

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

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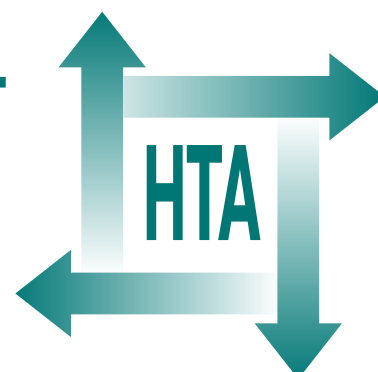
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## *Executive summary*

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## 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.

## Publication

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# NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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