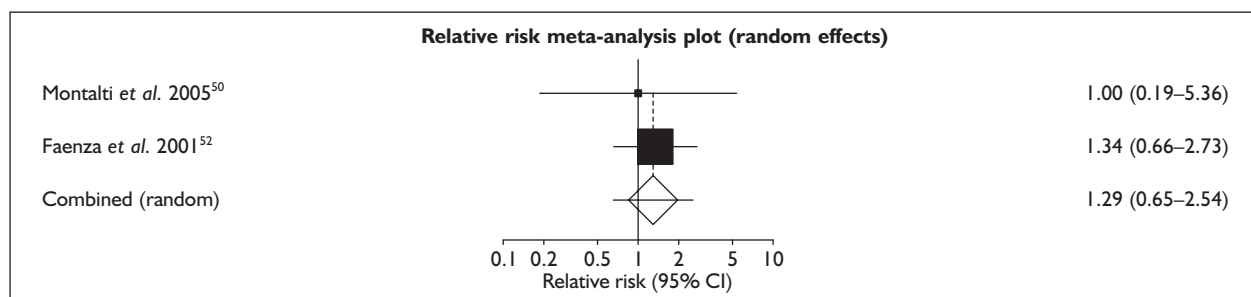
However, the British Transplantation Society's submission to NICE has highlighted the issue that care should be taken not to use Marshall's Soltran cold storage solution when other organs are being retrieved with the kidneys. This is because this solution is not safe for extended preservation of the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



**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.

## Subgroups

The heterogeneity of the studies included in this systematic review did not allow subgroup analyses.

## 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

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 graft survival was significantly better at 1 year with machine perfusion than cold storage. However, no significant differences were found between machine preservation (LifePort) and cold storage (ViaSpan) for mainly BSD donors with a smaller proportion of DCD donors (with an



**TABLE 16** Results of RCTs comparing ViaSpan with Celsior cold storage solution

Outcome	Study (follow-up)	Donor population	ViaSpan, n/N	Celsior, n/N	Effect	95% CI	p-value	Comment
DGF	Montalti et al. 2005, <sup>50</sup> RCT	BSD and DCD	13/25	12/25	RR 1.08	0.62 to 1.89	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT	BSD and DCD	61/269	40/172	RR 0.98	0.69 to 1.38	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT	BSD and DCD	30/80	31/99	RR 1.09	0.72 to 1.64	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT	BSD and DCD	4/269	4/172	RR 0.64	0.16 to 2.52	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT	BSD and DCD	6/88	7/99			NS	
Kidneys rejected post storage/pre transplant	Montalti et al. 2005, <sup>50</sup> RCT (1 year)	BSD and DCD	24/25	23/25	RR 1.04	0.91 to 1.20	NS	PenTAG calculation
	Montalti et al. 2005, <sup>50</sup> RCT (5 years)	BSD and DCD	22/25	20/25	RR 1.10	0.86 to 1.40	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT (1 month)	BSD and DCD	245/269	162/172	RR 1.00	0.96 to 1.01	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT (1 year)	BSD and DCD	245/269	162/172	RR 0.97	0.92 to 1.02	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT (2 years)	BSD and DCD	66/80	83/99	RR 0.90	0.77 to 1.04	NS	PenTAG calculation
Patient survival	Pedotti et al. 2004, <sup>51</sup> RCT (1 month)	BSD and DCD	269/269	172/172	RR 1.00	0.99 to 1.01	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT (1 year)	BSD and DCD	263/269	171/172	RR 0.98	0.96 to 1.01	NS	PenTAG calculation
	Montalti et al. 2005, <sup>50</sup> RCT (before discharge)	BSD and DCD	2/25	2/25	RR 1.00	0.15 to 6.55	NS	PenTAG calculation
Graft rejection	Faenza et al. 2001, <sup>52</sup> RCT (before discharge)	BSD and DCD	13/80	12/99	RR 1.22	0.59 to 2.53	NS	PenTAG calculation

Outcome	Study (follow-up)	Donor population	ViaSpan, n/N	Celsior, n/N	Effect	95% CI	p-value	Comment
Creatinine concentrations	Pedotti et al. 2004, <sup>51</sup> RCT (day 1)	BSD and DCD	Mean 220.4 µmol/l	Mean 200.8 µmol/l	DM 19.60	-121.00 to 160.20	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT (day 15)	BSD and DCD	Mean 671.8 µmol/l	Mean 663.0 µmol/l	DM 8.80	-1.78 to 29.39	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT (day 1)	BSD and DCD	Mean 3.9 mg/dl	Mean 2.9 mg/dl	DM 0.88	-0.08 to 1.84	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT (discharge)	BSD and DCD	Mean 2.2 mg/dl	Mean 1.9 mg/dl	DM 0.50	-0.40 to 1.40	NS	PenTAG calculation
Urinary output	Pedotti et al. 2004, <sup>51</sup> RCT (day 1)	BSD and DCD	Mean 2520 ml/24 hours	Mean 2180 ml/24 hours	DM 340.0	305.99, 374.01	NS	PenTAG calculation
	Pedotti et al. 2004, <sup>51</sup> RCT (day 15)	BSD and DCD	Mean 2500 ml/24 hours	Mean 2600 ml/24 hours	DM -100.0	-266.9 to 66.09	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT (day 1)	BSD and DCD	Mean 1568 ml/24 hours	Mean 2265 ml/24 hours	DM -697.1	-1586.43 to 192.23	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT (discharge)	BSD and DCD	Mean 1754 ml/24 hours	Mean 1971 ml/24 hours	DM -193.1	-691.91 to 304.99	NS	PenTAG calculation
Post-operative dialysis events	Montalti et al. 2005, <sup>50</sup> RCT	BSD and DCD	Mean (SD) 3.1 (4.9)	Mean (SD) 2.2 (3.8)	DM 0.90	-1.53 to 3.33	NS	PenTAG calculation
	Faenza et al. 2001, <sup>52</sup> RCT	BSD and DCD	Mean (SD) 1.9 (3.5)	Mean (SD) 1.0 (3.3)	DM 0.90	-0.08 to 1.88	NS	PenTAG calculation

BSD, brain stem dead; CI, confidence interval; DCD, donation after cardiac death; DGF, delayed graft function; DM, difference in means; NS, not significant; PNF, primary non-function; RCT, randomised controlled trial; RR, relative risk; SD, standard deviation.

average CIT of 15 hours) for the outcomes of DGE, PNF, patient survival and post-transplant duration of hospital stay. Subgroup analyses for DGF found no significant differences between standard criteria donors versus ECD, BSD versus DCD (main data set) or BSD versus DCD (extended data set).

5. (Academic-in-confidence information removed.)
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 multinational registry study showed that for a range of CITs, 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.

# Chapter 4

## Assessment of cost-effectiveness

### Some economic aspects of kidney preservation methods

Our reading of a broad range of studies in the field of organ transplantation and RRT 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 DGF), 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 PNF, 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 longer (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;<sup>27,38,64</sup> they will also have a greater risk of death while waiting for a kidney transplant than if they had been transplanted earlier.<sup>2</sup>

Few of our included effectiveness studies have reported post-storage kidney discard rates, and those that did showed no significant differences between storage methods. 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 RRT.

### Systematic review of existing cost-effectiveness evidence

#### 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.

#### Methods

##### Search strategy

The search strategy for economic evaluations and other economic studies is shown in Appendix 1. The range of sources searched is the same as for clinical effectiveness, with the addition of EconLit and NHS Economic Evaluation Database (EED).

##### 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, with the following exceptions:

- 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 report only average cost-effectiveness ratios will be included only 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).

### Data extraction strategy

Data were 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.

### 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 Consensus on Health Economics Criteria (CHEC) list questions developed by Evers and colleagues.<sup>65</sup>

### 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<sup>47</sup> on machine perfusion versus cold storage of donated kidneys. The other four citations reported one study which compared ViaSpan preservation solution with HTK<sup>66</sup> and two studies which compared ViaSpan with Euro Collins.<sup>67,68</sup> 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 HTA monograph by Wight and colleagues,<sup>47</sup> 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. Below, we review in more detail the cost-effectiveness analyses presented in these two technology assessment reports.

## Summary of existing evidence

### 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 *Tables 17* and *18*.

Wight and colleagues<sup>47</sup> produced a systematic review of economic studies of machine perfusion of kidneys, and also reviewed research on the hypothetical relationship between DGF and graft survival. These reviews helped inform an original probabilistic cost–utility analysis of machine perfusion versus cold storage, which was directly based on a model of the relationship between DGF and graft survival using data from a single transplant centre in the US (from 1985 to 1990).<sup>69</sup>

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 preservation systems.<sup>70,71</sup>

In a more recent technology assessment report, for a Canadian university hospital research group, Costa and colleagues<sup>49</sup> also examined the cost-effectiveness of machine perfusion versus cold storage of donated kidneys. Although in most respects this appears to be a relatively high quality model-based analysis, their cost-effectiveness results were expressed only in terms of the cost per DGF event avoided. As 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 1 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 RCTs 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.<sup>65</sup>

### 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

TABLE 17 Summary characteristics and methods of included studies

Author, year	Analysis type and year	Country, setting	Population	Comparators	Perspective	Sensitivity analyses
Wight et al. 2003 <sup>47</sup>	Model-based CUA, 2002	UK, NHS	Not stated – but implicitly initially successful transplant recipients (NHBDs and HBDS)	Machine perfusion (RM3 Waters machine) versus cold storage (solution not specified)	Health service (UK NHS)	PSA only (separately for DCD and BSD kidneys)
Costa et al. 2007 <sup>49</sup>	Model-based CEA, 2006	Canada, University Hospital	Not stated – but implicitly initially successful transplant recipients	Machine perfusion versus cold storage	McGill University Health Centre	PSA

BSD, brain stem dead; CEA, cost-effectiveness analysis; CUA, cost-utility analysis (generating costs per quality-adjusted life-year); DCD, donation after cardiac death; HBDS, heart-beating donors; NHBDs, non-heart-beating donors; PSA, probabilistic sensitivity analysis.

TABLE 18 Model characteristics and results of included studies

Author, year	Time horizon and 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, transplant management, HD, 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
Costa et al. 2007 <sup>49</sup>	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 80% (DCD) and 50–60% (BSD) of PSA simulations Machine perfusion dominates cold storage in 99.1% of PSA simulations

BSD, brain stem dead; CAPD, continuous ambulatory peritoneal dialysis; DCD, donation after cardiac death; DGF, delayed graft failure (need for dialysis within 7 days post transplant); HD, haemodialysis; PSA, probabilistic sensitivity analysis; QALY(s), quality-adjusted life-year(s); WTP, willingness to pay.

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 RRT or methods for expanding donor numbers. We examined several economic evaluations of alternative forms of RRT,<sup>38,72</sup> methods for enhancing the kidney donor pool,<sup>73,74</sup> alternative post-transplantation immunosuppressive regimes,<sup>75,76</sup> or the economics of transplantation in general,<sup>64</sup> 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.<sup>67,68,70,77</sup> Another older study, by Hornberger and colleagues,<sup>78</sup> has also highlighted the potential importance for cost-effectiveness analyses of including re-transplantation as a treatment pathway.

## Assessment of industry submissions to NICE

Two industry submissions were received by NICE; these 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.

### Organ Recovery Systems

The Organ Recovery Systems' submission consisted of a presentation of the 6-month follow-up results from the MPT<sup>62</sup> and a paper in press.<sup>54</sup> These are the same data that were considered in Machine perfusion systems versus cold storage solutions, Chapter 3, and will not be further reviewed here. A section of their submission referred to an economic study that is part of the MPT. 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 *et al.*<sup>47</sup> and Costa *et al.*<sup>49</sup> These studies were both systematic reviews with original economic analyses, and were also found by the

PenTAG systematic review (see above for our assessment of them).

### 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.<sup>50-52,57</sup> These studies are critiqued in Cold storage solution versus cold storage solution, Chapter 3. The other studies fell outside the inclusion criteria for this assessment because they had comparators that were excluded.

## The PenTAG cost-utility assessment

### Decision problem

The aim of this analysis was 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 versus cold storage with ViaSpan solution, in DCD kidney recipients [based on the Pulsatile Perfusion in Asystolic donor Renal Transplantation (PPART) study]
- machine perfusion with LifePort versus cold storage with ViaSpan solution, in both DCD and BSD kidney recipients (based on the MPT)
- machine perfusion with LifePort versus cold storage with Marshall's Soltran solution
- cold storage with ViaSpan versus 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.

### Summary of methods

A Markov (state transition) model was developed in Microsoft EXCEL<sup>®</sup> (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, i.e. 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 (PSS). A mixed-sex cohort, of 1000 adult kidney transplant recipients, is modelled until virtually all of the cohort (97%) has died. Five separate age groups (18–34, 35–44, 45–54, 55–64, 65+) are simulated in the model, and the results are aggregated to represent the incident population of adult kidney transplant recipients. The model uses a cycle length of 1 month.

### 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.<sup>53,62</sup> The PPART study provided effectiveness data relating only to DCD-donated kidneys, while the MPT 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<sup>56</sup> that also examined this comparison. We found only one study that compared LifePort with Marshall's Soltran;<sup>55</sup> 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 7 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 multinational registry study comparing ViaSpan with Marshall's Soltran.<sup>57</sup>

### 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 1-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 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: IGF (i.e. non-delayed graft function), DGF or death. A patient who experiences IGF will remain in this state (re-cycle arrow in the *Figure 11*) or will eventually experience kidney failure [move to the Failing kidneys (after IGF) state], or alternatively they may die.

### Model states

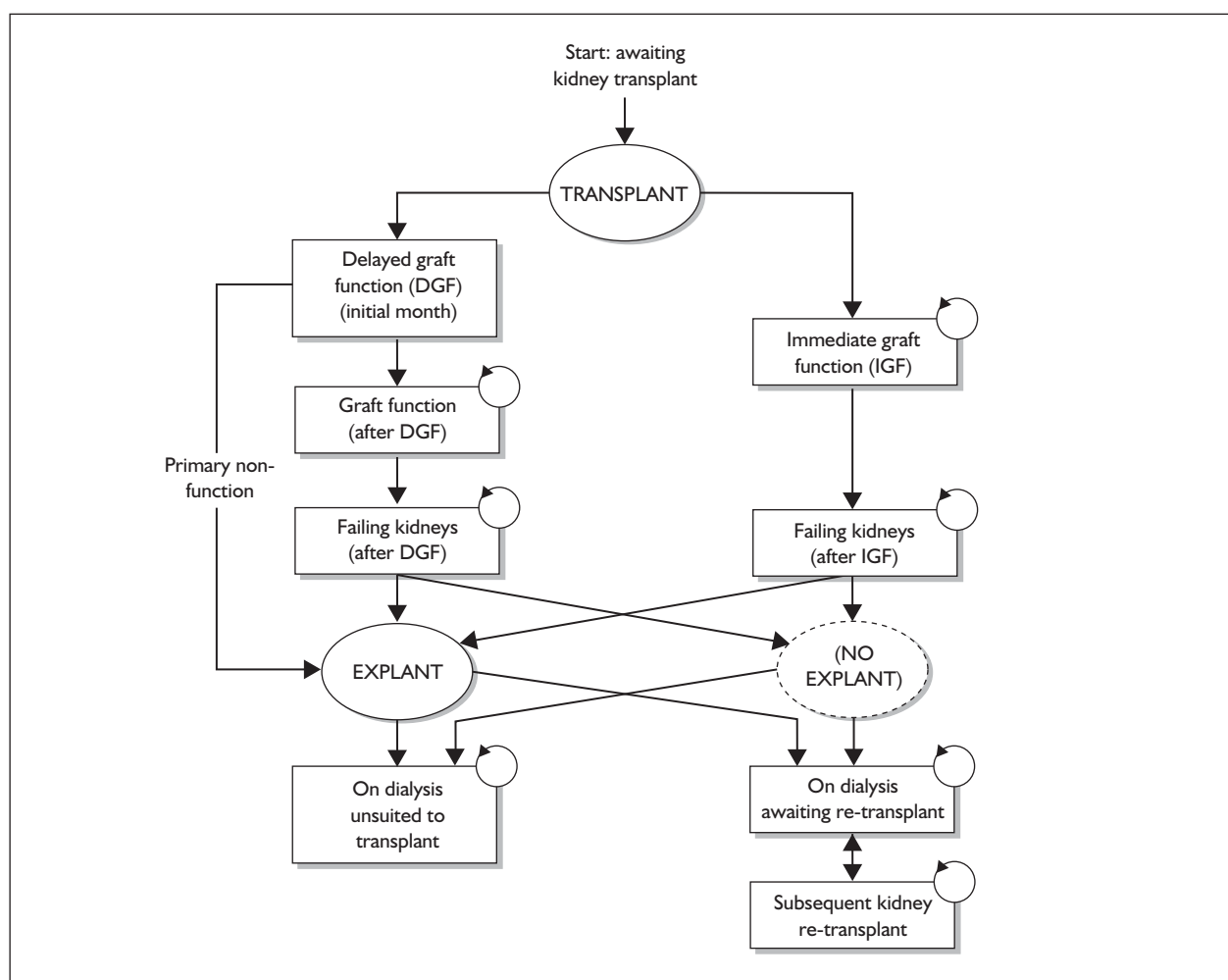
*Table 19* describes in more detail each of the states used in the model to capture the key aspects of the outcomes for kidney transplant patients.

### 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*). 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.

### 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



**FIGURE 11** Structure diagram of the PenTAG kidney transplant model.

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.<sup>79</sup> The age ranges were chosen to be consistent with data presented by the NHSBT and the UK Renal Registry (UKRR) (18–34, 35–44, 45–54, 55–64, 65+) and the proportion allocated to each age range in the model was 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 HD versus 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 dependent, which means that the

probability varies according to 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.

### 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. 1 month) following kidney transplant.
- All patients who experience PNF (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 (as no data were available to parameterise age groups separately).

**TABLE 19** 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 subgroup of patients comprises (1) those whose kidney graft will not have started working by the end of this month (i.e. primary non-function), and (2) 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 possible states of graft function for the re-transplant
Death	The time horizon of the model (the period for which the model is run) is set such that virtually all patients (97%) eventually end in this state

QALY, quality-adjusted life-year.

- In each age group, those patients who received re-transplant (after initial graft failure) are modelled as a homogeneous 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 rejoin 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 (e.g. BSD versus DCD) as 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 years 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 (e.g. 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. CIT, age of donor).
- The impacts of complications either during or post transplantation were not included in the model.

### 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.

### 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.<sup>80</sup>

## 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 *Figure 11*). 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 UKRR and the NHSBT.

### Sources of model parameters

For each cost–utility comparison an initial *standard data set* 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 data set 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 (e.g. differential costs for kidney storage, differential outcome data supplied in the relevant studies for the modelled comparison). The standard data set also provides a basis for sensitivity analysis, which is used to explore the relationships between model inputs and outputs.

The standard data set used to populate the model is shown in the following sections. Much of this

has been drawn from national registry sources, especially from the NHSBT and the UKRR.<sup>18,81</sup>

### Standard age group weightings

The proportion of deceased donor kidney transplantations in each age group was supplied by NHSBT statisticians (*Table 20*).

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.

### Costs estimates

Our cost comparison of the different methods for storing deceased donated kidneys includes the costs 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 PNF)
- 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 HD or PD, routine check-ups, drug treatment for anaemia).

### 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 was 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

**TABLE 20** Proportions of modelled adult transplant recipients in each age group between 1 January 2002 and 31 December 2004 [source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland]

	Age when transplant was received				
	18–34	35–44	45–54	55–64	65+
Proportion of transplants (%)	18.18	24.21	24.86	22.62	10.13

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.<sup>82</sup> 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<sup>83</sup>) 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 Recovery 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 21* shows how the cost per kidney stored was calculated.

### 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 the NHSBT. The vast majority are supplied with a satchel and the required accessories/consumables, costing £45.80 each (information supplied by the NHSBT); we use this figure in our base-case analyses. 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 the NHSBT indicate 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 22* shows the cost per litre (excluding VAT) of the different storage solutions compared in our analysis.

### Number and cost of kidney graft explantation

The NHSBT supplied data on the proportion of failed grafts which were explanted by time

**TABLE 21** 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 <sup>a</sup>	£69	£475 <sup>d</sup>	£544
From DCD donors only <sup>c</sup>	16 <sup>b</sup>	£262	£475 <sup>d</sup>	£737

BSD, brain stem dead; DCD, donation after cardiac death.

a Twenty-two transplant centres in the UK (excluding Glasgow and Edinburgh) transplanted 1332 kidneys in the year 2006–7.<sup>18</sup>

b Seventeen transplant centres in the UK with a DCD donor programme (excluding Glasgow and Edinburgh) transplanted 267 kidneys in the year 2006–7.<sup>18</sup>

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 used only for kidneys from DCD donors under present organ-sharing arrangements.

d Source: Organ Recovery Systems, industry submission.



**TABLE 22** 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 six 1-litre bags)
Marshall's Soltran	£9.60	Baxter e-catalog (web pages accessed 19 May 2008; product code FKB4708G at: <a href="http://www.ecomm.baxter.com/ecatalog/">http://www.ecomm.baxter.com/ecatalog/</a> )

since transplant. Our assumptions regarding the probability of kidney graft explantation following graft failure are shown under Kidney graft failure, later in this chapter.

Each kidney explant operation is given a unit cost of £4135, which is the weighted average of the 2006–7 national average unit costs for kidney major open procedures (Healthcare Resource Group codes LB02B – with intermediate complex co-morbidities, and LB02C – without complex co-morbidities: £3949 and £4424 respectively).

#### **Ongoing care costs with a functioning kidney transplant**

Table 23 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 postoperative rates, which would overestimate long-term rates. We have therefore suggested simply reducing rates of acute reduction, with the initial rate for the first 3 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.<sup>84</sup> We assumed that most transplant centres in the NHS use a triple regime involving (1) a calcineurin inhibitor (either ciclosporin or tacrolimus); (2) an antiproliferative agent (either azathioprine or mycophenolate mofetil; and (3) 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).

With these ingredient costs, the estimated monthly NHS cost of living with a functioning transplant is initially £2464, decreasing to £1386, and then to £567 per month from year 2 onwards.

#### **Ongoing care costs when on dialysis**

Table 24 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. As older patients are more likely to be on HD (rather than PD), 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 25).

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

#### **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 HHD or on PD, e.g. showers, bunkers or sheds for storing deliveries of dialysate bags).

#### **Summary of standard cost parameters**

Table 26 lists the standard values of each of the cost variables used to calibrate the model.

#### **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

TABLE 23 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 members <sup>a</sup>	£258	NSRC 2006–7	£1720 £860 £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 <sup>b</sup>	£1489	NSRC 2006–7	£223 £74 £15
Proportion of episodes of acute rejection requiring intravenous treatment with ATG	10%	Estimate by a transplant surgeon	£2960 <sup>c</sup>	Renal pharmacist, Plymouth Hospitals NHS Trust	NA
Immunosuppressive drug therapy	Various, but typically a triple regime involving (1) a calcineurin inhibitor; (2) an antiproliferative agent and (3) steroids <sup>d</sup>	Plymouth Hospitals NHS Trust and NICE Guidance <sup>d</sup>	Various	Drug Tariff 2006 and Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT) Fact Sheet 7	£417 (= £5000 per year ÷ 12)

ATG, antithymocyte globulin; NA, not applicable; NSRC, National Schedule of Reference Costs.

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

b 0.15 broadly reflects short-term rates reported in four published studies comparing machine perfusion with cold storage.<sup>54–56,65</sup> 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 125 mg ATG given intravenously (centrally given) per day for 3 days.

d Based on a regime involving ciclosporin or tacrolimus (as per current NICE guidance<sup>64</sup>) 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).



**TABLE 24** Costs associated with being on dialysis

Cost type	Units used	Source	Unit cost	Source	Monthly cost
Haemodialysis (HD) treatments	Three sessions per week	Standard practice throughout NHS	£158	NSRC 2006-7	£2049
Peritoneal dialysis (PD) treatments	Per day cost (as in NSRC) <sup>a</sup>	NSRC 2006-7	£44	NSRC 2006-7	£1338
Routine outpatient appointments	Two per year	Expert advice	£114	NSRC 2006-7	£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 <sup>81</sup>	£0.000754	BNF no. 55, <sup>86</sup> (epoietin alfa: Eprex <sup>®</sup> ) <sup>b</sup>	£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 <sup>81</sup>	£0.000754	BNF no. 55, <sup>86</sup> (epoietin alfa: Eprex <sup>®</sup> ) <sup>b</sup>	£155

BNF, British National Formulary; IU, international units; NSRC, National Schedule of Reference Costs; UKRR, UK Renal Registry.

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 a typical mix of alternative EPO drugs that might be used (epoietin beta and delta); however, they all have a similar cost per unit.

**TABLE 25** Data on the proportion of adult patients on different dialysis modalities [source: numbers read off from bar chart (Figure 4.10) in Chapter 4 of UK Renal Registry 10th Annual Report.<sup>81</sup> The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association]

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

**TABLE 26** Summary listing of standard cost data for Markov states

Parameter	Value	Source
<b>State costs (£s per patient per monthly cycle)</b>		
Patients with functioning graft		
Months 1–3 post transplant	£2464	See Ongoing care costs with a functioning kidney transplant
Months 4–12 post transplant	£1386	
Months 13+ post transplant	£567	
Patients on dialysis (by age group)		
18–34	£2034	See Ongoing care costs when on dialysis
35–44	£2040	
45–54	£2052	
55–64	£2060	
65+	£2117	
<b>Parameter</b>		
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 (1) in-hospital dialysis and (2) 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 transplant; see Ongoing care costs with a functioning kidney transplant
DTH: death	£0	
<b>Event costs (£s per patient)</b>		
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 with no explant	£0	
NSRC, National Schedule of Reference Costs.		

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 recently published systematic review (by Dale and colleagues 2008<sup>27</sup>) 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.

#### **Systematic search for comparative quality of life studies**

##### **Methods**

We conducted a bibliographic search for published papers which reported 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 EuroQol – 5 dimensions (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.<sup>33,87</sup>

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: different methods of storing donated kidneys; different immunosuppressive drug regimes; different modalities of RRT; and 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 ESRD, 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.<sup>24,28–30,32–35,88–97</sup> These were in addition to the two studies already found (for researching Chapter 1) which had used the SF-36 in both dialysis patients and kidney transplant recipients.<sup>23,34</sup> (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),<sup>92,93</sup> one was in HD patients only,<sup>89</sup> and one collected quality of life data in different types of dialysis patient and transplant recipients, but provided no comparative analysis across these groups.<sup>88</sup> None of the 18 studies found had used the EQ-5D quality of life instrument, and the only two remaining studies which had used the SF-36 were in dialysis and transplant patients with diabetes.<sup>24,34</sup> All of the remaining comparative studies had either used bespoke subjective or objective indicators of quality of life,<sup>28,32,33,94,96,97</sup> 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<sup>91</sup> and by Russell and colleagues<sup>95</sup> both used TTO or standard gamble methods to elicit utility weights from the patients themselves. In general, it seems that empirical quality of life studies in groups of patients on dialysis and/or with ESRD 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 KDQOL, the Quality of Life Index (QLI) or Parfrey’s health questionnaire for ESRD.<sup>98–103</sup>

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<sup>27</sup> 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.

### Results – review of cost–utility studies in ESRD

Seven recently published cost–utility analyses in ESRD and/or kidney transplant patients were identified (*Table 27*). This was not intended to be an exhaustive systematic review of such studies, but

TABLE 27 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 <sup>47</sup>	Machine perfusion vs cold storage of donated kidneys	Hornberger et al. 1997 <sup>78</sup>	Tx = 0.84 Dialysis after graft failure = 0.65 Difference = 0.19	
McEwan et al. 2006 <sup>75</sup>	Sirolimus vs tacrolimus for immunosuppression in Tx patients	Laupacis et al. 1996, <sup>104</sup> Gudex 1995, <sup>105</sup> Kiberd 1994 <sup>106</sup>	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 <sup>76</sup> (four industry-submitted analyses)	Different renal immunosuppression regimes	Hornberger et al. 1997, <sup>78</sup> Russell et al. 1992, <sup>95</sup> Booth-Clibborn et al. 1997 <sup>107</sup>	Differences = 0.19–0.3	Table 30 of <i>Health Technology Assessment publication</i> <sup>76</sup>
Woodroffe et al. 2005 <sup>76</sup> (own analysis)	Different renal immunosuppression regimes	Used modified Novartis model (i.e. values from Hornberger et al. 1997 <sup>78</sup> )	Tx = 0.84 Dialysis after graft failure = 0.65 Difference = 0.19	
Mendeloff et al. 2004 <sup>73</sup>	Different methods of organ procurement	Hornberger et al. 1997, <sup>78</sup> Russell et al. 1992 <sup>95</sup>	With Tx = 0.76 (low 0.74, high 0.84) Without Tx = 0.56 (low 0.41, high 0.68)	Three other sources were cited; two were unpublished reports and one was an abstract
Yen et al. 2004 <sup>108</sup>	Medicare coverage vs no coverage for immunosuppressive medications	Hornberger et al. 1997 <sup>78</sup>	Difference = 0.2 Tx = 0.84	
Rutten et al. 1993 <sup>68</sup>	ViaSpan solution vs EC solution for storing deceased kidneys	De Charro 1998 (PhD thesis)	Dialysis after graft failure = 0.68 Difference = 0.16	
De Wit et al. 1998 <sup>38</sup>	Two HD and two PD dialysis modalities	Own data (EQ-5D) for dialysis modalities For transplantation assumed = 0.90	Functioning graft = 0.8 On dialysis = 0.4 Difference = 0.4 Full care centre HD = 0.66 Limited care HD = 0.81 CAPD = 0.71 Continuous cycling PD = 0.81 Differences = 0.09 – 0.24	Possibly assumed figures

CAPD, continuous ambulatory peritoneal dialysis; EC, Euro Collins; HD, haemodialysis; PD, peritoneal dialysis; Tx, transplant.

was to give us an indication of the main previous sources of utility estimates in this patient group, and the consistency of these values.

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<sup>94,104,105,110</sup> (*Table 28*) [excluding the De Charro PhD thesis (cited in Rutten 1993<sup>68</sup>) and the De Wit and colleagues study<sup>38</sup> – in which the utility for living with a transplant had been assumed – and the analysis by Hornberger and colleagues,<sup>78</sup> whose utility values were drawn mainly from the 1992 study by Churchill and colleagues<sup>109</sup>).

The only studies reporting utility values for both dialysis and transplant patients had used the TTO method for eliciting preferences. (N.B. 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.)

A recently published systematic review of studies reporting utility values in ESRD, by Dale and colleagues,<sup>27</sup> also identified two studies which reported utility values derived from EQ-5D questionnaire completion by patients. The first, larger, study by Greiner and colleagues<sup>111</sup> reported EQ-5D-based utility values for 150 German transplant recipients, both before (when on dialysis) and up to 2 years post transplantation.

A smaller cross-sectional study ( $n = 27$  in each group) in Swedish kidney transplant recipients

also used the EQ-5D.<sup>112</sup> However, despite usefully matching dialysis and transplant recipients on a number of characteristics, it may not be as reliable as the German study because of the lower sample size, and because the values for HD patients were substantially lower than those for patients on PD; this is contrary to most other high quality studies, which usually show patients on HD (particularly home or satellite unit dialysis) having a better or similar quality of life to those on PD. In addition, their assessed utility difference between being on HD 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 28*).

The main characteristics and results of the Greiner and colleagues study are shown in *Table 29*. 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<sup>113</sup> has shown the EQ-5D to be a valid instrument for measuring health status in renal transplant patients.

#### Utility values used

*Table 30* 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 28** Published utility values for both dialysis and kidney transplant patients/health states (from primary studies)

Study	n	Transplant	Haemodialysis			Peritoneal dialysis		Method
			HHD	SHD	CHD	CAPD	Other	
Churchill et al. 1987 <sup>110</sup> (cited in Hornberger et al. 1997 <sup>78</sup> )	272 <sup>a</sup>	0.84	0.49		0.43	0.56		TTO
Russell et al. 1992 <sup>95</sup>	27 <sup>b</sup>	0.74	0.41					TTO
Gudex 1995 <sup>105</sup>	501	0.79	0.63		0.53			HMQ and Rosser scores
Laupacis et al. 1996 <sup>104</sup>	134	0.77	0.62 <sup>c</sup>					TTO

CAPD, continuous ambulatory peritoneal dialysis; CHD, centre/hospital haemodialysis; HHD, home (or self-) haemodialysis; HMQ, Health Measurement Questionnaire; SHD, satellite haemodialysis; TTO, time trade-off.

a  $n = 103$  transplant, 60 CHD, 57 HHD, 52 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.

**TABLE 29** Summary of utility elicitation study by Greiner and colleagues<sup>11</sup>

<b>Study design</b>	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 1, 3, 6, 12 months, and 'more than 1 year' after transplant)		
<b>Study strengths</b>	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)		
<b>Study weaknesses</b>	Small sample sizes at longer follow-up (risk of bias) Not clear whether UK population utility weights for EQ-5D were used <sup>a</sup> 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		
<b>Study results</b>	<b>Time point</b>	<b>n</b>	<b>EQ-5D utility weight</b>
	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.			

**TABLE 30** Summary listing of standard data for utilities in the model

Parameter	Utility	Source
<b>Transplant states (by age group)</b>		
18–34	0.83	Assumed 0.1 decrement subtracted from Health State Index norms (MVH National Survey Data 1993, CHE, University of York <sup>14</sup> )
35–44	0.81	
45–54	0.75	
55–64	0.70	
65+	0.66	
<b>Dialysis states (by age group)</b>		
18–34	0.71	0.12 decrement subtracted from corresponding living with transplant utility above (source: Greiner <i>et al.</i> 2001 <sup>11</sup> )
35–44	0.69	
45–54	0.63	
55–64	0.58	
65+	0.54	
The first month post transplant for those who experience delayed graft function includes 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.		

## Transition probabilities

### 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.

### 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 trial data using regression analysis. For three of the four comparisons presented here, the study data presented gave a good initial 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 the NHSBT (Table 31) to extrapolate the curves to provide a more reliable fit. Also for one comparison, ViaSpan versus LifePort, the PPART trial did not provide graft survival data beyond 3 months post transplantation and showed no significant differences between arms. Therefore, in this case, we chose to use the the NHSBT graft survival data to fit the Weibull survival parameters for the model.

### 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 dependent.

After graft failure, the model has two dialysis states: (1) receiving dialysis and waiting for further transplant; and (2) receiving dialysis unsuited to transplant. The relative probability of moving to each of the states is dependent on the age of the patient as outlined below.

**TABLE 31** Five-year graft survival following first kidney transplant in UK 2000–2 [source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland]

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

BSD, brain stem dead; CI, confidence interval; DCD, donation after cardiac death.

**TABLE 32** Proportion of patients in each age group suitable for re-transplant [source: numbers read from scatter plot chart (Figure 5.5) in Chapter 5 of UK Renal Registry Eighth Annual Report 2005<sup>115</sup> [source: The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association]

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

**TABLE 33** Kidney graft explant post graft failure, by months since transplant [source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland]

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



### Suitability for re-transplant after graft failure

The probabilities of a patient rejoining the waiting list for re-transplant after graft failure for each age were derived from the NHSBT data representing the proportion of dialysis patients in each age group actively waiting for transplant (*Table 32*).

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 dependent on the duration of graft function prior to failure. Early graft failures are far more likely to result in explantation. Data provided by the NHSBT (*Table 33*) were used in the model to sequentially decrease the probability of an explantation following a graft failure relative to the duration of graft function.

### 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

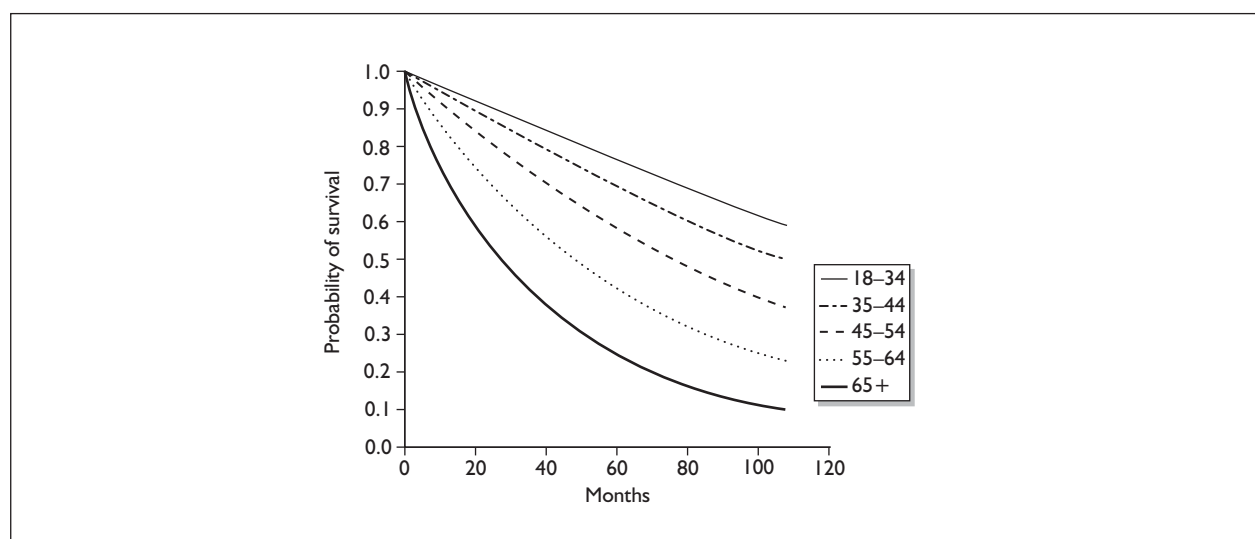
waiting time for a patient receiving a subsequent transplant is known to be age related. Transition probabilities for re-transplant were therefore calculated independently for each age group based on data for the known numbers of re-transplant supplied by the NHSBT.

### Patient survival

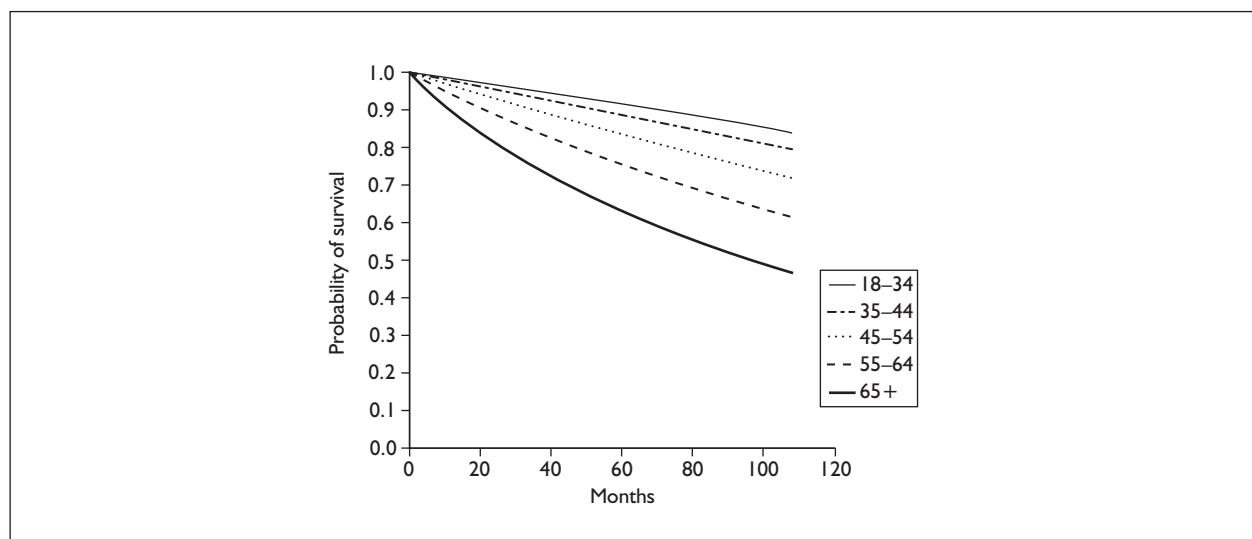
Renal Registry data<sup>81</sup> were used to derive patient survival curves by age group and treatment modality (dialysis or transplant) for the standard data set used in the model. For those patients on dialysis, regression analysis was used to fit Weibull curves to Kaplan–Meier survival data for each of the age groups modelled (as shown in *Figure 12*).

Survival probability for patients on transplant is recognised to be significantly higher than for those on dialysis. An extensive analysis by Wolfe and colleagues<sup>2</sup> revealed RR 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 the NHSBT for 5-year patient survival since transplant. To incorporate the improved survival of transplant patients relative to those on dialysis within the model, a HR of 0.327 was calculated as a weighted average based on the data presented by Wolfe and colleagues. This yielded the survival curves shown in *Figure 13*. Sensitivity analysis was used to explore the effects of changes to this HR on model outputs.

A summary of the parameters used in the PenTAG model is shown in *Table 34*.



**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). The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.]



**FIGURE 13** Standard patient survival curves by age group for patients with transplant. (Source: UK Renal Registry 10th Annual Report. The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.)

**TABLE 34** 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
<b>Age group weights (proportions)</b>		
18–34	18.18%	Data supplied by Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT) [personal communication to Rob Anderson from Alex Hudson (May 2008)]
35–44	24.21%	
45–54	24.86%	
55–64	22.62%	
65+	10.13%	
<b>Utilities by age group for transplant</b>		
18–34	0.83	Assumed 0.1 decrement applied to age related health utility norms.
35–44	0.81	
45–54	0.75	
55–64	0.70	
65+	0.66	
Decrement applied to all patients of dialysis	0.12	Greiner <i>et al.</i> 2002 <sup>111</sup> (see Quality of life – utility estimates in text)
<b>Dialysis costs (per month) by age group</b>		
18–34	£2034	Various costing sources – see Ongoing care costs when on dialysis in text (costs increase with age owing to increasing proportions on haemodialysis compared with peritoneal dialysis)
35–44	£2040	
45–54	£2052	
55–64	£2060	
65+	£2117	
<b>Operation costs</b>		
Transplant operation cost	£16,413	NSRC 2006–7
Explantation operation cost	£4134	NSRC 2006–7

**TABLE 34** Summary of PenTAG model parameters, values and sources (continued)

Parameter	Base-case value	Source
<b>Kidney storage costs (by arm)</b>		
ViaSpan (cold storage)	£262.53	See Cold storage boxes and solutions in text
Marshall's Soltran (cold storage)	£49.73	See Cold storage boxes and solutions in text
LifePort (machine perfusion)	£736.55	See Pulsatile perfusion machines and solutions in text (LifePort only)
<b>Patients with functioning graft (monthly cost)</b>		
Months 1–3 post transplant	£2463.60	See Ongoing care costs with a functioning kidney transplant in text
Months 4–12 post transplant	£1385.83	See Ongoing care costs with a functioning kidney transplant in text
Months 13+ post transplant	£567.47	See Ongoing care costs with a functioning kidney transplant in text
<b>Transitions</b>		
Proportion of transplants (DGF)	Various	Comparator-specific based on trial data
Proportion of transplants (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
<b>Suitability for re-transplant by age group</b>		
18–34	54%	Numbers read from scatterplot chart (Figure 5.5) in Chapter 5 of UK Renal Registry Eighth Annual Report 2005. See Dialysis and re-transplantation following graft failure in text
35–44	50%	
45–54	38%	
55–64	28%	
65+	10%	
<b>Patient survival</b>		
Patient survival with functioning graft	See above	Estimated survival curves based on Renal Registry and UK Transplant data. See Patient survival in text
Patient survival while on dialysis	See above	
DGF, delayed graft function; IGF, immediate graft function; NSRC, National Schedule of Reference Costs; PNF, primary non-function.		

## Results of PenTAG cost–utility analysis

Owing 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 able to make only the following comparisons:

- machine perfusion versus cold static storage solution
  - LifePort versus ViaSpan
  - LifePort versus Marshall's Soltran
- cold static storage solution versus cold static storage solution
  - ViaSpan versus Marshall's Soltran.

## Machine perfusion versus cold static storage *LifePort versus ViaSpan*

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

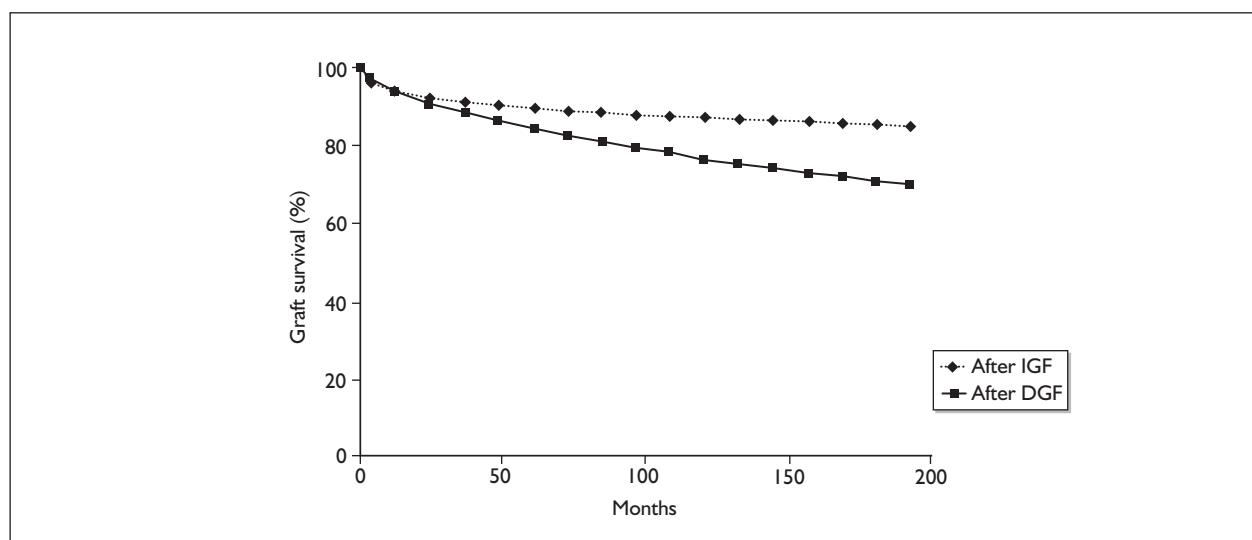
### **LifePort versus ViaSpan – PPART study with DCD kidney transplants in UK**

In order to model cost–utility outcomes based on the PPART trial data, the standard data set was modified with the differential data shown in *Table 35*. For each of the arms, data were drawn from the

**TABLE 35** 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	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)
Percentage of PNF	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)
Graft survival (all patients) at 3 months	(Academic-in-confidence information removed)	(Academic-in-confidence information removed)

DGF, delayed graft function; PNF, primary non-function.



**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 the PPART trial.

**TABLE 36** Base-case deterministic outputs from PenTAG model based on PPART trial data

	Discounted costs per patient (£)	Discounted benefits per patient (QALYs)	ICER
ViaSpan cold storage	139,205	9.19	
LifePort machine perfusion	141,319	9.13	Was dominated
Difference	2114	-0.066	
	<b>Undiscounted costs per patient (£)</b>	<b>Undiscounted benefits per patient (QALYs)</b>	<b>ICER</b>
ViaSpan cold storage	228,885	16.51	
LifePort machine perfusion	231,387	16.36	Was dominated
Difference	2502	-0.153	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

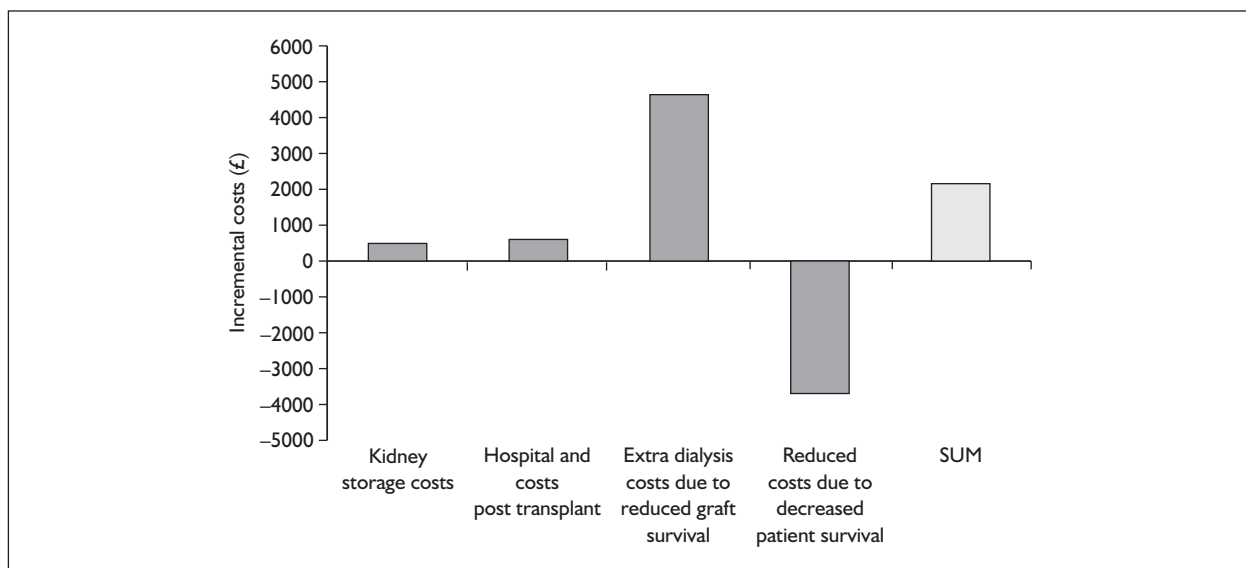
reported trial outcomes and differential costs based on the resource analysis (described above).

In order to fit graft survival curves for these data in the model, it was necessary to use data supplied by the NHSBT for 5-year graft survival (classified by IGF and DGF) as the single 3-month data point provided by this trial does not provide a basis for survival curve fitting. The survival curves shown in *Figure 14* were derived using the NHSBT data.

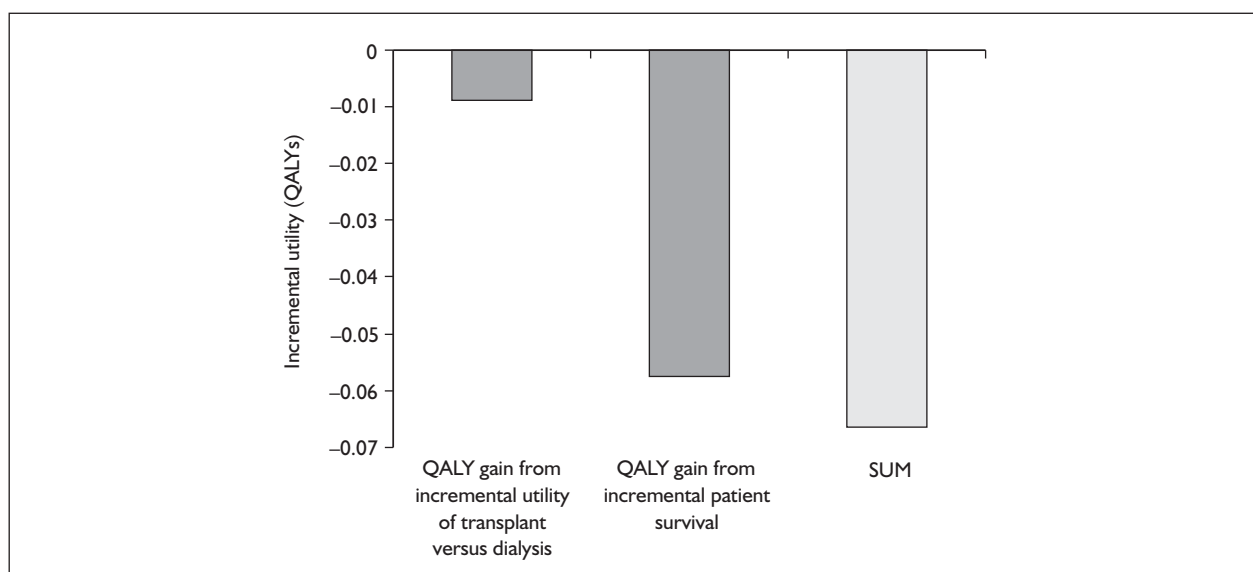
These data yielded the summary deterministic outputs from the model for cost and benefit differences shown in *Table 36*.

The outputs from the model show only very small differences between the arms for both 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 both was 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.



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



**FIGURE 16** Component analysis of utility gains LifePort vs ViaSpan. QALY(s), quality-adjusted life-year(s).

**TABLE 37** Events count output from PenTAG model based on PPART trial data

Description	ViaSpan	LifePort
Immediate graft function (IGF)	444	422
Delayed graft function (DGF)	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 transplant after graft failure	141	139
Re-transplants	97	119
Graft failures after re-transplant	66	81
Deaths in subsequent transplant	29	36
Deaths while waiting for re-transplant	64	77
Deaths on dialysis (transplant unsuited)	140	138

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

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.

The event counts that were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients are shown in *Table 37*.

#### **LifePort versus ViaSpan – the MPT in BSD and DCD patients in Germany, Belgium and the Netherlands**

In order to model cost–utility outcomes based on the MPT data, the standard data set was modified with the data drawn from the costing assumptions (described above) and the reported trial outcomes (*Table 38*).

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 the NHSBT for 5-year graft survival (classified by IGF and DGF) were used to extrapolate the HR for each population beyond the first year supplied in the trial data. This yielded the survival curves shown in *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.<sup>116</sup>

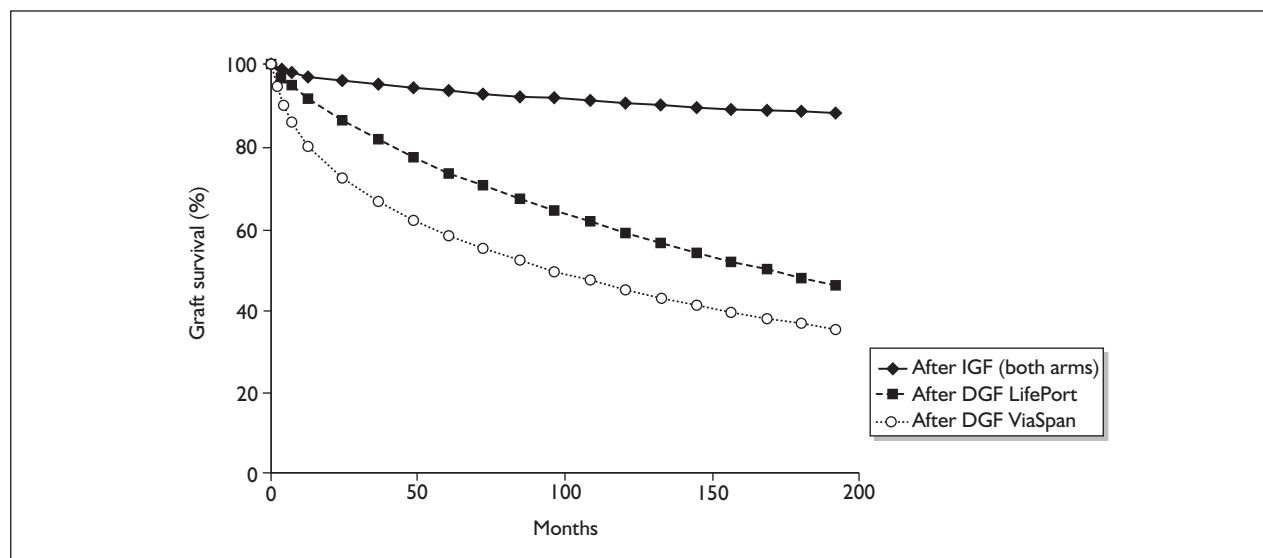
*Table 39* shows the base-case outputs from the model for each comparator arm. These are the deterministic model outputs with discounting and show the cost and utilities per patient for each treatment option, as well as the incremental values for costs and QALYs.

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

**TABLE 38** Summary of differential input parameters based on MPT data

Parameter	ViaSpan	LifePort
Storage cost per kidney	£262.53	£736.55
Proportion of DGF following transplant	26.5%	20.8%
Proportion of PNF	4.8%	2.1%
Graft survival (IGF patients)	98% at 1 year	98% at 1 year
Graft survival (DGF patients)	82% at 1 year	93% at 1 year

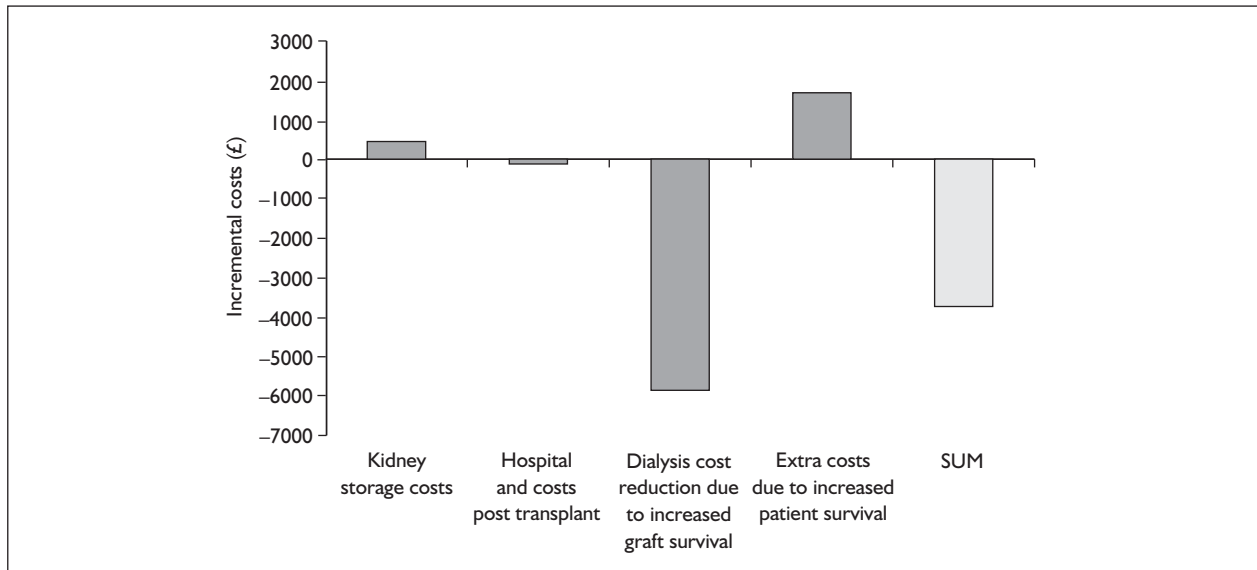
DGF, delayed graft function; IGF, immediate graft function; PNF, primary non-function.

**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 the MPT.**TABLE 39** Base-case deterministic outputs from PentAG model based on MPT data

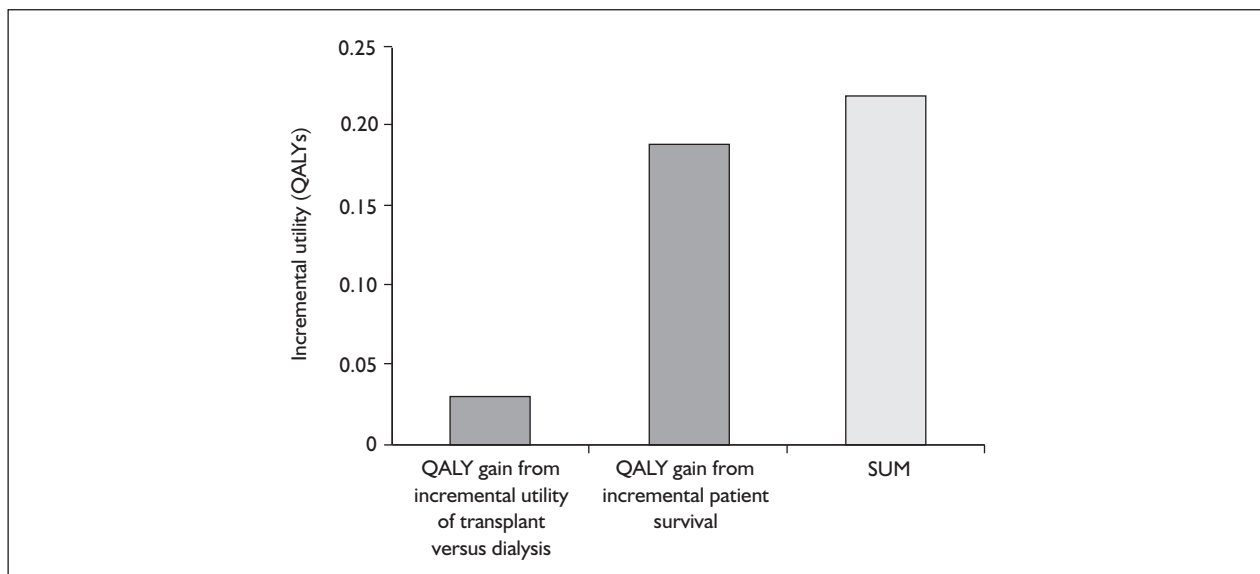
	Discounted costs per patient (£)	Discounted benefits per patient (QALYs)	ICER
ViaSpan cold storage	142,805	9.58	Was dominated
LifePort machine perfusion	139,110	9.79	
Difference	-3695	0.218	
	Undiscounted costs per patient (£)	Undiscounted benefits per patient (QALYs)	ICER
ViaSpan cold storage	232,301	17.20	Was dominated
LifePort machine perfusion	228,540	17.68	
Difference	-3761	0.485	

ICER; incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.





**FIGURE 18** Component analysis of incremental costs of LifePort vs ViaSpan (MPT data).



**FIGURE 19** Component analysis of utility gains of LifePort vs ViaSpan. QALY(s) quality-adjusted life-year(s).

compared with cold storage using the ViaSpan solution. Appendix 8 shows the breakdown of these results by age group.

The component analyses in *Figures 18* and *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 both the costs associated with kidney storage and those associated with increased survival (N.B. increased survival is associated with extra costs because either being on dialysis or having a working kidney graft incurs significant ongoing health-care costs).

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

The event counts in *Table 40* were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

**LifePort versus Marshall’s Soltran**

For the cost-utility comparison of Marshall’s Soltran solution versus LifePort MP, one clinical effectiveness study by Plata-Munoz and colleagues<sup>55</sup>

has been used to provide effectiveness data for this cost–utility analysis. The comparator-specific data shown in *Table 41* were input into the model in addition to the standard data set described above.

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 the NHSBT for 5-year graft survival (classified by IGF and DGF) were used to extrapolate beyond the 2-year results 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. *Figure 20* shows the survival curves for each arm that were employed in the model.

These data yielded the summary base-case outputs from the model for cost and benefit differences shown in *Table 42*.

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 with cold storage using the Marshall's solution. Appendix 8 shows the breakdown of these results by age group.

The component analyses in *Figures 21* and *22* show the breakdown of costs and utility gains between the comparator arms. These figures show that the

**TABLE 40** Events count output from PenTAG model based on MPT data

Description	ViaSpan	LifePort
Immediate graft function (IGF)	735	792
Delayed graft function (DGF)	265	208
Primary non-function	48	21
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 transplant after graft failure	132	119
Re-transplants	142	103
Graft failures after re-transplant	97	70
Deaths in subsequent transplant	44	31
Deaths while waiting for re-transplant	90	68
Deaths on dialysis (transplant unsuited)	131	118

**TABLE 41** Differential input data for compared arms based on Plata-Munoz et al.<sup>55</sup> data

	Marshall's Soltran	LifePort
Storage cost per kidney	£49.73	£736.55
Proportion of DGF following transplant	83%	53%
Proportion of PNF	0%	0%
Graft survival (all patients) at 2 years	90.0%	96.7%

DGF, delayed graft function; PNF, primary non-function.

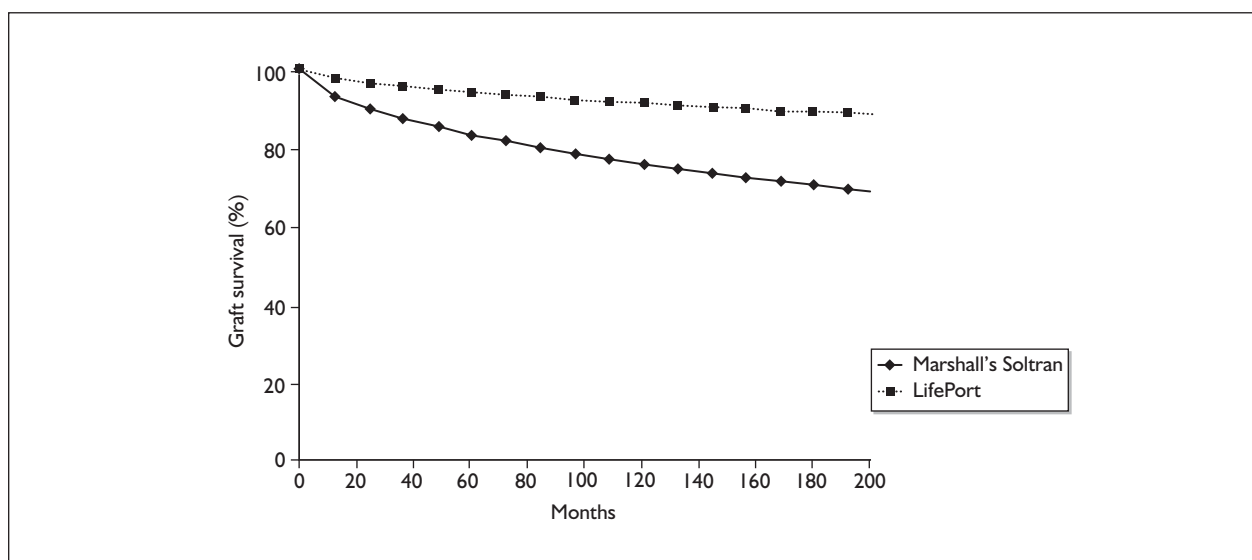


FIGURE 20 Weibull survival estimates of graft survival for each arm of comparison of Marshall's Soltran and LifePort.

TABLE 42 Base-case deterministic outputs from PenTAG model based on Plata-Munoz et al.<sup>55</sup> data

	Discounted costs per patient (£)	Discounted benefits per patient (QALYs)	ICER
Marshall's Soltran solution	144,332	8.55	Was dominated
LifePort machine perfusion	132,953	9.54	
Difference	-11,379	0.993	
	Undiscounted costs per patient (£)	Undiscounted benefits per patient (QALYs)	ICER
Marshall's Soltran solution	235,844	14.99	Was dominated
LifePort machine perfusion	220,662	17.54	
Difference	-15,182	2.551	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years

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 with Marshall's Soltran.

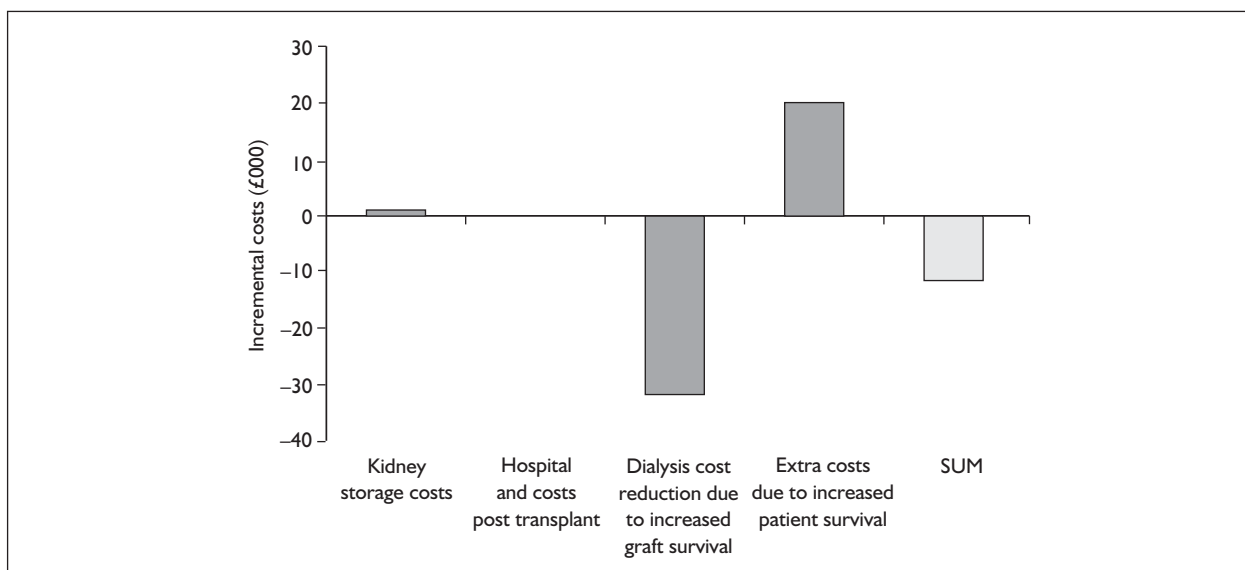
The event counts in Table 43 were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

**Cold storage solution versus cold storage solution**  
**ViaSpan versus Marshall's Soltran solution**

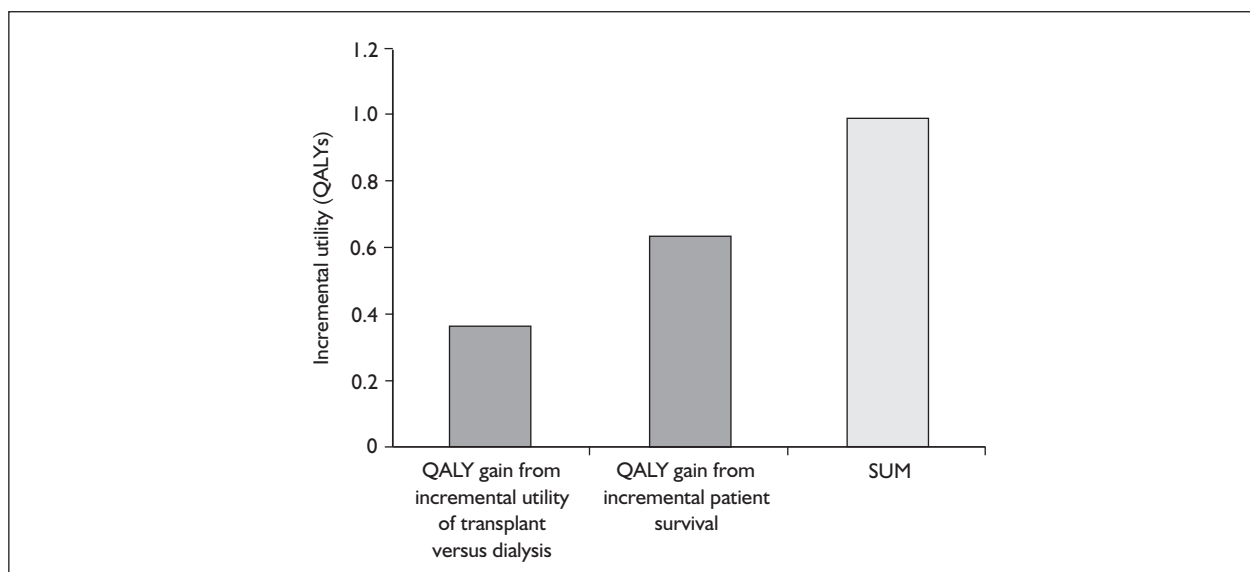
For the cost-utility comparison of Marshall's Soltran solution versus LifePort, one study (Opelz and Dohler<sup>57</sup>) satisfied our inclusion criteria. This registry data study provided inputs for graft

survival at 3 years. The between-arms data shown in Table 44 were put into the model in addition to the underlying standard data set.

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 were extracted from the study data and used to calculate representative Weibull parameters for each arm of the trial. As 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 survival curves for each arm shown in Figure 23 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



**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. QALY(s), quality-adjusted life-year(s).

to have the corresponding numerical data for graft survival from this trial in accordance with best practice for presenting survival data.<sup>116</sup>

Table 45 shows the summary base-case outputs from the model; these indicate that for the specific input parameters derived from this study, ViaSpan both results in lower overall costs of treatment and confers greater benefits to patients when compared with 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 in Figures 24 and 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.

The event counts in Table 46 were output by the model for this comparison for a cohort of 1000 simulated kidney graft recipients.

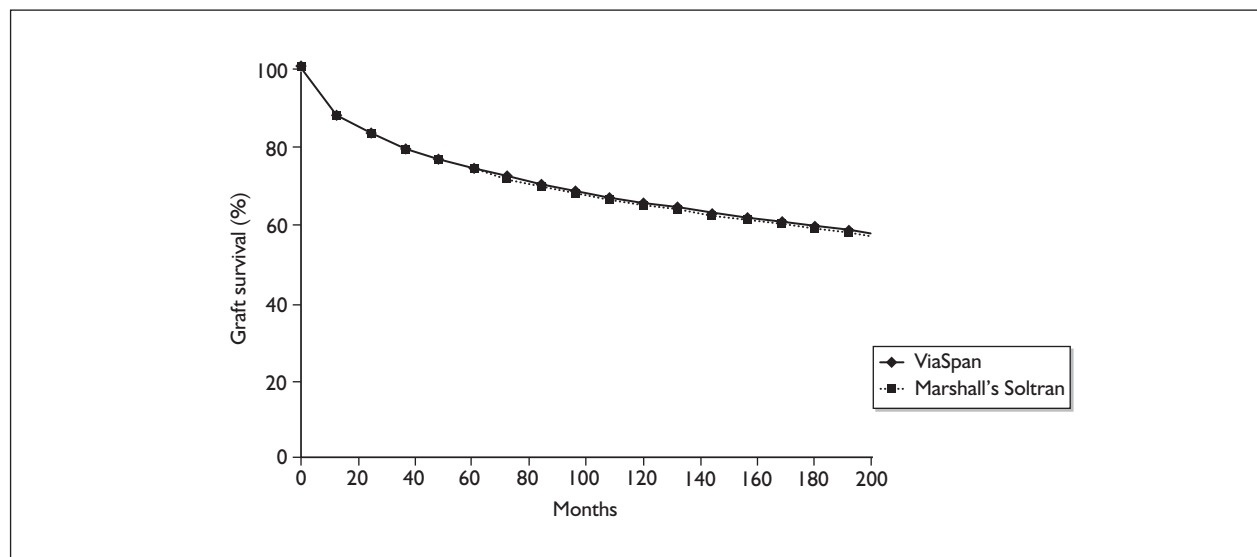
**TABLE 43** Events count output from PenTAG model based on Plata-Munoz et al.<sup>55</sup> data

Description	Marshall's Soltran	LifePort
Immediate graft function (IGF)	167	467
Delayed graft function (DGF)	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 transplant after graft failure	188	74
Re-transplants	129	49
Graft failures after re-transplant	88	34
Deaths in subsequent transplant	39	15
Deaths while waiting for re-transplant	85	34
Deaths on dialysis (transplant unsuited)	186	73

**TABLE 44** Differential input data for compared arms based on Opelz and Dohler<sup>57</sup> data

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

IGF, immediate graft function.

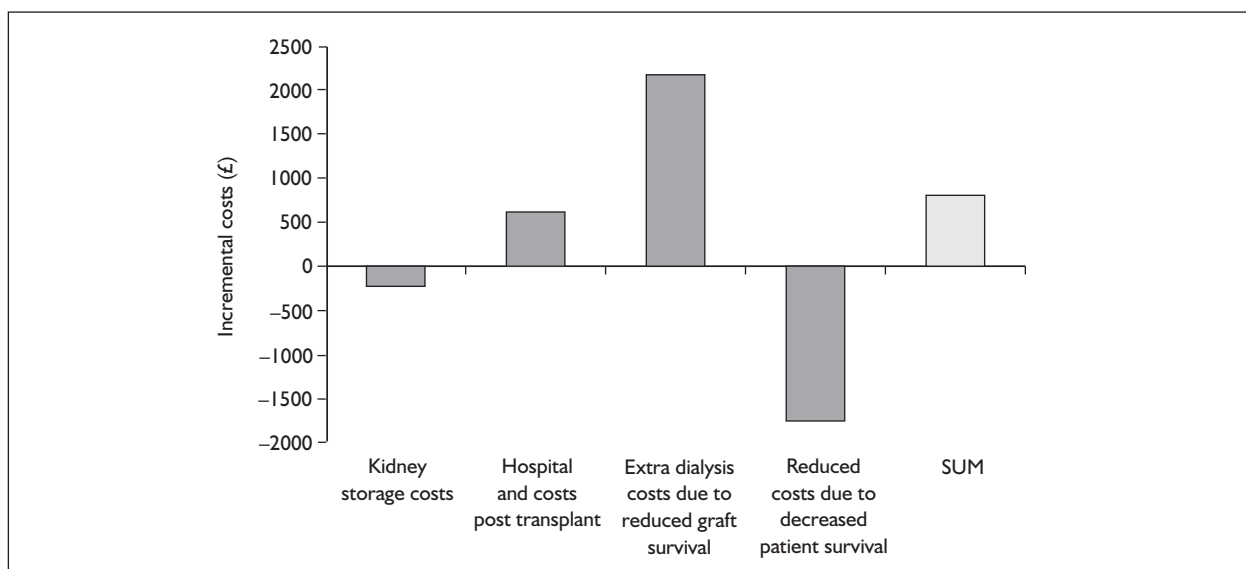
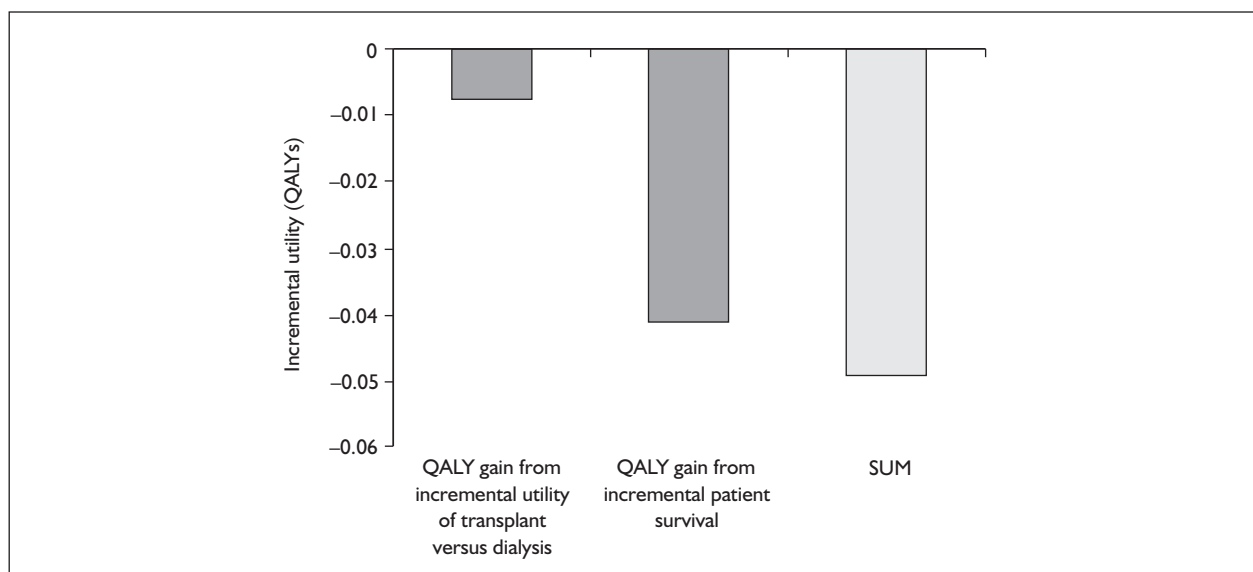


**FIGURE 23** Weibull survival estimates of graft survival for each arm of comparison of ViaSpan and Marshall's Soltran.

**TABLE 45** Base-case deterministic outputs from PenTAG model based on Opelz and Dohler<sup>57</sup> data

	<b>Discounted costs per patient (£)</b>	<b>Discounted benefits per patient (QALYs)</b>	<b>ICER</b>
ViaSpan solution	151,001	8.62	
Marshall's Soltran solution	151,826	8.57	Was dominated
Difference	825	-0.049	
	<b>Undiscounted costs per patient (£)</b>	<b>Undiscounted benefits per patient (QALYs)</b>	<b>ICER</b>
ViaSpan solution	242,714	14.78	
Marshall's Soltran solution	243,658	14.64	Was dominated
Difference	944	-0.141	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

**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. QALY(s), quality-adjusted life-year(s).

**TABLE 46** Events count output from PenTAG model based on Opelz and Dohler<sup>57</sup> data

Description	ViaSpan	Marshall's Soltran
Immediate graft function (IGF)	500	500
Delayed graft function (DGF)	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 transplant after graft failure	242	251
Re-transplants	170	177
Graft failures after re-transplant	116	121
Deaths in subsequent transplant	51	53
Deaths while waiting for re-transplant	107	111
Deaths on dialysis (transplant unsuited)	240	250

### 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 MPT, 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 are 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 in the MPT only two did so (functional DGF and graft survival). 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 shows very small differences

between the arms which, given the uncertainty in the input data, also gives little basis for any confident conclusions. However, ViaSpan was shown to dominate Marshall's Soltran.

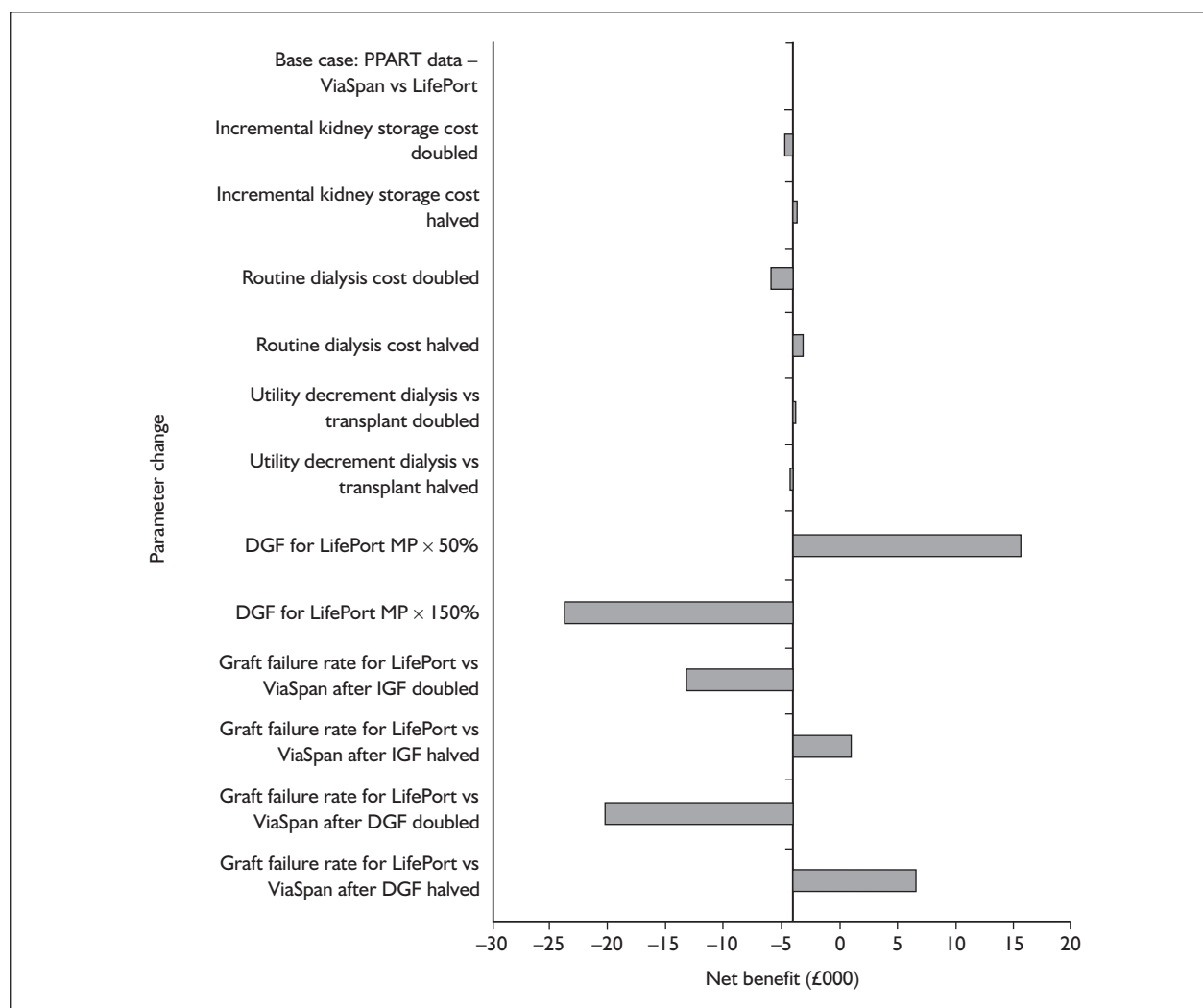
It should be noted that the differential costs of kidney storage associated with the different storage methods are relatively small when compared with the gains that result from any small improvement in effectiveness that can be demonstrated, e.g. through gains in graft survival. However, strong evidence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

### 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.





**FIGURE 26** Net benefit changes to LifePort vs ViaSpan (measured at a willingness to pay of £30,000 per QALY) caused by specific input parameter changes to model – PPART. DGF, delayed graft function; IGF, immediate graft function.

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

$$\text{Net benefit} = wQ - C$$

where  $Q$  = incremental benefit of comparison,  $C$  = incremental cost of comparison and  $W$  = willingness to pay for each additional unit of benefit.

### LifePort versus ViaSpan (PPART study with DCD donor kidney transplants)

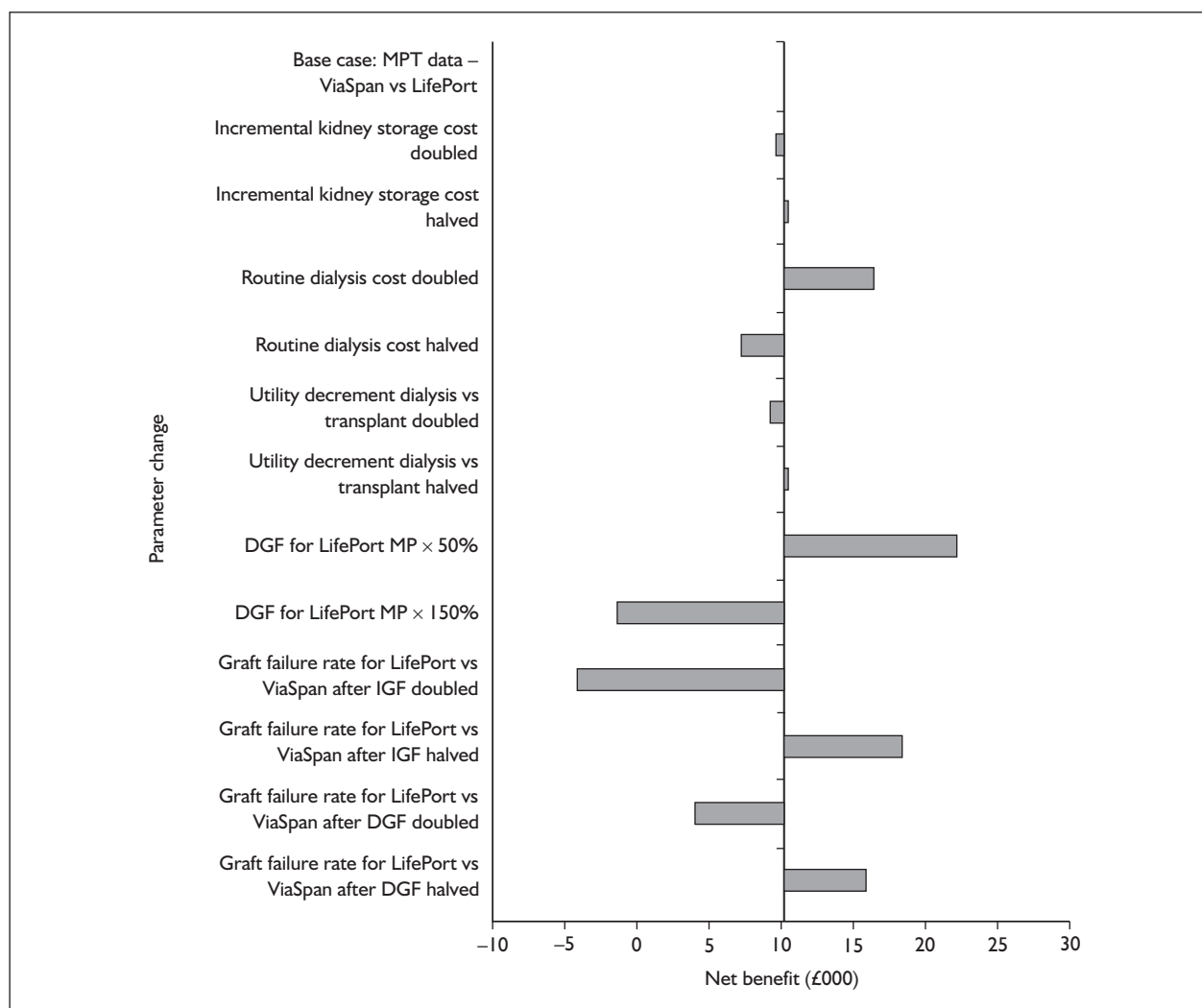
The tornado chart illustrated in *Figure 26* shows the output changes from the base case in the model induced by each of the listed changes in the input

parameter when the model is used to compare ViaSpan with LifePort, based on the data derived from the PPART trial.

In this comparison, the largest impact on 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 greatest 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.

### LifePort versus ViaSpan (MPT in BSD and DCD patients)

*Figure 27* shows the one-way sensitivity outputs from the model for the LifePort versus ViaSpan



**FIGURE 27** Net benefit changes to LifePort vs ViaSpan (measured at a willingness to pay of £30,000 per QALY) caused by specific input parameter changes to model – MPT. DGF, delayed graft function; IGF, immediate graft function.

comparison, based on the data derived from the MPT.

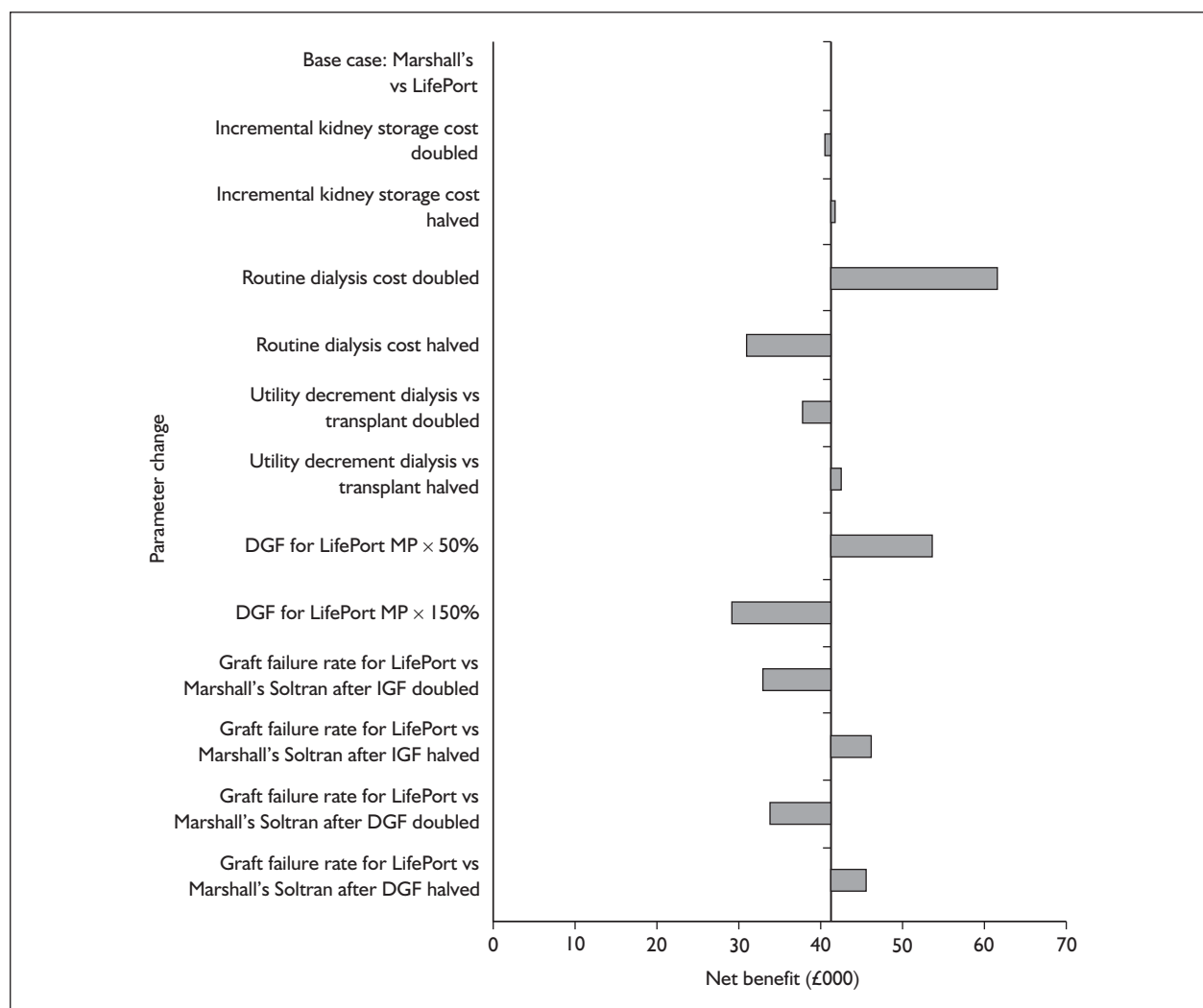
In this comparison the largest impact on net benefit output arises from changes to the effectiveness parameters and changes to dialysis costs. The latter result is explained by the fact that differential effectiveness levels inherent in the input parameters for this comparison mean that dialysis cost 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 on net benefit output. The per kidney storage costs have such little impact on the results that whether a machine is assumed to store 10 kidneys or 100 kidneys in a given year has a very small effect on the cost-effectiveness result (net benefit value). This

also means that these results would be insensitive to scenarios in which centres were assumed to have four or six machines, instead of the two per centre assumed in our model.

### Marshall’s Soltran versus LifePort

Figure 28 shows one-way sensitivity outputs from the model for the Marshall’s Soltran versus LifePort comparison.

For this comparison the largest impact on net benefit output arises from changes to the effectiveness parameters and changes to dialysis costs. High levels of DGF inherent in these 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



**FIGURE 28** Net benefit changes to LifePort vs Marshall's Soltran (measured at a willingness to pay of £30,000 per QALY) caused by specific input parameter changes to the model. DGF, delayed graft function; IGF, immediate graft function.

have had a small but significant effect on the net benefit. Cost of kidney storage has relatively little impact on net benefit output.

### Marshall's Soltran versus ViaSpan

The tornado chart illustrated in *Figure 29* shows one-way sensitivity outputs from the model for the ViaSpan versus Marshall's Soltran comparison.

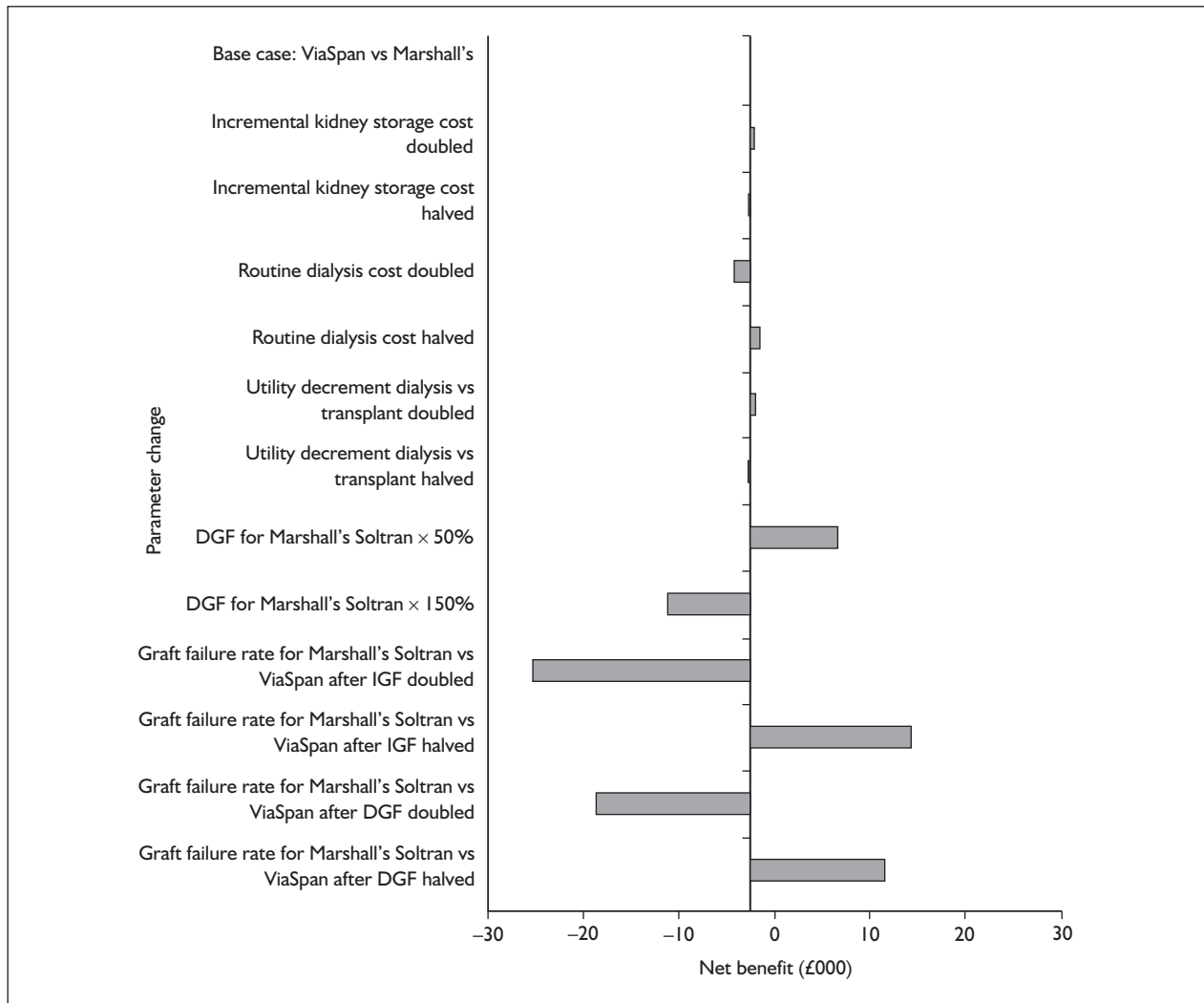
For this comparison the largest impact on net benefit output arises from changes to the effectiveness parameters related to differential graft failure rate for those patients in the model who experienced IGF. This reflects the fact that relatively low levels of DGF are recorded in this study. The lack of any differential impact of DGF on graft survival in the inputs also entails that changes to the HR 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.

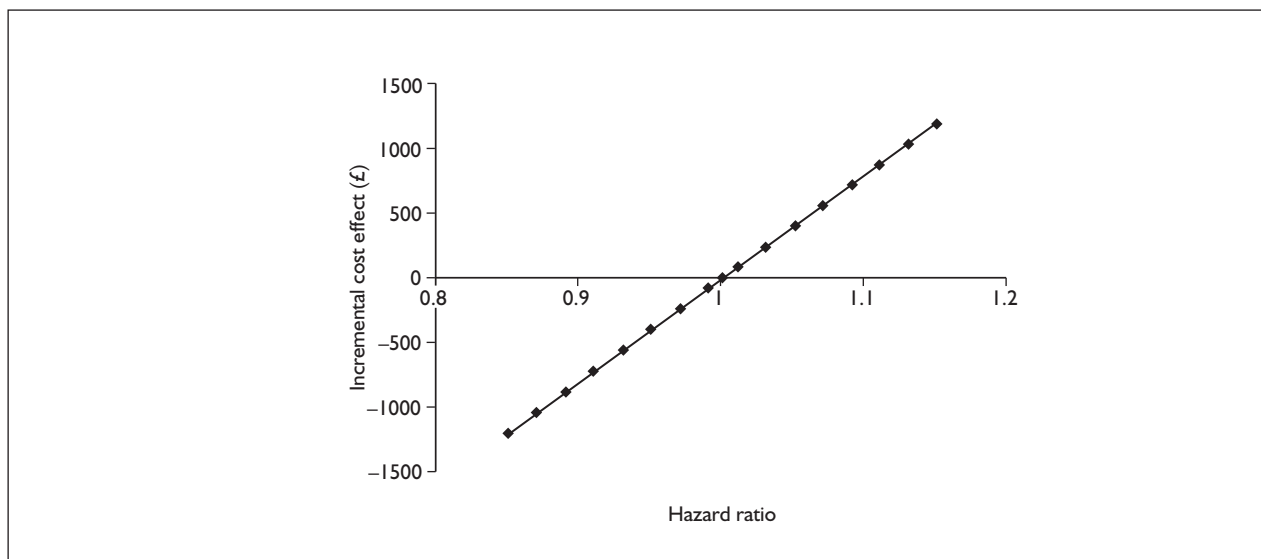
### General observations from the one-way sensitivity analyses

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.



**FIGURE 29** Net benefit changes to Marshall's Soltran vs ViaSpan (measured at a willingness to pay of £30,000 per QALY) caused by specific input parameter changes to the model. DGF, delayed graft function; IGF, immediate graft function.



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

- 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 those experiencing 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 versus DGF). For example, if very few patients in the model experience DGF, then graft survival changes for DGF patients have a small impact on the overall net benefit output.

A simple analysis was conducted using the graft survival data from the standard data set (see *Table 31*), where both comparators were given identical input parameters apart from graft survival, which was varied between the arms according to a HR. It can be seen from *Figure 30* that there is a relatively linear relationship between the HR for graft survival between comparators and cost savings over the range in this analysis. A graft survival HR of 0.1 between arms (which equates to about a 1% graft survival advantage after 5 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 HR for graft survival. Graphs showing the effect on incremental QALYs between arms and overall net benefit are included in Appendix 9.

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 (PSAs) presented below partly explore these potential interaction effects.

## Probabilistic sensitivity analysis

In order to explore the underlying parameter uncertainty on cost-effectiveness for the different comparisons, a 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 drawn randomly 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.

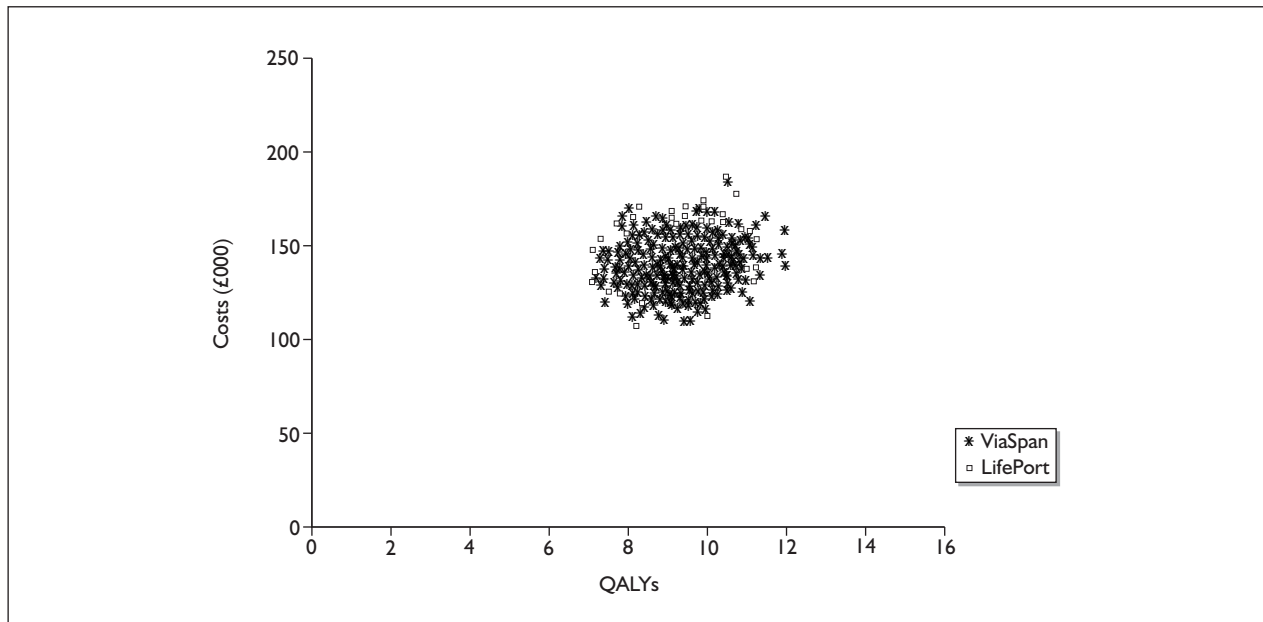
Outputs for the Monte Carlo simulation are shown for each of the comparisons below. For each comparison, these illustrate the incremental cost-effectiveness ratio (ICER) values for 1000 simulated trials. A cost-effectiveness acceptability curve (CEAC) has also been calculated showing, at different levels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

### Probabilistic sensitivity analysis for machine perfusion versus cold static storage *LifePort versus ViaSpan* **LifePort versus ViaSpan – PPART study with DCD donor kidney transplants**

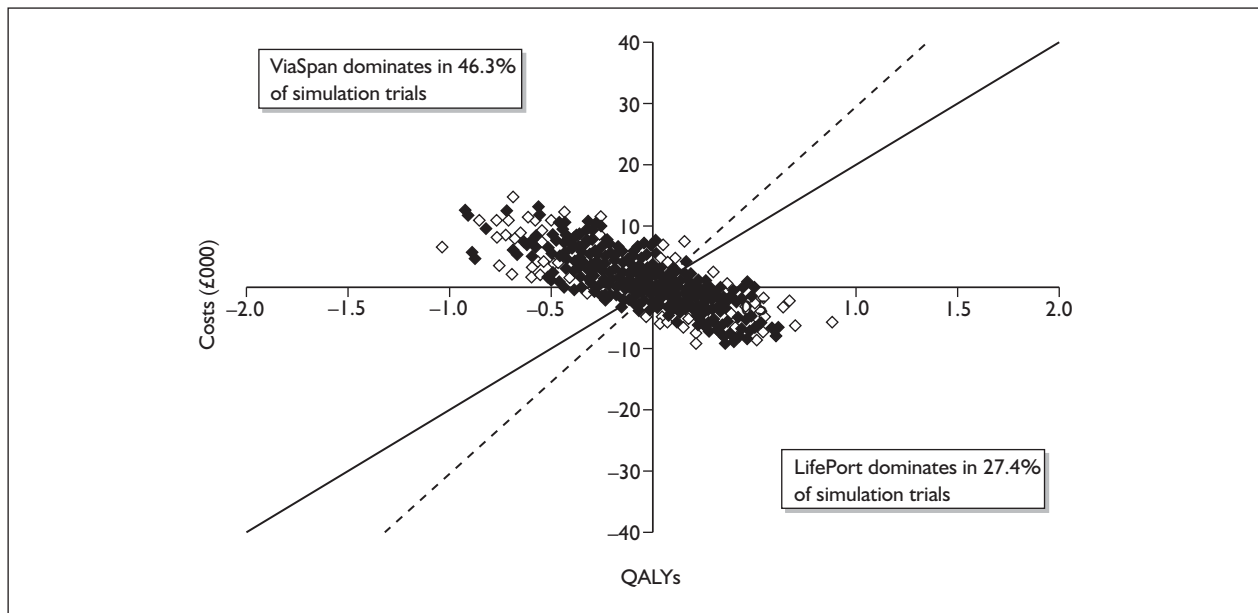
*Figure 31* shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation. These demonstrate the levels of uncertainty associated with the cost and effectiveness outputs from both arms of this comparison, when the parameter uncertainty is included in the model. The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

*Figure 32* represents the outputs shown in *Figure 31* in terms of the incremental costs and benefits of LifePort versus 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 33* shows the 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



**FIGURE 31** Scatter plot from probabilistic simulation based on PPART data for ViaSpan vs LifePort. QALYs, quality-adjusted life-years.



**FIGURE 32** Incremental cost-effectiveness ratio of LifePort vs ViaSpan based on PPART trial data. QALYs, quality-adjusted life-years.

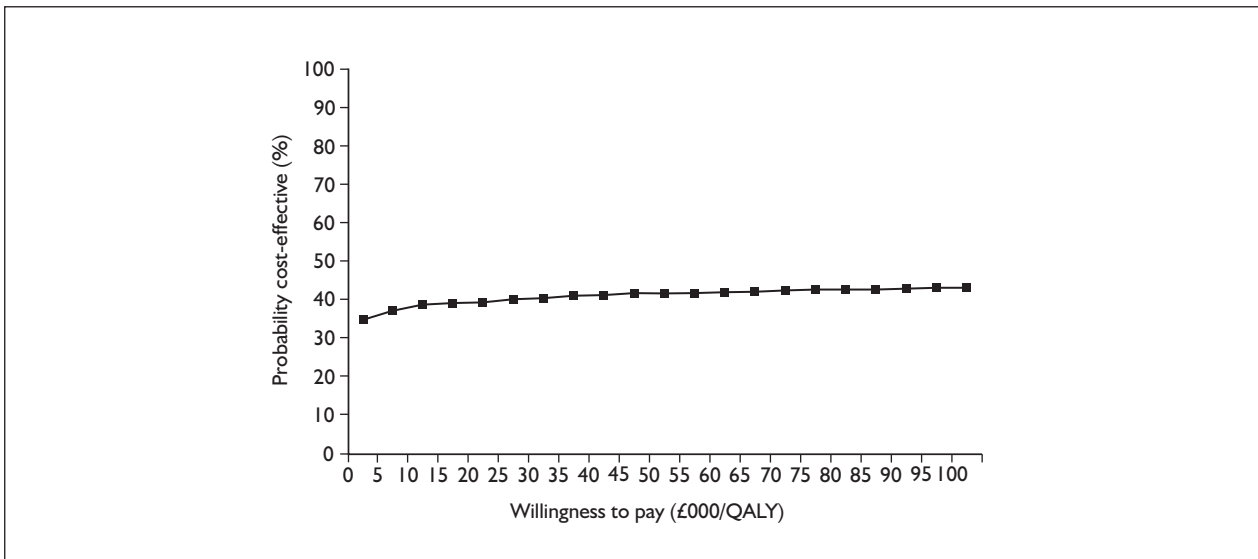
different levels of willingness to pay for each extra QALY conferred by adopting this treatment. This, in turn, shows that over a range of willingness-to-pay thresholds the model predicts around a 40% likelihood that LifePort will be cost-effective when compared with ViaSpan.

**LifePort versus ViaSpan – MPT in BSD and DCD patients**

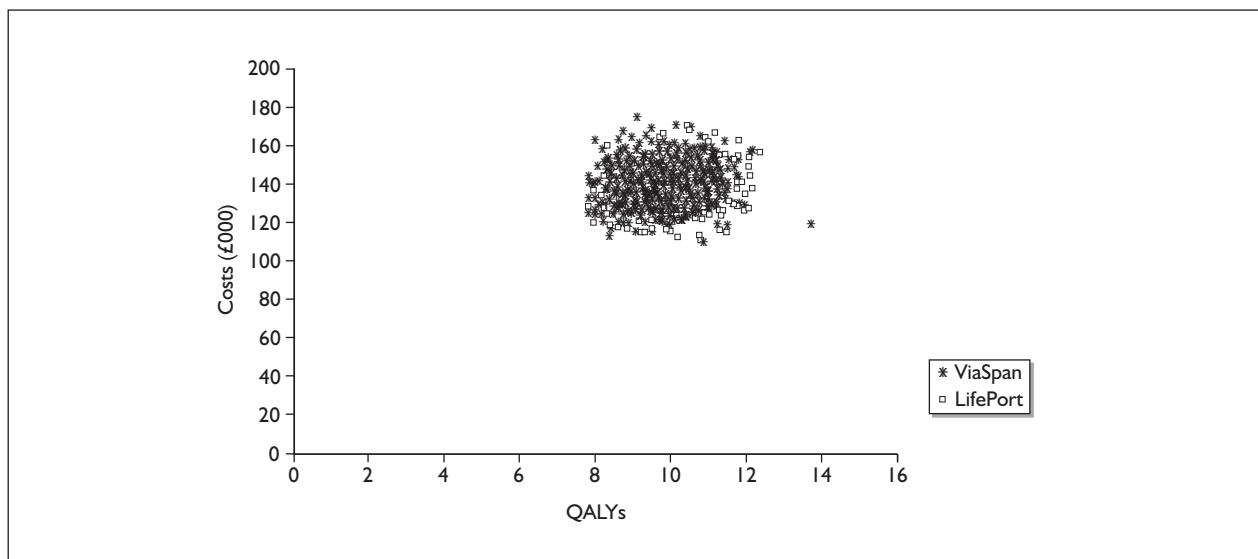
Figure 34 shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation based on the inputs from the MPT

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 35 represents the outputs shown above in terms of the incremental costs and benefits of LifePort versus ViaSpan. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000



**FIGURE 33** Cost-effectiveness acceptability curve for LifePort vs ViaSpan: PPAR trial data. QALY, quality-adjusted life-year.



**FIGURE 34** Scatter plot from probabilistic simulation based on MPT data for LifePort vs ViaSpan. QALYs, quality-adjusted life-years.

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.

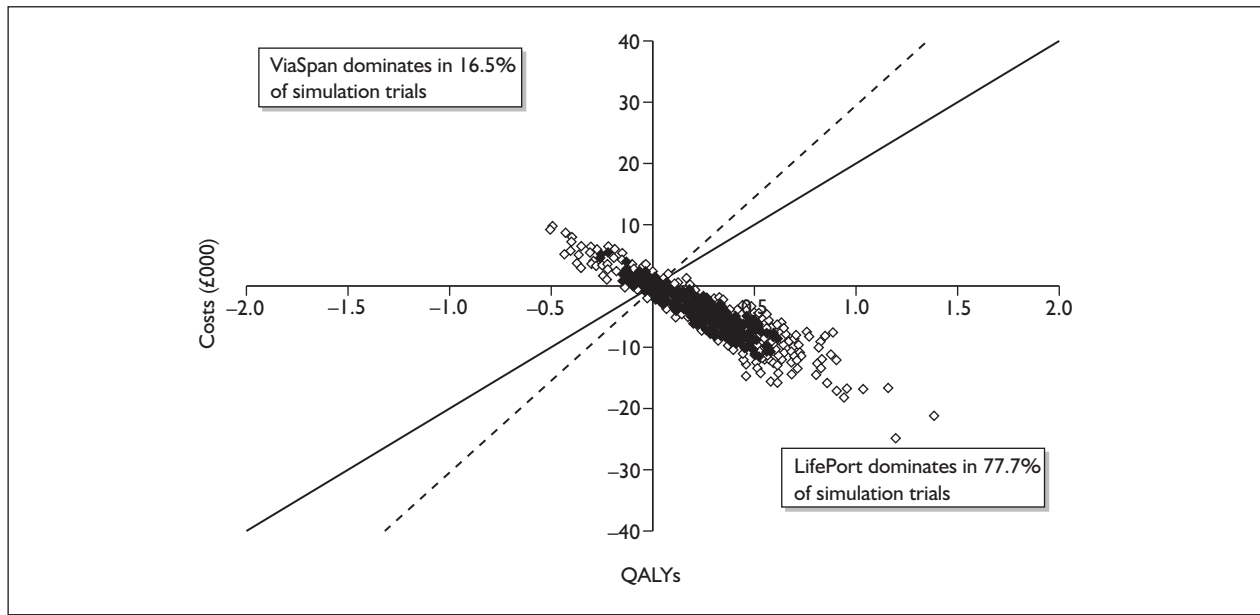
Figure 36 shows the CEAC for the comparison of LifePort with ViaSpan based on the MPT data. This shows the probability based on the PSA outputs that the LifePort storage option is cost-effective over a range of different levels of willingness to

pay for each extra QALY conferred by adopting this treatment. It indicates that there is an 80% probability that LifePort is cost-effective across the willingness-to-pay range.

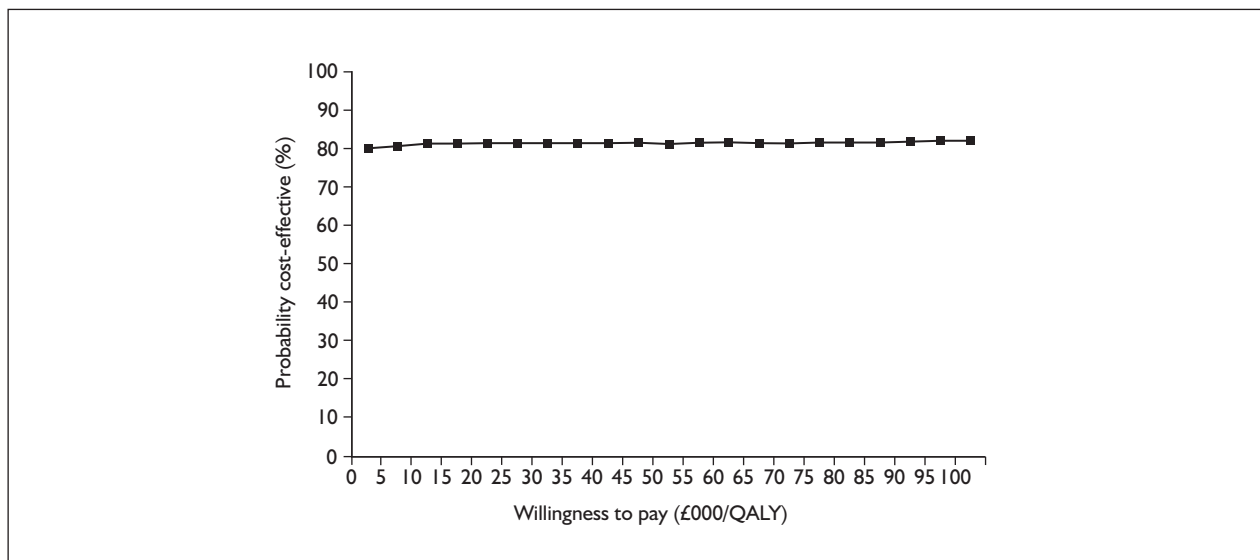
#### **LifePort versus Marshall's Soltran**

Figure 37 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 versus LifePort machine preservation. The distribution of output points illustrates the levels of uncertainty associated with the cost and effectiveness outputs from both





**FIGURE 35** Incremental cost-effectiveness ratio of LifePort MP vs ViaSpan based on MPT data. QALYs, quality-adjusted life-years.



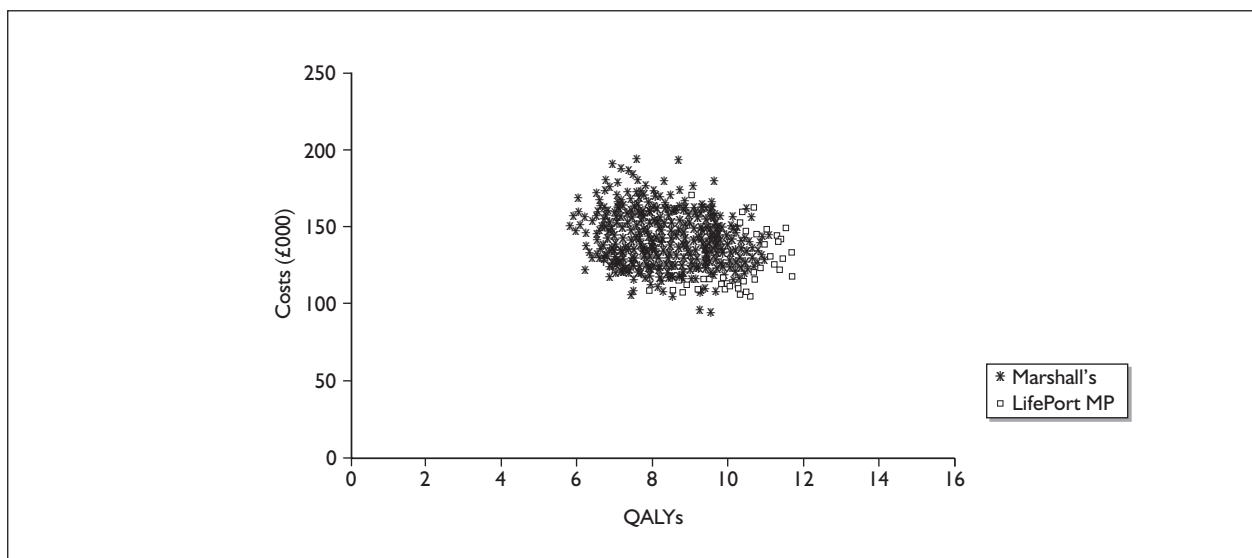
**FIGURE 36** Cost-effectiveness acceptability curve for LifePort vs ViaSpan based on MPT data. QALY, quality-adjusted life-year.

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.

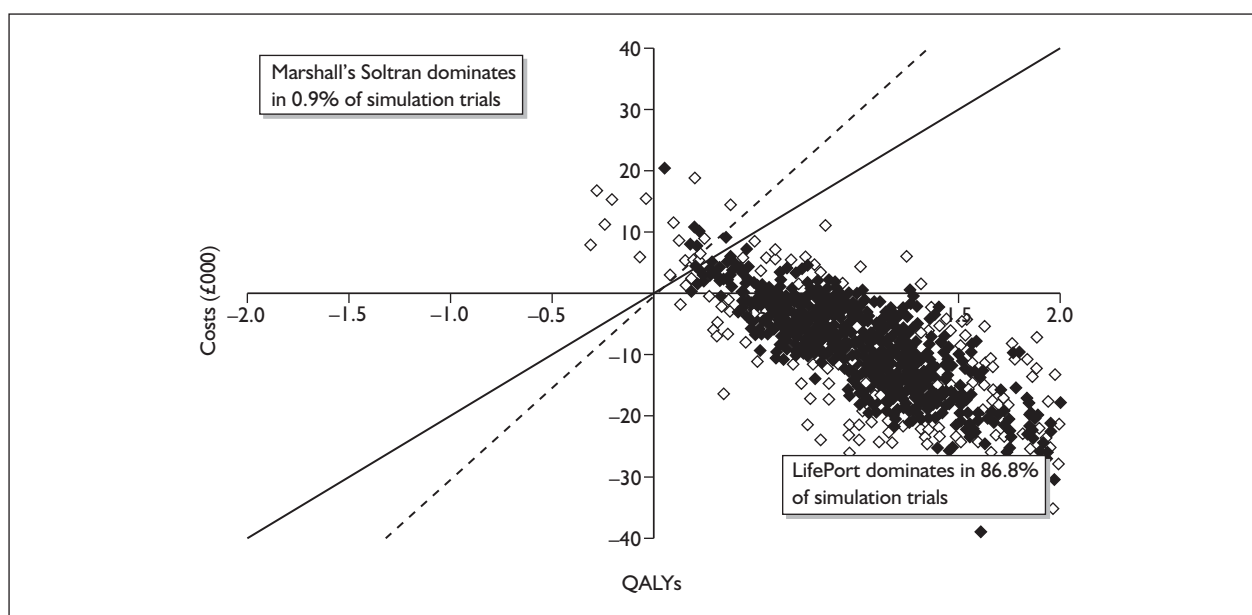
Figure 38 represents the outputs shown above in terms of the incremental costs and benefits of LifePort versus Marshall’s Soltran. Net benefit thresholds are shown for willingness-to-pay thresholds of £20,000 per QALY (solid line) and

£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 Marshall’s Soltran in a great number of the simulation trials.

Figure 39 shows the CEAC 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, these are not RCT data and these outputs should be treated with caution.



**FIGURE 37** Scatter plot from probabilistic simulation for Marshall's Soltran vs LifePort. CS, cold storage; MP, machine perfusion; QALYs, quality-adjusted life-years.



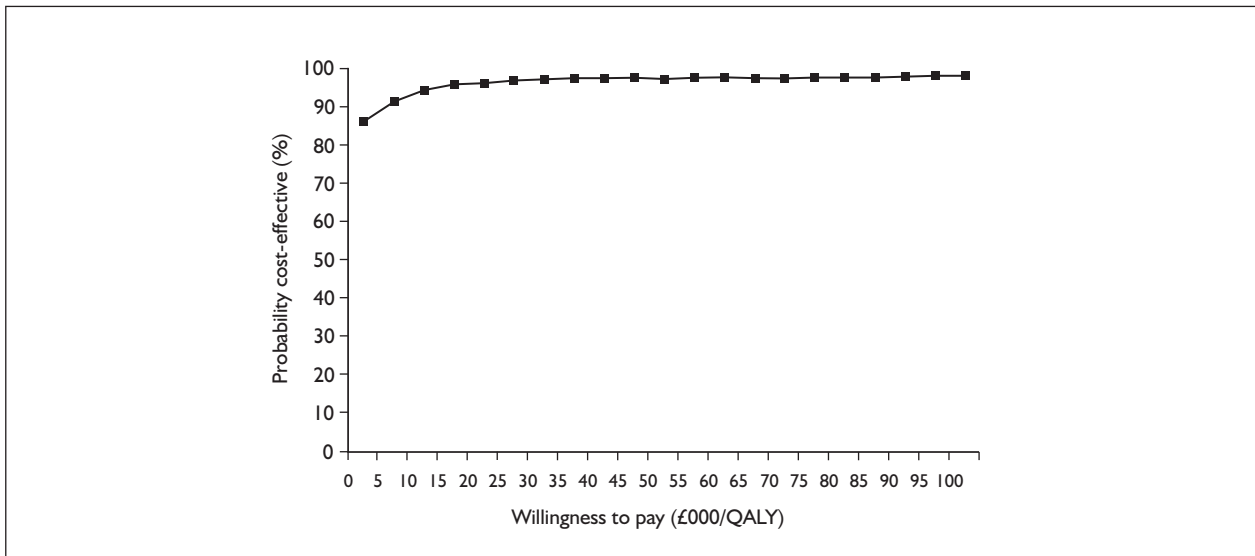
**FIGURE 38** Incremental cost-effectiveness of LifePort vs Marshall's Soltran. QALYs, quality-adjusted life-years.

### Cold storage solution versus cold storage solution ViaSpan versus Marshall's Soltran

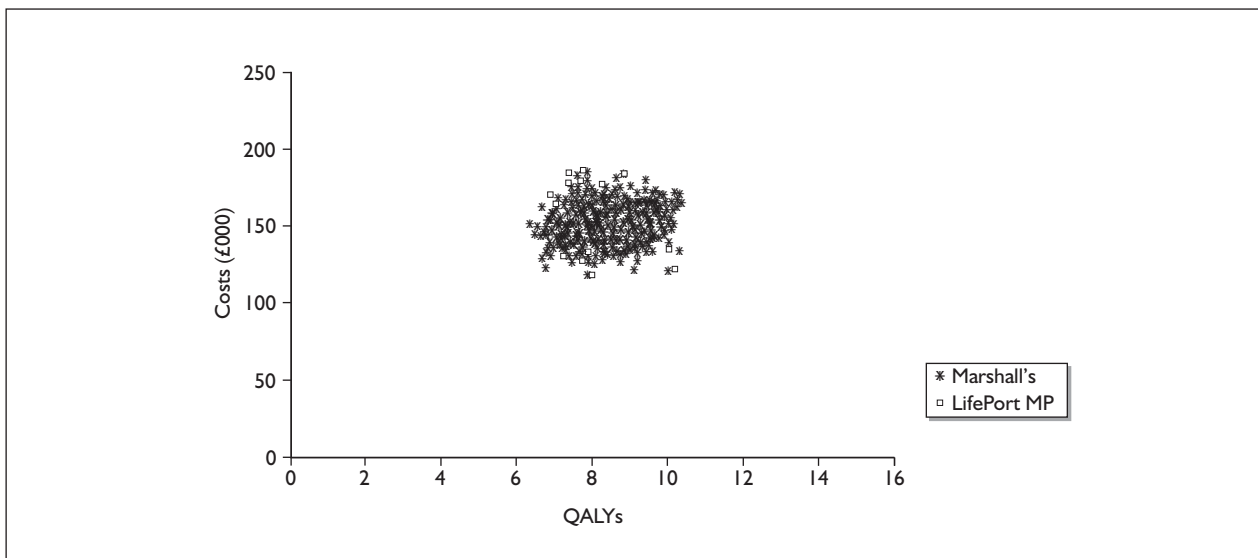
Figure 40 shows the scatter plot outputs from the model for 1000 trial runs of the probabilistic simulation based on the trial data for cold storage with Marshall's solution versus LifePort machine preservation. The distribution of output points illustrates the levels of uncertainty associated with the 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 41 represents the outputs in Figure 40 in terms of the incremental costs and benefits of LifePort versus 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 that of ViaSpan. It should be noted that these outputs are based on a single study.



**FIGURE 39** Cost-effectiveness acceptability curve for LifePort vs Marshall's Soltran. QALYs, quality-adjusted life-years.



**FIGURE 40** Scatter plot from probabilistic simulation for Marshall's Soltran vs ViaSpan. QALYs, quality-adjusted life-years.

Figure 42 shows the CEAC 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.

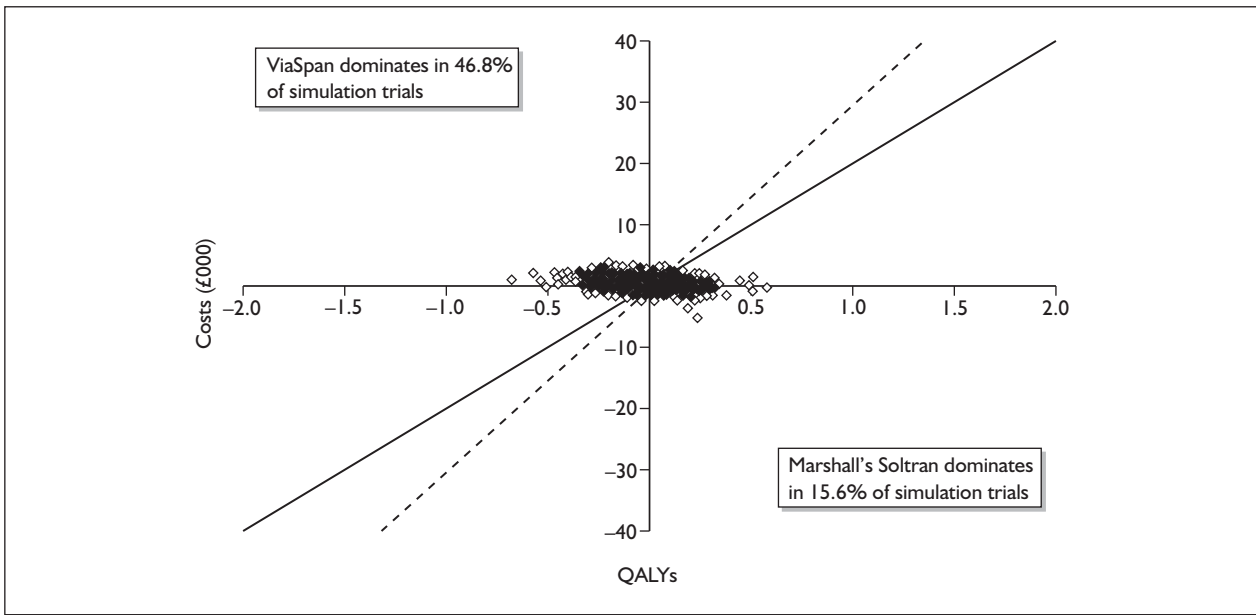
**Summary of probabilistic sensitivity analysis outputs**

In general, because the outputs of the PSA embody the inherent uncertainty associated with model inputs, they provide a more balanced picture of the

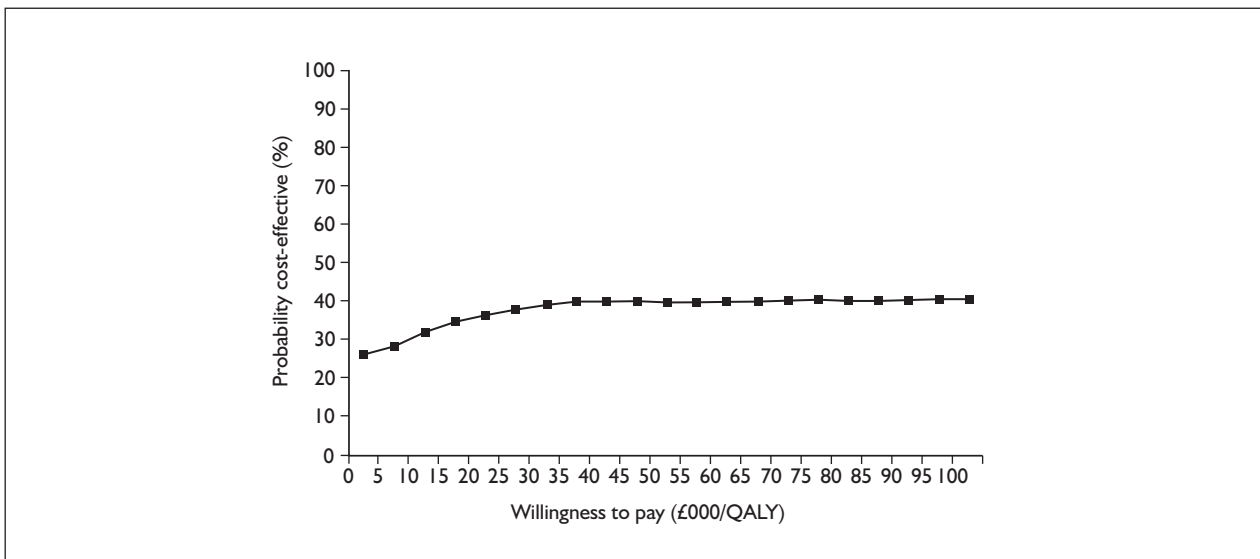
comparisons undertaken in this cost-effectiveness analysis than the simple deterministic outputs.

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



**FIGURE 41** Incremental cost-effectiveness of Marshall's Soltran vs ViaSpan. QALYs, quality-adjusted life-years.



**FIGURE 42** Cost-effectiveness acceptability curve for Marshall's Soltran vs ViaSpan. QALY, quality-adjusted life-year.

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.

## Summary of cost-effectiveness

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 from 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 ViaSpan yield contrasting cost-utility results.
5. The comparison based on the PPART study shows that ViaSpan both is 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 MPT data shows, in contrast, that for the deterministic outputs, LifePort both is cheaper and confers greater QALYs when compared with 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.
6. The comparison of Marshall's Soltran with LifePort indicates, in the deterministic model, that LifePort both is cheaper and confers more QALYs than the use of Marshall's Soltran as a storage method. The PSA analysis confirms this finding; however, the sample size and non-randomised nature of the underlying study data indicate that these outputs should be interpreted with caution.
7. 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's 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 is included in the model.
8. 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.

## Chapter 5

# Assessment of factors relevant to the NHS and other parties

### 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 PNF 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<sup>47</sup> 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.<sup>117</sup> 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  $\alpha$ -glutathione-S-transferase (GST) concentrations

may be a means of predicting which kidneys will not work post transplant.<sup>45,118–120</sup>

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.<sup>45,121–131</sup> A number of different methods for testing viability had been evaluated, including perfusion flow rates, biomarkers and weight gain of the graft.

Overall, the debate continues. Matsuno and colleagues<sup>129</sup> believe that perfusion flow can predict PNF rates in DCD grafts, but Sonnenday and colleagues<sup>131</sup> doubt the reliability of perfusion parameters to guide kidney selection. Balupuri and colleagues<sup>45</sup> 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%. The use of multiple measures was also advocated by Kosieradzki and colleagues,<sup>121</sup> who developed a set of parameters (tissue flow, vascular resistance, lactate dehydrogenase 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 that of Metcalfe and colleagues,<sup>123</sup> who reported that IRVR did not predict PNF, and Mozes and colleagues,<sup>128</sup> who found that renal resistance was not a reliable predictor of graft viability. Gok and colleagues<sup>124–127</sup> looked at alternative biomarkers 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). Wilson and colleagues<sup>130</sup> explored whether the varying weight of perfused kidneys could be used to predict viability, but found that this was not so. More recently, de Vries and colleagues<sup>122</sup> 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.

Further work is required to determine better ways of assessing organ viability after retrieval – particularly kidneys from uncontrolled non-heart-beating donors (a subgroup 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.

### **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, followed by some bench work before implantation. 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 watertight. 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 do 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 Safety, Chapter 3, 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.

### **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 that owns the machine. Thus, while there is a national system for sharing BSD organs, including a nationally organised supply of storage equipment (boxes and related consumables are provided by the NHSBT), 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<sup>46</sup> has indicated that organ retrieval and transport arrangements (including the central employment of transplant co-ordinators by the NHSBT) 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.

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.<sup>57,70</sup>

### **Impact of dialysis versus 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.<sup>26,104</sup> For example, in Canadian patients, Laupacis and colleagues<sup>104</sup> found that the proportion of people in employment increased from 30% before transplantation to 45% after transplantation. Furthermore, of those with functioning grafts 2 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,<sup>36</sup> 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% versus 26%).

Additionally, it is inevitable that people on HD (except HHD) will, in general, only be able to work part-time. Satellite unit or hospital HD is usually provided as three sessions per week, with each session typically lasting between 3 and 4 hours.<sup>132</sup>



## Chapter 6

### 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.

#### Principal findings

##### Clinical effectiveness

###### *Machine perfusion versus cold storage*

Unfortunately we are unable to provide a clear answer to the issue of comparing machine perfusion with cold storage in DCD kidneys. There were two recent RCTs of this comparison, one of which (PPART,  $n = 90$ ) (academic-in-confidence information removed), while the other (MPT,  $n = 672$ ) produced a non-significant result in favour of machine perfusion for most short-term outcomes (e.g. DGF, PNF), but showed a small significant difference in graft survival at 12 months in favour of machine perfusion (HR at 12 months 0.39,  $p = 0.03$ ). However, 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 five transplant centres in the UK) (academic-in-confidence information removed).

In contrast, the MPT included mostly BSD and some DCD donor kidneys (294 BSD, 42 DCD). Although there was no significant difference in DGF or PNF between the two storage methods, their 12-month follow-up results indicate improved graft survival with machine perfusion. A subgroup analysis included additionally-recruited DCD participants ( $n = 82$ ), but also failed to show any

difference in DGF (their designated primary outcome) between types of donor. It would therefore be speculative to extrapolate the full trial findings, using largely BSD donor kidneys, to DCD kidneys and their recipients. From the MPT, for the key outcome of 1-year graft survival it does seem that there may be an advantage from machine perfusion in BSD-donated kidneys. Other outcomes fail to show a benefit for either storage method, at least when CIT is between about 3 and 30 hours (mean 15 hours). It is paradoxical that this trial, with mostly BSD kidneys, gives stronger indications of the relative effectiveness of machine perfusion than the trial in DCD kidneys (which would, theoretically, be expected to benefit more from the technology). This result may not hold with longer cold ischaemic or at post-transplant follow-up times.

The only study we found comparing LifePort with Marshall's Soltran (Plata-Munoz and colleagues<sup>55</sup>) had many potentially confounding factors: it wasn't randomised; for the first 2 years all kidneys were perfused with Marshall's Soltran and 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 7 years older than 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 study's 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 CITs.

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 not finished collecting and analysing their results and/or have not published them fully.

No existing systematic reviews that met our assessment criteria were identified.

## Cost-effectiveness

### 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,<sup>47</sup> 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 DGF 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). The other economic evaluation, by Costa and colleagues,<sup>49</sup> 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.

### 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 versus cold storage with Marshall's Soltran; and cold storage with ViaSpan versus cold storage with Marshall's Soltran. In each case, however, the base-case deterministic results should be viewed with considerable caution, owing to both 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 versus cold storage

*Deterministic analysis* 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 MPT, 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 QALYs and lower lifetime costs than machine perfusion. However, the effectiveness data used for this comparison are 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 PSAs 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 (88%) 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 PSAs 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 versus cold storage**

*Deterministic analysis* When Marshall's Soltran cold storage solution is compared with 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.

### **Strengths and limitations of the systematic review of clinical effectiveness**

#### **Strengths**

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

#### **Limitations**

- The search strategy was limited to English language publications owing 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 MPT included DCD donors ( $n = 84$ ), this trial was predominantly of BSD donors ( $n = 588$ ). Subgroup 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 5 of the 11 included studies were RCTs; this meant that some of the comparisons (LifePort versus RM3, LifePort versus Marshall's Soltran and Marshall's versus 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.
- (Academic-in-confidence information removed.) We do not know what effect this may have had on the results.

### **Strengths and limitations of the cost-utility analysis**

#### **Strengths**

- 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 IGE, DGF and PNF, 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 DGF (e.g. more days of in-hospital dialysis) and PNF (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 lifelong return to dialysis.

- The analyses make best use of recently available effectiveness data from two RCTs of machine perfusion with LifePort compared with cold storage with UW ViaSpan. Wherever possible, our four cost–utility analyses have 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 RRT patients (the UKRR) or kidney transplant recipients (annual activity reports or specific data supplied by NHSBT 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 DGF, PNF and graft survival.

## Limitations

- 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 MPT had to be read from a graph, as this information was not available in the text; this may have led to an under- or overestimate 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).<sup>26,33,87</sup> The Greiner *et al.* study,<sup>111</sup> 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 2 years post transplant (although with smaller respondent numbers at 1 and 2 years' follow-up, which may have introduced some bias). The Swedish study,<sup>112</sup> which we could alternatively have used, was also based on EQ-5D health status assessment in both transplant recipients and those on dialysis. It would have provided a substantially larger estimated utility decrement for dialysis versus a functioning transplant (of 0.21 with PD and 0.44 with HD). However, this was in three smaller ( $n = 27$ ) but matched samples of transplant, HD and PD patients. Also, the difference between HD and living with a kidney transplant is very high relative to other values in the literature and, contrary to most other studies,<sup>22,133,134</sup> also assesses quality of life on PD to be much better than on HD.

- Cost of being on dialysis. Although, in general, we have been able to use good data in the UK on the mix of RRT 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 HD or different forms of PD, 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 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 the NHSBT on the specific immunosuppressive drug regimes being used with kidney transplant recipients, and hopefully have 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. As 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, they were 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 with ViaSpan indicate their equivalence.

### Uncertainties

The primary area of uncertainty in this assessment is whether machine perfusion generates improvements in the short and long term in graft survival compared with cold storage. Despite a threefold difference in the estimated per kidney cost of storage between LifePort and ViaSpan,

the absolute difference (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 (1) 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 intraregionally retrieved organs; and (2) 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 DGF 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 CIT, deceased donor type or other factors. Although, for one of our cost–utility analyses (PPART trial of LifePort versus UW ViaSpan, where only 3-month outcome data were available) we used historical (NHSBT-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.

## Other relevant factors

### Determinants of graft survival

As reported earlier, Opelz and Dohler<sup>57</sup> analysed data from the multinational 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 and 2005 ( $n = 91,674$ ). They found that increasing levels of cold ischaemia up to 18 hours did not appreciably affect graft survival. However, at 19–24

hours there was a RR incurred of 1.09, 25–36 hours RR 1.16 and > 36 hours RR 1.30 ( $p < 0.001$ ). However, this gradual decrease in graft survival with CIT > 18 hours 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 to 1.39,  $p = 0.011$ ).

They also found that the quality of human leucocyte antigen (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 an even shorter ischaemic time of 0–3 hours bring rates of graft survival close to those of living donors.<sup>135</sup>

## Chapter 7

# 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 trials’ results is relied upon. The two RCTs for this comparison (academic-in-confidence information removed); Moers *et al.*’s 12-month graft survival findings were statistically significant. 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 people’s lifetimes.

The effectiveness data used in the model for the comparison of LifePort with 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 owing 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 (1-year graft survival) outcomes.

### 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 potential solution may be for the NHSBT 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.<sup>46</sup> The NHSBT 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.

### Suggested research priorities

A number of research priorities have emerged from this assessment:

1. As graft and patient survival have multifactorial determinants, there is a need for sufficiently large RCTs of comparators of interest to allow for appropriate analysis of subgroups, which may in turn better identify those combinations of donor kidney, types of recipient or storage characteristics (such as length of CIT) in which machine preservation appears to be most effective at improving short-term and long-term outcomes.
2. If evaluators of kidney preservation technologies are to rely upon DGF 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 CIT, donor type and tissue matching).
3. 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.

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 comorbidities, 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.

In addition, the NHSBT 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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### Competing interests of Expert Advisory Group

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

### Contribution of authors

Jacob Akoh (Consultant Surgeon) provided clinical input into the design of the model, advised on clinical matters and contributed to the editing of the report. Rob Anderson (Senior Lecturer in Health Economics) 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, and was overall director of the project and is guarantor of the report. Mary Bond (Research Fellow) provided overall project management, wrote the protocol, assessed abstracts and titles for inclusion and exclusion, conducted the effectiveness systematic review, contributed to writing and editing the

report, and contributed to the design of the model. Martin Hoyle (Research Fellow) provided support in the execution of the economic model and checked calculations within it, and contributed to editing of some parts of the report. Tiffany Moxam (Information Scientist) wrote and ran the search strategies for clinical and cost-effectiveness, and assessed abstracts and titles for inclusion and exclusion. Martin Pitt (Senior Research Fellow) led the design, development and execution of the economic model, and contributed to writing and editing the report (Chapter 4).

### About PenTAG

The Peninsula Technology Assessment Group (PenTAG) 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 multidisciplinary 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:

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. *Health Technol Assess* 2002;**6**(31).

The effectiveness and cost-effectiveness of imatinib (STI 571) in chronic myeloid leukaemia: a systematic review. *Health Technol Assess* 2002;**6**(33).

Systematic review of endoscopic sinus surgery for nasal polyps. *Health Technol Assess* 2003;**7**(17).

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol Assess* 2004;**8**(3).

The effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. *Health Technol Assess* 2004;**8**(28).

Do the findings of case series studies vary significantly according to methodological characteristics? *Health Technol Assess* 2005;**9**(2).

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic modelling. *Health Technol Assess* 2005;**9**(29).

The effectiveness and cost-effectiveness of dual chamber pacemakers compared with single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(43).

The effectiveness and cost-effectiveness of surveillance of Barrett's oesophagus: exploring the uncertainty. *Health Technol Assess* 2005;**10**(8).

The cost-effectiveness of testing for hepatitis C (HCV) in former injecting drug users: systematic review and economic evaluation. *Health Technol Assess* 2005;**10**(32).

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation. *Health Technol Assess* 2005;**11**(18).

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation. *Health Technol Assess* 2005;**11**(45).

The effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model. *Health Technol Assess* 2005;**11**(47).

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over. *Health Technol Assess* 2007;**12**(19).

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess* 2007;**12**(20).

The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technol Assess* 2009 (in press).



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# Appendix I

## 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 of different methods of storing donated kidneys. Databases searched for the clinical effectiveness sections of the review are listed below with the search strategy used.

### 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. ADJ ORGAN ADJ TRANSPLANT\$6).TW.
8. (NO
9. 6 AND 3
10. 1 OR 2 OR 7
11. (SOLID N-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.
12. (DONOR\$2 OR DONOUR\$2) NEAR (MARGINAL OR EXPANDED OR EXTENDED OR HIGH-RISK)
13. 9 OR 10 OR 11
14. 12 AND 6
15. 13 OR 8
16. PULSATILE-FLOW#.DE.
17. MACHINE\$2.TW. AND PULSAT\$4.TW.
18. LIFEPORT.TW.
19. RM3.TI,AB.
20. (MACHINE\$2 OR PULSAT\$4).TW. AND (PERFUS\$4 OR PRESERV\$4 OR SYSTEM).TW.
21. WATER\$2 ADJ RM3
22. KIDNEY.W..MJ.OR RENAL OR KIDNEY\$3
23. WATER\$2 NEAR PRESERVATION AND 21
24. WATER\$2 ADJ MEDICAL ADJ SYSTEM\$2



25. WATER\$2 NEXT RENAL\$2
26. 24 AND 21
27. KIDNEY\$2 NEXT TRANSPORT\$4 AND 22
28. UNIVERSITY ADJ OF ADJ WISCONSIN OR UW ADJ SOLUTION\$2
29. CELSIOR
30. MARSHALL'S NEAR SOLUTION
31. VIASPAN
32. SOLTRAN
33. BELZER\$
34. PERFUSION#.W..DE. AND (machine OR pulsat\$4).TW.
35. (cold OR ice OR static OR hypo OR thermic).TI,AB. AND (storage OR preserv\$5).TI,AB
36. (histidine AND tryptophan) OR HTK
37. 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
38. 36 AND 14
39. LG=EN
40. 37 AND 38
41. PT=EDITORIAL OR PT=LETTER
42. ANIMAL=YES NOT HUMAN ADJ =YES
43. 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 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. 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 to date)**

Dialog DataStar: online 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 OR 4 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 to date)**

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, Science & Technology edition) (1990 to date)**

Years searched: 2003 to date

Search date: 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 (HTA)  
database on the CRD website**

Search date: 29 November 2007  
Search strategy same as for DARE

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

**NRR (National Research Register)**

2007, issue 4  
Source: [www.nrr.nhs.uk/](http://www.nrr.nhs.uk/)  
Search date: 21 November 2007  
NB Includes information added until September 2007

**ReFeR: Research Findings  
Register (now withdrawn)**

Source: [www.refer.nhs.uk/](http://www.refer.nhs.uk/)  
Search date: 21 November 2007

**Current Controlled Trials including  
MRC Trials database**

Source: <http://controlled-trials.com/>  
Search date: 20 November 2007

**US Food and Drug Administration (FDA)**

Source: [www.fda.gov/](http://www.fda.gov/)  
Search date: 5 May 2008

- (a) Center for Drug evaluation and Research: Adverse Events reporting system.
- (b) Center for Devices & Radiological Health

**Medical Healthcare &  
Regulatory Authority**

Source: [www.mhra.gov.uk/](http://www.mhra.gov.uk/)  
Search date: 5 May 2008

**Databases and their search  
terms for the systematic review  
of economic evaluations  
MEDLINE (1950 to date)**

Dialog DataStar: online version  
Search date: 8 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: online 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 above)

**ISI Web of Knowledge (SCI-  
Expanded) (1970 to date)**

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.

**Databases and search terms  
for the review of quality of  
life and utility studies  
MEDLINE (1950 to date)**

Dialog DataStar: online 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.

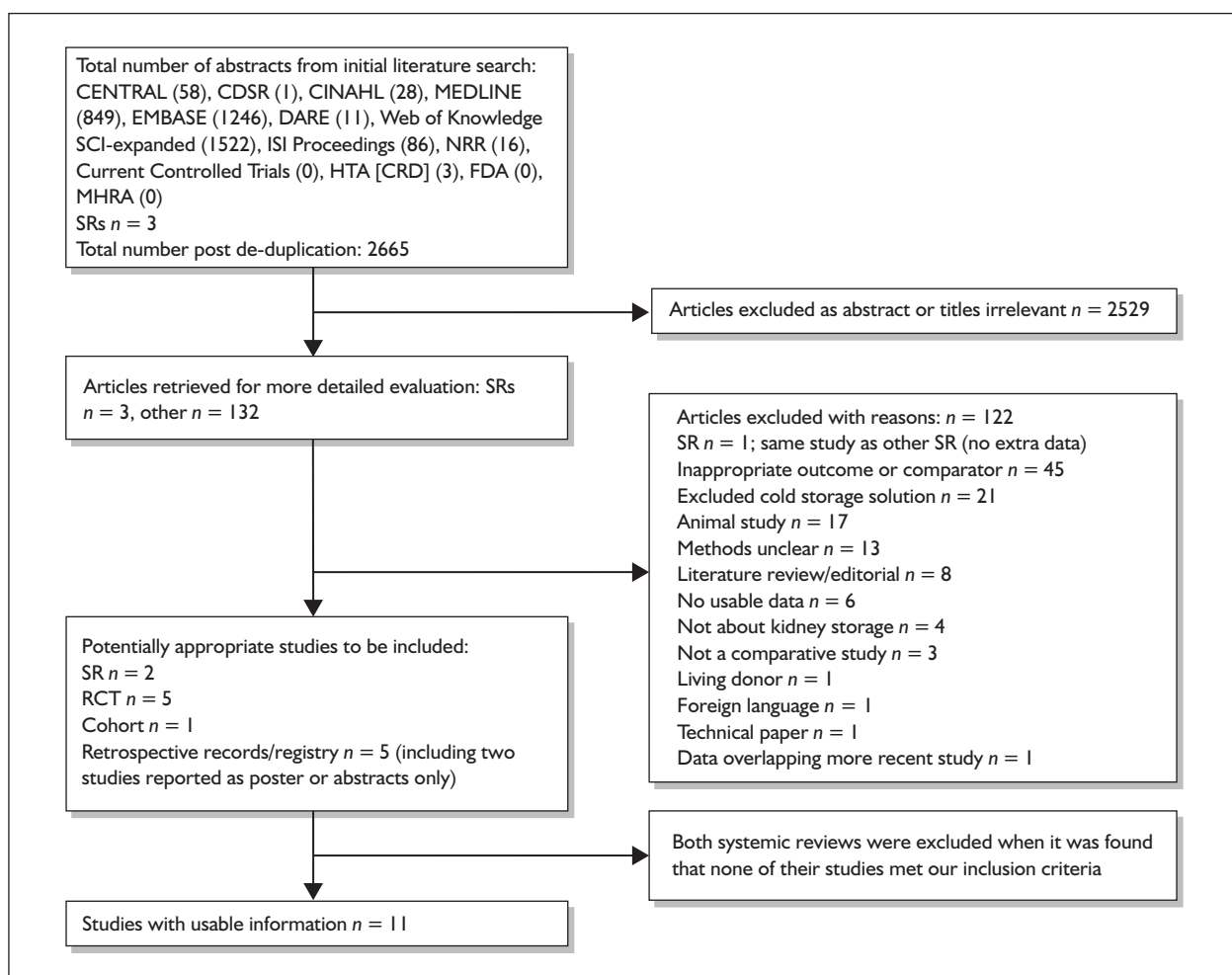
TTO.TI,AB. OR VAS.TI,AB.

(VISUAL ADJ (ANALOG OR ANALOGUE)).TI,AB.

(PATIENT ADJ PREFERENC\$2).TI,AB.

## Appendix 2

### Study identification



**FIGURE 43** QUOROM flow diagram for the identification of studies in this systematic review. RCT, randomised controlled trial; SR, systematic review.



# Appendix 3

## Data extraction tables

## STORAGE OF DONATED KIDNEYS: Data Extraction

Moustafellos et al. (2008)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Retrospective record review	<b>ARM 1:</b> <b>LifePort</b>	<b>Number enrolled:</b> 36	<b>Primary outcome measure:</b> Immediate renal function
<b>Country (countries):</b> UK	Intervention: Machine perfusion Number enrolled: 18	<b>Attrition / dropout:</b> -	<b>Secondary outcome measure(s):</b> Delayed graft function Length of hospitalisation Mean creatinine levels at discharge
<b>Number of centres:</b> 1	<b>ARM 2:</b> <b>University of Wisconsin cold storage solution</b>	<b>Inclusion criteria:</b> Class III or IV DCD donors	<b>Method of assessing outcomes:</b> DGF not defined
<b>Recruitment dates:</b> 2004-2006	Intervention: Cold storage Number enrolled: 18	<b>Exclusion criteria:</b> -	
<b>Length of follow-up:</b> -			
<b>Source of funding:</b> not reported			

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	LifePort				University of Wisconsin cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age years -recipient	18	-	36.3[a]	0	18	-	54.5[b]	0	-18.2	0	<0.001[c]
Gender (n male)	18	13	-	-	18	10	-	-	-	-	-
HLA mismatches	18	-	2.4	0	18	-	2.1	0	-	-	-

#### Notes

[a] range (20-66)

[b] range (36 -69)

[c] student's t-test (calculated by reviewer)

### RESULTS

Outcome	LifePort				University of Wisconsin cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Cold ischemia (mins)	18	-	909	-	18	-	999	-	-90	0	<0.001[b]
Creatinine (umol/L at discharge)	18	-	385.6	-	18	-	503.1	-	-118	0	<0.001[b]
Death due to infection	18	1	-	-	18	0	-	-	3	4.96	0.468[a]
DGF RR	18	5	-	-	18	16	-	-	0.313	1.48	<0.001[a]
Hospitalisation (days)	18	-	8.1	1.8	18	-	14.1	3.1	-6	0.845	<0.001[b]
IRF	18	13	-	-	18	2	-	-	6.5	1.98	<0.001[a]
Rejection of graft	18	0	-	-	18	0	-	-	1	7.2	1.000[a]

#### LOSS OF GRAFT

Post-operative period	18	0	-	-	18	0	-	-	1	7.2	1.000[a]
Surgical technique/preparation	18	-	-	-	18	0	-	-	1	7.2	1.000[a]

#### Notes

[a] chi-square test (calculated by reviewer)

[b] student's t-test (calculated by reviewer)

### ASSESSMENT OF STUDY QUALITY

1. Were inclusion criteria appropriate?  
YES
2. Was the method of selection reported?  
NO
3. Was the method of allocation reported?  
NO
4. were I and C groups treated the same?  
NO - the groups received different induction therapies
5. Were I and C groups similar at baseline?  
NO - The cold storage group were older by an average of 18 years
6. Were assessors blinded to allocation?  
NOT REPORTED



**STORAGE OF DONATED KIDNEYS: Data Extraction****Moustafellos et al. (2007)**

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7. **Was the follow up time adequate?**  
NOT REPORTED
8. **How were missing data accounted for?**  
NOT REPORTED
9. **Were confounders accounted for in analysis?**  
NOT REPORTED
10. **Was inter centre variability reported?**  
NA
11. **Are the results generalisable?**  
NO - method of allocation to group is unknown (not randomised), the groups have baseline differences and the numbers are small (36)
12. **Are conflict of interests declared?**  
NO

## STORAGE OF DONATED KIDNEYS: Data Extraction

Plata-Munoz et al. (2008)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> cohort study	<b>ARM 1:</b> <b>LifePort</b>	<b>Number enrolled:</b> 60	<b>Primary outcome measure:</b> not specified
<b>Country (countries):</b> UK	Intervention: Machine perfusion Number enrolled: 30	<b>Attrition / dropout:</b> -	<b>Secondary outcome measure(s):</b> Primary non function PNF Delayed graft function DGF Immediate graft function IGF Acute rejection 1 year graft function 1 year graft survival 1 year patient survival Length of hospitalisation Warm ischaemic time Cold ischaemic time Serum creatinine HLA matching
<b>Number of centres:</b> 1	<b>ARM 2:</b> <b>Marshall cold storage solution</b>	<b>Inclusion criteria:</b> DCD Maastricht category III <65 years	<b>Method of assessing outcomes:</b> DGF: the need for dialysis during the first week after transplantation, excluding those episodes of dialysis secondary to fluid overload or hyperkalaemia during the first 24 hours post-transplant.
<b>Recruitment dates:</b> March 2002 - December 2005	Intervention: Cold storage Number enrolled: 30	<b>Exclusion criteria:</b> Donors: Diabetes Primary renal disease Systemic sepsis Malignancy	
<b>Length of follow-up:</b> 1 year			
<b>Source of funding:</b> -			

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	LifePort				Marshall cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Implantation time (mins)	30	-	55[j]	-	30	-	40[h]	-	15	-	-
<b>DONOR</b>											
Age	30	-	41.6	2.9	30	-	40.3	2.6	1.3	0.711	0.073[o]
Cerebrovascular disease	30	11	-	-	30	12	-	-	0.917	1.39	0.791[a]
Creatinine clearance (umol/L)	30	-	95[j]	-	30	-	103[k]	-	-	-	-
Gender (n male)	30	17	-	-	30	18	-	-	0.944	1.24	0.793[a]
Hypertension	30	3	-	-	30	5	-	-	0.6	1.98	0.448[a]
<b>HLA MISMATCHES</b>											
0	30	1	-	-	30	1	-	-	1	4.02	1.000[a]
1-2	30	8	-	-	30	14	-	-	0.571	1.43	0.108[a]
3-4	30	18	-	-	30	15	-	-	1.2	1.27	0.436[a]
5-6	30	1	-	-	30	0	-	-	3	5.02	0.472[a]
<b>INDUCTION THERAPY</b>											
Alemtuzimab	30	15	-	-	30	1	-	-	15	2.72	<0.001[a]
Anti-thymocyte Globuline	30	2	-	-	30	28	-	-	0.0714	1.98	<0.001[a]
Basiliximab	30	13	-	-	30	1	-	-	13	2.73	<0.001[a]
<b>MAINTENANCE THERAPY</b>											
Prednisolone	30	15	-	-	30	30	-	-	0.508	1.2	<0.001[a]
Tacrolimus/Sir + MMF	30	30	-	-	30	30[j]	-	-	1	1.03	1.000[a]
<b>PRE-IMPLANTATION DATA</b>											
Cold ischaemic time > 24 hrs	30	7	-	-	30	5	-	-	1.4	1.69	0.519[a]
Cold ischaemic time 14-18 hrs	30	9	-	-	30	8	-	-	1.13	1.51	0.774[a]
Cold ischaemic time 18-24 hrs	30	10	-	-	30	12	-	-	-	-	-
Cold ischaemic time (mins)	30	-	1115[e]	0	30	-	1076[d]	0	-	-	-
Cold ischaemic time <12 hrs	30	0	-	-	30	1	-	-	0.333	5.02	0.472[a]
Cold ischaemic time <14 hrs	30	4	-	-	30	4	-	-	1	1.93	1.000[a]
Warm ischaemic time (mins)	30	-	18[b]	-	30	-	18.5[c]	-	-0.5	-	-
<b>RECIPIENT</b>											
Age	30	-	47[m]	-	30	-	54[n]	-	-7	-	-
Days on waiting list	30	-	493[g]	-	30	-	410[f]	-	83	-	-
First transplant	30	25	-	-	30	29	-	-	0.862	1.09	0.085[a]
Gender (n male)	30	20	-	-	30	19	-	-	1.05	1.21	0.787[a]
Highly sensitized PRA (>85%)	30	2	-	-	30	1	-	-	2	3.31	0.554[a]
Pre-transplant antibodies	30	16	-	-	30	10	-	-	1.6	1.36	0.118[a]

#### Notes

[a] *chi-square test (calculated by reviewer)*

## STORAGE OF DONATED KIDNEYS: Data Extraction

### Plata-Munoz et al. (2008)

- [b] Median, inter-quartile range (13-30)  
 [c] Median, inter-quartile range (15-23)  
 [d] Median, inter-quartile range (876-1320)  
 [e] Median, inter-quartile range (918-1363)  
 [f] Median, range (176-683)  
 [g] Median, range (291-1220)  
 [h] Median, range (32-60)  
 [i] Median, range (43-630)  
 [j] Median, range (65-106)  
 [k] Median, range (69-120)  
 [l] MMF Mycophenolate of Mophetil  
 [m] range 20 - 69 years  
 [n] range 34 - 76 years  
 [o] student's t-test (calculated by reviewer)

### RESULTS

Outcome	LifePort				Marshall cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Acute rejection	30	4	-	-	30	2	-	-	2	2.29	0.389[a]
Creatinine (umol/L at 1 month)	30	-	199	20	30	-	282	33	-83	7.05	<0.001[b]
Creatinine day 7 (umol/L)	30	-	259	27	30	-	461	33	-202	7.78	<0.001[b]
GF 1 year	30	-	154	9	30	-	193	25	-39	4.85	<0.001[b]
GF 6 months	30	-	163	10	30	-	201	21	-38	4.25	<0.001[b]
Graft loss	30	1	-	-	30	1	-	-	1	4.02	1.000[a]
Graft survival (1 year)	30	30	-	-	30	28	-	-	1.07	1.06	0.237[a]
Graft survival (2 year)	30	29	-	-	30	27	-	-	1.07	1.07	0.301[a]
Hospitalisation (days)	30	-	10	-	30	-	14	-	-4	-	-
IRF	30	17	-	-	30	4	-	-	4.25	1.64	<0.001[a]
Patient loss	30	1	-	-	30	1	-	-	1	4.02	1.000[a]
Patient survival (1 year)	30	30	-	-	30	28	-	-	1.07	1.06	0.237[a]
Patient survival (2 year)	30	29	-	-	30	27	-	-	1.07	1.07	0.301[a]
PNF	30	0	-	-	30	0	-	-	-	-	-
Serum Creatinine mmol/dl (1 year)	30	-	112	14.9	30	-	184	23	-72	5	<0.001[b]
<b>DGF</b>											
DGF total	30	16	-	-	30	25	-	-	0.64	1.21	0.012[a]
First 15 transplants	30	8	-	-	30	14	-	-	0.571	1.43	0.108[a]
Second 15 transplants	30	8	-	-	30	12	-	-	0.667	1.46	0.273[a]

#### Notes

- [a] chi-square test (calculated by reviewer)  
 [b] student's t-test (calculated by reviewer)

### ASSESSMENT OF STUDY QUALITY

- Were inclusion criteria appropriate?  
YES
- Was the study prospective?  
YES
- Was method of selection reported?  
NO
- Was the method of allocation reported?  
YES
- Were I and C groups treated the same other than the intervention?  
UNCLEAR
- were I and C groups similar at baseline?  
NO - The machine preservation recipients were younger
- Were I and C groups assessed the same?  
UNCLEAR
- Was there a power calculation?  
NO - Not applicable
- Were assessors blind to allocation?  
UNCLEAR
- Was follow up time adequate to show outcomes to change?  
YES



## STORAGE OF DONATED KIDNEYS: Data Extraction

### Plata-Munoz et al. (2008)

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11. Was analysis by ITT?  
UNCLEAR
12. Was attrition reported?  
NO
13. Were missing data accounted for?  
UNCLEAR
14. Were confounders accounted for in analysis?  
UNCLEAR
15. Was inter centre variability reported?  
NA
16. Are the results generalisable?  
PARTIALLY - To DCD III donors
17. Was ethical approval given?  
NOT REPORTED
18. Were conflict of interest declared?  
NO

## STORAGE OF DONATED KIDNEYS: Data Extraction

Guarrera et al. (2007)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Retrospective record review	<b>ARM 1:</b> <b>RM3</b>	<b>Number enrolled:</b> 774	<b>Primary outcome measure:</b> DGF
<b>Country (countries):</b> USA	Intervention: Machine perfusion Number enrolled: 280	<b>Attrition / dropout:</b> 190 kidneys were discarded after storage (RM3 = 98 (26%), LifePort = 91 (23%), ns)	<b>Secondary outcome measure(s):</b> Graft function, 6 months, 1 year Graft survival Primary non-function Recipient 1 year SCr (mg/dL)
<b>Number of centres:</b> 1	<b>ARM 2:</b> <b>LifePort</b>	<b>Inclusion criteria:</b> ECD: Donor age > 60 years Donor age > 50 -59 + hypertension Diabetes > 5 years GFR < 70 ml/min or an admit serum creatinine of >1.5 mg/dl Any DCD a serum creatinine level that doubles from admit to final Other: prolonged cold ischaemia, disseminated intravascular coagulopathy	<b>Method of assessing outcomes:</b> Abstract and poster only
<b>Recruitment dates:</b> Dec 2001 - Sep 2006	Intervention: Machine perfusion Number enrolled: 305	<b>Exclusion criteria:</b> -	
<b>Length of follow-up:</b> 1 year			
<b>Source of funding:</b> -			

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	RM3				LifePort				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
<b>DONOR</b>											
Age years	378	-	52[g]	-	396	-	51[d]	-	1	-	[h]
DCD	378	75	-	-	396	96	-	-	0.851	1.14	0.213[a]
Hx of Hypertension	378	185	-	-	396	198	-	-	0.979	1.08	0.769[a]
<b>ETHNIC GROUP - DONOR</b>											
African American	378	91	-	-	396	103	-	-	0.962	1.12	0.744[a]
Caucasian	378	249	-	-	396	253	-	-	1.07	1.03	0.038[a]
Hispanic	378	34	-	-	396	32	-	-	1.16	1.26	0.528[a]
Other	378	4	-	-	396	8	-	-	0.545	1.83	0.309[a]
<b>RECIPIENT</b>											
Admit creatinine	378	-	1[c]	0.3	396	-	1.1[b]	0.5	-0.1	0.0338	0.003[h]
Age years	378	-	52.4[f]	-	396	-	50.5[e]	-	1.9	-	[h]

#### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *range 0.2 - 15.3*  
 [c] *range 0.2 - 2.3*  
 [d] *range 11 -79 years*  
 [e] *range 11-79*  
 [f] *range 2-80*  
 [g] *range 2-80 years*  
 [h] *student's t-test (calculated by reviewer)*

### RESULTS

Outcome	RM3				LifePort				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Cold ischemia (hours)	378	-	23[m]	-	396	-	24.3[l]	-	-1.3	-	[n]
Creatinine 1 year (mg/dL)	289	-	1.91	0.9	305	-	1.83	1.1	0.08	0.0823	0.331[n]
DCD	280	-	-	-	305	-	-	-	0.851	1.14	0.213[a]
DGF	289	90	-	-	396	162	-	-	0.761	1.11	0.009[a]
Discard rate	378	98	-	-	396	91	-	-	1.13	1.13	0.340[a]
Flow of solution (CC/min)	280	-	129[k]	-	305	-	145[j]	-	-16	-	[n]
PNF	378	11	-	-	396	8	-	-	1.44	1.58	0.424[a]
Renal resistance (map/flow)	280	-	0.32[b]	-	305	-	0.28[d]	-	0.04	0	<0.001[n]
Total cold ischaemia (hours)	378	-	23	-	398	-	24.3	-	-1.3	0	<0.001[n]
Transplanted > 60 yrs	378	92	-	-	396	85	-	-	1.13	1.14	0.341[a]

## STORAGE OF DONATED KIDNEYS: Data Extraction

### Guarrera et al. (2007)

Outcome	RM3				LifePort				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
<b><u>GRAFT FUNCTION</u></b>											
1 year	378	347	-	-	396	339	-	-	1.07	1.03	0.007[a]
Final creatinine	378	-	1.46[c]	0.8	396	-	1.5[e]	0.9	-0.04	0.0611	0.513[n]
Glomerular filtration rate	378	-	91.2[i]	-	396	-	95[h]	-	-3.8	-	[n]
<b><u>GRAFT SURVIVAL</u></b>											
1 year	378	366[f]	-	-	396	367[g]	-	-	1.04	1.02	0.010[a]
<b><u>PATIENT SURVIVAL</u></b>											
1 year	378	366	-	-	396	367	-	-	1.04	1.02	0.010[a]

#### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *range 0.05-9.99*  
 [c] *range 0.2 - 4.6*  
 [d] *range 0.28-1.06*  
 [e] *range 0.4 - 10.8*  
 [f] *range 0.7-10.6*  
 [g] *range 0.8-11.3*  
 [h] *range 17-198*  
 [i] *range 23.8-182*  
 [j] *range 39-199*  
 [k] *range 5-218*  
 [l] *range 8-58*  
 [m] *range 9-47.5*  
 [n] *student's t-test (calculated by reviewer)*

### ASSESSMENT OF STUDY QUALITY

1. Were inclusion criteria appropriate?  
YES
2. Was the method of selection reported?  
YES
3. Was the method of allocation reported?  
YES
4. were I and C groups treated the same?  
UNCLEAR
5. Were I and C groups similar at baseline?  
YES
6. Were assessors blinded to allocation?  
NOT REPORTED
7. Was the follow up time adequate?  
NOT REPORTED
8. How were missing data accounted for?  
NOT REPORTED
9. Were confounders accounted for in analysis?  
NOT REPORTED
10. Was inter centre variability reported?  
NA
11. Are the results generalisable?  
PARTIALLY - As the study was not randomised and use of machines sequential other variables may have influenced the outcomes
12. Are conflict of interests declared?  
NO

## STORAGE OF DONATED KIDNEYS: Data Extraction

Kazimi et al. (2007)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Retrospective record review  <b>Country (countries):</b> USA  <b>Number of centres:</b> 1  <b>Recruitment dates:</b> Feb 2005 - Nov 2006  <b>Length of follow-up:</b> not reported  <b>Source of funding:</b> not reported	<b>ARM 1:</b> <i>Lifeport</i> Intervention: Machine perfusion Number enrolled: 52  <b>ARM 2:</b> <i>RM3</i> Intervention: Machine perfusion Number enrolled: 37	<b>Number enrolled:</b> 89  <b>Attrition / dropout:</b> -  <b>Inclusion criteria:</b> Renal allografts brought in or handled by the perfusion laboratory that were either: kidney kidney/liver kidney/pancreas  <b>Exclusion criteria:</b> -	<b>Primary outcome measure:</b> Graft survival- GS  <b>Secondary outcome measure(s):</b> Post-transplant dialysis length of hospital stay rate of improvement in creatinine levels  <b>Method of assessing outcomes:</b> Abstract and poster only  Outcome data were from the transplant registry database. Analysis used SPSS. Chi-square and Mann-Whitney tests were used for group comparisons, p<0.05 was considered significant.  The LifePort machine has been used most recently, therefore there are issues about confounding variables and bias

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	Lifeport				RM3				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age years -recipient	52	-	48	-	37	-	46	-	2	-	[b]
DONOR -age	52	-	30	-	37	-	32	-	-2	-	[b]
DONOR- terminal creatinine	52	-	1	-	37	-	1.1	-	-0.1	-	[b]
Pre-op Creatinine - recipient	52	-	5.4	-	37	-	8.2	-	-2.8	-	[b]
Sex (n male)-recipient	52	42	-	-	37	20	-	-	1.49	1.18	0.007[a]
<b>DONOR TYPE</b>											
BSD	52	51	-	-	37	36	-	-	1.01	1.03	0.807[a]
DCD	52	1	-	-	37	1	-	-	0.712	4.05	0.807[a]
<b>ETHNIC GROUP - RECIPIENT</b>											
black	52	8	-	-	37	11	-	-	0.517	1.51	0.104[a]
Other	52	6	-	-	37	2	-	-	2.13	2.2	0.319[a]
White	52	38	-	-	37	24	-	-	1.13	1.16	0.406[a]
<b>TRANSPLANT TYPE</b>											
kidney or kidney/pancreas (import)	52	4	-	-	37	6	-	-	0.474	1.84	0.210[a]
kidney or kidney/pancreas (local)	52	29	-	-	37	27	-	-	-	-	-
kidney/liver (local)	52	19	-	-	37	4	-	-	3.38	1.66	0.006[a]

#### Notes

[a] *chi-square test (calculated by reviewer)*

[b] *student's t-test (calculated by reviewer)*

### RESULTS

Outcome	Lifeport				RM3				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
% change in creatinine at 48 hrs post Tx	52	-	28	-	37	-	35	-	-7	-	[b]
% change in creatinine at hospital discharge	52	-	65	-	37	-	71	-	-6	-	[b]
Hospitalisation (days)	52	-	15	-	37	-	9	-	6	-	[b]
post transplant dialysis	52	2	-	-	37	2	-	-	0.712	2.66	0.726[a]
<b>GRAFT SURVIVAL</b>											
30 days	52	49	-	-	37	36	-	-	0.968	1.04	0.491[a]
90 days	41	37	-	-	36	35	-	-	0.928	1.06	0.215[a]

#### Notes

[a] *chi-square test (calculated by reviewer)*

[b] *student's t-test (calculated by reviewer)*



## STORAGE OF DONATED KIDNEYS: Data Extraction

Kazimi et al. (2007)

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### ASSESSMENT OF STUDY QUALITY

1. **Were inclusion criteria appropriate?**  
UNCLEAR - This was a poster presentation, therefore information is limited
2. **Was the method of selection reported?**  
YES
3. **Was the method of allocation reported?**  
NO
4. **were I and C groups treated the same?**  
UNCLEAR
5. **Were I and C groups similar at baseline?**  
NO - There were more men in the RM3 group ( $p < 0.01$ ) and more participants in the LifePort group ( $p < 0.02$ )
6. **Were assessors blinded to allocation?**  
NOT REPORTED
7. **Was the follow up time adequate?**  
NOT REPORTED
8. **How were missing data accounted for?**  
NOT REPORTED
9. **Were confounders accounted for in analysis?**  
NOT REPORTED
10. **Was inter centre variability reported?**  
YES - in baseline characteristics but not in the results
11. **Are the results generalisable?**  
NO - this was a non randomised study with the RM3 being used historically before the LifePort machine, other confounding variables may have biased the result
12. **Are conflict of interests declared?**  
NO

## STORAGE OF DONATED KIDNEYS: Data Extraction

### Opelz & Dohler (2007)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Retrospective record review  <b>Country (countries):</b> 26 countries in Europe, North America and Australia  <b>Number of centres:</b> 195  <b>Recruitment dates:</b> 1990 - 2005  <b>Length of follow-up:</b> 3,6,12 months and then yearly  <b>Source of funding:</b> -	<b>ARM 1:</b> <i>University of Wisconsin cold storage solution</i>  Intervention: Cold storage Number enrolled: 53560  <b>ARM 2:</b> <i>Marshall cold storage solution</i>  Intervention: Cold storage Number enrolled: 5047	<b>Number enrolled:</b> 58607  <b>Attrition / dropout:</b> -  <b>Inclusion criteria:</b> kidneys transplanted from deceased donors  <b>Exclusion criteria:</b> -	<b>Primary outcome measure:</b> Graft survival  <b>Secondary outcome measure(s):</b> Death censored functional survival  <b>Method of assessing outcomes:</b> Analysis was limited to transplants between 1990 -2004. DGF data was not collected due to lack of standardisation. Graft survival rates and death censored functional graft survival rates were analysed with Kaplan Meier methods. Logistic regression and Cox regression analysis were used on covariables.  These data are a subset taken from the Collaborative Transplant Study <a href="http://www.ctstransplant.org">www.ctstransplant.org</a>

### CHARACTERISTICS OF PARTICIPANTS

### RESULTS

Outcome	University of Wisconsin cold storage solution				Marshall cold storage solution				Comparison			
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P	
<b>GRAFT SURVIVAL 3 YEARS FOLLOW UP</b>												
>36 hours of cold ischaemia	2486	1855	-	-	303	220	-	-	1.03	1.04	0.449[a]	
0-18 hours of cold ischaemia	24258	19746	-	-	2225	1782	-	-	1.02	1.01	0.129[a]	
19-24 hours of cold ischaemia	16147	12756	-	-	1636	1260	-	-	1.03	1.01	0.062[a]	
25-36 hours of cold ischaemia	11158	8636	-	-	944	709	-	-	1.03	1.02	0.107[a]	

#### Notes

[a] *chi-square test (calculated by reviewer)*

### ASSESSMENT OF STUDY QUALITY

1. Were inclusion criteria appropriate?  
YES
2. Was the method of selection reported?  
YES
3. Was the method of allocation reported?  
NO
4. were I and C groups treated the same?  
UNCLEAR
5. Were I and C groups similar at baseline?  
UNCLEAR
6. Were assessors blinded to allocation?  
NOT REPORTED
7. Was the follow up time adequate?  
YES
8. How were missing data accounted for?  
NOT REPORTED
9. Were confounders accounted for in analysis?  
NOT REPORTED
10. Was inter centre variability reported?  
NO
11. Are the results generalisable?  
YES - Due to very large sample size

## STORAGE OF DONATED KIDNEYS: Data Extraction

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### Opelz & Dohler (2007)

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12. Are conflict of interests declared?

NO

## STORAGE OF DONATED KIDNEYS: Data Extraction

Montalti et al. (2005)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Prospective multi-centre RCT  <b>Country (countries):</b> Italy  <b>Number of centres:</b> 2 Bologna and Palma  <b>Recruitment dates:</b> Nov 1998 - Sept 2000  <b>Length of follow-up:</b> 5 years  <b>Source of funding:</b> Not reported	<b>ARM 1:</b> <i>University of Wisconsin cold storage solution</i> Intervention: Cold storage Number enrolled: 25  <i>As 6 kidneys from the 30 randomised to this group were rejected it is assumed that one of the kidneys randomised to Celsior solution was changed to UW.</i>  <b>ARM 2:</b> <i>Celsior cold storage solution</i> Intervention: Cold storage Number enrolled: 25	<b>Number enrolled:</b> 60  <b>Attrition / dropout:</b> 10 kidneys were rejected following histologic examination (UW =6, Celsior =4)  <b>Inclusion criteria:</b> Deceased multiple organ donors > 60 years  <b>Exclusion criteria:</b> -	<b>Primary outcome measure:</b> Delayed graft function DGF  <b>Secondary outcome measure(s):</b> urinary output serum creatinine  <b>Method of assessing outcomes:</b> Graft survival was calculated using Kaplan Meier analysis  DGF - the absence of life-sustaining renal function requiring one or more dialysis session within the first days after transplantation

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
<b>DONOR</b>											
Age years	25	-	66.2	4.1	25	-	66.4	4.2	-0.2	1.17	0.865[a]
Terminal creatinine	25	-	1.2	0.9	25	-	1	0.3	0.2	0.19	0.297[a]
Urinary output per hour (mL)	25	-	248	130	25	-	236	60	12	28.6	0.677[a]
<b>RECIPIENT</b>											
Age years	25	-	54.5	7.4	25	-	55.2	8.3	-0.7	2.22	0.754[a]

#### Notes

[a] student's t-test (calculated by reviewer)

### RESULTS

Outcome	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
A mismatches	25	-	0.9	-	25	-	0.9	-	0	-	[b]
Acute rejection	25	2	-	-	25	2	-	-	1	2.61	1.000[a]
B mismatches	25	-	1.1	-	25	-	0.9	-	0.2	-	[b]
Cold ischaemic time (hours)	25	-	19	6.5	25	-	18	4.5	1	1.58	0.530[b]
DGF	25	13	-	-	25	12	-	-	1.08	1.33	0.777[a]
DR mismatches	25	-	1.2	-	25	-	0.8	-	0.4	-	[b]
Panel reactive antibodies	25	-	18.2	22.3	25	-	13.3	18.3	4.9	5.77	0.400[b]
Post-operative dialysis	25	-	3.1	4.9	25	-	2.2	3.8	-	-	-
Warm ischaemic time (mins)	25	-	46.9	17.9	25	-	42.4	11	4.5	4.2	0.290[b]
<b>GRAFT SURVIVAL</b>											
1 year	25	24	-	-	25	23	-	-	1.04	1.07	0.552[a]
5 years	25	22	-	-	25	20	-	-	1.1	1.13	0.440[a]

#### Notes

[a] chi-square test (calculated by reviewer)

[b] student's t-test (calculated by reviewer)

### ASSESSMENT OF STUDY QUALITY

- Are the study aims clearly described and focused?  
YES
- Is study design appropriate to answer these aims?  
YES
- Are there explicit inclusion and exclusion criteria for the study?  
PARTIAL
- Are methods of randomisation adequate?  
NOT REPORTED

## STORAGE OF DONATED KIDNEYS: Data Extraction

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### Montalti et al. (2005)

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5. Was there concealed randomised allocation?  
UNCLEAR
6. Are sample characteristics adequately described?  
YES - Extended criteria donors
7. Are there significant differences between the cohorts?  
NO
8. Was the follow up time adequate for outcomes to change?  
YES
9. Do analyses attempt to control for confounders?  
CAN'T TELL
10. Is there a power calculation?  
CAN'T TELL
11. Is the sample size sufficient?  
NOT ANALYSED
12. Is primary outcome measure objective?  
OBJECTIVE
13. Are secondary outcome measures objective?  
OBJECTIVE
14. Were outcome assessors blind to exposure status?  
CAN'T TELL
15. Are drop-out rates similar between intervention and controls?  
CAN'T TELL
16. was analysis by ITT  
NOT REPORTED
17. Inter centre variability reported?  
NO
18. Are the results generalisable?  
PARTIALLY - The donors were over 60 years old, this may affect the quality of their kidneys
19. Was ethical approval given?  
NOT REPORTED
20. Were all groups treated similarly?  
CAN'T TELL
21. Were all participants accounted for?  
YES

## STORAGE OF DONATED KIDNEYS: Data Extraction

Marcen et al. (2005)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Retrospective record review  <b>Country (countries):</b> Spain  <b>Number of centres:</b> 1  <b>Recruitment dates:</b> Jan 1997 - Oct 2001  <b>Length of follow-up:</b> 12 months  <b>Source of funding:</b> -	<b>ARM 1:</b> <i>University of Wisconsin cold storage solution</i>  Intervention: Cold storage Number enrolled: 138  <b>ARM 2:</b> <i>Celsior cold storage solution</i>  Intervention: Cold storage Number enrolled: 39	<b>Number enrolled:</b> 177  <b>Attrition / dropout:</b> -  <b>Inclusion criteria:</b> Deceased donors Brain death diagnosed BSD  <b>Exclusion criteria:</b> -	<b>Primary outcome measure:</b> Delayed graft function DGF  <b>Secondary outcome measure(s):</b> Primary non-fuction PNF Serum creatinine Graft survival GS  <b>Method of assessing outcomes:</b> Chi-squared test to compare categorical data, with t test and Mann-Whitney tests as indicated. Graft survival was calculated using the Kaplan -Meiter method.

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age- donor (years)	138	-	42.3	16.9	39	-	38.1	12.5	4.2	2.46	0.090[b]
Age years -recipient	138	-	49.5	14.4	39	-	43.3	13	6.2	2.42	0.011[b]
DONOR- terminal creatinine	138	-	1.1	0.6	39	-	0.9	0.8	0.2	0.138	0.149[b]
RECIPIENT body mass index (kg/m2)	138	-	24.4	5.5	39	-	24	5.8	0.4	1.04	0.701[b]
RECIPIENT Sex (n male)	138	85	-	-	39	23	-	-	1.04	1.16	0.767[a]
RECIPIENT time on dialysis prior to Tx (years)	138	-	2.5	2.7	39	-	2	1.6	0.5	0.344	0.148[b]

#### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *student's t-test (calculated by reviewer)*

Characteristic	N	k	Mean	SD
Age years -recipient	177	-	48.1	13.5
RECIPIENT Sex (n male)	177	107	-	-
RECIPIENT time on dialysis prior to Tx (years)	17	-	2.4	2.5

### RESULTS

Outcome	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Acute rejection	138	23	-	-	39	2	-	-	-	-	-
Acute rejection RR	138	-	-	-	39	-	-	-	3.25	2.04	0.068[a]
Cold ischemia (hours)	138	-	17.5	4.3	39	-	16.9	3.7	-	-	-
Cold ischemia (hours) RR	138	-	-	-	39	-	-	-	0.6	0.696	0.390[b]
Creatinine (umol/L at 1 month)	138	-	1.9	0.9	39	-	1.5	0.5	-	-	-
Creatinine (umol/L at 1 month) RR	138	-	-	-	39	-	-	-	0.4	0.111	<0.001[b]
Creatinine (umol/L at 12 months)	-	-	-	-	39	-	1.35	0.4	-	-	-
Creatinine (umol/L at 12 months) RR	138	-	1.63	0.5	-	-	-	-	-	-	-
Creatinine (umol/L at 12 months) RR	138	-	-	-	39	-	-	-	0.28	0.0769	<0.001[b]
DGF RR	-	-	-	-	39	9	-	-	-	-	-
DGF RR	138	54	-	-	39	-	-	-	1.7	1.36	0.064[a]
Graft survival (12 months)	138	121	-	-	39	38	-	-	-	-	-
Graft survival (12 months) RR	138	-	-	-	39	-	-	-	0.9	1.04	0.075[a]
PNF	138	8	-	-	39	1	-	-	-	-	-
PNF RR	138	-	-	-	39	-	-	-	2.26	2.84	0.417[a]
Rejection of graft	138	23	-	-	39	2	-	-	-	-	-
Rejection of graft RR	138	-	-	-	39	-	-	-	3.25	2.04	0.068[a]

#### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *student's t-test (calculated by reviewer)*

## STORAGE OF DONATED KIDNEYS: Data Extraction

**Marcen et al. (2005)**

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### ASSESSMENT OF STUDY QUALITY

1. **Were inclusion criteria appropriate?**  
YES
2. **Was the method of selection reported?**  
YES
3. **Was the method of allocation reported?**  
NO
4. **were I and C groups treated the same?**  
UNCLEAR
5. **Were I and C groups similar at baseline?**  
NO - recipients in the UW group were older, there were many more people in the UW group
6. **Were assessors blinded to allocation?**  
NOT REPORTED
7. **Was the follow up time adequate?**  
YES
8. **How were missing data accounted for?**  
NOT REPORTED
9. **Were confounders accounted for in analysis?**  
NOT REPORTED
10. **Was inter centre variability reported?**  
NA
11. **Are the results generalisable?**  
PARTIALLY - This was not a RCT and so biases may have been present and the numbers in the two groups are very unbalanced
12. **Are conflict of interests declared?**  
NO



## STORAGE OF DONATED KIDNEYS: Data Extraction

Pedotti et al. (2004)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Prospective multi-centre RCT  <b>Country (countries):</b> Italy  <b>Number of centres:</b> 16  <b>Recruitment dates:</b> March 2000- Dec 2001  <b>Length of follow-up:</b> 12 months  <b>Source of funding:</b> -	<b>ARM 1:</b> <i>University of Wisconsin cold storage solution</i> Intervention: Cold storage Number enrolled: 269  <b>ARM 2:</b> <i>Celsior cold storage solution</i> Intervention: Cold storage Number enrolled: 172	<b>Number enrolled:</b> 441  <b>Attrition / dropout:</b> -  <b>Inclusion criteria:</b> Deceased multi-organ donors  <b>Exclusion criteria:</b> non-multi organ donors from non NITp programme centres from centres where included perfusion solutions not available paediatric patients regrafts transplants with missing or incomplete data on follow-up were excluded from analysis	<b>Primary outcome measure:</b> not specified  <b>Secondary outcome measure(s):</b> DGF PNF Patient survival PS Graft survival GS Creatinine levels Urine output  <b>Method of assessing outcomes:</b> Analysis was conducted by the NITp Reference Centre using SAS v 8. Statistical techniques used were t tests for continuous variables, chi-square for parametric variables. Log transformation was used when necessary. Survival was calculated using the actuarial method. Logistic multivariate analyses were performed to find the role of determinant factors on graft and patient survival.

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age- donor (years)	269	-	45.4	17.2	172	-	46.1	17.2	-0.7	1.68	0.677[b]
Age years -recipient	269	-	46	13.6	172	-	45.3	14	0.7	1.35	0.605[b]
Cold ischaemic time (hours)	269	-	15.3	4.8	172	-	15.1	4.3	0.2	0.439	0.649[b]
<b>HLA MISMATCHES (A, B, DR)</b>											
0-1	269	47	-	-	172	24	-	-	1.25	1.26	0.327[a]
2-4	269	214	-	-	172	138	-	-	0.992	1.05	0.862[a]
5-6	269	8	-	-	172	10	-	-	0.512	1.59	0.142[a]
<b>PANEL REACTIVE ANTIBODIES</b>											
> 30%	269	9	-	-	172	7	-	-	0.822	1.64	0.692[a]
≤ 30%	269	260	-	-	172	165	-	-	1.01	1.02	0.692[a]

#### Notes

[a] *chi-square test (calculated by reviewer)*

[b] *student's t-test (calculated by reviewer)*

### RESULTS

Outcome	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Acute tubular necrosis	269	28	-	-	172	19	-	-	0.942	1.32	0.832[a]
DGF	269	61	-	-	172	40	-	-	0.975	1.2	0.888[a]
PNF	269	4	-	-	172	4	-	-	0.639	2.01	0.520[a]
<b>COMPLICATIONS</b>											
Infection	269	12	-	-	172	7	-	-	1.1	1.59	0.844[a]
Medical	269	38	-	-	172	31	-	-	0.784	1.25	0.272[a]
none	269	155	-	-	172	85	-	-	-	-	-
Rejection	269	59	-	-	172	31	-	-	1.22	1.22	0.320[a]
Surgical	269	17	-	-	172	20	-	-	0.543	1.37	0.050[a]
<b>CREATININE</b>											
day 1 (µmol/L)[b]	269	-	671.8	102.9	172	-	663	110.4	8.8	10.5	0.402[c]
day 10 (µmol/L)[b]	269	-	246.6	-881.2	172	-	236.7	-549.4	9.9	68.1	0.885[c]
day 15 (µmol/L)[b]	269	-	220.4	-847.7	172	-	200.8	-652.4	19.6	71.7	0.785[c]
day 5 (µmol/L)[b]	269	-	371.3	-463.6	172	-	353.6	-451	17.7	44.5	0.691[c]
<b>GRAFT SURVIVAL</b>											
1 month	269	258	-	-	172	165	-	-	1	1.02	0.992[a]
1 year	269	245	-	-	172	162	-	-	0.967	1.03	0.233[a]

## STORAGE OF DONATED KIDNEYS: Data Extraction

Pedotti et al. (2004)

Outcome	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
<b><u>PATIENT SURVIVAL</u></b>											
1 month	269	269	-	-	172	172	-	-	1	1	0.822[a]
1 year	269	263	-	-	172	171	-	-	0.983	1.01	0.177[a]
<b><u>URINE OUTPUT</u></b>											
day 1 (mL/24hrs)[b]	269	-	2520	259.4	172	-	2180	-93.68	340	17.4	<0.001[c]
day 10 (mL/24hrs)[b]	269	-	2500	159	172	-	2500	1024	0	78.7	1.000[c]
day 15 (mL/24hrs)[b]	269	-	2500	1305	172	-	2600	381.4	-100	84.7	0.239[c]
day 5 (mL/24hrs)[b]	269	-	2500	150.6	172	-	2600	1512	-100	116	0.388[c]

### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *MEDIAN*  
 [c] *student's t-test (calculated by reviewer)*

### ASSESSMENT OF STUDY QUALITY

- Are the study aims clearly described and focused?  
YES
- Is study design appropriate to answer these aims?  
YES
- Are there explicit inclusion and exclusion criteria for the study?  
PARTIAL
- Are methods of randomisation adequate?  
NO - from a list
- Was there concealed randomised allocation?  
NO
- Are sample characteristics adequately described?  
YES
- Are there significant differences between the cohorts?  
NO
- Was the follow up time adequate for outcomes to change?  
YES
- Do analyses attempt to control for confounders?  
CAN'T TELL
- Is there a power calculation?  
CAN'T TELL
- Is the sample size sufficient?  
NOT ANALYSED
- Is primary outcome measure objective?  
OBJECTIVE
- Are secondary outcome measures objective?  
OBJECTIVE
- Were outcome assessors blind to exposure status?  
CAN'T TELL
- Are drop-out rates similar between intervention and controls?  
CAN'T TELL
- was analysis by ITT  
NOT REPORTED
- Inter centre variability reported?  
NO
- Are the results generalisable?  
YES
- Was ethical approval given?  
NOT REPORTED
- Were all groups treated similarly?  
YES
- Were all participants accounted for?  
CAN'T TELL

## STORAGE OF DONATED KIDNEYS: Data Extraction

Faenza et al. (2001)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Prospective multi-centre RCT  <b>Country (countries):</b> Italy  <b>Number of centres:</b> 4  <b>Recruitment dates:</b> Sept 1998 - Sept 2000  <b>Length of follow-up:</b> 2 years  <b>Source of funding:</b> -	<b>ARM 1:</b> <i>University of Wisconsin cold storage solution</i> Intervention: Cold storage Number enrolled: 88  <b>ARM 2:</b> <i>Celsior cold storage solution</i> Intervention: Cold storage Number enrolled: 99	<b>Number enrolled:</b> 187  <b>Attrition / dropout:</b> 13 kidneys were not transplanted (UW = 6, C = 7); these were from marginal donors and rejected on histological grounds by the same pathologist  <b>Inclusion criteria:</b> Donors and recipients > 15 years old multiple organ donors  <b>Exclusion criteria:</b> recipient had already had a transplant	<b>Primary outcome measure:</b> not specified  <b>Secondary outcome measure(s):</b> Delayed graft function DGF Serum creatinine Urinary output Post transplantation dialysis  <b>Method of assessing outcomes:</b> univariate analyses with Mann-Whitney test and chi-square test to assess differences between groups were used. Graft survival was calculated using Kaplan Meier analysis.

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age- donor (years)	88	-	52.9	17.6	99	-	48.6	18.8	4.3	2.66	0.108[a]
Age years -recipient	88	-	46.6	11.4	99	-	46.9	11.7	-0.3	1.69	0.859[a]
DONOR terminal creatinine	88	-	1	0.5	99	-	1.1	0.8	-0.1	0.0965	0.301[a]
DONOR urinary output per hour (mL)	88	-	193.3	139.6	99	-	221.3	165.3	-28	22.3	0.211[a]
RECIPIENT Panel reactive antibodies	88	-	8	12	99	-	12.6	19.3	-4.6	2.32	0.049[a]

#### Notes

[a] student's t-test (calculated by reviewer)

### RESULTS

Outcome	University of Wisconsin cold storage solution				Celsior cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
A mismatches	88	-	1.4	-	99	-	1.1	-	0.3	-	[b]
Acute rejection	88	13	-	-	99	12	-	-	-	-	-
B mismatches	88	-	1.1	-	99	-	1.3	-	-0.2	-	[b]
Cold ischemia (hours)	88	-	16.7	5	99	-	16.5	6.6	0.2	0.851	0.814[b]
DGF	88	30	-	-	99	31	-	-	1.09	1.23	0.686[a]
DR mismatches	88	-	0.8	-	99	-	0.8	-	0	-	[b]
Graft survival (2 year)	88	66	-	-	99	83	-	-	0.895	1.08	0.134[a]
Number of rejection episodes before discharge	88	-	-	-	99	-	-	-	1.22	1.45	0.595[a]
Post-operative dialysis	88	-	1.9	3.5	99	-	1	3.3	0.9	0.499	0.073[b]
Warm ischaemic time (mins)	88	-	35.1	14.2	99	-	38.3	14.1	-3.2	2.07	0.124[b]

#### COLD ISCHAEMIA > 17 HOURS

Creatinine (mg/dL at discharge)	41	-	2.2	1.5	45	-	1.9	1.08	0.3	0.284	0.294[b]
Creatinine day 1 (mg/dL)	41	-	7.08	2.4	45	-	6.2	2.1	0.88	0.488	0.075[b]
Creatinine day 15 (mg/dL)	41	-	3.2	2.2	45	-	2.7	2.02	0.5	0.457	0.277[b]
Creatinine day 3 (mg/dL)	41	-	6.2	3.3	45	-	5.1	3.4	1.1	0.723	0.132[b]
Creatinine day 5 (mg/dL)	41	-	5.3	3.4	45	-	4.6	3.3	0.7	0.724	0.336[b]
Creatinine day 7 (mg/dL)	41	-	4.7	3.4	45	-	4.2	3.3	0.5	0.724	0.492[b]
DGF	41	18	-	-	45	18	-	-	1.1	1.29	0.714[a]
Post-transplantation dialysis rate	41	-	3.9	-	45	-	2.9	-	1	-	[b]
Urinary output discharge (mL/24hrs)	41	-	1754	1153	45	-	1971	1210	-217	255	0.397[b]
Urine output day 1 (mL/24hrs)	41	-	1568	1549	45	-	2265	2575	-697	454	0.128[b]
Urine output day 15 (mL/24hrs)	41	-	1731	1121	45	-	1924	1236	-193	254	0.449[b]
Urine output day 3 (mL/24hrs)	41	-	1622	1477	45	-	1633	1472	-11.2	318	0.972[b]
Urine output day 5 (mL/24hrs)	41	-	1627	1671	45	-	1730	1138	-104	311	0.740[b]
Urine output day 7 (mL/24hrs)	41	-	1651	1228	45	-	1824	1174	-172	260	0.509[b]

#### Notes

[a] chi-square test (calculated by reviewer)

[b] student's t-test (calculated by reviewer)

## STORAGE OF DONATED KIDNEYS: Data Extraction

Faenza et al. (2001)

### ASSESSMENT OF STUDY QUALITY

1. Are the study aims clearly described and focused?  
YES
2. Is study design appropriate to answer these aims?  
YES
3. Are there explicit inclusion and exclusion criteria for the study?  
YES
4. Are methods of randomisation adequate?  
NOT REPORTED
5. Was there concealed randomised allocation?  
UNCLEAR
6. Are sample characteristics adequately described?  
YES
7. Are there significant differences between the cohorts?  
NO
8. Was the follow up time adequate for outcomes to change?  
YES
9. Do analyses attempt to control for confounders?  
CAN'T TELL
10. Is there a power calculation?  
CAN'T TELL
11. Is the sample size sufficient?  
NOT ANALYSED
12. Is primary outcome measure objective?  
OBJECTIVE
13. Are secondary outcome measures objective?  
OBJECTIVE
14. Were outcome assessors blind to exposure status?  
CAN'T TELL
15. Are drop-out rates similar between intervention and controls?  
YES
16. was analysis by ITT  
NOT REPORTED
17. Inter centre variability reported?  
NO
18. Are the results generalisable?  
YES
19. Was ethical approval given?  
NOT REPORTED
20. Were all groups treated similarly?  
YES
21. Were all participants accounted for?  
YES

## STORAGE OF DONATED KIDNEYS: Data Extraction

Moers et al. (2009)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<p><b>Study design:</b> Prospective multi-centre RCT</p> <p><b>Country (countries):</b> Netherlands, Belgium, Germany</p> <p><b>Number of centres:</b> -</p> <p><b>Recruitment dates:</b> Nov 2005- Nov 2006</p> <p><b>Length of follow-up:</b> 1 year</p> <p><b>Source of funding:</b> Organ Recovery Systems</p>	<p><b>ARM 1:</b> <b>LifePort</b> Intervention: Machine perfusion Number enrolled: 336</p> <p><b>ARM 2:</b> <b>University of Wisconsin and some HTK</b> Intervention: Cold storage Number enrolled: 336 <i>UW was the preferred cold storage solution but HTK was allowed, data were not disaggregated</i></p>	<p><b>Number enrolled:</b> 1086</p> <p><b>Attrition / dropout:</b> Excluded post randomisation &amp; prior to storage: donor procedure cancelled = 28, one or both kidneys not transplantable = 140, combined organ offer =2, other reasons =40</p> <p>MP exclusions: kidney rejected at transplant centre =4, technical failure of MP = 7, due to exclusion of contralateral organ = 10, death of contralateral organ recipient = 1, contralateral organ lost to follow up = 1.</p> <p>Cold storage exclusions: kidney rejected at transplant centre = 10, due to exclusion of contralateral organ = 11, recipient died one day after transplantation (not related to transplant) = 1, lost to follow up = 1.</p> <p><b>Inclusion criteria:</b> Deceased donors ≥16 years providing kidney pairs BSD and DCD, Maastricht categories III &amp; IV kidney pairs must go to different recipients</p> <p><b>Exclusion criteria:</b> Donors &gt; 60 years Multiple organ transplant of recipient Only one kidney from a donor transplanted</p> <p>Recipients non-transplant related death in first week after transplant</p>	<p><b>Primary outcome measure:</b> Delayed graft function DGF</p> <p><b>Secondary outcome measure(s):</b> Primary non-function Duration of DGF Serum creatinine Hyperkalemia Calcineruin inhibitor toxicity Duration of hospital stay Acute rejection Graft survival - 1 year Patient survival - 1 year</p> <p><b>Method of assessing outcomes:</b> The study is powered to detect a 10% change in DGF at 80% with p&lt;0.05, giving an expected sample size of N = 300. The data will be analysed using posterior stratification of preservation time, HLA matches, recent PRA level, recipient age, 1st/retransplant, length of time on dialysis, donor type and donor age. Correlation of perfusate function to post-transplant graft function and survival analysis. There will also be a cost-benefit analysis with reference to graft outcome and survival. Fischers exact test used for discrete variables Mann-Whitney test used for continuous variables</p> <p>DATA WERE NOT ANALYSED AS ITT</p> <p>DGF: any dialysis requirement within 7 days post transplant Paired design; one kidney in the donor randomised to machine perfusion and the other automatically to cold storage. Randomisation was carried out by Euro Transplant at donor using block randomisation.</p>

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	LifePort				University of Wisconsin and some HTK				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Age years -recipient	336	-	53[e]	-	336	-	52[c]	-	1	-	[h]
Cold ischaemic time (hours)	336	-	15[g]	-	336	-	15[f]	-	0	-	[h]
Discard rate @ recipient centre	336	-	-	-	336	-	-	-	0.4	1.8	0.105[a]
Discard rate due to kidney quality @ recipient centre	336	4	-	-	336	10	-	-	-	-	-
HLA mismatches	336	54	-	-	336	50	-	-	1.08	1.2	0.670[a]
Pre-Tx dialysis duration (years)	336	-	4.5[d]	-	336	-	4.4[b]	-	0.1	-	[h]
Previous transplants	336	77	-	-	336	71	-	-	1.08	1.16	0.576[a]
<b>PANEL REACTIVE ANTIBODIES</b>											
>84%	336	4	-	-	336	3	-	-	1.3	1.51	0.524[a]
0-5 %	336	297	-	-	336	304	-	-	0.977	1.03	0.380[a]
6-84%	336	35	-	-	336	29	-	-	1.22	1.12	0.082[a]

#### Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *MEDIAN range ( 0.19-24 )*  
 [c] *MEDIAN range ( 2 -70 )*  
 [d] *MEDIAN range (0.15-18)*  
 [e] *MEDIAN range (11-79 )*  
 [f] *MEDIAN range (2.5-29.7 )*  
 [g] *MEDIAN range (3.5-26.3)*  
 [h] *student's t-test (calculated by reviewer)*

## STORAGE OF DONATED KIDNEYS: Data Extraction

### Moers et al. (2009)

Characteristic	N	k	Mean	SD
Age- donor (years)	336	-	51[i]	-
DONOR BSD	336	294	-	-
DONOR DCD	336	42	-	-

#### Notes

[i] range (16 -81)

### RESULTS

Outcome	LifePort				University of Wisconsin and some HTK				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
Acute rejection within 14 days	336	44	-	-	336	46	-	-	0.957	1.22	0.821[a]
CNI toxicity within 14 days	336	21	-	-	336	19	-	-	1.11	1.36	0.744[a]
Creatinine clearance @ day 14 (ml/mol)[b]	336	-	42	-	336	-	40	-	-	-	-
DGF	336	70	-	-	336	89	-	-	0.787	1.15	0.085[a]
DGF duration (days)[b]	336	-	10	-	336	-	13	-	-3	-	[c]
Functional DGF	336	77	-	-	336	101	-	-	0.762	1.14	0.036[a]
Graft survival (12 months)	336	329	-	-	336	316	-	-	1.04	1.02	0.011[a]
Graft survival (6 months)	336	329	-	-	336	319	-	-	1.03	1.02	0.038[a]
Hospitalisation (days)[b]	336	-	19	-	336	-	18	-	1	-	[c]
Patient survival (12 months)	336	326	-	-	336	326	-	-	1	1.01	1.000[a]
Patient survival (6 months)	336	329	-	-	336	329	-	-	1	1.01	1.000[a]
PNF	336	7	-	-	336	16	-	-	0.438	1.56	0.056[a]
<b>DGF</b>											
Cold ischemia (hours)	336	-	-	-	336	-	-	-	1.07	0	.002
DCD donor vs. BSD donor	336	-	-	-	336	-	-	-	10.1	0	<0.001
Donor age (yrs)	336	-	-	-	336	-	-	-	1.03	0	.003
Duration of pre-transplant dialysis (yrs)	336	-	-	-	336	-	-	-	1.07	0	.06
HLA mismatches	336	-	-	-	336	-	-	-	1.11	0	.17
MP vs. CS	336	-	-	-	336	-	-	-	0.63	0	.02
PRA levels (0-5%, 6-84%, >84%)	336	-	-	-	336	-	-	-	1.01	0	.38
Recipient age (yrs)	336	-	-	-	336	-	-	-	1.01	0	.21
Re-transplant vs. first transplant	336	-	-	-	336	-	-	-	2.75	0	<0.001
<b>GRAFT FAILURE</b>											
Cold ischemia (hours)	336	-	-	-	336	-	-	-	1.04	0	0.28
DCD donor vs. BSD donor	336	-	-	-	336	-	-	-	1.32	0	0.67
Donor age (yrs)	336	-	-	-	336	-	-	-	1.06	0	0.002
Duration of pre-transplant dialysis (yrs)	336	-	-	-	336	-	-	-	0.97	0	0.63
HLA mismatches	336	-	-	-	336	-	-	-	1.22	0	0.15
MP vs. CS	336	-	-	-	336	-	-	-	0.46	0	0.05
Recipient age (yrs)	336	-	-	-	336	-	-	-	0.97	0	0.07
Re-transplant vs. first transplant	336	-	-	-	336	-	-	-	1.85	0	0.13

#### Notes

[a] *chi-square test (calculated by reviewer)*

[b] *MEDIAN*

[c] *student's t-test (calculated by reviewer)*

### ASSESSMENT OF STUDY QUALITY

1. Are the study aims clearly described and focused?

YES

2. Is study design appropriate to answer these aims?

YES

3. Are there explicit inclusion and exclusion criteria for the study?

YES

4. Are methods of randomisation adequate?

YES - Block randomisation, separate lists for each region. Kidneys were allocated from a central office. Switching allowed between arms if MP not possible for technical reasons

5. Was there concealed randomised allocation?

YES

6. Are sample characteristics adequately described?

YES

**STORAGE OF DONATED KIDNEYS: Data Extraction****Moers et al. (2009)**

7. Are there significant differences between the cohorts?  
NO
8. Was the follow up time adequate for outcomes to change?  
YES
9. Do analyses attempt to control for confounders?  
YES - MATCHED COHORTS
10. Is there a power calculation?  
YES
11. Is the sample size sufficient?  
YES
12. Is primary outcome measure objective?  
OBJECTIVE
13. Are secondary outcome measures objective?  
OBJECTIVE
14. Were outcome assessors blind to exposure status?  
YES
15. Are drop-out rates similar between intervention and controls?  
YES
16. was analysis by ITT  
NO
17. Inter centre variability reported?  
NO
18. Are the results generalisable?  
YES
19. Was ethical approval given?  
YES
20. Were all groups treated similarly?  
CAN'T TELL
21. Were all participants accounted for?  
CAN'T TELL



## STORAGE OF DONATED KIDNEYS: Data Extraction

### Watson (2006)

DESIGN	ARM(S)	PARTICIPANTS	ANALYSIS
<b>Study design:</b> Prospective multi-centre RCT  <b>Country (countries):</b> UK  <b>Number of centres:</b> 5  <b>Recruitment dates:</b> -  <b>Length of follow-up:</b> 5 years  <b>Source of funding:</b> Novartis Pharma and Organ Recovery Systems	<b>ARM 1:</b> <b>LifePort</b> Intervention: Machine perfusion Number enrolled: 45  <i>43 kidneys were actually treated with MP</i>  <b>ARM 2:</b> <b>University of Wisconsin cold storage solution</b> Intervention: Cold storage Number enrolled: 45  <i>47 kidneys were actually treated with CS</i>	<b>Number enrolled:</b> 93  <b>Attrition / dropout:</b> 3 discarded: 1= anatomical reasons, 2=failed to receive allocated treatment  <b>Inclusion criteria:</b> DCD donors > 17 years old  <b>Exclusion criteria:</b> Recipients are excluded if they show: Positive crossmatch Previous non-renal transplant No consent	<b>Primary outcome measure:</b> Delayed graft function DGF  <b>Secondary outcome measure(s):</b> Measured at 3 and 12 months and 5 years: Creatinine reduction ratio day 0 -5 (CRR05) <30% Creatinine reduction ratio day 1 -2 (CRR2) <30% Mean creatinine reduction ratios Patient survival Graft survival Renal function measured using calculated GFR Non function rate Time to last dialysis post transplant Acute rejection incidence Cost comparison at one year  <b>Method of assessing outcomes:</b> The kidneys from each donor are randomised to each treatment group, by the left or right kidney and by order of transplant. A power calculation showed that 205 participants would give 90% power to detect a difference between the groups in a fixed sample size analysis. However, for ethical reasons a sequential design was adopted where patients are recruited until there is sufficient evidence, based on the primary endpoint, to reject the null hypothesis ie that there is no difference between the two methods of preservation. Randomisation is through the duty office of Organ Donation and Transplantation Directorate of NHS Blood and Transplant who also monitor data collection and determine the end of the study. Analysis was by ITT. As the data are paired McNemar's exact test is used to determine if graft function is associated with the method of kidney storage.  DGF - the need for dialysis in the first 7 days following kidney transplantation

### CHARACTERISTICS OF PARTICIPANTS

Characteristic	LifePort				University of Wisconsin cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
<b>RECIPIENT</b>											
Age years	45	-	50.3	13.2	45	-	48.6	13.9	1.7	2.86	0.553[b]
First transplant	39	-	-	-	40	-	-	-	-	-	-[a]
Gender (n male)	31	-	-	-	33	-	-	-	-	-	-[a]
Height (cm)	45	-	168.9	10.5	44	-	172.6	9.6	-3.7	2.13	0.086[b]
Months of pre-transplant dialysis	44	-	52.8	53.8	45	-	44.4	39.1	8.4	9.99	0.403[b]
Re-graft	6	-	-	-	5	-	-	-	-	-	-
Sensitised	4	-	-	-	5	-	-	-	-	-	-[a]
Serum albumin at transplant (gm/l)	45	-	39	5.4	45	-	39.1	6.4	-0.1	1.25	0.936[b]
Serum calcium (corrected for albumin) pre-tx (mmol/l)	44	-	2.3	0.1	44	-	2.3	0.2	0	0.0337	1.000[b]
Serum creatinine pre-transplant (umol/l)	44	-	701.7	292	44	-	677.8	227.2	23.9	55.8	0.669[b]
Serum urea at transplant (mmol/l)	44	-	17.1	8.1	44	-	15.3	7	1.8	1.61	0.268[b]
weight (kg)	45	-	73.2	13.5	45	-	77	14.6	-3.8	2.96	0.203[b]
<b>RECIPIENT ETHNICITY</b>											
Non-white	4	-	-	-	7	-	-	-	-	-	-[a]
White	41	-	-	-	38	-	-	-	-	-	-[a]
<b>RECIPIENT HLA MISMATCH LEVEL</b>											

## STORAGE OF DONATED KIDNEYS: Data Extraction

## Watson (2006)

Characteristic	LifePort				University of Wisconsin cold storage solution				Comparison		
	N	k	Mean	SD	N	k	Mean	SD	Est	SEM	P
3	27	-	-	-	23	-	-	-	-	-	-[a]
4	6	-	-	-	7	-	-	-	-	-	-[a]
<u>RECIPIENT TYPE OF DIALYSIS AT ADMISSION</u>											
Haemodialysis	28	-	-	-	28	-	-	-	-	-	-[a]
No dialysis	3	-	-	-	3	-	-	-	-	-	-[a]
Peritoneal dialysis	14	-	-	-	14	-	-	-	-	-	-[a]

## Notes

- [a] *chi-square test (calculated by reviewer)*  
 [b] *student's t-test (calculated by reviewer)*

## RESULTS

(Academic-in-confidence information removed)

## ASSESSMENT OF STUDY QUALITY

- Are the study aims clearly described and focused?  
YES
- Is study design appropriate to answer these aims?  
YES
- Are there explicit inclusion and exclusion criteria for the study?  
YES
- Are methods of randomisation adequate?  
YES - kidneys are randomised to treatment group and order of transplantation
- Was there concealed randomised allocation?  
YES
- Are sample characteristics adequately described?  
YES
- Are there significant differences between the cohorts?  
NO
- Was the follow up time adequate for outcomes to change?  
YES - this is an ongoing 5 year trial for which we have 3 month data
- Do analyses attempt to control for confounders?  
N/A

## STORAGE OF DONATED KIDNEYS: Data Extraction

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### Watson (2006)

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9. Do analyses attempt to control for confounders?  
N/A
10. Is there a power calculation?  
YES
11. Is the sample size sufficient?  
YES
12. Is primary outcome measure objective?  
OBJECTIVE
13. Are secondary outcome measures objective?  
OBJECTIVE
14. Were outcome assessors blind to exposure status?  
CAN'T TELL
15. Are drop-out rates similar between intervention and controls?  
YES - no drop out at 3 months
16. Was analysis by ITT  
YES
17. Inter centre variability reported?  
YES - this is planned but not yet available
18. Are the results generalisable?  
YES
19. Was ethical approval given?  
YES
20. Were all groups treated similarly?  
YES
21. Were all participants accounted for?  
YES

## Appendix 4

### Excluded studies

Stored kidneys	Reason for exclusion
Pulsatile perfusion is beneficial in expanded criteria donor kidney transplantation. <i>Nat Clin Pract Nephrol</i> 2006; <b>2</b> (9):470–1	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. <i>Transplant Proc</i> 1993; <b>25</b> (4):2561–2	Inappropriate outcome or comparator
Alijani MR, Cutler JA, Delvalle CJ, Morres DN, Fawzy A, Pechan BW <i>et al.</i> Single-donor cold-storage versus machine perfusion in cadaver kidney preservation. <i>Transplantation</i> 1985; <b>40</b> (6):659–61	Wrong cold storage solution
Baatard R, Pradier F, Dantal J, Karam G, Cantarovich D, Hourmant M <i>et al.</i> Prospective randomized comparison of University of Wisconsin and UW-modified, lacking hydroxyethyl-starch, cold-storage solutions in kidney transplantation. <i>Transplantation</i> 1993; <b>55</b> (1):31–5	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. <i>Am J Transplant</i> 2007; <b>7</b> (1109 Suppl. 2):432	Inappropriate outcome or comparator
Baldan N, Rigotti P, Furian L, Sarzo G, Cadrobbi R, Valente ML <i>et al.</i> Celsior <sup>®</sup> , a new organ preservation solution, in kidney and pancreas experimental transplantation. <i>Transplantation</i> 2000; <b>69</b> (8):S200	Animal study
Balupuri S, Buckley PE, Mantle D, Manas DM, Talbot D. Outcomes of pulsatile preservation and viability assessment of NHBD kidneys. <i>Transplantation</i> 2000; <b>69</b> (8):S334–S335	Not a comparative study
Barber WH, Deierhoi MH, Phillips MG, Diethelm AG. Preservation by pulsatile perfusion improves early renal-allograft function. <i>Transplant Proc</i> 1988; <b>20</b> (5):865–8	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. <i>Transplant Proc</i> 1991; <b>23</b> (5):2394–5	Wrong cold storage solution
Barry JM, Farnsworth MA, Metcalfe JB, Bennett WM. Human kidney preservation – comparison of simple cold storage to machine perfusion. <i>Kidney Int</i> 1978; <b>14</b> (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. <i>Transplant Proc</i> 1979; <b>11</b> (1):459–64	Wrong cold storage solution
Belzer FO. Perfusion preservation versus cold storage. <i>Transplant Proc</i> 1985; <b>17</b> (III):1515–17	Literature review or editorial
Belzer FO, Hoffman RM, Stratta RJ, Dalessandro A, Pirsch J, Kalayoglu M <i>et al.</i> Combined cold-storage perfusion preservation of the kidney with a new synthetic perfusate. <i>Transplant Proc</i> 1989; <b>21</b> (1):1240–1	Wrong cold storage solution
Benoit G, Jaber N, Moukarzel M, Bensadoun H, Blanchet P, Charpentier B <i>et al.</i> Incidence of arterial and venous complications in kidney transplantation – role of the kidney preservation solution. <i>Transplant Proc</i> 1994; <b>26</b> (1):295–6	Inappropriate outcome or comparator
Berenguer I, Pedemonte G, Rodriguez-Martinez D, Alvarado A, Martinez C, Del Canizo JF <i>et al.</i> Comparative study of the hypothermic preservation and pulsatile perfusion effects in autotransplanted ischemic kidneys. <i>Int J Artif Organs</i> 2005; <b>28</b> (9):888 (abstract #79–888)	Animal study
Booster MH, Wijnen RMH, Yin M, Tiebosch ATM, Heineman E, Maessen JG <i>et al.</i> Enhanced resistance to the effects of normothermic ischemia in kidneys using pulsatile machine perfusion. <i>Transplant Proc</i> 1993; <b>25</b> (6):3006–11	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. <i>Am J Transplant</i> 2007; <b>7</b> :286 (abstract #532)	Methods unclear
Burdick JF, Rosendale JD, McBride MA, Kauffman HM, Bennett LE. National impact of pulsatile perfusion on cadaveric kidney transplantation. <i>Transplantation</i> 1997; <b>64</b> (12):1730–3	Methods unclear
Cerra FB, Raza S, Andres GA, Siegel JH. Structural injury produced by pulsatile perfusion vs cold storage renal preservation. <i>Surg Forum</i> 1975; <b>26</b> :313–15	Animal study

continued

Stored kidneys	Reason for exclusion
Cho SI, Bradley JW, Nabseth DC. Graft survival of perfused vs nonperfused cadaver kidneys. <i>Surg Forum</i> 1975;(-):351–2	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. <i>Am J Transplant</i> 2005;5(537):293	Methods unclear
Clark EA, Terasaki PI, Opelz G, Mickey MR. Cadaver kidney transplant failures at one month. <i>New Engl J Med</i> 1974;291(21):1099–102	Inappropriate outcome or comparator
Cooper J, Kimmelstiel F, Lin J, McCabe R. Improved kidney preservation by post cold-storage machine perfusion. <i>Cryobiology</i> 1988;25(6):513–14	Animal study
Corry RJ. A critical comparison of cold storage and dynamic perfusion of cadaver renal allografts. <i>Dial Transplant</i> 1979;8(3):207–10	Inappropriate outcome or comparator
Daemen JH, Heineman E, Kootstra G. Viability assessment of non-heart-beating donor kidneys during machine preservation. <i>Transplant Proc</i> 1995;27(5):2906–7	Inappropriate outcome or comparator
Daemen JHC, De Wit RJ, Bronkhorst MWG, Marcar ML, Yin M, Heineman E et al. Short-term outcome of kidney transplants from non-heart-beating donors after preservation by machine perfusion. <i>Transplant Int</i> 1996;9(Suppl. 1):S76–S80	Inappropriate outcome or comparator
Daemen JHC, de Vries B, Oomen APA, DeMeester J, Kootstra G. Effect of machine perfusion preservation on delayed graft function in non-heart-beating donor kidneys early results. <i>Transplant Int</i> 1997;10(4):317–22	Inappropriate outcome or comparator
Daemen JHC, de Vries B, Kootstra G. The effect of machine perfusion preservation on early function of non-heart-beating donor kidneys. <i>Transplant Proc</i> 1997;29(8):3489	Methods unclear
Degawa H, Matsuno N, Iwamoto H, Hama K, Nakamura Y, Narumi Y et al. Primary nonfunctioning grafts in cadaveric kidney transplantation. <i>Transplant Proc</i> 2000;32(7):1903–4	Methods unclear
Fabre E, Paradis V, Conti M, Eschwege P, Benoit G. Is renal preservation with pulsatile perfusion a model for reperfusion? <i>Transplant Proc</i> 2000;32(8):2742–3	Animal study
Florence LS, Christensen LL, Wolfe RA, Galloway J, Distant D, Hull D et al. 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. <i>Am J Transplant</i> 2007;7(1346, Suppl. 2):493	Methods unclear
Fuller BJ, Pegg DE. Assessment of renal preservation by normothermic bloodless perfusion. <i>Cryobiology</i> 1976;13(2):177–84	Inappropriate outcome or comparator
Gage F, Ali M, Alijani MR, Aquino AO, Barhyte DY, Callender CO et al. Comparison of static versus pulsatile preservation of matched-paired kidneys. <i>Transplant Proc</i> 1997;29(8):3644–5	Inappropriate outcome or comparator
Garcia JA, Holm A, Lagunas J, Camarena A. Static cold storage vs hypothermic pulsatile preservation in cadaveric kidney transplantation in a single institution (Mexico City). <i>Transplantation</i> 1999;67(7):591	Wrong cold storage solution
Goldstein MJ, Guarrera JV, Abreu-Goris M, Kapur S. Pulsatile-machine preservation versus colds storage in mate renal allografts. <i>Am J Transplant</i> 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. <i>Transplantation</i> 1977;23(5):437–43	Animal study
Grundmann R, Kurten K. Mechanical perfusion vs hypothermic storage for the preservation of hypotensively damaged kidneys. <i>Cryobiology</i> 1983;20(6):732–3	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. <i>Transplantation</i> 2004;77(8):1264–8	Inappropriate outcome or comparator
Guarrera JV, Polyak MMR, Arrington B, Boykin J, Brown T, Jean-Jacques M et al. Pushing the envelope in renal preservation: Improved results with novel perfusate modifications for pulsatile machine perfusion of cadaver kidneys. <i>Transplant Proc</i> 2004;36(5):1257–60	Inappropriate outcome or comparator
Halloran P, Aprile M. A Randomized prospective trial of cold-storage versus pulsatile perfusion for cadaver kidney preservation. <i>Transplantation</i> 1987;43(6):827–32	Wrong cold storage solution
Healthcare Insurance Board. <i>Preservation of non-heart-beating kidney donors – primary research</i> . Healthcare Insurance Board; 1998	Foreign language

Stored kidneys	Reason for exclusion
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. <i>Transplant Proc</i> 1987; <b>19</b> (1):2046	Wrong cold storage solution
Helfrich GB, Cutler JA, Kelley DJ, Delvalle CJ, Morres DN, Pechan BW <i>et al.</i> Cold-storage (CS) versus machine perfusion (MP) for preservation of cadaver kidneys from the same donor. <i>Kidney Int</i> 1985; <b>27</b> (1):342	Wrong cold storage solution
Henry ML, Tso P, Elkhammas EA, Davies EA, Pelletier RP, Bumgardner GL <i>et al.</i> Immediate renal allograft function following pulsatile preservation. <i>Transplantation</i> 2000; <b>69</b> (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. <i>J Heart Lung Transplant</i> 2007; <b>26</b> (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. <i>Transplant Proc</i> 1988; <b>20</b> (5):882–4	Not a comparative study
Jacobbi LM, Gage F, Kravitz D. Machine preservation is an effective evaluation measure for kidneys from asystolic donors. <i>Am J Kidney Dis</i> 2003; <b>41</b> (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. <i>Transplant Proc</i> 1989; <b>21</b> (1):1254–5	Animal study
Johnson CP, Roza AM, Adams MB. Local procurement with pulsatile perfusion gives excellent results and minimizes initial cost associated with renal transplantation. <i>Transplant Proc</i> 1990; <b>22</b> (2):385–7	Not a comparative study
Kievit JK, Oomen APA, de Vries B, Heineman E, Kootstra G. Update on the results of non-heart-beating donor kidney transplants. <i>Transplant Proc</i> 1997; <b>29</b> (7):2989–91	Inappropriate outcome or comparator
Koning OH, van Bockel JH, van der Woude FJ, 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. <i>Transplant Proc</i> 1995; <b>27</b> (1):752–3	Inappropriate outcome or comparator
Koyama H, Cecka JM, Terasaki PI. A comparison of cadaver donor kidney storage methods – pump perfusion and cold-storage solutions. <i>Clin Transplant</i> 1993; <b>7</b> (2):199–205	Inappropriate outcome or comparator
Kozaki M, Miyamoto K, Tamaki I, Sakurai E, Tokuchi M, Sugie S <i>et al.</i> Comparative study of hypothermic pulsatile and nonpulsatile perfusion for kidney preservation. <i>Artif Organs</i> 1984; <b>8</b> (2):245	No usable data
Kozaki K, Sakurai E, Tamaki I, Matsuno N, Saito A, Furuhashi K <i>et al.</i> Usefulness of continuous hypothermic perfusion preservation for cadaveric renal crafts in poor condition. <i>Transplant Proc</i> 1995; <b>27</b> (1):757–8	Wrong cold storage solution
Kozaki K, Sakurai E, Uchiyama M, Matsuno N, Kozaki M, Nagao T. Usefulness of continuous hypothermic perfusion preservation for cadaveric renal high risk grafts. <i>Transplantation</i> 1999; <b>67</b> (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. <i>Transplant Proc</i> 2000; <b>32</b> (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. <i>Transplant Proc</i> 2002; <b>34</b> (7):2592–7	Inappropriate outcome or comparator
Kumar MSA, Samhan M, Alsabawi N, Alabdullah IH, Silva OSG, White AG <i>et al.</i> Preservation of cadaveric kidneys longer than 48 hours – comparison between Euro-Collins solution, UW solution, and machine perfusion. <i>Transplant Proc</i> 1991; <b>23</b> (5):2392–3	Inappropriate outcome or comparator
Kumar MSA, Stephan R, Chui J, Brezin J, Lyons P, Katz SM <i>et al.</i> Comparative study of cadaver donor kidneys preserved in University of Wisconsin solution for less than or longer than 30 hours. <i>Transplant Proc</i> 1993; <b>25</b> (3):2265–6	Inappropriate outcome or comparator
Kusaka M, Kubota Y, Sasaki H, Maruyama T, Hayakawa K, Shiroki R <i>et al.</i> Is pulsatile perfusion necessary for renal transplantation engrafting kidneys from cardiac death donors? <i>Transplant Proc</i> 2006; <b>38</b> (10):3388–9	Methods unclear

continued

Stored kidneys	Reason for exclusion
Kwiatkowski A, Danielewicz R, Polak W, Michalak G, Paczek L, Walaszewski J <i>et al.</i> Storage by continuous hypothermic perfusion for kidney harvested from hemodynamically unstable donors. <i>Transplant Proc</i> 1996; <b>28</b> (1):306–7	Inappropriate outcome or comparator
Kwiatkowski A, Wszola M, Kosieradzki M, Danielewicz R, Ostrowski K, Domagala P <i>et al.</i> Machine perfusion preservation improves renal allograft survival. <i>Am J Transplant</i> 2007; <b>7</b> (8):1942–7	Inappropriate outcome or comparator
Kyllonen LEJ, Salmela KT, Eklund BH, Halme LEH, Hockerstedt KA, Isoniemi HM <i>et al.</i> Long-term results of 1047 cadaveric kidney transplantations with special emphasis on initial graft function and rejection. <i>Transplant Int</i> 2000; <b>13</b> (2):122–8	Not about kidney storage
Laskowski IA, Pratschke J, Wilhelm MJ, Paz D, Tilney NL. Non-heart-beating kidney donors. <i>Clin Transplant</i> 1999; <b>13</b> (4):281–6	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. <i>Transplant Proc</i> 1977; <b>9</b> (3):1517–19	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. <i>Transplant Proc</i> 1995; <b>27</b> (5):2962–4	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. <i>Clin Transplant</i> 1996; <b>10</b> (3):233–6	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. <i>Transplant Proc</i> 2000; <b>32</b> (1):186–7	Not about kidney storage
Marshall VC, Ross H, Scott D. Cadaveric renal allografts – comparison of preservation by ice storage and continuous perfusion. <i>Aust N Z J Surg</i> 1977; <b>47</b> (1):111	No usable data
Marshall VC, Biguzas M, Jablonski P, Scott DF, Howden BO, Thomas AC <i>et al.</i> UW solution for Kidney Preservation. <i>Transplant Proc</i> 1990; <b>22</b> (2):496–7	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. <i>Transplant Proc</i> 1993; <b>25</b> (6):3095–6	Inappropriate outcome or comparator
Matsuno N, Kozaki M, Sakurai E, Uchiyama M, Iwahori T, Kozaki K <i>et al.</i> Effect of combination insitu cooling and machine perfusion preservation on non-heart-beating donor kidney procurement. <i>Transplant Proc</i> 1993; <b>25</b> (1):1516–17	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. <i>Transplantation</i> 1994; <b>57</b> (2):293–4	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. <i>Transplant Proc</i> 1996; <b>28</b> (3):1551–2	Inappropriate outcome or comparator
Matsuno N, Kozaki K, Degawa H, Narumi Y, Suzuki N, Kikuchi K <i>et al.</i> Importance of machine perfusion flow in kidney preservation. <i>Transplant Proc</i> 1999; <b>31</b> (5):2004–5	Inappropriate outcome or comparator
Matsuoka L, Shah T, Aswad S, Bunnapradist S, Cho Y, Mendez RG <i>et al.</i> Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. <i>Am J Transplant</i> 2006; <b>6</b> (6):1473–8	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. <i>Transplantation</i> 1990; <b>50</b> (2):230–3	Wrong cold storage solution
Merkel FK, Geroulis N, Thornton B, Jensik SC. Perfusion Preservation of human cadaver kidneys – an 8-year experience. <i>Transplant Proc</i> 1982; <b>14</b> (1):86–7	Inappropriate outcome or comparator
Mittal VK, Kaplan MP, Rosenberg JC, Allaben RA, Toledo-Pereyra LH. Pulsatile perfusion: better than hypothermic storage with cyclosporine as an immunosuppressant. <i>Dial Transplant</i> 1985; <b>14</b> (3):136–40	Wrong cold storage solution
Mittal VK, Toledo P, Kaplan MP, Rosenberg JC, Allaben RD. Effect of preservation method on function in the cyclosporine era. <i>Transplant Proc</i> 1985; <b>17</b> (6):2815–17	Inappropriate outcome or comparator
Mohacsi PJ, Herbert KL, Thompson JF. Human kidney preservation with University of Wisconsin solution – an initial report of the Australian experience. <i>Transplant Proc</i> 1992; <b>24</b> (1):256–7	Inappropriate outcome or comparator



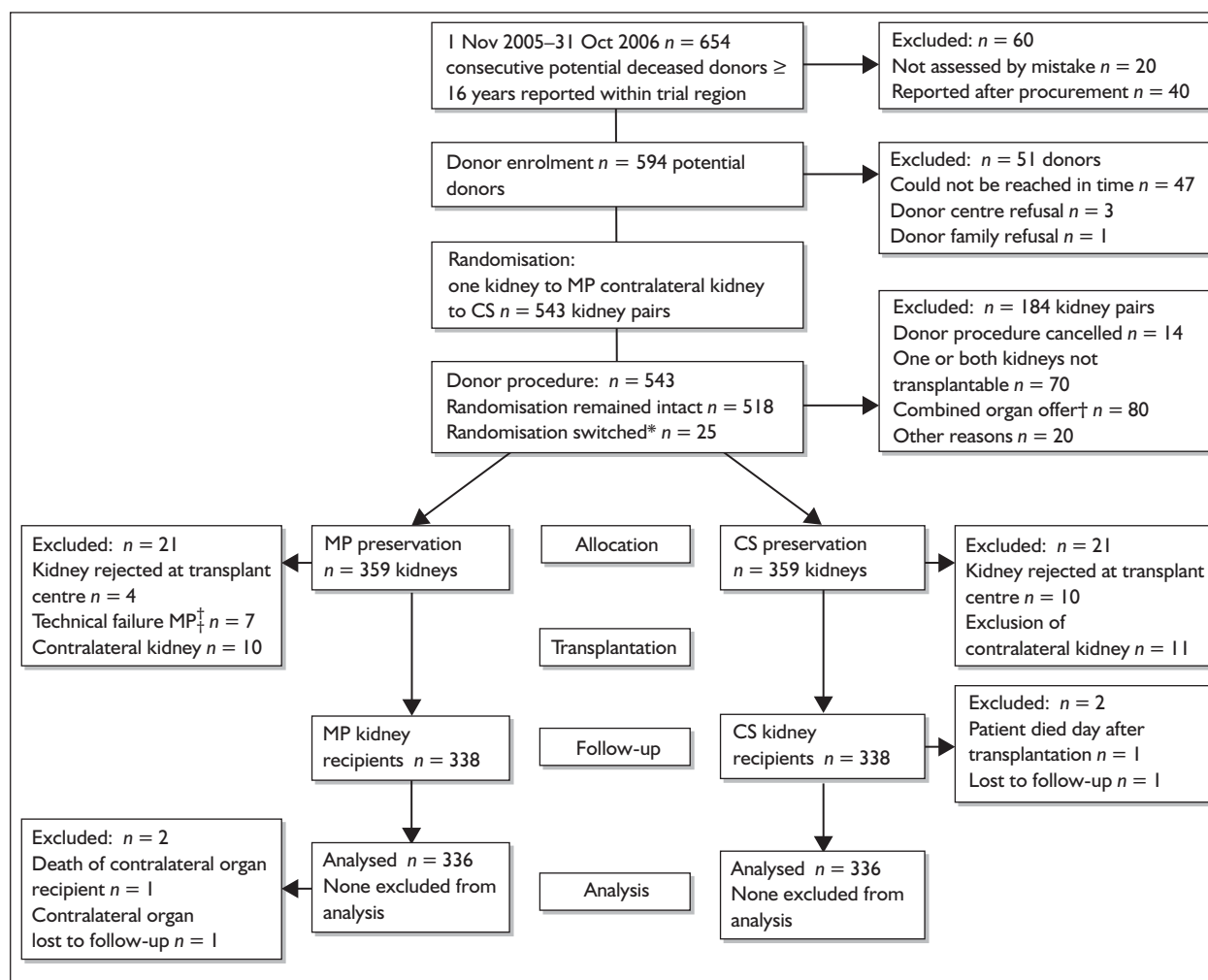
Stored kidneys	Reason for exclusion
Mozes MF, Finch WT, Reckard CR, Merkel FK, Cohen C. Comparison of cold storage and machine perfusion in the preservation of cadaver kidneys – a prospective, randomized study. <i>Transplant Proc</i> 1985;17(1):1474–7	Inappropriate outcome or comparator
Muhlbacher F, Langer F, Mittermayer C. Preservation solutions for transplantation. <i>Transplant Proc</i> 1999;31(5):2069–70	Literature review or editorial
Net M, Lara EE, Peri L, Saval N, Calsamiglia J, Agusti E <i>et al.</i> Pulsatile renal perfusion machine: viability prediction and improved preservation of marginal kidneys. <i>Am J Transplant</i> 2007;7(194, Suppl. 2):197	No usable data
Nghiem DD, Schukal JA, Corry RJ. Cadaver kidney preservation beyond 40 hours – superiority of machine preservation over cold storage. <i>Transplant Proc</i> 1986;18(3):564–5	Inappropriate outcome or comparator
Nicholson M. Kidney transplantation from asystolic donors. <i>Br J Hosp Med</i> 1996;55(1–2):51–6	Literature review or editorial
Nunes P, Mota A, Figueiredo A, Macário F, Rolo F, Dias V <i>et al.</i> Efficacy of renal preservation: comparative study of Celsior and University of Wisconsin solutions. <i>Transplant Proc</i> 2007;39(8):2478–9	Included living donors
Opelz G, Terasaki PI. Advantage of cold storage over machine perfusion for preservation of cadaver kidneys. <i>Transplantation</i> 1982;33(1):64–8	Wrong cold storage solution
Opelz G, Wujciak T. Comparative analysis of kidney preservation methods. <i>Transplant Proc</i> 1996;28(1):87–90	Data overlap with more recent study
Orlic P, Zelic M, Petrosic N, Maricic A, Zambelli M, Bacic I <i>et al.</i> Use of non-heart-beating donors: preliminary experience with perfusion <i>in situ</i> . <i>Transplant Proc</i> 1999;31(5):2097–8	Not about kidney storage
Peri L, Net M, Saval N, Lara E, Agud A, Ruiz A <i>et al.</i> Pulsatile perfusion kidney preservation improves kidney preservation and provides information about organ viability. <i>Eur Urol Suppl.</i> 2007;6(2):93	Methods unclear
Pirsch JD, D'Alessandro AM, Knechtle SJ, Kalayoglu M, Belzer FO, Sollinger HW. Simultaneous kidney–pancreas transplantation at the University of Wisconsin. <i>Transplant Proc</i> 1993;25(4):33–4	Inappropriate outcome or comparator
Plata-Munoz JJ, Contractor H, Muthusamy A, Shina S, Roy D, Darby C <i>et al.</i> Central role of pulsatile perfusion on preservation of kidneys from controlled non-heart-beating donors. <i>Am J Transplant</i> 2007;7(188, Suppl. 2):195	Methods unclear
Ploeg RJ, Goossens D, Camesi D, McAnulty JF, Southard JH, Belzer FO. Kidney preservation with Belzer's new pancreas preservation solution. <i>Cryobiology</i> 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. <i>Transplant Proc</i> 1988;20(1):935–8	Animal study
Polyak MM, Arrington B, Hardy MA, Stubenbord WT, Kinkhabwala M. The state of renal preservation for transplantation in New York. <i>Transplant Proc</i> 1999;31(5):2091–3	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. <i>Transplantation</i> 1999;67(9):S562	Methods unclear
Polyak MMR, Arrington BO, Stubenbord WT, Boykin J, Brown T, Jean-Jacques MA <i>et al.</i> The influence of pulsatile preservation on renal transplantation in the 1990s. <i>Transplantation</i> 2000;69(2):249–58	Inappropriate outcome or comparator
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 preservation. <i>Transplantation</i> 2000;69(8):S262	Technical paper
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. <i>Cryobiology</i> 1984;21(6):701–2	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. <i>Cryobiology</i> 1985;22(2):161–7	Animal study
Rosenthal JT, Herman JB, Taylor RJ, Broznick B, Hakala TR. Comparison of pulsatile machine perfusion with cold storage for cadaver kidney preservation. <i>Transplantation</i> 1984;37(4):425–6	Wrong cold storage solution

continued

Stored kidneys	Reason for exclusion
Santiago EA, Mason RV, Campos RA, Moberg AW, Najarian JS, Mozes MF. Comparative analysis of perfusion and nonperfusion methods for renal preservation. <i>Surgery</i> 1972; <b>72</b> (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. <i>Am J Transplant</i> 2005; <b>5</b> (7):1681–8	Methods unclear
Scott DF, Atkins RC. Results of ice storage and perfusion storage of kidneys prior to transplantation. <i>Aust N Z J Med</i> 1974; <b>4</b> (4):436	Wrong cold storage solution
Scott DF, Whiteside D, Redhead J, Atkins RC. Ice storage versus perfusion for preservation of kidneys before transplantation. <i>Br Med J</i> 1974; <b>4</b> (5936):76–7	Wrong cold storage solution
Sellers MT, Gallichio MH, Hudson SL, Young CJ, Bynon JS, Eckhoff DE <i>et al.</i> Improved outcomes in cadaveric renal allografts with pulsatile preservation. <i>Clin Transplant</i> 2000; <b>14</b> (6):543–9	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. <i>Lancet</i> 1975; <b>2</b> (7929):287–90	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. <i>Aust N Z J Med</i> 1976; <b>6</b> (1):94	No usable data
Slooff MJH, Vanderwijk J, Rijkman BG, Kootstra G. Machine perfusion versus cold storage for preservation of kidneys before transplantation. <i>Arch Chir Neerl</i> 1978; <b>30</b> (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. <i>Transplantation</i> 1978; <b>26</b> (4):228–32	Animal study
Stratta RJ, Moore PS, Farney AC, Rogers J, Hartmann EL, Reeves-Daniel A <i>et al.</i> Influence of pulsatile perfusion preservation on outcomes in kidney transplantation from expanded criteria donors. <i>J Am Coll Surg</i> 2007; <b>204</b> (5):873–82	Inappropriate outcome or comparator
Suarez JF, Riera L, Franco E, Ruiz R, Roig M, Torras J <i>et al.</i> Preservation of kidneys from marginal donors with pulsatile perfusion machine. <i>Transplant Proc</i> 1999; <b>31</b> (6):2292–3	Inappropriate outcome or comparator
Szust J, Olson L, Cravero L. A comparison of OPO pulsatile machine preservation practices and results. <i>J Transplant Coord</i> 1999; <b>9</b> (2):97–100	Literature review or editorial
Tisone G, Orlando G, Pisani F, Iaria G, Negrini S, Pollicita S <i>et al.</i> Gravity perfusion versus high-pressure perfusion in kidney transplantation: results from a prospective randomized study. <i>Transplant Proc</i> 1999; <b>31</b> (8):3386–7	Inappropriate outcome or comparator
Toledo P, Whitten JL, Baskin S, McNichol LJ. Extending the limits of renal preservation (greater than or equal to 40 hours) – effect of preservation method and immunosuppressive regimen. <i>Transplant Proc</i> 1988; <b>20</b> (5):938–9	Inappropriate outcome or comparator
van der Vliet JA, 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. <i>Transplant Proc</i> 2001; <b>33</b> (1–2):847	Inappropriate outcome or comparator
Vaughn WK, Mendezpicon G, Humphries AL. Cold storage versus perfusion for cadaver kidneys transplanted by Seopf institutions. <i>Cryobiology</i> 1979; <b>16</b> (6):619	Methods unclear
Veller MG, Botha JR, Britz RS, Gecelter GR, Beale PG, Margolius LP <i>et al.</i> Renal allograft preservation – a comparison of University of Wisconsin solution and of hypothermic continuous pulsatile perfusion. <i>Clin Transplant</i> 1994; <b>8</b> (2):97–100	Inappropriate outcome or comparator
Weinerth JL, Hendrix PC, Anderson EE. Preservation of the cadaveric kidney for transplantation. <i>South Med J</i> 1974; <b>67</b> (12):1457–8	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. <i>Health Technol Assess</i> 2003; <b>7</b> (25)	No usable data
Xenos ES. Perfusion storage versus static storage in kidney transplantation: is one method superior to the other? <i>Nephrol Dial Transplant</i> 1997; <b>12</b> (2):253–4	Literature review or editorial
Yland MJ, Anaise D, Ishimaru M, Rapaport FT. New pulsatile perfusion method for nonheart-beating cadaveric donor organs – a preliminary report. <i>Transplant Proc</i> 1993; <b>25</b> (6):3087–90	Inappropriate outcome or comparator
Yland MJ, Nakayama Y, Abe Y, Rapaport FT. Organ preservation by a new pulsatile perfusion method and apparatus. <i>Transplant Proc</i> 1995; <b>27</b> (2):1879–82	Inappropriate outcome or comparator
Zongli H, Zhilian M, Jingqin L, Haikuan Z. Preservation of cadaveric kidney allografts. <i>Transplant Proc</i> 1992; <b>24</b> (4):1351–2	Wrong cold storage solution

## Appendix 5

### Flow of kidneys in the Machine Preservation Trial



**FIGURE 44** Flow chart of recruited kidneys in the Machine Preservation Trial. \*Switching randomisation was only allowed when vascular anatomy made one kidney less suitable for the machine. †Whenever one or both kidneys were offered together with another organ to one recipient. ‡None of these failures rendered the graft unsuitable for transplantation. When machine perfusion failed, the kidney was automatically cold stored inside the machine. §Cause of death was not transplant related. [Source: Moers C, Smits J, Maathuis MH, Treckmann J, van Gelder F, Napieralski B et al. Transplantation after hypothermic machine preservation versus static cold storage of deceased donor kidneys: a prospective randomized controlled trial. *N Engl J Med* 2009;**360**(1):7–19. Copyright © 2009 Massachusetts Medical Society. All rights reserved.]



## Appendix 6

### CHEC list assessment of economic evaluations

Criteria	Wight <i>et al.</i> 2003 <sup>47</sup>	Costa <i>et al.</i> 2007 <sup>49</sup>
	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

CS, cold storage; DGF, delayed graft function; MP, machine perfusion; NA, not available; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years.  
 The CHEC list for assessing quality of economic evaluations (Evers *et al.* 2005<sup>65</sup>) incorporates all but one of the widely-used critical appraisal questions recommended by Drummond *et al.* 2005.<sup>82</sup>



# Appendix 7

## PenTAG model transitions

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)

DGF, delayed graft function; DYU, on dialysis unsuitable for re-transplant; DYW, on dialysis awaiting re-transplant; FKD, failing kidney after delayed graft function; FKI, failing kidney after immediate graft function; IGF, immediate graft function; STX, subsequent transplant.





## Appendix 8

### Base-case outputs from the PenTAG model by age group

#### Summary age-related outputs for each comparison

**TABLE 47** *LifePort versus ViaSpan, PPART trial – summary model outputs by age group*

Age group	Incremental costs (£)	Incremental QALYs	ICER
ViaSpan 18–34	173,086	12.69	
LifePort 18–34	176,034	12.63	Is dominated
Difference	2948	–0.06	
ViaSpan 35–44	154,771	10.97	
LifePort 35–44	157,324	10.91	Is dominated
Difference	2553	–0.06	
ViaSpan 45–54	137,699	8.84	
LifePort 45–54	139,793	8.77	Is dominated
Difference	2094	–0.07	
ViaSpan 55–64	117,754	6.84	
LifePort 55–64	119,277	6.77	Is dominated
Difference	1522	–0.07	
ViaSpan 65+	92,794	4.78	
LifePort 65+	93,728	4.71	Is dominated
Difference	934	–0.07	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.  
All incremental costs and QALYs shown are summary totals discounted at 3.5%.

**TABLE 48** LifePort versus ViaSpan, MPT trial – summary model outputs by age group

Age group	Incremental costs (£)	Incremental QALYs	ICER
ViaSpan 18–34	178,347	13.23	Is dominated
LifePort 18–34	172,446	13.45	
Difference	–5902	0.22	
ViaSpan 35–44	159,370	11.44	Is dominated
LifePort 35–44	154,557	11.66	
Difference	–4813	0.22	
ViaSpan 45–54	141,320	9.22	Is dominated
LifePort 45–54	137,741	9.45	
Difference	–3579	0.23	
ViaSpan 55–64	120,075	7.12	Is dominated
LifePort 55–64	117,933	7.34	
Difference	–2142	0.22	
ViaSpan 65+	93,828	4.94	Is dominated
LifePort 65+	93,018	5.13	
Difference	–811	0.19	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.  
All incremental costs and QALYs shown are summary totals discounted at 3.5%.

**TABLE 49** LifePort versus Marshall's Soltran – summary model outputs by age group

Age group	Incremental costs (£)	Incremental QALYs	ICER
Marshall's Soltran 18–34	181,279	11.90	Is dominated
LifePort 18–34	162,191	13.06	
Difference	–19088	1.16	
Marshall's Soltran 35–44	161,068	10.25	Is dominated
LifePort 35–44	146,627	11.35	
Difference	–14441	1.10	
Marshall's Soltran 45–54	142,460	8.18	Is dominated
LifePort 45–54	131,941	9.20	
Difference	–10519	1.02	
Marshall's Soltran 55–64	121,016	6.29	Is dominated
LifePort 55–64	114,412	7.16	
Difference	–6604	0.87	
Marshall's Soltran 65+	94,691	4.38	Is dominated
LifePort 65+	91,691	5.02	
Difference	–3000	0.63	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.  
All incremental costs and QALYs shown are summary totals discounted at 3.5%.

**TABLE 50** *ViaSpan versus Marshall's Soltran— summary model outputs by age group*

Age group	Incremental costs (£)	Incremental QALYs	ICER
ViaSpan 18–34	192,205	12.06	
Marshall's Soltran 18–34	193,675	12.01	Is dominated
Difference	1470	–0.05	
ViaSpan 35–44	169,671	10.35	
Marshall's Soltran 35–44	170,772	10.29	Is dominated
Difference	1101	–0.05	
ViaSpan 45–54	148,749	8.24	
Marshall's Soltran 45–54	149,511	8.19	Is dominated
Difference	762	–0.05	
ViaSpan 55–64	124,849	6.31	
Marshall's Soltran 55–64	125,257	6.26	Is dominated
Difference	409	–0.05	
ViaSpan 65+	963,61	4.39	
Marshall's Soltran 65+	964,50	4.36	Is dominated
Difference	89	–0	

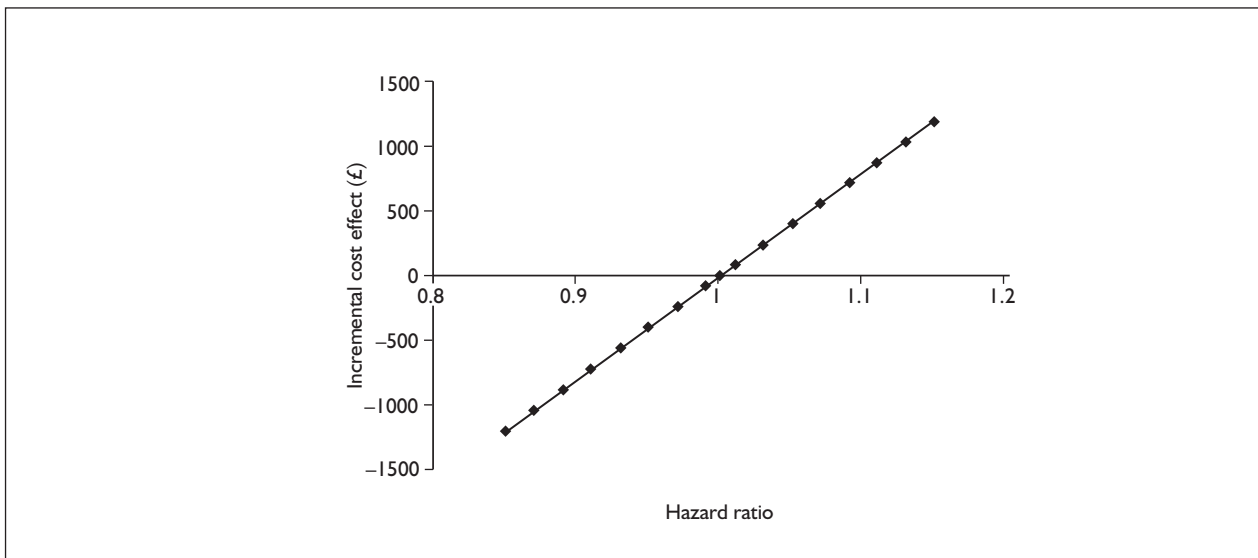
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.  
All incremental costs and QALYs shown are summary totals discounted at 3.5%.



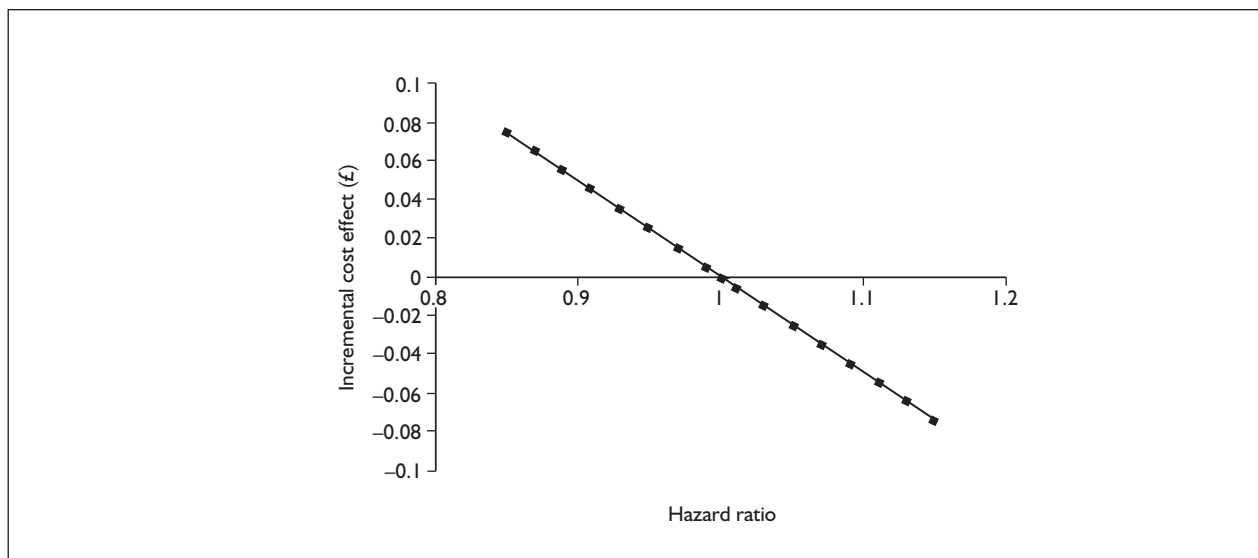
## Appendix 9

### Hazard ratios for graft survival

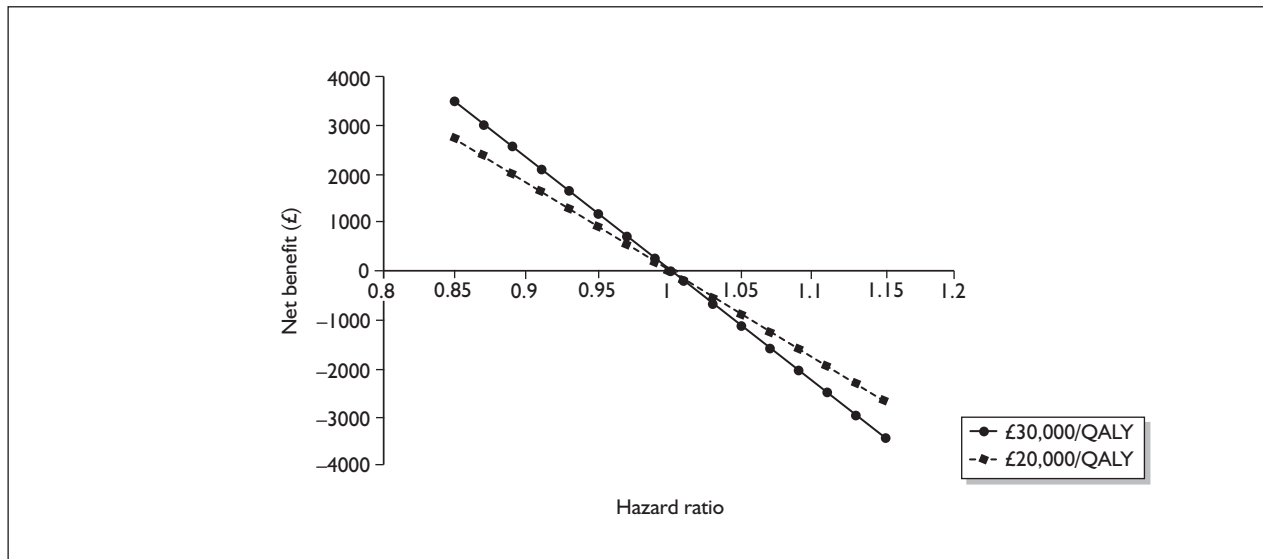
The effect of changes to the HR for graft survival between arms is shown in *Figures 45–47*.



**FIGURE 45** Cost effect of incremental hazard ratio for graft survival between comparator arms.



**FIGURE 46** QALY effect of incremental hazard ratio for graft survival between comparator arms.



**FIGURE 47** Net benefit effect of incremental hazard ratio for graft survival between comparator arms.



# Appendix 10

## Probabilistic sensitivity analyses

In 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 51* lists the standard data set parameters and distributions used in the model for the PSA. The variance attached to each parameter has been assessed from the available evidence (e.g. CIs). Where such data have not been available, estimates of the variance have been used to characterise the distribution.

**TABLE 51** Sampled distributions for fixed values of standard data set used in probabilistic sensitivity analysis

	Mean value (%)	SE (%)	Distribution
<b>Age group weightings</b>			
18–34	18.18	1.8	Normal
35–44	24.21	2.4	Normal
45–54	24.86	2.5	Normal
55–64	22.62	2.3	Normal
65+	10.13	1.0	Normal
	Mean value	Range	Distribution
<b>Utilities</b>			
Decrement for transplant vs age norms	0.1	0–0.2	Uniform
Decrement for dialysis vs transplant	0.12	0.07–0.17	Uniform
	Mean value	SE	Distribution
<b>Costs (£)</b>			
Storage costs			
Marshall's Soltran	49.73	5.84	Normal
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
<b>Functioning graft costs</b>			
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	16,413	3059	Normal
Explant operation cost	4134	656	Normal
Dialysis costs			

*continued*

**TABLE 51** Sampled distributions for fixed values of standard data set used in probabilistic sensitivity analysis (continued)

	Mean value (%)	SE (%)	Distribution
Peritoneal dialysis per month	1793.6	35.8	Normal
Haemodialysis per month	23,30.03	46.6	Normal
Outpatient reviews per month	19.12	8.14	Normal
<b>Peritoneal dialysis by age group (%)</b>			
18–34	58.8	1.8	Normal
35–44	57.7	0.4	Normal
45–54	55.4	1.0	Normal
55–64	53.9	2.0	Normal
65+	43.2	3.2	Normal
<b>Transitions</b>			
<i>Graft failures suitable for re-transplant by age group (%)</i>			
18–34	0.27	0.023	Normal
35–44	0.25	0.031	Normal
45–54	0.19	0.026	Normal
55–64	0.14	0.026	Normal
65+	0.05	0.016	Normal
<i>Probability of re-transplant from wait list by age group</i>			
18–34	0.0224	0.022	Normal
35–44	0.0222	0.022	Normal
45–54	0.0191	0.019	Normal
55–64	0.0143	0.014	Normal
65+	0.0051	0.005	Normal
<i>Probability per month of re-transplant failure</i>	0.0058	0.0006	Normal
SE, standard error.			

### 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 IGF
- graft survival for patients who experienced graft function after DGF.

Standard regression methods were used to calculate the lambda and gamma coefficients 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 data set

used in the model and did not vary between the arms or comparisons.

Graft survival curves (bullet points 3 and 4) 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 52*.

For the 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 coefficients drawn from a bivariate 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 coefficients in the model is described below.

### Method for estimation of standard error and correlation coefficient values for lambda and gamma used in the PSA

Standard error values for the survival curves were calculated using estimates of the 95% CIs 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 bivariate normal parameterisation of this matrix was then conducted using regression techniques to calculate the respective lambda and gamma means, standard errors and the correlation coefficient 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 covariance of the survival curve and the estimated correlation between the lambda and gamma coefficients.

The standard error values and correlation coefficient for each of the sample lambda and gamma distributions for both the patient survival curves and the graft survival curves for each comparator arm are shown in *Tables 52–56*.

**TABLE 52** Weibull coefficients used for patient survival curves (patients with functioning graft) in probabilistic sensitivity analysis

Age group	Mean value	Range	Distribution
<b>18–34</b>			
Lambda coefficient	0.0009	0.0002	Normal
Gamma coefficient	1.1230	0.0200	Normal
Correlation coefficient	–0.9961		
<b>35–44</b>			
Lambda coefficient	0.0013	0.0001	Normal
Gamma coefficient	1.1062	0.0400	Normal
Correlation coefficient	–0.9961		
<b>45–54</b>			
Lambda coefficient	0.0028	0.0005	Normal
Gamma coefficient	1.0183	0.0500	Normal
Correlation coefficient	–0.9947		
<b>55–64</b>			
Lambda coefficient	0.0066	0.0002	Normal
Gamma coefficient	0.9180	0.0200	Normal
Correlation coefficient	–0.9947		
<b>65+</b>			
Lambda coefficient	0.0013	0.0009	Normal
Gamma coefficient	0.8713	0.0243	Normal
Correlation coefficient	–0.8995		

**TABLE 53** Weibull coefficients used for graft survival curves in probabilistic sensitivity analysis for PPART data comparison of ViaSpan versus LifePort

	Mean value	SE	Distribution
<b>Storage costs (£)</b>			
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
	Mean value	Alpha, beta	Distribution
<b>DGF post transplant (%)</b>			
ViaSpan	55.6	(25,20)	Beta
LifePort	57.8	(26,19)	Beta
<b>Primary non-function (%)</b>			
ViaSpan	2.2	(1,24)	Beta
LifePort	0	(1,49)	Beta
	Mean value	SE	Distribution
<b>Graft survival post IGF</b>			
<i>ViaSpan and LifePort – Weibull coefficients</i>			
Lambda	0.0256	0.0055	Normal
Gamma	0.3499	0.1065	Normal
Correlation coefficient	-0.8967		
<b>Graft survival post DGF</b>			
<i>ViaSpan and LifePort – Weibull coefficients</i>			
Lambda	0.0118	0.0033	Normal
Gamma	0.6494	0.0580	Normal
Correlation coefficient	-0.8599		
DGF, delayed graft function; IGF, immediate graft function; SE, standard error.			

**TABLE 54** Weibull coefficients used for graft survival curves in probabilistic sensitivity analysis for MPT data comparison of ViaSpan versus LifePort

	Mean value	SE	Distribution
<b>Storage costs (£)</b>			
ViaSpan	262.53	5.84	Normal
LifePort	736.55	100.08	Normal
	Mean value	Alpha, beta	Distribution
<b>DGF post transplant (%)</b>			
ViaSpan	26.5	(89, 247)	Beta
LifePort	20.8	(70,266)	Beta
<b>Primary non-function (%)</b>			
ViaSpan	4.8	(16,220)	Beta
LifePort	2.1	(7,229)	Beta
	Mean value	SE	Distribution
<b>Graft survival post IGF</b>			
<i>ViaSpan and LifePort – Weibull coefficients</i>			
Lambda	0.0052	0.0021	Normal
Gamma	0.5923	0.1445	Normal
Correlation	-0.9101		
<b>Graft survival post DGF</b>			
<i>ViaSpan – Weibull coefficients</i>			
Lambda	0.0542	0.0201	Normal
Gamma	0.5592	0.0974	Normal
Correlation	-0.7000		
<i>LifePort – Weibull coefficients</i>			
Lambda	0.0111	0.0025	Normal
Gamma	0.8057	0.1024	Normal
Correlation	-0.9214		
DGF, delayed graft function; IGF, immediate graft function; SE, standard error.			

**TABLE 55** Weibull coefficients used for graft survival curves in probabilistic sensitivity analysis for comparison of Marshall's Soltran versus LifePort

	Mean value	SE	Distribution
<b>Storage costs (£)</b>			
Marshall's Soltran	49.73	5.84	Normal
LifePort	736.55	100.08	Normal
	Mean value	Alpha, beta	Distribution
<b>DGF post transplant (%)</b>			
Marshall's Soltran	83.3	(25, 5)	Beta
LifePort	53.3	(16,14)	Beta
	Mean value	SE	Distribution
<b>Graft survival (all patients)</b>			
<i>Marshall's Soltran – Weibull coefficients</i>			
Lambda	0.0157	0.00527	Normal
Gamma	0.5975	0.19	Normal
Correlation coefficient	-0.823		
<i>LifePort – Weibull coefficients</i>			
Lambda	0.0052	0.0012	Normal
Gamma	0.5975	0.162	Normal
Correlation coefficient	-0.8782		
DGF, delayed graft function; SE, standard error.			

**TABLE 56** Weibull coefficients used for graft survival curves in probabilistic sensitivity analysis for comparison of ViaSpan versus Marshall's Soltran

	Mean value	SE	Distribution
<b>Graft survival (all patients)</b>			
<i>ViaSpan – Weibull coefficients</i>			
Lambda	0.0358	0	NA
Gamma	0.5158	0	NA
Correlation coefficient	NA		
<i>Marshall's Soltran – Weibull coefficients</i>			
Lambda	0.0390	0.006129	Normal
Gamma	0.5158	0.04089	Normal
Correlation coefficient	-0.99586		
NA, not applicable; SE, standard error.			



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Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).

By Donnan PT, McLernon D, Dillon JF, Ryder S, Roderick P, Sullivan F, *et al.*

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A systematic review of presumed consent systems for deceased organ donation.

By Rithalia A, McDaid C, Suekarran S, Norman G, Myers L, Sowden A.

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Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial.

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A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).

By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al.*

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Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making.

By Andronis L, Barton P, Bryan S.

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By Ward S, Pilgrim H, Hind D.

Docetaxel for the adjuvant treatment of early node-positive breast cancer: a single technology appraisal.

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The use of paclitaxel in the management of early stage breast cancer.

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Rituximab for the first-line treatment of stage III/IV follicular non-Hodgkin's lymphoma.

By Dundar Y, Bagust A, Hounsome J, McLeod C, Boland A, Davis H, *et al.*

Bortezomib for the treatment of multiple myeloma patients.

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Fludarabine phosphate for the first-line treatment of chronic lymphocytic leukaemia.

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Cetuximab plus radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck.

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Psychological interventions for postnatal depression: cluster randomised trial and economic evaluation. The PoNDER trial.

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The effect of different treatment durations of clopidogrel in patients with non-ST-segment elevation acute coronary syndromes: a systematic review and value of information analysis.

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Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care.

By Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, *et al.*

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A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial.

By Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al.*, on behalf of the 3CPO study investigators.

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Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation.

By Ara R, Pandor A, Stevens J, Rees A, Rafia R.

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Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation.

By Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al.*

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Methods to identify postnatal depression in primary care: an integrated evidence synthesis and value of information analysis.

By Hewitt CE, Gilbody SM, Brealey S, Paulden M, Palmer S, Mann R, *et al.*

**No. 37**

A double-blind randomised placebo-controlled trial of topical intranasal corticosteroids in 4- to 11-year-old children with persistent bilateral otitis media with effusion in primary care.

By Williamson I, Bengt S, Barton S, Petrou S, Letley L, Fasey N, *et al.*





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