Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Protocol

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1 PROJECT TITLE

The effectiveness and cost-effectiveness of machine perfusion systems and cold static storage of donated kidneys

2 TAR TEAM PenTAG

3 Plain English Summary

This project will review the evidence for the use of cold machine perfusion systems and cold storage solutions for the preservation of donated kidneys from deceased heart-beating and non-heart-beating donors. Cold machine perfusion pumps a preservation solution through the retrieved donor kidney whilst it is being transported to the recipient or stored awaiting implantation, with the aim of supplying nutrients and removing waste products. Cold storage is a simple system of preserving the donated kidney by surrounding it in preservation fluid and keeping it cool by packing it in an ice box. The assessment will also assess whether these treatments are likely to be considered good value for money for the NHS.

4 The decision problem

4.1 Purpose

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

Most kidneys for transplantation are obtained from cadaveric 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. The availability of organs from this type of donor has declined by about 20% over the last decade, possibly because of a reduction in fatal road traffic accidents and a decrease in the number of deaths from intracranial haemorrhage.

One means of expanding the donor pool is to use organs retrieved from non-heart-beating donors (people in whom the process of organ retrieval begins after cessation of heartbeat). Non-heart-beating donors fall into five categories according to the modified Maastricht criteria.

Category 1: Dead on arrival at hospital. In this case the moment of sudden death must have been witnessed and the time at which it occurred documented as well as pre-admission resuscitation.

Category 2: Unsuccessful resuscitation. These individuals have undergone cardiopulmonary resuscitation following collapse, usually in the Accident and Emergency department.

Category 3: Awaiting cardiac arrest. These are a group of people for whom imminent death is inevitable, but who do not fulfil criteria for brainstem death testing.

Category 4: Cardiac arrest in a brainstem dead cadaver. A donor falls into this category if death has been diagnosed by brainstem criteria and then unexpected cardiac arrest occurs before organ retrieval has taken place.

Category 5: Unexpected cardiac arrest in an ITU or critical care unit. This category has been added to the other four recently.

The use of kidneys from non-heart-beating donors is not new. Before the concept of brainstem death was legally defined in the 1970s, all cadaveric kidneys came from non-heart-beating donors.

The critical difference between organs from non-heart-beating and heart-beating donors is the duration of ‘warm ischaemic time’. This is the time when the donor is asystolic before the kidney has been removed or perfusion begun. This asystolic warm period does not occur in heart-beating donors. Cold ischaemic time is from the start of cold perfusion, through the organ recovery and cold storage period until it is removed from the ice and the anastomois period of re-implanting in the recipient begins. This last anastomois period is also referred to as warm ischaemic; however, the kidney is still cold until it begins to warm up when perfused by the recipients’ blood. Both warm ischaemic time and cold ischaemic time are damaging to organs but, after retrieval, cooling the organ suppresses the metabolic rate and so reduces the rate of damage. In static cold storage, the kidney is simply flushed through with a preservation solution, and kept on ice.

In non-heart-beating donors (particularly uncontrolled non-heart-beating donors, in categories 1, 2 and 5) warm ischaemic time may be prolonged. As a result, kidneys from non-heart-beating donors tend to suffer higher rates of primary non-function (when the graft never works), delayed graft function and reduced long term graft survival than those from heart-beating donors. Delayed graft function is a delay in recovery of renal function post transplantation. It gives rise to the need for continuing dialysis, longer hospitalisation and is also associated with poorer long term outcome.

Transplants from non-heart-beating donors accounted for 288 (20%) of the 1440 kidney transplants conducted in the financial year 2006-2007. At present kidneys from non-heart-beating donors are only used for patients on the local waiting list, and are not shared through the national allocation system.

A second means of expanding the pool of heart-beating donors is through the use of extended criteria donors (marginal donor kidneys). These are kidneys from donors who, in the past would not normally meet the criteria for donation. The extended criteria include kidneys from donors who are either over sixty, or are over fifty and with two or more of the following features (2) a history of hypertension, (3) death by cerebral vascular accident, (3) terminal creatinine levels greater than 1.5mg/dl. Kidneys from extended criteria donors have a lower chance of long term success and a higher incidence of delayed graft function.

4.2 The interventions to be compared

In machine perfusion, core cooling of the organ is achieved by pumping cold preservation solution through it. Machine perfusion also provides nutrients and some oxygen, carries away toxic metabolites and provides ‘buffering’ (reducing build up of lactic acid). In theory this should reduce the damage associated with cold ischaemic time. Machine perfusion can be used to preserve grafts from both heart-beating and non-heart-beating donors. It is suggested that machine perfusion may also allow the selection of the kidneys for transplantation. Up to 10% of kidneys from non-heart-beating donors never function after transplantation (known as primary non-function).

Two commercially available machine perfusion systems have been identified: the LifePort Kidney Transporter (Organ Recovery Systems) and Waters' RM3 Renal Preservation System (Waters Medical Sytems). 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).

In cold static storage, the kidney is flushed through with a preservation solution, and kept in this solution in a bag, on ice. Two preservation solutions are widely used in the NHS; Marshall’s, (Soltran, Baxter Healthcare) and University of Wisconsin (Viaspan, Bristol Myers Squibb). The preservation solutions used in cold static storage are different from those used in machine perfusion.

4.3 The place of machine perfusion in kidney transplants

Machine perfusion has been used 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. As the numbers of heart-beating donors decreased and kidneys were increasingly sought from non-heart-beating

donors (and thereby exposed to longer warm ischaemic time), interest in machine perfusion has returned.

Currently there are 29 kidney transplant centres in England and Wales, at least five of which use machine perfusion as well as cold storage.

4.4 Population

Recipients of deceased donor kidney transplants from heart-beating and non-heart-beating donors

4.5 Interventions

Machine perfusion systems for kidney preservation including:

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

Kidney preservation by initial flushing with and preservation in these (cold static) storage solutions:

- Marshall's solution (Soltran)
- University of Wisconsin (cold storage) solution (ViaSpan)

4.6 Alternatives to be compared

Each intervention will be compared with the others

4.7 Sub-groups to be examined

If the evidence allows, the appraisal will consider the following subgroups:

- Recipients of kidneys from HB or NHB donors
- Recipients of kidneys from controlled NHB donors
- Recipients of kidneys from uncontrolled NHB donors
- Recipients of kidneys from extended criteria HB donors

4.8 Outcomes to be examined

The outcome measures to be considered include:

- Incidence and duration of delayed graft function
- Incidence of primary non-function
- Rejection rates
- Graft survival
- Graft function (glomerular filtration rate)

- Patient survival
- Health-related quality of life
- Cost-effectiveness

4.9 Other considerations

If the evidence allows, the appraisal will consider the implications of assessing graft-viability using machine perfusion and the comparative ease of use of machine perfusion systems where this may impact on the clinical and/or cost-effectiveness.

5 Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for clinical effectiveness of machine perfusion systems and cold (static) storage of donated kidneys. The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination[1].

5.1 Search Strategy

Refer to Appendix 1a for details of the sources to be searched and the draft search strategy for MEDLINE.

The search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases
- Internet
- Scrutiny of references of included studies
- Contact with the machine and solution manufacturers through NICE
- MHRA
- Contact with experts in the field

5.2 Study Selection Criteria and procedures

Types of studies to be included

For the reviews of clinical effectiveness, systematic reviews of RCTs, single RCTs, quasi-experimental (where allocation to intervention or control group is determined by the investigator but without randomisation or allocation concealment), data registry designs and unpublished ongoing trials will be included. Studies will only be included if they are relevant to the comparators, population and outcomes of interest (as specified in section 2).

Types of studies to be excluded

- Uncontrolled studies
- Non-comparative studies
- Animal models

- Preclinical and biological studies
- Narrative reviews, editorials, opinions

Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

Study selection process:

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Data extraction strategy

Data will be extracted from included studies by one reviewer using a standardised data extraction form and checked by another reviewer. Discrepancies will be resolved by discussion, with the involvement of a third reviewer if necessary.

Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed according to criteria suggested by NHS CRD Report No.4, according to study type.[1] One reviewer assesses whether each study meets each of the quality criteria for that study type and these judgements are checked by a second reviewer. Any disagreement will be resolved by consensus and if necessary a third reviewer will be consulted.

Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention to treat analyses.

If meta-analysis is conducted it will be carried out using fixed or random effects models, using Review Manager or STATA software. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic and methods such as meta-regression.

6 Methods for synthesis of evidence of cost-effectiveness

a) Systematic review of economic evaluations

6.1 Search strategy

The search strategy for economic evaluations and other economic studies is shown in Appendix 1b. The range of sources searched are the same as those for clinical effectiveness as well as NHS EED and Econlit.

6.2 Study selection criteria and procedures

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

Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies.)

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

Based on the above inclusion/exclusion criteria, study selection will be made independently by two reviewers. Discrepancies will be resolved by discussion, with involvement of third reviewer when necessary.

Study quality assessment

The methodological quality of the economic evaluations will be assessed according to internationally accepted criteria such as the CHEC list questions developed by Evers et al[2]. Any studies based on decision models will also be assessed against the ISPOR guidelines for good practice in decision analytic modelling[3].

Data extraction strategy

Data will be extracted by one researcher into two summary tables: one to describe the study design of each economic evaluation and the other to describe the main results.

In study design table: author and year; model type or trial based; study design (e.g. CEA, CUA or cost-analysis); service setting/country; study population; comparators; research question; perspective, time horizon, and discounting; main costs included; main outcomes included; sensitivity analyses conducted; and other notable design features.

For modelling-based economic evaluations a supplementary Study Design table will record further descriptions of: model structure (and note its consistency with the study perspective, and knowledge of disease/treatment processes; sources of transition & chance node probabilities; sources of utility values; sources of resource use and unit costs; handling of heterogeneity in populations; evidence of validation (e.g. debugging, calibration against external data, comparison with other models).

In the Results table: for each comparator: we are going to show; incremental cost; incremental effectiveness/utility and incremental cost-effectiveness ratio(s). Excluded comparators on the basis of dominance or extended dominance will also be noted. The original authors' conclusions will be noted, and also any issues they raise concerning the generalisability of results. Finally the

reviewers' comments on study quality and generalisability (in relation to the TAR scope) of their results will be recorded.

Synthesis of extracted evidence

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base.

b) Economic Modelling

A new cost-effectiveness analysis may be carried out from the perspective of the UK NHS and PSS using a decision analytic model. Such a new analysis will be conducted if, in the TAR team's judgement, the existing published evidence (and/or the analyses submitted by manufacturers) is insufficiently relevant to the current decision problem. The evaluation will be constrained by available evidence. If possible, the incremental cost-effectiveness of the different kidney preservation interventions will be estimated in terms of cost per QALY gained.

Model structure will be determined on the basis of available research evidence and clinical expert opinion.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from sponsor submission to NICE.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be identified from NHS and PSS reference costs or, where these are not relevant, will be extracted from published work and/or sponsor submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

To reflect health related quality of life, utility values will be sought either directly from relevant research literature or indirectly from quality of life studies.

Analysis of uncertainty will focus on cost utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Search strategies for additional information regarding model parameters or topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the methodological discussion paper ' Methods for establishing parameter values for decision analytic models' commissioned by the UK Dept. of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs other UK studies will be considered if appropriate.

ICERs estimated from consultee models will be compared with the respective ICERs from the Assessment Group's model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained

6.3 Further considerations

A life-time time horizon will be taken for our analysis.

The perspective will be that of the National Health Services and Personal Social Services. Both cost and outcomes (QALYs) will be discounted at 3.5% [4].

7 Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than February 28th 2008. Data arriving after this date will not be considered.

Economic evaluations included in the company submissions, will be assessed against NICE's guidance on the Methods of Technology Appraisal, and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used.

Any 'commercial in confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

8 Competing interests of authors

None

9 Appendices

Appendix 1 - clinical effectiveness searches – draft Medline search

1. SEARCH: KIDNEY-TRANSPLANTATION#.DE.
2. SEARCH: (RENAL OR KIDNEY$3) NEAR (TRANSPLANT$6 OR PRESERV$ OR REPLACE$ OR DONOR$ OR DONOUR$ OR DONATE$ OR RECIEVE$)
3. SEARCH: TISSUE-DONORS#.DE. OR ORGAN-PRESERVATION-SOLUTIONS.DE. OR ORGAN-PRESERVATION.DE. OR TISSUE-PRESERVATION#.DE.
4. SEARCH: KIDNEY.W..MJ.
5. SEARCH: KIDNEY$3 OR RENAL
6. SEARCH: 4 OR 5
7. SEARCH: 6 AND 3
8. SEARCH: 1 OR 2 OR 7
9. SEARCH: (SOLID ADJ ORGAN ADJ TRANSPLANT$6).TW.
10. SEARCH: (NON-HEART-BEATING OR NON ADJ HEART ADJ BEATING OR NHBD OR HEART ADJ BEATING OR HEART-BEATING OR CADAV$4 OR BRAIN ADJ DEAD).TW.
11. SEARCH: (DONOR$2 OR DONOUR$2) NEAR (MARGINAL OR EXPANDED OR

EXTENDED OR HIGH-RISK)

12. SEARCH: 9 OR 10 OR 11
13. SEARCH: 12 AND 6
14. SEARCH: 13 OR 8
15. SEARCH: PULSATILE-FLOW#.DE.
16. SEARCH: PERFUSION#.W..DE.
17. SEARCH: MACHINE$2.TW. AND PULSAT$4.TW.
18. SEARCH: LIFEPORT.TW.
19. SEARCH: RM3.TI,AB.
20. SEARCH: (MACHINE$2 OR PULSAT$4).TW. AND (PERFUS$4 OR PRESERV$4 OR SYSTEM).TW.
21. SEARCH: (COLD OR ICE OR STATIC) AND (STORAGE OR PRESERV$5)
22. SEARCH: UNIVERSITY ADJ OF ADJ WISCONSIN OR UW ADJ SOLUTION$2
23. SEARCH: EUROCOLLINS
24. SEARCH: HISTIDINE AND TRYPTOPHAN OR HTK
25. SEARCH: CELSIOR
26. SEARCH: MARSHALLS NEAR SOLUTION
27. SEARCH: VIASPAN
28. SEARCH: SOLTRAN
29. SEARCH: BELZER$
30. SEARCH: 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. SEARCH: 15 OR 16 OR 17 OR 18 OR 19 OR 20
32. SEARCH: 31 AND 14
33. SEARCH: 30 AND 14
34. SEARCH: 32 OR 33
35. SEARCH: 32 AND HUMAN=YES
36. SEARCH: PT=EDITORIAL OR PT=LETTER
37. SEARCH: 35 NOT 36
38. SEARCH: PT=RANDOMIZED-CONTROLLED-TRIAL
39. SEARCH: RANDOMIZED-CONTROLLED-TRIALS#.DE.
40. SEARCH: RANDOM$6.TW. AND PLACEBO$2.TW.
41. SEARCH: (SINGL$2 OR DOUBLE$2 OR TRIPLE$2 OR TREBLE$2).TW. AND (BLIN$2 OR MASK$2).TW.
42. SEARCH: 38 OR 39 OR 40 OR 41

Reference List

(1) NHS Centre for Reviews and Dissemination. Undertaking Systematic Reviews of Research on Effectiveness. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001.

(2) Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International Journal of Technology Assessment in Health Care 2005; 21(2):240-254.

(3) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health 2003; 6(1):9-17.

(4) National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. 2004. London, National Institute for Clinical Excellence.