Health Technology Assessment 2003; Vol. 7: No. 25

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

J Wight
J Chilcott
M Holmes
N Brewer

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

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

J Wight
J Chilcott*
M Holmes
N Brewer

The School of Health and Related Research (ScHARR), University of Sheffield, UK

*Corresponding author

Declared competing interests of authors: none

Published September 2003

This report should be referenced as follows:

Wight J, Chilcott J, Holmes M, Brewer N. The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. *Health Technol Assess* 2003;**7**(25).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE.

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme and funded as project number 01/35/01. Technology assessment reports are completed in a limited time to inform decisions in key areas by bringing together evidence on the use of the technology concerned.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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.

HTA Programme Director: Professor Kent Woods
Series Editors: Professor Andrew Stevens, Dr Ken Stein, Professor John Gabbay, Dr Ruairidh Milne, Dr Chris Hyde and Dr Rob Riemsma
Managing Editors: Sally Bailey and Sarah Llewellyn Lloyd

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2003

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to HMSO, The Copyright Unit, St Clements House, 2–16 Colegate, Norwich, NR3 1BQ.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

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

J Wight, J Chilcott,* M Holmes and N Brewer

The School of Health and Related Research (ScHARR), University of Sheffield, UK
*Corresponding author

Objectives: To evaluate the clinical and cost-effectiveness of machine perfusion (MP) compared to cold storage (CS), as a means of preserving kidneys prior to transplantation. Transplantation of kidneys from both heart-beating donors (HBDs) and non-heart-beating donors (NHBDs) is considered. Finally to review whether the use of MP can allow valid testing of kidney viability prior to transplantation.
Data sources: Fifteen electronic bibliographic databases were searched. The reference lists of relevant articles and sponsor submissions were hand searched and various health service research-related resources were consulted via the Internet.
Review methods: A literature search was undertaken to identify relevant studies and a meta-analysis performed on the studies that had appropriate comparator groups and reported sufficient data. A structured review examined tests of viability of kidneys on MP. Economic modelling was used to determine the cost-effectiveness and cost–utility of MP.
Results: The meta-analysis suggested that the use of MP, as compared with CS, is associated with a relative risk of delayed graft function (DGF) of 0.804 (95% confidence limits 0.672 to 0.961). There was no evidence to suggest that this effect is different in kidneys taken from HBDs as opposed to NHBDs. Meta-analysis of 1-year graft survival data showed no significant effect, but the studies, even when aggregated, were severely underpowered with respect to the likely impact on graft survival. The size of effects demonstrated were in line with those predicted by an indirect model of graft survival based on the association of DGF with graft loss. The economic assessment indicated that it is unlikely that in the UK health setting complete cost recovery will be obtained from a reduction in the incidence of DGF. The probability that MP is cheaper and more effective than CS in the long term was estimated at around 80% for NHBD recipients and 50–60% for HBD recipients. Flow characteristics of the perfusate of kidneys undergoing MP may be an indicator of kidney viability, but data were inadequate to calculate the sensitivity and specificity of any test based on this. The concentration of α-glutathione-S-transferase (a marker of cell damage) in the perfusate may be the basis of a valid test. A threshold of 2800 mg/100 g gave a sensitivity of 93% and specificity of 33% (and hence a likelihood ratio of 1.41).
Conclusions: The baseline analysis indicated that in the long-term MP would be expected to be cheaper and more effective than CS for both HBD and NHBD recipients. A definitive study of the clinical benefit of MP in order to establish its effect on DGF and longer term graft survival would be valuable, together with an economic evaluation of the benefits. While direct evidence relating to improvements in graft survival would be preferable, the small predicted improvement indicates that a very large sample size would be required. In addition to seeking direct evidence of the impact on DGF, research quantifying the impact of DGF on graft survival in this technology is required. Research is also needed to establish whether a valid test (or combination of tests) of kidney viability can be developed.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Contents

List of abbreviations

ALG	anti-lymphocyte globulin
ATN	acute tubular necrosis
BMJ	*British Medical Journal*
CAPD	continuous ambulatory peritoneal dialysis
CS	cold storage
CyA	cyclosporine A
DGF	delayed graft function
DRF	delayed renal function
α-GST	α-glutathione-S-transferase
HBD	heart-beating donor
HD	haemodialysis
IF	immediate function
IRR	intra-renal vascular resistance
LDH	lactate dehydrogenase
LL	lower limit
MO	membrane oxygenation
MP	machine perfusion
MPS	Marshall's perfusion solution
NHBD	non-heart-beating donor
NS	not significant
PNF	primary non-function
PPF	plasma protein fraction
PRA	panel reactive antibodies
QALY	quality-adjusted life-year
RCT	randomised controlled trial
ROC	receiver operating characteristics
RR	relative risk
UL	upper limit
UW	University of Wisconsin

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 at the end of the table.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Executive summary

Objectives

The aim of this review is to evaluate the clinical and cost-effectiveness of machine perfusion (MP), as opposed to cold storage (CS), as a means of preserving kidneys which are to be transplanted. It examines the use of MP for kidneys from both heart-beating donors (HBDs) and non-heart-beating donors (NHBDs), and the impact on graft function immediately post-transplantation as well as in the longer term. In addition, it examines whether or not the use of MP can allow valid testing of kidney viability prior to transplantation.

Background

There is a continuing (and growing) mismatch between the number of kidneys available for transplantation and the number of patients on the waiting list. One possible way to increase the supply of kidneys for transplantation would be to extend the range of donors. This could include NHBDs as well as donors with other adverse characteristics. Kidneys taken from such donors tend to suffer higher rates of primary non-function, delayed graft function (DGF) and reduced longer term survival than those taken from ideal donors.

It has been suggested that MP may lead to a reduction in DGF and an increase in graft survival. MP may also allow the valid testing of the viability of kidneys taken from 'marginal' donors (thus avoiding the transplantation of non-viable kidneys). This could then contribute to the safe extension of criteria for donor recruitment, and hence increase the transplantation rate. A reduction in DGF would also, *per se*, be cost saving – which may make the use of these machines cost-effective.

Methods

A literature search was undertaken to identify relevant studies. A meta-analysis was undertaken of those that had appropriate comparator groups and reported sufficient data. A structured review was undertaken of studies examining tests of viability of kidneys on MP. Economic modelling was used to determine the cost-effectiveness and cost–utility of MP.

Evidence available

Twenty papers (reporting 16 studies) were identified that reported on the clinical outcome of the use of MP and that had appropriate comparator groups. These were published between 1971 and 2001. In the majority of these, pairs of kidneys were split, with one being machine perfused and the other preserved using cold storage. Overall the studies were small and of poor quality, with only four of the 16 studies scoring two on the Jadad scale (none scored more).

Twenty-six papers were identified which reported studies of tests of kidney viability. Most were of limited quality, with non-ideal outcome measures and poor design. Only one contained sufficient information to be able to calculate the sensitivity and specificity of a test of viability.

Summary of findings

The meta-analysis suggests that the use of MP, as compared with CS, is associated with a relative risk of DGF of 0.804 (95% confidence limits 0.672 to 0.961). There was no evidence to suggest that this effect is different in kidneys taken from HBDs as opposed to NHBDs. Meta-analysis of 1-year graft survival data showed no significant effect, but the studies, even when aggregated, were severely underpowered with respect to the likely impact on graft survival. The size of effects demonstrated were in line with those predicted by an indirect model of graft survival based on the association of DGF with graft loss.

There is some evidence that the flow characteristics of the perfusate of kidneys undergoing MP may be an indicator of kidney viability, but data are inadequate to calculate the sensitivity and specificity of any test based on this. The concentration of α-glutathione-S-transferase (a marker of cell damage) in the perfusate may be the basis of a valid test. A threshold of 2800 μg/100 g

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

gives a sensitivity of 93% and specificity of 33% (and hence a likelihood ratio of 1.41).

The published economic evidence is of poor quality and the generalisability of the US studies to a UK healthcare setting is low. The economic assessment indicates that it is unlikely that in the UK health setting complete cost recovery will be obtained from a reduction in the incidence of DGF.

The baseline analysis indicates that in the long-term MP would be expected to be cheaper and more effective than CS for both HBD and NHBD recipients. The probability that this is the case is estimated at around 80% for NHBD recipients and 50–60% for HBD recipients.

Future research

A definitive study of the clinical benefit of MP (in the context of the current state of development of transplantation) needs to be undertaken, in order to establish its effect on DGF and longer term graft survival. Ideally this would be accompanied by an economic evaluation of the benefits.

While direct evidence relating to improvements in graft survival would be preferable, the small predicted improvement indicates that a very large sample size would be required in order to detect statistically significant results. In addition to seeking better direct evidence of the impact of MP on DGF rates, further research on quantifying the predicted impact of DGF on graft survival in this technology would be warranted.

Further research is also needed to establish whether or not a valid test (or combination of tests) of kidney viability can be developed. This should be accompanied by work with all interested parties (including patients) to establish what an appropriate trade-off between false-positive and false-negative results of such test(s) would be.

Chapter 1

Aim of the review

The aim of this review is to evaluate the clinical and cost-effectiveness of machine perfusion (MP), as opposed to cold storage (CS), as a means of preserving kidneys which are to be transplanted. It examines the use of MP for kidneys from both heart-beating donors (HBDs) and non-heart-beating donors (NHBDs), and the impact on both graft function immediately post-transplantation and in the longer term. In addition, it examines whether or not the use of MP can allow valid testing of kidney viability prior to transplantation.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Chapter 2
Background

Underlying problem

Transplantation is the best treatment for patients with end-stage renal failure. It provides the most favourable clinical outcomes, including the best quality of life for the patient. It is also the most cost-effective treatment option available. Unfortunately, demand for kidneys for transplantation (as measured by the number of people on the transplant waiting list, which may be an underestimate of the demand that would exist if supply were not limited) exceeds the current supply of cadaveric kidneys, with the effect that the waiting list is ever lengthening. As a consequence, there is increasing pressure to look for alternative sources of organs. This may be achieved either by extending the criteria for cadaveric organ retrieval, such as using older donors or NHBDs, or by increasing the use of live, related or unrelated, donors.

Ever since the development of kidney transplantation in the 1960s, the importance of ensuring successful preservation of the organ between retrieval and implantation has been recognised. Ischaemia is profoundly damaging to the kidney. It deprives the kidney of oxygen and nutrients, which leads to a cascade of cellular damage, resulting promptly in irreversible damage to the organ. Two approaches were developed to limit this damage, both deriving from animal experimentation, and both have persisted, although the details have changed over the years. These are cold (static) storage (CS) and machine (pulsatile) perfusion (MP).

Cooling the kidney suppresses the metabolic rate and so reduces damage. In simple CS, the kidney vasculature is simply flushed through with preservation solution and then kept on ice. Over the years the solution used for flushing has improved, in particular through the development and use of hypertonic 'intracellular' solutions which limit intracellular oedema and acidosis. The alternative approach is to use a machine to pump a cold perfusate through the organ, which is intended to allow metabolism to continue by supplying oxygen and nutrients and removing the metabolic end products. Again, the perfusate used has evolved over the years, in an attempt to limit damage and provide adequate substrate for the (reduced) metabolism.

Over the past 30 years, there has been a continuing debate as to the relative merits of each of these approaches. In the 1970s, the majority of kidneys were preserved by MP, as it was maintained that this gave an improved chance of both immediate and longer term function. However, by the mid-1980s the situation had reversed, with the majority of kidneys being preserved by CS. The main reason for this was that large-scale studies of transplantation outcome[1–4] failed to find any survival advantage for kidneys preserved by MP. Consequently, the disadvantages of MP – the need for a machine, disposables and technician, and the risk of equipment failure, particularly in earlier years, as compared with the simplicity and low cost of CS – meant that the use of the approach could not be justified.

With the increasing interest, in recent years, in the possibility of extending the donor criteria, primarily to include older donors and NHBDs, there has been a resurgence of interest in the use of MP to preserve kidneys. This is because of the belief that MP leads to a reduced rate of delayed graft function (DGF) – the delay in recovery of normal renal function post-transplantation caused most commonly by acute tubular necrosis, which leads to the need for dialysis for some days, sometimes weeks, postoperatively. DGF is seen following 23–33% of transplants from HBDs,[5] but is substantially more common following transplantation from NHBDs,[6] no doubt because of the inevitable period of warm ischaemia which these kidneys undergo.

DGF gives rise to the need for continuing dialysis and longer hospitalisation (and hence increased costs), and is associated with poorer long-term outcome.[7] Attempts to reduce the rate of DGF through the use of machine preservation may therefore be justified, in both clinical and economic terms, particularly if it allows for the successful extension of the donor pool to include 'expanded criteria' donors.

A further reason for the renewed interest in MP is the possibility that it gives for viability testing of

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

the *ex vivo* organ. With NHBDs, up to 10% of transplants never function – so-called primary non-function. Since this does not appear to depend on recipient factors (it is extremely uncommon in HBD kidney transplants), it must presumably be a result of damage to the transplanted organ prior to implantation. Clearly, if these organs could be identified as damaged beyond recovery prior to implantation, then the operation, and with it the clinical, emotional and financial costs, could be avoided. In the early stages of the development of MP, kidney viability was assessed by measuring perfusate pressures and flow rates. More recently, attention has been focused on the measurement of markers of cell damage, such as α-glutathione-S-transferase (α-GST) in the perfusate, but none have been developed which reliably predict renal function post-transplantation. One reason for this is hypothermia, which, while greatly reducing the amount of renal damage, also makes evaluation of renal function impossible. As a result there is now also renewed interest in normothermic machine preservation,[8] although this remains, as yet, completely experimental.

Technology assessed

Both the machines used for perfusion and the perfusate solutions used for CS and MP have developed over the three or more decades during which they have been available. Because of the scarcity of recent studies on MP, we have included in this review studies dating back as far as 1971. Inevitably, studies undertaken at that time used less advanced machines and perfusates. It would clearly be unreasonable to compare the results achieved then with those that we might expect to achieve now (not only because of the changes in preservation techniques, but also because of other advances in transplantation surgery). However, we have taken the view that the comparison of MP and CS, at the respective stages of development of those techniques at the time, can give useful information as to their relative merits now. We have therefore included in the review all studies comparing MP with CS, with no limitation as to type of machine or perfusate used.

In order to establish whether or not the relative merits of MP and CS are different with modern perfusate solutions, we separately analysed those studies that used University of Wisconsin (UW) solution (described later).

Outcomes measured

The primary outcome of interest in renal transplantation is long-term graft survival (i.e. avoidance of dialysis). This is ideally measured using actuarial techniques over a period of some time (5 years or more). DGF is also of interest, not only because rapid recovery from the operation and the avoidance of postoperative dialysis are in themselves desirable, but also because of its possible link with long-term survival. Most studies of kidney preservation methods do not report on graft function beyond 1 year, and in some cases only short-term function (i.e. DGF) is reported. In many cases, not all transplants are followed-up for as long as 1 year, and in some cases the absolute numbers included in longer term follow-up are not explicit.

Current service provision

Of the 30 renal transplant units currently functioning in the UK, the majority do not use MP for kidney preservation. Only two units are known to use perfusion machines on a regular basis, both of them centres which have active NHBD programmes. The Leicester Unit uses a Waters machine, whereas the one in use in Newcastle was manufactured locally using parts from dialysis and other machines.[9] MP is thought to be equally infrequently used in other European countries (one exception being the Maastricht Unit, which has an active NHBD programme). However, in the USA it is more popular, with 12 out of 44 responding centres in a recent survey reporting that they used them.[10]

Research question and scope

The aim of the review is to evaluate the clinical and cost-effectiveness of MP in both HBDs and NHBDs. The specific questions which we sought to address were as follows:

1. What is the comparative clinical and cost-effectiveness of pulsatile preservation and static (cold) preservation for ex-NHBD and ex-HBD kidneys?
2. What is the comparative clinical and cost-effectiveness of hypo- and normothermic perfusion?
3. What is the comparative clinical and cost-effectiveness of perfusion with acellular and blood-based perfusates?

4. Can pulsatile perfusion allow valid viability testing of kidneys, and what are the possible implications of this?

Unfortunately, with regard to the second and third of these questions, no relevant studies undertaken in humans were identified in the literature. Consideration was given to reviewing the animal experimentation literature, but this was not possible in the time available and so these questions could not be pursued further.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

The review was undertaken as systematically as time allowed. The aim was to locate and appraise relevant trials, reviews and cost-effectiveness studies.

Search strategy

The search aimed to identify all literature relating to static CS and MP preservation systems for preserving kidneys from HBDs and NHBDs in humans. The main searches were conducted in September and October 2001, and a specific economics search was performed in January 2002. A citation search was performed in the Science and Social Science Citation Indexes in February 2002 to identify any papers that cited the included studies. The resulting list was then compared with the studies that had already been identified and any relevant articles that were not already held were obtained.

Sources searched

The following 15 electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature (including current research):

1. Biological Abstracts
2. CCTR (Cochrane Controlled Trials Register)
3. CDSR (Cochrane Database of Systematic Reviews)
4. CINAHL
5. EBM Reviews
6. EMBASE
7. HEED (Health Economic Evaluations Database)
8. HIMC (Health Information Management Consortium – comprising DH-Data, the King's Fund Database and HELMIS)
9. MEDLINE
10. NHS DARE (Database of Assessments of Reviews of Effectiveness)
11. NHS EED (Economic Evaluations Database)
12. NHS HTA (Health Technology Assessment)
13. PreMedline
14. Science Citation Index
15. Social Sciences Citation Index.

In addition, the reference lists of relevant articles and sponsor submissions were hand searched and various health services research-related resources were consulted via the Internet. These included health economics and HTA organisations, guideline-producing agencies, generic research and trials registers and specialist sites. The other sources searched were as follows:

1. British Organ Donor Society
2. British Transplantation Society
3. CCOHTA (Canadian Coordinating Centre for Health Technology Assessment)
4. Copernic
5. eGuidelines
6. European Society for Organ Transplantation (The)
7. National Guideline Clearinghouse
8. NCCHTA (National Coordinating Centre for Health Technology Assessment)
9. NHS CRD (Centre for Reviews and Dissemination), University of York
10. Renal Association (The)
11. ScHARR Library Catalogue
12. SIGN (Scottish Intercollegiate Guidelines Network)
13. TRIP (Turning Research into Practice) Database
14. UK Transplant Support Service Authority (The)
15. Wessex DEC (Development and Evaluation Committee) Reports.

Search terms

A combination of free-text and thesaurus terms was used. 'Population' search terms (e.g. kidney, renal, transplantation, preservation, donor) were combined with 'intervention' terms (e.g. machine, pulsatile, perfusion, non-heart-beating, heart-beating, perfusate, Belzer, gluconate, albumin). This was supplemented by a specific basic search on the cost of DGF using terms such as cost, cost-effectiveness, economic cost–benefit analysis AND delay, graft, function AND renal, kidney (MEDLINE, EMBASE, CCTR, NHS EED and HEED). Copies of the search strategies used in the major databases are included in Appendix 1.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Search restrictions

No date, language or study/publication type restrictions were applied to the main searches. An economic evaluations filter was used for the kidney preservation systems – economics search (refer to Appendix 2).

Results of the search

Over 1400 references were identified by the search strategy, of which 307 were duplicates. These were then assessed for inclusion in a series of stages, as shown in *Figure 1*.

Data quality assessment

Primary studies were scored using the Jadad scale[11] (see Appendix 3). Quality assessment and data extraction were undertaken by one reviewer and checked by a second, with any disagreements being resolved through discussion.

Excluded studies

Criteria for exclusion of studies from consideration were as follows:

- animal studies
- non-comparative studies or reports
- studies in languages other than English, French or Spanish.

Results of the review

Clinical effectiveness of MP versus CP

Results – studies identified

Forty-five review or discussion articles were identified that addressed the relative merits of CS and MP. Only one of these[12] was a review of published literature. It reviewed nine studies published between 1990 and 2000, and concluded that MP led to 'immediate function rates of approximately 90% versus immediate function rates of about 70 to 80% in centres that use static storage'. However, of these nine studies, three have no comparator groups, in three the comparisons are with dissimilar groups of kidneys and one is based on registry data, which is open to bias. Only two of the primary studies are reports of appropriate comparisons, and they are included in our analysis below.[13,14]

A total of 62 reports were identified of studies which compared CS with MP as means of preserving kidneys for transplantation. These dated from 1971 to 2001. The majority were from the USA, with a few from Europe, Australia, South Africa, Canada and Japan. In the majority of these reports the comparisons were not randomised. In some studies, kidneys were allocated to CS or MP

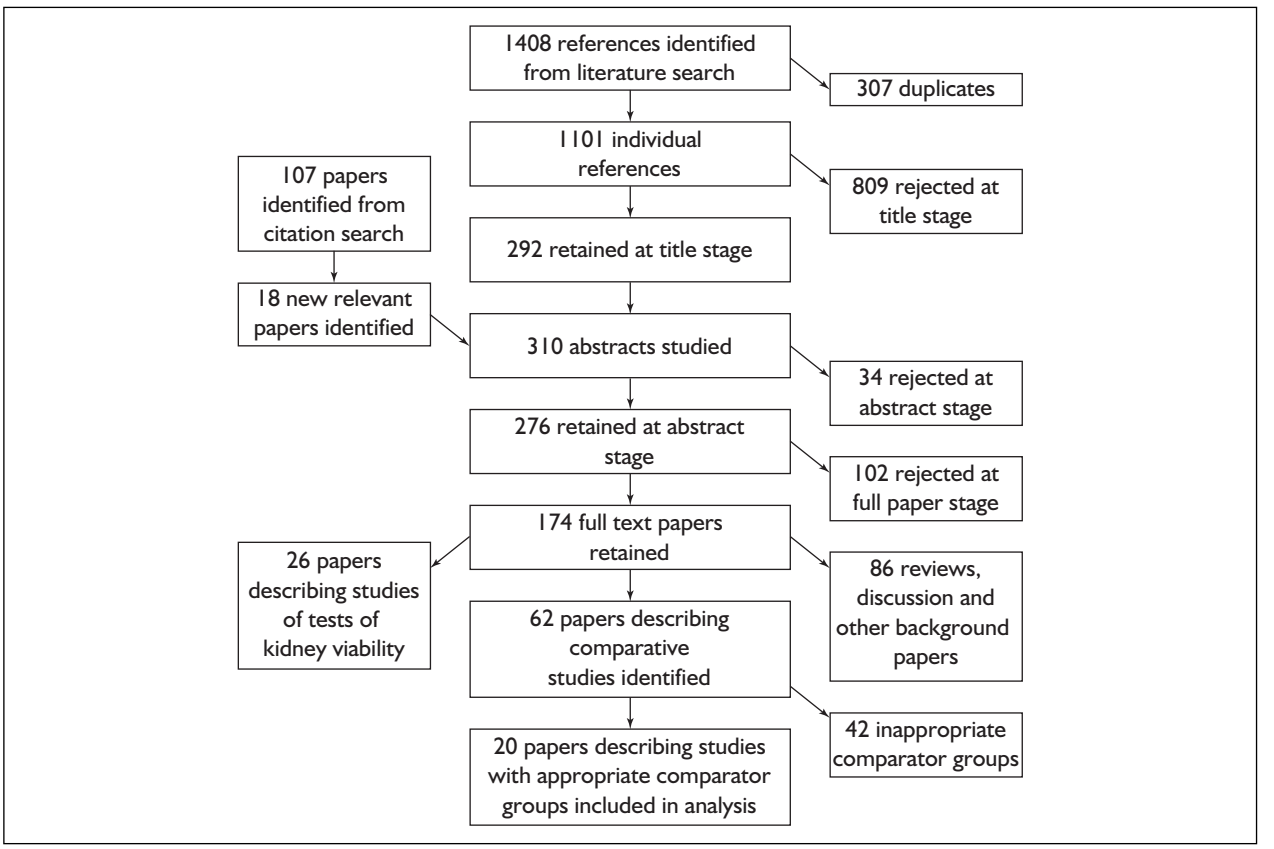

FIGURE 1 *Flowchart showing identification and inclusion of studies for review*

on an historical basis (e.g. before and after the acquisition of a perfusion machine,[15–20] or before and after a change of policy with regard to the use of the machine[21]). In others, kidneys were selected for one particular preservation modality for specific reasons, such as MP being reserved for kidneys harvested at night,[22] those where tissue typing was not done at the time of harvest or for marginal donors.[23–26] In some studies, MP was the preferred means of preservation, and CS was only used if there were anatomical considerations which made perfusion difficult.[27,28]

In most studies, however, no rationale was given for allocation of kidneys to one or other preservation modality, and there can be no assumption that the two groups of kidneys are equivalent. This includes those studies which are based on transplant registry data,[29–32] where although the larger numbers of patients included (and the inclusion of data from more than one centre) ought to give external validity to the studies, one cannot exclude the possibility of systematic bias in the allocation of kidneys to preservation modality and the submission of data to the registries.

Studies with appropriate comparator groups

Only one study was identified in which kidney donors were explicitly randomised to preservation by MP or CS.[33] In this the authors state that they chose to randomise donors, rather than kidneys, in order to overcome any possible bias against cold-stored kidneys by the host centre. (This might lead them to machine perfuse the 'better' kidneys, or to keep more machine perfused kidneys and 'export' more cold-stored kidneys. In either case there would be a bias in favour of MP.) In one study kidneys are described as having been allocated in a random fashion to preservation modality, but no further details are given, there is no suggestion that pairs of kidneys were split between modalities and the numbers in each treatment group are very dissimilar.[34]

There are 18 reports of studies in which the kidneys from a single donor were split, one being preserved by MP and the other by CS. In three of these,[35–37] the allocation within pairs is said to have been random. In two others,[14,38] the allocation is said to have been alternate, i.e. donor pairs were split right kidney to MP, left kidney to CS, and vice versa, alternately.

In the remaining 13 reports, the method of allocation of the two kidneys to the preservation modality is not stated. In these cases, a decision will have been made with regard to the allocation, and there is therefore the possibility of bias.

There are two stages in the allocation of a kidney to a preservation modality, and its subsequent transplantation, at which bias may be introduced. These are the allocation of kidneys to preservation modality and the subsequent allocation of preserved kidney to recipient. Ideally, both of these steps should be randomised in order to avoid bias by known and unknown confounders. In practice, the allocation of kidney to recipient will be largely governed by the tissue type match (at least in the past two decades, during which time this has emerged as of crucial importance in determining graft function and the avoidance of rejection). Although for most donors there are two harvested kidneys, and hence for any recipient there are in theory two kidneys available, which will be equally matched to the recipient and could be or have been randomised with respect to preservation modality, this is not universally the case.

Only three studies can be taken to have explicitly addressed the second step. These are the ones in which donors were randomised[33] and two studies in which donated kidney pairs were split between preservation modalities and then randomly assigned to recipients.[13,36]

None of the studies made any mention of blinding, either of the recipients or of the surgeons or conductors of the studies, to the preservation method used. Although it would be difficult to imagine how non-blinding of recipients would impact on the outcome, it is feasible that non-blinding of surgeons might. The main outcome measure used is DGF, most commonly taken to mean the requirement for dialysis in the first week post-transplantation. Although most such cases will be unambiguous, one can easily imagine marginal cases in which a decision whether or not to dialyse a patient could be influenced by knowledge of the preservation modality of the transplanted kidney. It would be logistically feasible, of course, to blind those clinicians responsible for post-transplant care to the preservation modality of the kidney, but this does not appear ever to have been done.

Another problem that may arise stems from the use of MP as a means by which to assess the viability of the kidney before transplantation. Although the reliability of this approach is controversial, the fact that some transplant teams have used it, and rejected kidneys after harvesting

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

but prior to transplantation, gives rise to the possibility that those which are eventually transplanted are a selected subset of those harvested. This would potentially allow for the introduction of bias if rejected kidneys are not included in the analysis.

The evidence base is therefore clearly less than ideal. However, the purpose of randomisation is to minimise the chance of bias due to inequality of treatment groups with respect to known or unknown confounders. Although it is theoretically possible that there may be within-donor-pair differences between kidneys which may affect the outcome of transplantation, this is unlikely. Donor factors which influence the outcome of transplantation (e.g. age, pre-mortem drug exposure) will affect both kidneys equally. This reduces the importance of within-pair randomisation of kidneys to preservation modality, and for this reason we have included studies in which kidney pairs are allocated to the two modalities even when this is not explicitly stated to have been done in a random way. The failure of studies to address or report on the second stage of allocation (of preserved kidneys to recipients) does remain a concern.

The reports which were included in the final analysis were the one study with randomisation of donors,[33] the one with randomisation of kidneys[34] and the 18 reports in which donor kidney pairs were split and one allocated to each preservation modality. Of these, there are two sets of three, by Marshall, and colleagues[39–41] and Matsuno and colleagues[37,42,43] which appear to relate to the same study. In these cases data were taken from the papers which contained the most detailed reports of the studies.[37,40] A total of 16 studies thus remained available for analysis. Details are given in *Table 1*. Details of the 42 comparative studies which were not included in the analysis are given in Appendix 6.

Quality of included studies

Overall the quality of the studies was poor, as assessed by the Jadad score. Out of a possible score of five (based on randomisation, blinding and adequate description of drop-outs and those lost to follow-up), four studies scored two, seven scored one and nine scored zero.

The studies were for the most part small, and therefore almost certainly insufficiently powered to detect a real difference in outcomes between CS and MP. None reported any sample size calculation. In order to have an 80% power of detecting a fall in DGF rate from 30 to 15% in MP compared with CS, at a significance level of 5%, a study would have to include at least 119 patients. Only three recruited as many as this.[33,35,40] To detect lesser differences in DGF rates, even greater numbers would be required. Studies were even more seriously underpowered with regard to detecting likely differences in longer term graft survival rates. For example, to detect a change in 1-year survival from 70 to 75% at the same power and significance levels would require recruiting at least 1256 patients.

One of the most significant factors determining the immediate function of a kidney post-transplant is whether or not it was from an HBD or NHBD. It is important, therefore, to distinguish between the two when assessing the impact of MP. Unfortunately, not all studies state explicitly whether the donors were HBDs or not, although in most of these cases one can make a reasonable assumption, based on knowledge of what was standard practice at the time. There is also heterogeneity with respect to whether or not the study was restricted to first transplants,[13] or whether subsequent transplants were also included.[14,34,35,40,50] In most cases, this is not stated.

Information with regard to drop-outs from the studies is only given in three cases.[33,38,51] In the other studies there is an assumption that there were no drop-outs.

The earlier studies used a variety of perfusates for kidneys kept in CS, including hypertonic citrate,[40] Sacks II,[45] Collins C_3[45] or TP-II.[46] From 1985 to 1993 studies used Collins or Euro-Collins solution, and from 1993 onwards UW solution was used. The most commonly used machine for perfusing kidneys was the Waters MOX 100. Other machines used included the Belzer LI 400,[44,45] Gambro[33,40,51] and a Nikiso APS-02.[37] Earlier studies used cryoprecipitated plasma as a perfusate,[13,37,40,44,45] while later ones used plasma protein fraction,[38,46] silica-gel plasma perfusate,[14,35,36] plasmanate,[33,34,51] 5% albumin[33] or UW gluconate (Viaspan).[50] (Van der Vliet and colleagues[51] reported using 'Belzer solution'. This is assumed to be UW solution, as that was developed by Belzer, and is known to be in standard use.)

Three studies were of kidneys taken from NHBDs.[37,40,51] Five studies explicitly stated that the kidneys came from HBDs,[13,34,35,48,49] and the remainder did not specify whether the donors were heart beating or not. It is likely that in all such cases they were HBDs, with the possible exception

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 1 *Controlled studies*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Sterling,[44] 1971	0	Richmond, Virginia, USA	CS 2–8 h vs CS 4–10 h followed by machine perfusion (Belzer's LI 400 with cryoprecipitated human plasma) 6–19 h	Donated pairs allocated (method not stated) one each to CS and MP	Post-transplantation ATN (not defined), serum creatinine post-transplantation	5 CS 5 MP	4/5 kidneys in each group had ATN for 5–21 days. Serum creatinine all 2.0 mg% or below at 1–7 months post-transplantation	Kidneys in MP group also had period of CS. Perfusion fluid for CS not stated. Text does not state whether HBD or NHBD, but date of study suggests probably NHBD. No data on matching
Marshall,[39] 1977	0	Melbourne, Australia	CS (hypertonic citrate) mean 14 h, vs MP (Gambro with cryoprecipitated plasma) mean 16 h	Donated pairs allocated (method not stated) one each to CS and MP	Early function, graft survival	34 CS 31 MP	Immediate function in 20/34 (60%) CS, 17/31 (55%) MP. 20 grafts followed-up for 1 year – 5/10 graft survival for both CS and MP	Early result of continuing trial. All NHBD. Two kidneys lost due to mechanical failure of MP. No data on matching
Marshall,[40] 1977	1	Melbourne, Australia	CS (hypertonic citrate) mean ischaemic time 13 h vs MP (Gambro with cryoprecipitated plasma) mean ischaemic time 16 h	Donated pairs allocated ('as far as possible … randomised') one each to CS and MP	ATN (= dialysis in first week), 3-month and 1-year graft survival	68 CS 62 MP	ATN, 3-month, 1-year survival: 34/68 (50%), 28/52 (54%), 10/27 (37%) CS, 33/62 (53%), 24/58 (50%), 18/42 (43%) MP. NS. Overall 1-year graft survival less [11/36 (31%) vs 17/33 (52%)] in grafts with ATN vs no ATN	112 first grafts, 18 second grafts (split between CS and MP not stated). All NHBD. Presumably includes patients in Ref. 39. No data on matching

continued

TABLE I *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Beck,[45] 1979	0	Torrance, California, USA	CS (19 Sacks II, 6 Collins C_3) vs MP (19 LI 400, 5 T-1450, 1 Waters, all with cryoprecipitated plasma)	'Common donor' – method of allocation not stated	Dialysis requirement at 1 month	25 CS 25 MP	14/25 (56%) grafts did not require dialysis at 1 month in both CS and MP	Delay in total adenine nucleotide pool estimated from warm and cold ischaemia, reported to be good predictor of function. No further data on HBD/NHBD, matching, 1st/subs. tx. Protocol modified during study, and 'an improved rate of success for MP was observed following protocol modifications'
Marshall,[41] 1980	0	Melbourne, Australia	CS mean ischaemic time 14 h vs MP mean ischaemic time 16 h	'Matched donor pairs'	1-year graft survival	101 CS 80 MP	1-year graft survival 55% in CS, 49% for MP.	Presumably includes same patients as Marshall and colleagues.[39,40] No further information included
Toledo-Pereyra,[46] 1983	0	Detroit, Michigan, USA	CS (TP-II solution) mean ischaemic time 23 h vs MP (Waters MOX 100 + PPF) mean ischaemic time 19 h	Donated pairs allocated (method not stated) one to each of CS and MP	ATN (= dialysis within 2 weeks), 1-year graft survival	10 CS 10 MP	ATN and 1-year graft survival: 2/10, 9/10 in CS, 5/10, 8/10 in MP	All first transplants. Immunosuppression with prednisolone and azathioprine ± ALG. No further data on HBD/NHBD, matching, 1st/subs. tx

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 1 *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Mozes,[35] 1985	1	Chicago, Illinois, USA	CS (Euro-Collins) mean ischaemic time 32.8 h vs MP (Waters MOX 100 + silica gel plasma perfusate) mean ischaemic time 35.1 h	Donated pairs allocated randomly one each to CS and MP	ATN (= dialysis in first week), 3-month, 1-year graft survival	96 donors 94 CS 93 MP	Primary non-function in 2/94 CS, 9/93 MP. ATN in 51/94 (54%) CS, 40/93 (43%) MP ($p > 0.06$). 3-month, 1-year actuarial graft survival 52% in CS with ATN, 71% in CS without, 54% in MP with ATN, 74% in MP without. Significant difference in ATN rate in CS group between those with preservation time greater (48/79) and less than (4/15) 24 h. 1-year graft survival significantly lower in patients who had ATN in both CS and MP groups	All HBD. Warm ischaemia in 16 donors, >10 minutes in 4. 38 patients treated with azathioprine and steroids only, 120 with azathioprine, steroids and ALG, 29 with cyclosporine. 154 1st tx, 33 secondary. No significant difference between groups with respect to HLA matching. Not clear if any patients died with functioning grafts within 1 year, and if so how analysed. Note ATN rates substantially higher than in Rosenthal and colleagues[47]

continued

TABLE I *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Alijani,[38] 1985	1	Washington DC, USA	CS (Euro-Collins) mean 29 h vs MP (Waters MOX 100 + PPF) mean 32 h	Donated pairs allocated alternately R and L each to CS and MP	ATN (= dialysis in first week)	38 donors, but only 29 CS, 29 MP analysed because in 8 one of pair not used, in one preservation mode changed	ATN in 18/29 (62%) CS, 5/29 (17%) MP. No case of ATN in MP kidney where CS pair did not also have ATN. Higher mean nos of dialyses required in CS with ATN (2.8) vs MP with ATN (2.4). In CS kidneys, ATN more common with increasing preservation time. 'Graft and patient survival of both groups at 1 year does not appear to be altered significantly by the method of preservation'	Patient level data available. No further data on HBD/NHBD, matching, 1st/subs. tx, immunosuppression
Heil,[36] 1987	2	Minneapolis, Minnesota, USA	CS (Euro-Collins) vs MP (Waters MOX 100 with silica gel fractionated plasma)	Donated pairs allocated randomly (sealed envelopes) to CS and MP, and then randomly allocated to recipients	DRF (= need for dialysis post-transplant), 1-year graft survival	27 CS 27 MP	No statistically significant difference in DRF: CS 11/27 (41%), MP 14/27 (52%). 1-year graft survival greater in MP: 20/27 (74%) in CS, 24/27 (89%) in MP ($p < 0.05$). DRF in CS lasted longer than in MP (14.9 vs 9.9 days, $p < 0.05$)	No further data on HBD/NHBD, matching, 1st/subs. tx, immunosuppression. Data on graft survival ambiguous: not clear if it refers to all grafts or only those that suffered DRF

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 1 *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Halloran,[33] 1987	2	Toronto, Canada	CS (modified Collins) mean total storage 27.7 h vs MP [Waters (most) or Gambro with plasmanate or 5% albumin] mean total storage 30.5 h	Randomisation of donors	Delayed function, requirement for dialysis in first week post-transplant, graft failures at 12 months	107 donors randomised, yielding 208 kidneys. 12 discarded after randomisation. Follow-up data available for 194 kidneys, 90 CS, 91 MP, 13 randomised to MP, but received CS	Complete data available on 176 patients who received kidneys per allocation. Delayed function, dialysis required in first week, higher in CS than MP: 40/90 (44%), 33/90 (37%), in CS, 28/91 (31%), 24/91 (26%), in MP. 12-month graft survival: 69.5% in CS 74.9% in MP. NS.	Randomisation of donors chosen over randomisation of kidneys in order to overcome possible bias against CS kidneys by host centre. Comment that criteria for post-tx dialysis and DGF vary between centres. Some costing data. 41% of CS, 43% of MP received cyclosporine. Matching equivalent in both groups. 75.6% CS, 76.9% MP were first transplant. No further data on HBD/NHBD
Mendez,[48] 1987	0	Los Angeles, California, USA	CS (Collins) vs MP (Waters MOX100 with Belzer's plasmanate)	Donated pairs allocated (method not stated) one to each of CS and MP	Immediate function (= urine output >1000 ml/day more than pre transplant), 1-year graft survival	26 CS 26 MP	No immediate function, 1-year graft survival: 17/26 (65.4%), 15/26 (57.7%) in CS, 9/26 (34.6%), 19/26 (73.1%) in MP	HBD. All patients received CyA + prednisolone. No data on ischaemic time, matching, first/sub. transplants

continued

TABLE I *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Jaffers,[34] 1989	2	San Antonio, Texas, USA	CS (Collins) vs MP (Waters MOX 100 with plasmanate)	'Random' (not paired)	ATN (= lack of decline of creatinine over 4 days post-tx). 1-year survival	33 CS 68 MP	ATN and 1-year survival 15/33 (45.5%), 25/33 (75.8%) in CS, 19/68 (27.9%), 50/68 (73.5%) in MP. ATN significantly higher in CS preserved >24 h 10/16 (62.5%) than in CS <24 h or MP <24 or >24 h 1-year survival greater if no ATN (53/67, 79.1%) than if ATN (22/34, 64.7%)	All HBD. All received cyclosporine. 90 first grafts, 11 sub. No difference in matching between groups
Merio,[14] 1990	1	Ann Arbor, Michigan, USA	CS (Euro-Collins) mean preservation 22 h vs MP (Waters MOX 100 with silica gel fraction) mean preservation 21 h	Donated pairs allocated alternately R and L each to CS and MP	Postoperative creatinine levels at 1, 7, 30 days, postoperative dialysis	51 CS 51 MP	No significant difference in postoperative dialysis requirement: 16/51 (31%) in CS, 21/51 (41%) in MP. Ischaemia >24 h associated with higher rate of dialysis in both groups. Of paired kidneys, in 32% only the MP kidney recipient required dialysis, cf 23% only CS recipient	Majority received cyclosporine. 44 first tx in CS, 41 first tx in MP. Matching similar between groups. No further data on HBD/NHBD
Matsuno,[42] 1993	0	Tokyo, Japan	CS (Euro-Collins or UW) mean preservation 7 h vs MP (LPS 02 with cryoprecipitated plasma) mean preservation 13 hour.	Not explicitly stated, though suggestion in results that they were paired	Immediate function, ATN, postoperative HD days, best serum creatinine, 1-month and 2-year graft survival	'12 pairs of grafts'	Results presented in a confusing manner, with discrepancies between text and table, no absolute data and no statistical analysis	NHBD. No useful data

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 1 *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Matsuno,[43] 1993	1	Tokyo, Japan	CS vs MP	For each pair of kidneys, one on CS, one on MP.		14 CS 14 MP	Postoperative HD requirement said to be less, and serum creatinine said to be lower, in MP than in CS, but no data or statistical analysis included	NHBD. May be an overlap with previous study[42]
Matsuno,[37] 1994	1	Tokyo, Japan	CS (4 Euro-Collins, 9 UW) mean preservation 6.1 h vs MP (Nikiso APS-02 with cryoprecipitated plasma) mean preservation 11.9 h	Donated pairs allocated randomly R and L each to CS and MP	ATN (= dialysis in first week), 1-month survival, best serum creatinine	13 CS 13 MP	Immediate function, primary non-function, ATN, postoperative HD days, 1-month graft survival: 1/13 (7.6%), 1/13 (7.6%), 11/13 (86.4%), 12.4 days, 10/13 (76.9%) in CS; 5/13 (8.5%), 0/13, 8/13 (61.5%), 8 days, 13/13 in MP	NHBD. Probably same study as Matsuno and colleagues.[43] Mean 0.9 B matches, 1.2 DR matches in CS, 0.7 and 1.2 in MP. Immunosuppression with prednisolone, azathioprine and ALG, then prednisolone + azathioprine + cyclosporine
Veller,[13] 1994	1	Johannesburg, South Africa	CS (UW) mean preservation 18 h vs MP (Waters 1000 with cryoprecipitated plasma) mean preservation 19 h	Donated pairs split (allocation method not stated) to CS and MP, then allocated randomly	ATN (= dialysis in first week), DGF (clinically assessed), 1-year graft survival.	18 CS 18 MP	ATN, DGF, 1-year survival: 5/18 (28%), 8/18 (44%), 83% in CS, cf. 6/18 (33%), 8/18 (44%), 82% in MP. In kidneys preserved >24 h, ATN in 2/2 CS, 2/5 MP	HBD. First transplants only. No data on matching, immunosuppression

continued

TABLE I *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Gage,[49] 1997	0	Washington, DC, USA	CS (UW) mean preservation time 20 h, vs MP (Waters MOX) with albumin (n = 11, mean preservation time 24 h) or MPS (n = 14, mean preservation time 19 h) perfusates	'Matched pairs' retrospectively analysed	DGF (= dialysis in first week), 1-year graft function	25 CS 25 MP	DGF in 6/25 (24%) CS, vs 3/25 (12%) MP (none on MPS, 3 on albumin). All kidneys functioning at 1 year	All described as 'brain dead', hence presumably HBD. No data on matching or immunosuppression
Kosieradzki,[50] 1999	0	Warsaw, Poland	CS (UW) mean ischaemic time 27 h vs MP [UW, Waters MOX 100 with UW gluconate (Viaspan)] mean ischaemic time 34 h	Donor pairs split CS and MP. Not stated as random	ATN (= dialysis in first week), number of rejection episodes, 1-year graft function	38 CS 38 MP	ATN, patients with rejection episodes, mean episodes per patient, 1-year graft survival: 17/38 (45%), 19, 1.06, 33/37 (89%) in CS, 11/38 (29%), 13, 0.57, 35/37 (95%) in MP. ($p < 0.05$ for ATN, NS for other results.) One death from myocardial infarction in MP group. Mean no. of dialyses in ATN patients 2.8 in CS, 1.54 in MP. One primary non-functioning kidney in CS group	Some results given in terms of 'study' and 'control' groups without explicitly defining them: taken to be MP and CS respectively. 'Haemodynamically unstable cadaveric donors'. All treated with cyclosporine. 69 first tx, 7 subs. Matching equivalent between groups. Immunosuppression with prednisolone + azathioprine + cyclosporine.

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE I *Controlled studies (cont'd)*

Author, year	Jadad score	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
van der Vliet[51] 2001	2	Nijmegen, The Netherlands	CS (UW) mean preservation time 23 h, vs MP (Gambro with Belzer) mean preservation time 25 h.	Donated pairs allocated randomly R and L each to CS and MP	Immediate function, DGF (not defined) serum creatinine at 3 months, 1-year graft survival	5 lost to follow-up. 36 CS 35 MP	Immediate function, 3-month creatinine, 1-year survival: 8/36 (22%), 162 (mol, 84.2% in CS, 15/35 (43%), 174 μmol, 76.3% in MP. NS. Primary non-function in 4/36 (11%) CS, 6/35 (17%) MP. DGF primary non-function in 28 CS, 20 MP	NHBD. No differences in number of retransplants and HLA mismatches between groups. No data on immunosuppression

ATM, acute tubular necrosis; NS, not significant; tx, transplant; CyA, cyclosporine A; HD, haemodialysis; ALG, anti-lymphocyte globulin; DRF, delayed renal function; PPF, plasma proteins fraction.

TABLE 2 *Delayed graft function*

		CS				MP						
Study	***N* (total)**	***n***	**Number with DGF**	**Percent with DGF**	**Ischaemic time (h)**	***n***	**Number with DGF**	**Percent with DGF**	**Ischaemic time (h)**	**Relative risk**	**Lower limit RR**	**Upper limit RR**
Sterling[44]	10	5	4	80.0		5	4	80.0		1.00	0.54	1.86
Marshall[40]	130	68	34	50.0	13	62	33	53.2	16	1.06	0.76	1.49
Toledo-Pereyra[46]	20	10	2	20.0	23	10	5	50.0	19	2.50	0.63	10.00
Mozes[35]	187	94	51	54.3	33	93	40	43.0	35	0.79	0.59	1.07
Alijani[38]	58	29	18	62.1	29	29	5	17.2	32	0.28	0.12	0.65
Heil[36]	54	27	11	40.7		27	14	51.9		1.27	0.71	2.28
Halloran[33]	181	90	33	36.7	28	91	24	26.4	31	0.72	0.46	1.11
Mendez[48]	52	26	17	65.4		26	9	34.6		0.53	0.29	0.96
Jaffers[34]	101	33	15	45.5		68	19	27.9		0.61	0.36	1.05
Merion[14]	102	51	16	31.4	22	51	21	41.2	21	1.31	0.78	2.21
Matsuno[37]	26	13	11	84.6	6	13	8	61.5	12	0.73	0.45	1.19
Veller[13]	36	18	5	27.8	18	18	6	33.3	19	1.20	0.45	3.23
Gage[49]	50	25	6	24.0	20	25	3	12.0	21	0.50	0.14	1.78
Kosieradzki[50]	76	38	18	47.4	27	38	11	28.9	34	0.61	0.34	1.11
van der Vliet[51]	71	36	28	77.8	23	35	20	57.1	25	0.73	0.53	1.03
Total	1154	563	269	47.8		591	222	37.6				

of the earliest study,[44] dating from 1971. Five studies[14,34,35,40,50] included second and subsequent transplants, while two[13,46] explicitly stated that all were first transplants. The remainder of the studies did not state whether or not second and subsequent transplants were included. Information on immunosuppression used was only included in eight studies.[14,33–35,37,46,48,50] Seven studies[14,33–35,37,50,51] explicitly state that the extent of tissue type matching between donor and recipient was similar in both MP and CS kidneys. In the other studies no information is given about this.

Information on the length of preservation time is available in 11 studies.[13,14,33–35,37,38,40,46,49–51] In these, the mean preservation time for CS kidneys varied from 6[37] to 33 h,[35] and for MP from 12[37] to 35 h.[35] (It should be noted that MP did not necessarily last for the whole time that kidneys were ischaemic – in many cases it was only used for part of the time, and kidneys were simply kept in CS for the rest of the time.) In nine of the 11 studies the ischaemic time was longer in MP than in CS kidneys, with the difference varying between –4 h (i.e. CS kidneys had a 4 h shorter ischaemic time) and +7 h.

Immediate graft function

The outcome for which most information is available is the immediate graft function post-transplantation. Most commonly, this is reported as the requirement for dialysis in the first week postoperatively,[13,33,35,37,38,40,49,50] although in other cases it is reported as dialysis requirement in the first 2 weeks,[46] as urine output[48] or decline in creatinine over 4 days postoperatively.[34] In some papers the presence of acute tubular necrosis (ATN) or DGF was reported as an outcome, although the diagnostic criteria for this were not specified.[44,51] One paper only reported dialysis requirement at 1 month,[45] and this was taken to be too long after the operation to be considered a good measure of immediate function, and therefore excluded from further analyses.

Information was therefore available for 15 studies (see *Table 2*). In these, the incidence of DGF in kidneys preserved by CS varied between 20[46] and 84.6%.[37] The three studies with NHBDs and the oldest study all reported high rates of DGF. The incidence of DGF in the MP kidneys varied from 12[49] to 80%.[44] The relative risk of DGF in kidneys preserved by MP as compared with CS within individual studies varied from 0.5[49] to 2.5.[46]

A funnel plot of the logarithm of the relative risk against study size (*Figure 2*) demonstrates no evidence of publication bias in the studies. The two largest studies give relative risks nearest to the point estimate, as is to be expected, while the relative risks in smaller studies are evenly distributed about this figure.

Meta-analysis of all 15 studies, using a random effects model, gave a point estimate for the relative risk of 0.804, with 95% confidence limits of 0.672 to 0.961 and a p value of 0.017 (see *Figure 3*). This implies that overall a 20% reduction in the incidence of DGF is achieved by using MP.

Because of the heterogeneity of the studies, meta-analyses were undertaken of various groupings of the studies (see *Figure 4*). The point estimate for the relative risk for the three NHBD studies is 0.847 (p = 0.21, CI 0.653 to 1.098). For the five specified HBD studies it is 0.718 (p = 0.005, CI 0.572 to 0.903), and for the studies in which the donor status was not specified it is 0.865 (p = 0.46, CI 0.587 to 1.275). When these latter two groups were combined the point estimate is 0.788 (p = 0.049, CI 0.621 to 0.999).

Meta-analysis of the two studies in which UW solution was used as the perfusate gives a point estimate of the relative risk of 0.703 (p = 0.019, CI 0.524 to 0.943).

Meta-analysis of those five studies which explicitly included second and subsequent transplants gives a point estimate of 0.863 (p = 0.26, CI 0.667 to 1.116), and of those studies which were confined to first transplants or where detail was not given gives a point estimate of 0.763 (p = 0.037, CI 0.591 to 0.984).

All studies with mean ischaemic times of >24 h reported a relative risk of <1.

Overall, therefore, there is evidence that MP of kidneys leads to a 20% reduction in DGF following transplantation. Such evidence as is available suggests that this applies equally to HBDs and NHBDs, and to first and subsequent transplants. Based on only two studies, it would appear that the benefit in kidneys perfused with UW solution may be even greater. There is also a suggestion that the benefits are greater with longer ischaemic times.

Only two studies reported the duration of DGF,[36,37] although two others reported the number of dialyses required.[38,50] Where graft function is delayed, it appears to be delayed

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

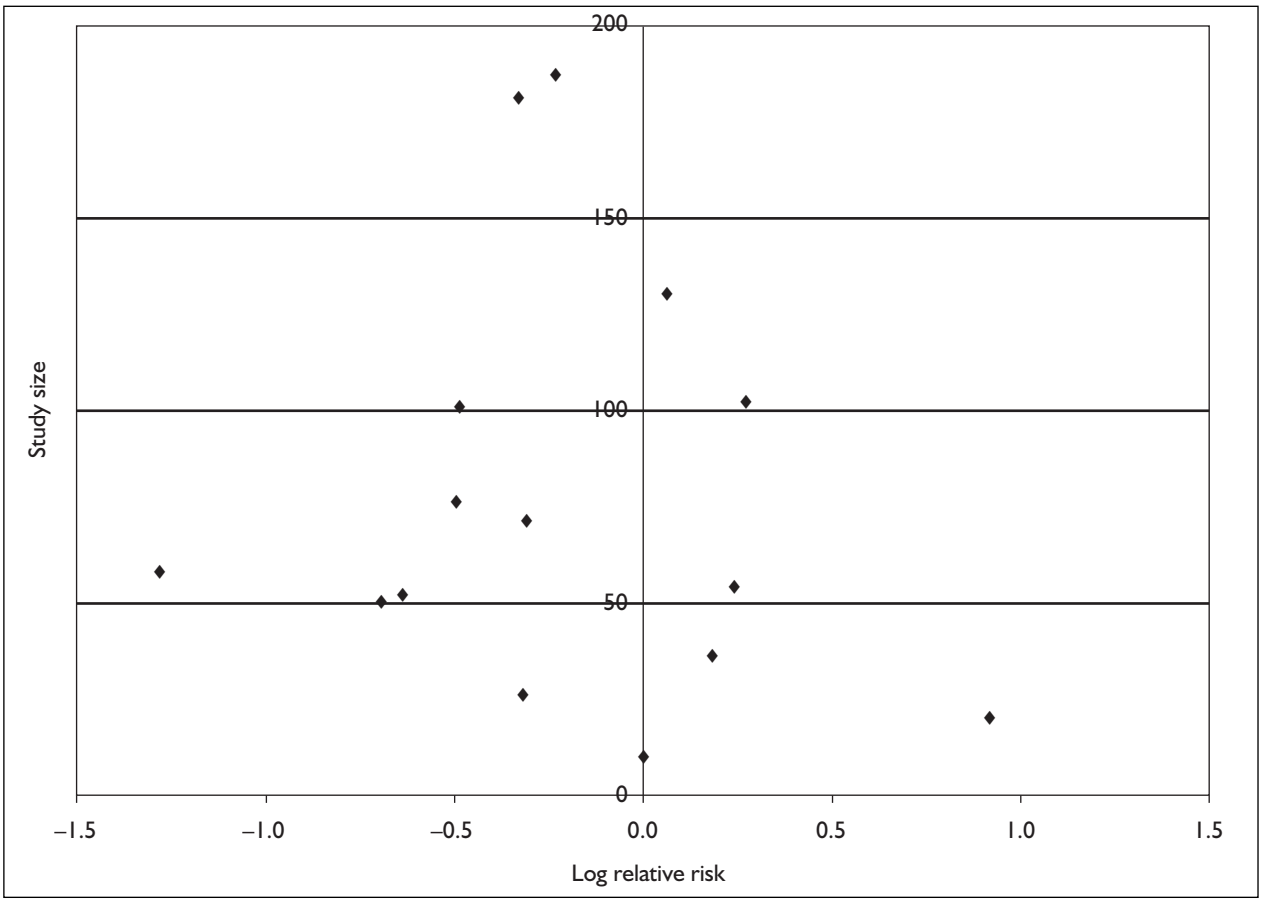

FIGURE 2 *Funnel plot of studies*

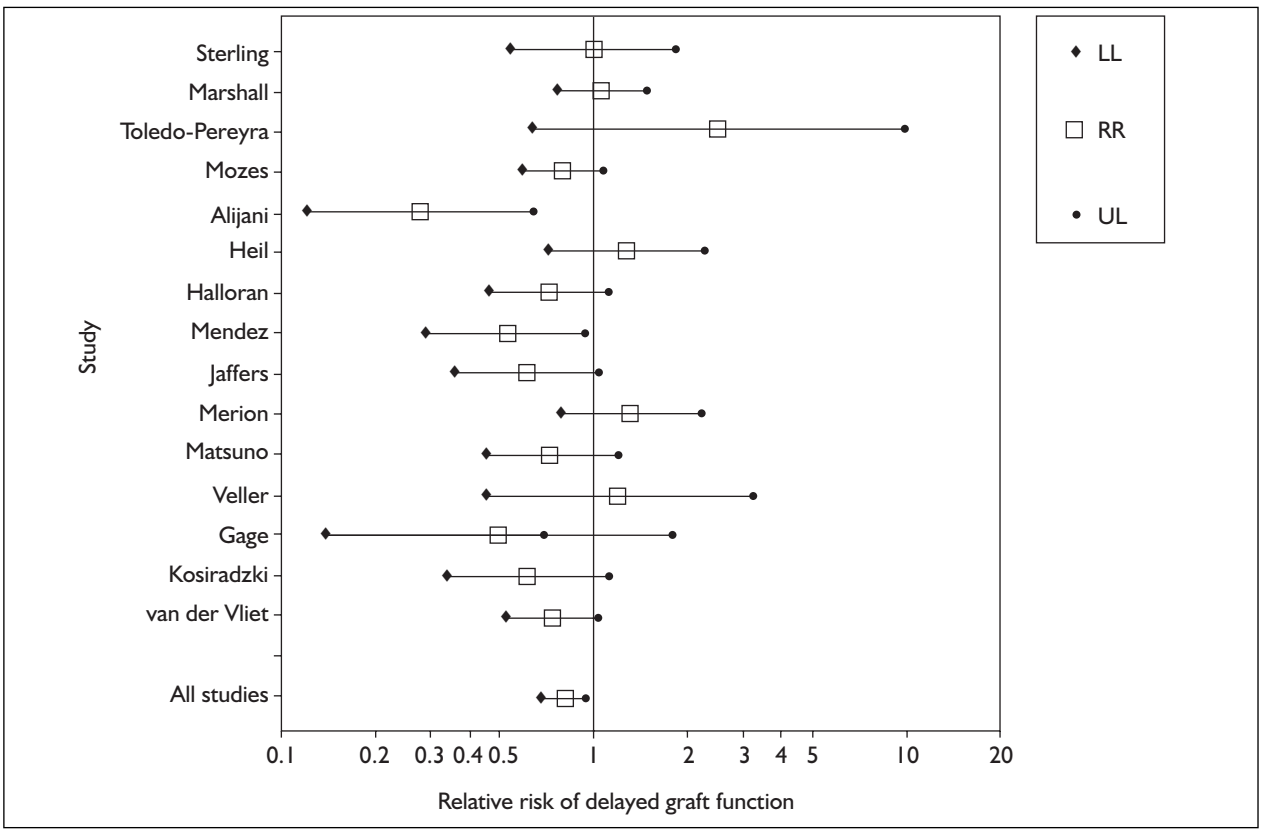

FIGURE 3 *Box and whisker plot of relative risk of DGF by study*

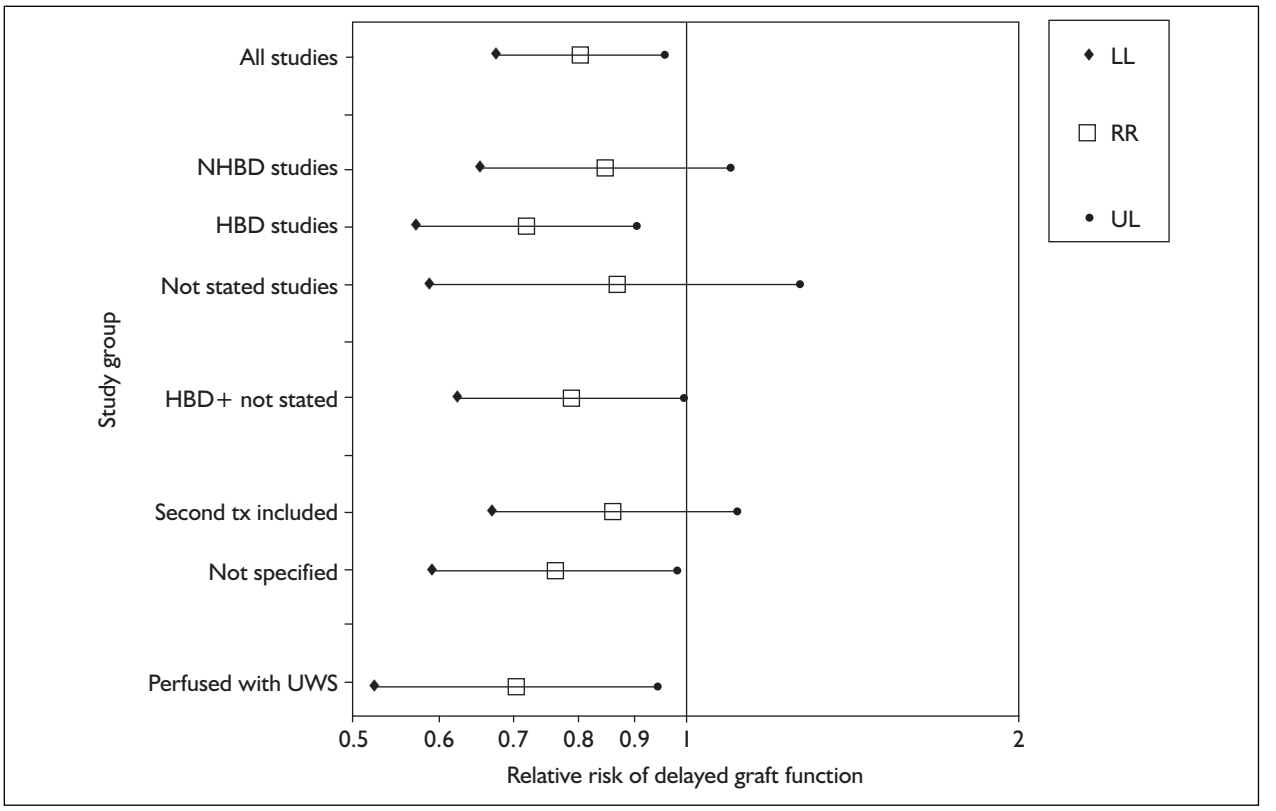

FIGURE 4 *Box and whisker plot of relative risk of DGF by grouping of study*

longer in CS than in MP kidneys: 14.9 vs 9.9 days in one study[36] and 12.4 vs 8 days in the other.[37] Similarly, the reported number of dialyses required in patients who received CS as opposed to MP kidneys appears to be greater: 2.8 vs 2.4 in one study,[38] 2.8 vs 1.54 in another.[50]

Longer term graft survival

The 1-year graft survival was reported in nine studies.[13,34,36,40,46,48–51] In five of these,[34,36,46,48,49] all patients recruited to the study were followed for 1 year, and a true 1-year graft survival figure given. In two,[40,50] not all patients were followed-up for the year, and in two others,[13,51] the percentage 1-year survival is quoted without stating how many patients were followed-up for this length of time. Details are given in *Table 3*.

Meta-analysis was undertaken of those seven studies which reported absolute numbers of grafts surviving or not for 1 year.[34,36,40,46,48–50] A total of 420 patients were included. The graft survival rate in CS kidneys varied from 37 to 100% between studies, and in MP kidneys between 42.9 and 100%. The relative risk of graft survival in MP as compared with CS kidneys varied from 0.89 to 1.27. Meta-analysis gave a point estimate of the relative risk of 1.025 (p = 0.44, CI 0.963 to 1.090) (see *Figure 5*). There is thus no evidence from these studies that MP of kidneys, despite leading to a reduction in DGF, leads to an increase in graft survival over 1 year. However, in view of the number of patients included in the studies, and the earlier comments about power, it is possible that a real effect could have been missed.

Testing viability of kidneys *ex vivo*

One of the claimed advantages of MP systems is that they enable assessment to take place of the viability of the kidney(s) prior to transplantation. In the early years of kidney transplantation the use of MP was routine in many centres, particularly in the USA, and perfusate pressures and flows were monitored in the belief (based on animal studies) that poor perfusion of the organ was an indication of non-viability. Criteria were set for the adequacy of perfusion, which if not met led to the discarding of the organ. However, after the introduction of brain death criteria in the mid-1970s, and the near abandonment of NHBDs as a source of kidneys, primary non-function (PNF) of transplants (i.e. transplants that never function) became extremely uncommon, and testing for kidney viability thus less of a concern. Moreover, there was a general shift to the use of CS, as it was seen as cheaper, simpler and as effective as MP.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 3 *One-year graft survival*

		CS			MP					
Study	***N* (total)**	***n***	**Functioning at 1 year**	**Percent functioning at 1 year**	***n***	**Functioning at 1 year**	**Percent functioning at 1 year**	**Relative risk**	**LL RR**	**UL RR**
Marshall[40]	69	27	10	37.0	42	18	42.9	1.16	0.63	2.12
Toledo-Pereyra[46]	20	10	9	90.0	10	8	80.0	0.89	0.61	1.29
Heil[36]	54	27	20	74.1	27	24	88.9	1.20	0.93	1.56
Mendez[48]	52	26	15	57.7	26	19	73.1	1.27	0.85	1.90
Jaffers[34]	101	33	25	75.8	68	50	73.5	0.97	0.76	1.23
Veller[13]				83.0			82.0			
Gage[49]	50	25	25	100.0	25	25	100.0	1.00	1.00	1.00
Kosieradzki[50]	74	37	33	89.2	37	35	94.6	1.06	0.93	1.22
van der Vliet[51]				84.2			76.3			
Total	420	185	137	74.1	235	179	76.2			

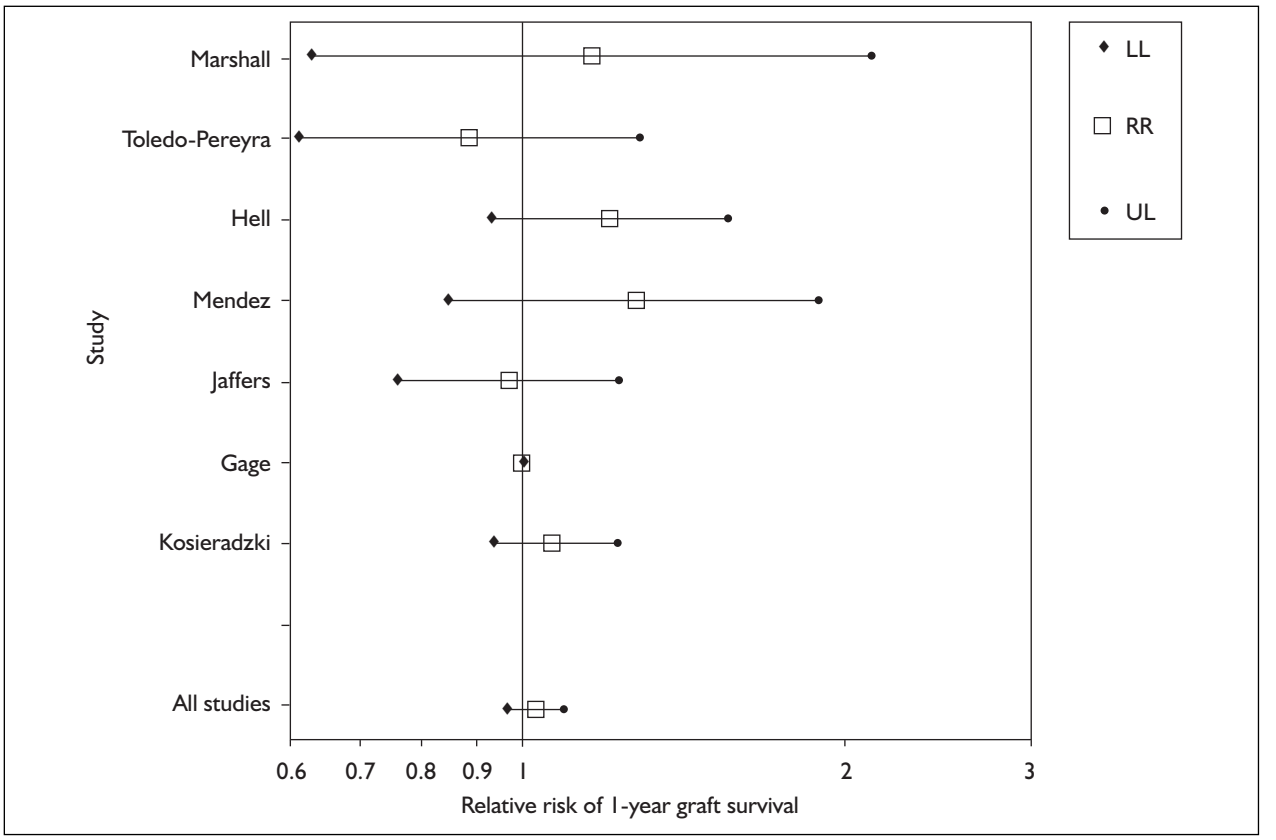

FIGURE 5 *Relative risk of 1-year graft survival by author*

In recent years, the mismatch between supply and demand for kidneys has led to the use of 'extended donor' kidneys (e.g. older, hypertensive, diabetic) and NHBDs, which do have a significant incidence of PNF. With this has come a renewed interest in the possibility of testing for viability on MP. This has included monitoring of perfusate pressures and flows, and also testing for markers of cell damage, such as lactate dehydrogenase (LDH) and α-GST.

In assessing any proposed test of the viability of kidneys, the 'gold standard' against which it must be compared is the actual outcome for kidneys transplanted. The ideal study of viability testing would involve collecting data prospectively on kidneys that are below, as well as above, whatever threshold is postulated, in order to determine whether those below the threshold do not function post-transplantation as well as those above. Only in this way could the sensitivity and specificity of any proposed test for viability be established. In effect this means that some kidneys have to be transplanted which fail to meet the proposed threshold.

The main aim of viability testing has to be the identification of non-viable kidneys, so that their transplantation can be avoided. Some studies have examined the use of viability testing to identify kidneys that suffer DGF or ATN. While this may be of both clinical and research interest, it is not the ultimate aim of viability testing, as a kidney which is known to be at a high risk of DGF is not likely to be rejected for that reason alone.

Papers identified for review

Twenty-six papers, reporting 18 studies, were identified which reported the use of tests for viability of human kidneys on MP. Of these, nine[52–60] were published between 1974 and 1981, reporting seven studies of the use of perfusate flow characteristics and biochemical markers. A further 17 papers published since 1993 have been identified,[61–77] reporting 11 studies. Details of all studies are given in *Table 4*.

Studies published between 1974 and 1981

Of the nine studies published between 1974 and 1981, eight[52,53,55–60] did not report on PNF, and of these, two studies[52,58] explicitly discarded a number of kidneys on the grounds of poor perfusion prior to transplantation, thus clearly making it impossible to report on outcomes of those kidneys below the chosen threshold. Three studies[53,55,59] reported no statistically significant correlation

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 4 *Studies of viability testing*

Author, year	Centre	Test examined	Number of kidneys (total)	Preselected?	Source	Outcomes reported	Results	Comments
Baxby,[52] 1974	Newcastle, UK	Perfusate flow and pressure	41	4 kk rejected because of positive cross-match, 5 because of poor flow, high perfusion pressure	Not stated	pH and lactate levels on perfusion in IF and DGF groups	32 kk transplanted. 4 excluded from analysis because of early rejection or hypotension. 12/28 immediate function, 16/28 delayed function. Fall in pH on perfusion greater, lactate at 1 h lower, in IF than DF group. Lactate of 20 mg/100 ml said to distinguish between IF and DF kk	
Sampson, 1977;[53] 1978[54]	Wisconsin, USA	Perfusate flow	100	No kk rejected on grounds of poor perfusion	HBD	PNF, duration of ATN, serum creatinine at 3, 12 months in kk with flow <80, 80–100, >100 ml/minute^{-1}	No significant differences in outcomes between three different groups. Significant difference in duration of ATN (but not PNF) between kidneys with decreasing and increasing flow on perfusion	
Burleson,[55] 1978	Syracuse, New York, USA	'Perfusate data'	63	No kk rejected on grounds of poor perfusion	HBD and NHBD	Presence of ATN. (Graft survival and histology also reported, but not related to perfusion data)	'No differences were apparent in the perfusion data that allow discrimination …'	'Perfusion data' appear to include lactate concentration (in abstract) as well as flow rate, etc.
Feinfeld,[56] 1978	New York, USA	Ligandin (α-GST) in perfusate	13	No	Not stated	Post-transplant oliguric renal failure (based on urine vol. <200 ml/24 h, no rejection, good blood flow)	8/8 α-GST +ve kidneys (mean concentration 3.4 μM minute^{-1}) had acute oliguric renal failure, 5/5 α-GST –ve kidneys did not ($p < 0.001$, Fisher's exact test)	Tested for α-GST using immunodiffusion analysis

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 4 *Studies of viability testing (cont'd)*

Author, year	Centre	Test examined	Number of kidneys(total)	Preselected?	Source	Outcomes reported	Results	Comments
Horpacsy, 1978,[57] 1979[58]	Berlin, Germany	Perfusate flow, LDH, lactate and pH.	105[57] 101[58]	24/105 discarded 'because of signs of avitality'	Not stated	Duration of dialysis post-op., time to fall of creatinine to below 2 mg%.	Correlation results include only 49 cases – detail of selection not given. Correlation observed between perfusate flow and time to creatinine <2 mg%. ($r = 0.48$, $p < 0.01$.) No correlation with LDH or lactate	Study primarily a comparison of two different albumin solutions for perfusion
Sy,[59] 1980	Detroit, Michigan, USA	Perfusate pressure and flow, pH, gases	50	Not stated	Not stated	Long-term actual graft survival in kk with flow > or <175 ml/minute^{-1}	Difference in graft survival between high- and low-flow kidneys did not reach statistical significance	
Cho,[60] 1981	New York, USA	Ligandin (α-GST) in perfusate	24 (12 pairs) in study 1, 12 in study 2	Yes – in study 1 only those kidneys where both of pair functioned similarly were included	Not stated	Immediate function	Study 1: α-GST activity higher in the perfusate of 8 kk with ATN than 16 without (144 vs 43 μM minute^{-1}, $p < 0.0002$) Study 2: α-GST activity not significantly higher in the ultrafiltrate of 2 kk with ATN than 10 without (42 vs 4 μM minute^{-1}, p = NS)	α-GST measured by spectrophotometric assay

continued

TABLE 4 *Studies of viability testing (cont'd)*

Author, year	Centre	Test examined	Number of kidneys(total)	Preselected?	Source	Outcomes reported	Results	Comments
Tesi, 1993[61] 1994[62]	Columbus, Ohio, USA	Pump parameters	87	13/87 'did not meet minimal pump perfusion parameters and were discarded' – i.e. renal resistance >0.4, or flow <70 ml/minute^{-1}	37/74 from donors aged >60 years	Patient and graft survival, ATN, 72-h urine output, hospital stay, 10- and 30-day creatinine	Results based on 69 kidneys transplanted in centre. Pump parameters failed to predict ATN. Authors claim that study shows that by rejecting kidneys with poor flow, low ATN rates were achieved, thus supporting the accuracy of perfusion characteristics in predicting a good functioning kidney	Conclusions not supported by data
Daemen,[63] 1995	Maastricht, The Netherlands	Perfusate characteristics (IRR), LDH, pH	38	11/38 rejected – reasons not stated, but in analysis stated to have had higher IRR and LDH	NHBD	Perfusate characteristics including, LDH, pH in ever functioning and non-functioning kk	No significant differences between functioning and non-functioning kidneys in terms of IRR, LDH or pH	
Matsuno, 1994,[64] 1996,[65] 1998[66]	Tokyo, Japan	Perfusate flow rate	63[64] 71[65] 77[66]	5/63 had flow of <0.4 ml minute^{-1} g^{-1} and were not transplanted.[64] 4/71 discarded[65]	NHBD	'Kidney function after transplantation'	All 58 transplanted kidneys showed good function.[64] Authors claim that this vindicates use of threshold for selecting kidneys. 62 kidneys with flow >0.4 ml minute^{-1} g^{-1} all had good function, 5 with flow less than this had PNF.[65] Extended to 68 kk with good flow[66]	

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 4 *Studies of viability testing (cont'd)*

Author, year	Centre	Test examined	Number of kidneys(total)	Preselected?	Source	Outcomes reported	Results	Comments
Polyak, 1997,[67] 1999[68]	New York, USA	Perfusate flow	111[67] 100[68]	Not stated	Extended donors	Discharge creatinine, length of stay, immediate function, DGF in DGF, cf. IF kidneys	Kidneys that experienced DGF had lower flow and increased resistance on perfusion. Ionised calcium in perfusate increased in DGF[68]	No mention of PNF
Danielewicz,[69] 1997	Warsaw, Poland	Perfusion parameters (pressure, flow, IRR, pH, gases, lactate, LDH)	63 donors, 86 transplants.	'8 recipients excluded because early acute rejection proven histologically'	'Ischaemically damaged' – implied NHBD	Perfusion characteristics in DGF, cf. IF kk	2 kidneys never functioned, 4 patients died. Perfusate flow lower, renal resistance higher, LDH and lactate higher in delayed function kk ($n = 26$) cf. IF ($n = 54$)	Authors claim that a combination of factors allows prediction of outcome of graft in 60% of cases
Kievit,[70] 1997	Maastricht, The Netherlands	α-GST and π-GST in perfusate	28	Yes – 6 not transplanted for variety of reasons	19 NHBD, 9 'marginal' HBD	PNF vs life-sustaining function	α-GST ($\mu g\ l^{-1}$) and π-GST ($\mu mol\ l^{-1}$) concentration 1042, 185 in 19 functioning kk, 2649, 263 in 3 non-functioning kk. ($p < 0.05$ for α-GST, NS for α-GST)	α-GST measured by immunoassay, corrected for kidney weight
Kievit,[71] 1997	Maastricht, The Netherlands	α-GST in perfusate	107	Yes – 32/91 NHBD kk not transplanted because of poor perfusion characteristics, etc.	91 NHBD, 16 HBD	PNF vs life-sustaining function	α-GST(μg/100 g) concentration at 8 h: 455, 1107, 2113 in 16 HBD KK (all functioning), 49 functioning NHBD kk, and 10 non-functioning NHBD kk. ($p = 0.0033$). If a threshold α-GST concentration of 2800 used, sensitivity = 93%, specificity = 33%	Possibly included kk in study above.[70] 6/10 PNF kk said to be 'vital' – i.e. failed due to rejection or thrombosis. If these are classified as 'functioning' then sensitivity = 94%, specificity = 75%

continued

TABLE 4 *Studies of viability testing (cont'd)*

Author, year	Centre	Test examined	Number of kidneys (total)	Preselected?	Source	Outcomes reported	Results	Comments
Balupuri,[77,73] 2000	Newcastle, UK	α-GST, perfusate flow, IRR	43[72] 22[73]	Yes – 9 kk rejected due to high α-GST, IRR. 3 others excluded for other reasons. 28 transplanted,[72] 7 kk rejected.[73]	NHBD	Immediate graft function	1 PNF, 2 graft losses due to rejection, thrombosis, 2 deaths. IF in 2, DGF in 22[72]	Threshold for α-GST not explicit. Authors claim results vindicate selection of kidneys for transplantation in this way
Matsuno, 1999,[74] 2000[75]	Tokyo, Japan	Perfusate pressure and flow	80[74] 66[75]	Yes – flow <0.4 ml minute^{-1} g^{-1} – discarded	NHBD	Immediate graft function in kk with flow 0.4–0.65 (low), 0.65– 0.9 (medium), >0.9 (high) ml minute^{-1} g^{-1}	PNF in 7/27 (26%), 2/30 (7%), 0/23 (0%) in low-, medium- and high-flow groups. Longer time to urine vol. >2 L, longer ATN, higher best creatinine in low-cf. high-flow groups.[74] PNF in 7/25 (28%), 1/22 (4.5%), 0/19 (0%) in low-, medium- and high-flow groups[75]	
Kozaki,[76] 2000	Tokyo, Japan	Perfusion data	10	Yes – 10 kidneys with low flow, high resistance	6 from NHBD, 4 from HBD	IF	6/10 kidneys transplanted. All had PNF	No control group. No details about selection. Discrepancy about figures in tables
Kwiatkowski,[77] 2001	Warsaw, Poland	Perfusion data – flow, resistance, lactate	260	Yes – 13 kk not transplanted for 'different reasons' (trauma, infection). 4 not transplanted because of poor perfusion (criteria not stated)	HBD	Perfusion characteristics in DGF cf. IF kk	Results given on 234 grafts (not all kk accounted for). 143 IF, 84, DGF, 7 PNF. Resistance lower, flow higher in first 4 h of perfusion, lactate lower at 4 h in IF cf. DF group. No data given for PNF group. Claim combination of factors can predict IF cf. DGF	

kk, kidneys. IRR, intra-renal vascular resistance.

between flow characteristics and graft function immediately postoperatively, whereas two[57,58] did. One[52] claimed that lactate level after 1 h predicted delayed, as opposed to immediate, graft function.

Two studies[56,60] examined the use of ligandin (later identified as α-GST) concentration in the perfusate as a marker of viability. Neither reported PNF. Although the assays used and the way in which the results are presented differed between the two studies, both reported a highly significant correlation between the ligandin concentration and acute oliguric renal failure or ATN in kidneys post-transplantation, with high ligandin levels being predictive of renal failure.

The one study that explicitly did not discard any kidneys and did report on the incidence of PNF found no correlation between flow rates and outcome.[54]

Studies published since 1993

Since 1993 there has been renewed interest in the assessment of kidneys on perfusion, no doubt associated with the desire to extend the range of possible kidney donors. A further 17 papers have been identified,[61–77] reporting 11 studies, all but one[77] of which were in NHBD or 'extended donor' kidneys. In only one of these[67,68] studies were kidneys not rejected from transplantation due to perfusion characteristics (thus making it impossible to assess how they would have performed if transplanted). However, this study did not report any cases of PNF.

In three studies,[61,64–66,72,73] the fact that the majority of kidneys, preselected for transplantation using perfusion criteria, functioned postoperatively is put forward as vindication of those criteria. Clearly, without a proper control group, this conclusion is not justified. Four studies[63,67–69,74,75,77] reported on the perfusion flow characteristics of kidneys which post-transplantation had immediate function (IF) or DGF. One of these[63] reported no differences in the perfusion characteristics, but the other three all reported higher flow, lower vascular resistance and lower lactate and LDH levels in kidneys with IF compared with DGF.

One study[74,75] categorised kidneys into three different groups according to the perfusate flow, and reported higher PNF in the low-flow group. The same group[76] reported the outcome of six kidneys which failed to meet their normal perfusate flow criteria for transplantation, but were nevertheless transplanted – all had PNF.

Two studies[70,71] from the same centre (and possibly with some overlap) reported on the use of α-GST in the perfusate as a marker of viability. In both studies, some kidneys were discarded because of poor flow characteristics prior to transplantation, but nevertheless, the α-GST concentration in the perfusate was shown to be statistically significantly higher in kidneys that never functioned post-transplant than in those that did. In one of these studies[71] there are enough data to calculate the sensitivity and specificity of the use of a threshold concentration of α-GST of 2800 μg/100 g as a discriminatory test. This gives a sensitivity of 93% and a specificity of 33% (and hence a likelihood ratio of 1.41). Of the 10 kidneys in this study which never functioned, six were said to be 'vital', that is, they were thought to have had the potential to function at transplantation, but failed owing to rejection or thrombosis. If these are classified as 'functioning' then the sensitivity becomes 94%, and the specificity 75% (likelihood ratio 3.76). If this were confirmed, using this test with this threshold would lead to six out of every 100 viable kidneys being rejected (hence not transplanted, and wasted), and one in four non-viable kidneys being transplanted (and subsequently not working).

Overall, there is little evidence that non-viable kidneys can be accurately identified when on MP. While there is some evidence that high vascular resistance and poor flow rates are associated with DGF and in some cases with PNF, it is not possible to state what the sensitivity or specificity of different flow thresholds would be. The use of α-GST concentration in the perfusate appears promising as a means of identifying non-viable kidneys, but further investigation would be required to establish the sensitivity and specificity of different thresholds of α-GST concentration.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Chapter 4

Economic analysis

Overview of economic assessment

The literature search identified a limited number of direct assessments and no randomised controlled trials (RCTs) that evaluate the economic outcomes of the use of MP systems in the preservation of kidneys. The evidence shows that DGF may increase graft survival and it has been hypothesised that MP through reducing DGF may lead to improvements in long-term graft survival. The clinical review in Chapter 3 indicates a statistically significant impact of MP on DGF: however, graft survival outcomes at 1 year are not consistently statistically significant.

The economic analysis therefore includes a review of the effects of DGF on graft survival and an economic model to predict the potential impact of MP on long-term graft survival. The immediate short-term effect of MP on DGF and long-term clinical effect of MP is included in a model-based evaluation. As one of the most significant factors in determining DGF post-transplantation is whether or not it was from an HBD or NHBD, this evaluation compares the effects and costs of MP on these kidneys.

Methods

The systematic review described in Chapter 3 included an economic evaluations filter for economic assessments of MP. Methodological details of this filter are presented in Appendix 2.

Economic assessments were critically appraised according to the *British Medical Journal* (*BMJ*) guidelines and are presented in Appendix 4.

A broad topic search was undertaken for papers which examined the link between DGF and long-term graft survival. This search was used to identify assessments that estimate the long-term impact of DGF on graft survival.

The long-term impact of DGF on graft survival was estimated using Cox proportional hazards modelling.

Results of systematic review of economic studies of MP

The systematic search for health economic studies of MP identified four articles of relevance. Two of these reported the same study.[25,26] All four studies took place in the USA and none reported economic benefit measurements and valuation in any detail.

In summary, the evidence presented is poor according to the economic criteria set down in the *BMJ* guidelines. Three of the studies[25,26,78] were single-centre observational studies and one was a retrospective analysis of a US registry database. The three observational studies were not randomised and both explicitly state that marginal kidneys were targeted to specified preservation systems, thereby introducing serious bias. Overall, there is a lack of information on how the economic analysis was conducted and a poor description of the benefits and methods used. All studies presented crude cost minimisation evaluations based upon the demonstration of clinical benefit in terms of reduced DGF.

These studies claimed complete cost recovery from reduced short-term costs of dialysis and hospitalisation in the US system, associated with the reduction of DGF. In addition to the poor quality of these studies, there is insufficient information to make a direct comparison with the UK healthcare system.

Results of review of the relationship between DGF and graft loss

Details of the literature on the link between DGF and long-term graft survival identified through topic review can be found in Appendix 5, together with a summary of the objectives and methodologies described in these papers.

Of the 18 papers identified that considered the role of DGF as a predictor of graft loss, two did not find DGF to be a statistically significant

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

prognostic factor of graft survival.[79,80] Of the remaining papers, three found DGF to be either the only prognostic factor or the primary prognostic factor for graft loss.[18,81,82] One found DGF with acute rejection predicted poor 5-year graft survival but when DGF was adjusted for acute rejection it was not associated with decreased graft survival.[83] The remaining 12 studies all found DGF to be significantly associated with graft loss. On balance, the published studies show that DGF is associated with higher rates of graft loss.

The link between DGF and long-term graft loss is quantified in the following section.

Model of long-term graft loss

Methods for quantifying the relationship between DGF and long-term graft loss

Two types of statistical analysis have been used in the literature to explore the occurrence of graft loss:

- simple descriptive statistics, that is the mean and standard deviation of graft loss at selected time points for the study populations sub-grouped according to the factors of interest;
- multivariate or univariate Cox proportional hazards modelling.

We focused on the proportional hazards analyses, as this allows graft loss to be assessed over a continuous time period, rather than at discrete time points. It allows the effects of many prognostic factors to be assessed together, and their relative contribution to predicting graft loss to be determined.

The basis of the Cox proportional hazards model is that the hazard or instantaneous risk, for example of graft loss, at any point in time is assumed to be proportional to each of the prognostic factors. The hazard at any point in time for an individual is defined as the probability of the adverse event occurring in a very short time interval given that the individual has survived to the start of that interval without experiencing the event.

The Cox model is a semi-parametric model and makes no assumption about the underlying graft survival characteristics of the population not experiencing DGF. Thus, while the model allows comparisons of risks to be made between populations, no absolute measure of graft survival is obtained. Further, insufficient information is typically reported to quantify the baseline hazard and hence produce a complete graft survival analysis. Clearly, to assess the benefits in terms of graft survival, and hence graft years gained, some measure of baseline graft survival, that is, graft survival following CS of kidneys, is required.

In order to fulfil the modelling requirements to quantify the link between DGF and graft survival, studies needed to fulfil the following criteria:

- analysis of risk factors for graft loss
- delayed graft function assessed as potential factor for graft loss
- Cox proportional hazards model used
- Kaplan–Meier graft survival data for DGF versus no DGF presented in order to estimate baseline survival.

Review of the studies reporting Cox models for graft loss

The seven studies that presented Cox proportional hazards models were selected for further investigation on this basis. The selected studies were then searched for data that could be used in the modelling process. Of these studies only two presented Kaplan–Meier survival data for DGF versus no DGF.[81,84] Only the Feldman study[84] supplied sufficient information to allow calibration of a model of graft loss.

It would be preferable to be able to model long-term graft loss with a multivariate model including all identified prognostic factors. However, it is impossible to calibrate such a model as insufficient data on the prognostic characteristics of the study population are presented in these two studies.

The model of graft loss

The Feldman study[84] was a prospective observational single centre study investigating 338 recipients of cadaveric allografts transplanted between 1985 and 1990 at the University of Pennsylvania Medical Center. The study evaluated the relationship of DGF to acute rejection and long-term survival of cadaveric allografts.

Graft survival rates were estimated by the Kaplan–Meier method. A univariate analysis was undertaken and the variables found to be significantly associated with graft loss were introduced into a multivariate Cox's proportional hazards model. The univariate analysis identified 10 clinical baseline variables as prognostic factors for graft survival (*Table 5*).

TABLE 5 *Rate ratios of allograft failure from univariate proportional hazards analysis*

Variable	Rate ratio	*p*-Value	95% Confidence interval
Delayed allograft function (any vs none)	2.25	<0.001	1.46 to 3.48
Rejection during first 30 days	1.95	0.002	1.28 to 2.98
Rejection after 30 days	3.01	<0.001	1.91 to 5.03
Cold ischaemia time 31–36 h	0.52	0.03	0.29 to 0.96
Recipient race (non-white vs white)	2.94	<0.001	1.92 to 4.35
Recipient age ≤ 30 years	1.7	0.02	1.08 to 2.06
Prior renal transplant (any vs none)	1.53	0.0001	1.18 to 1.98
T cell PRA (>0% vs 0%)	1.58	0.04	1.01 to 2.47
Prior blood transfusions (>5 vs ≤ 5)	1.74	0.02	1.08 to 2.81

PRA, panel reactive antibodies.

TABLE 6 *Rate ratios of allograft failure from multivariate proportional hazards analysis*

Variable	Rate ratio	*p*-Value	95% Confidence interval
Delayed allograft function (any vs none)	1.72	0.02	1.07 to 2.76
Rejection (any vs none in first 30 days)	1.99	<0.01	1.23 to 3.21
Rejection beyond 30 days	3.53	<0.01	2.08 to 6.00
Non-white vs white recipient race	2.78	<0.01	1.78 to 4.35
Prior renal transplant (any vs none)	1.38	0.04	1.02 to 1.87

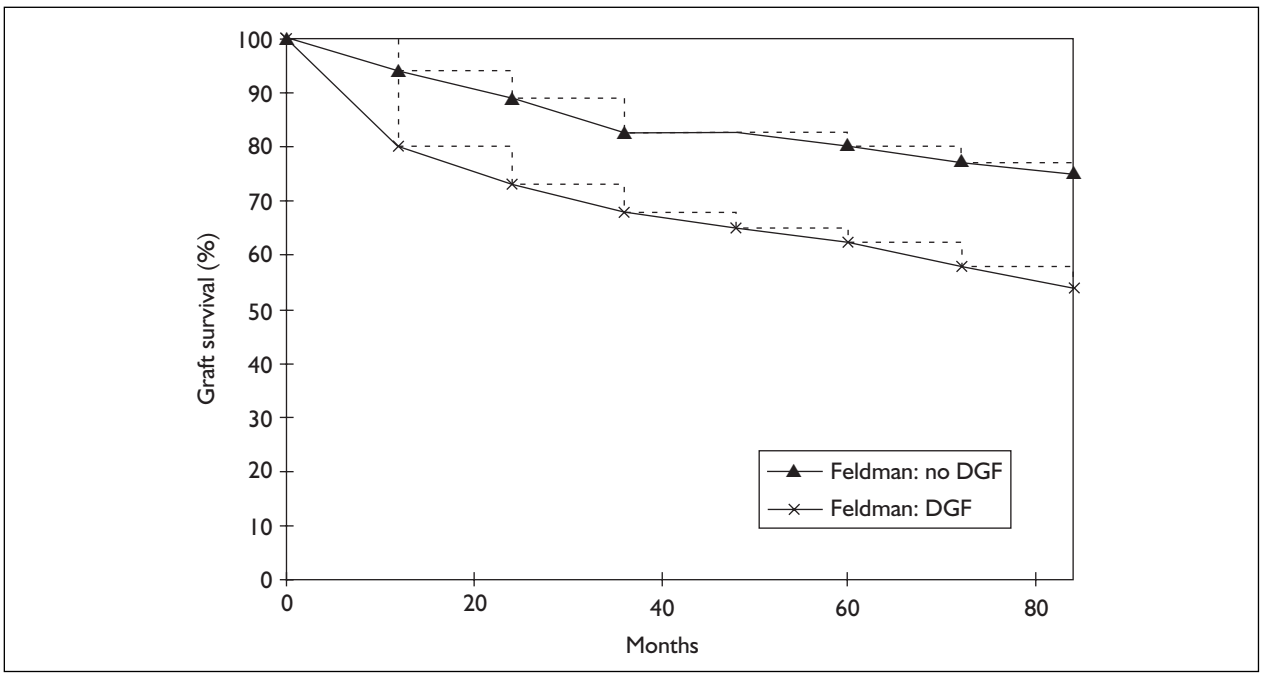

FIGURE 6 *Kaplan–Meier graft survival plots under DGF and no DGF*

These factors identified in the univariate analyses were included in the multivariate analysis and, of these, five were found to be statistically significantly associated with graft loss, confirming their strong association with the long-term prognosis of graft survival (*Table 6*).

In order to assess the benefits in terms of survival, and hence life-years gained, some measure of baseline survival is required. *Figure 6* gives the Feldman[84] actuarial Kaplan–Meier graft survival estimates, estimated from the published graph, for transplant patients experiencing DGF and no DGF. The figure shows the Kaplan–Meier step functions (- - - -) together with simple straight-line interpolations between the interval end-points.

In order to estimate the benefits in terms of graft survival and life years gained, it is necessary to find a mathematical formula that best fits the

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

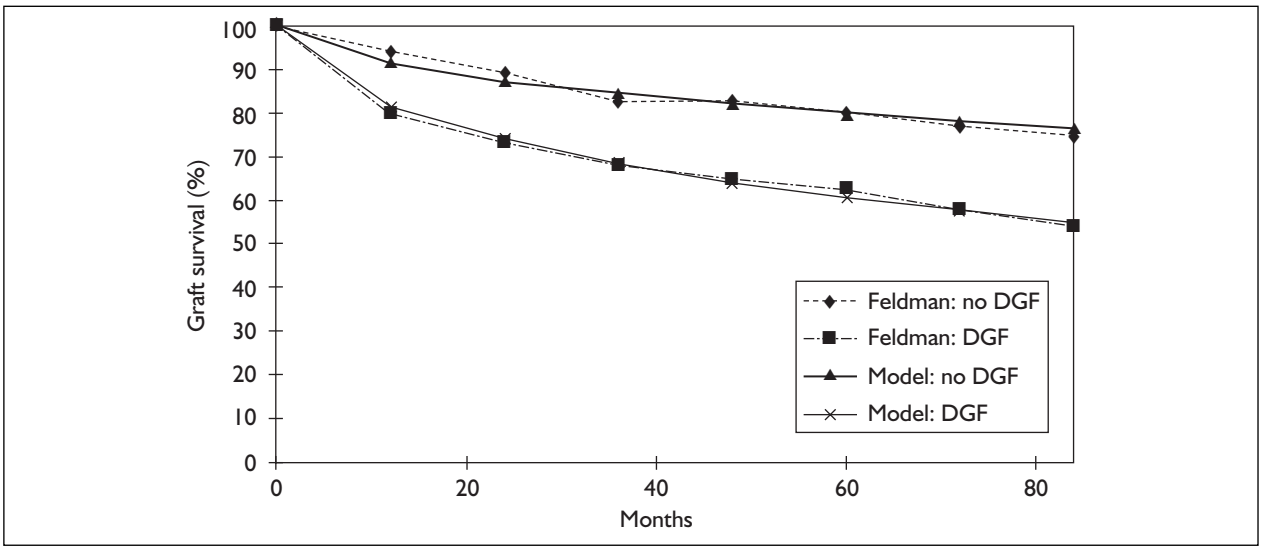

FIGURE 7 *Empirical survival plots and best fitted survival from Cox proportional hazards model with Weibull baseline hazard function*

existing data (from the Feldman study[84]), which can then be used to describe the impact of DGF on survival, and extrapolated over a longer time period. Equations which describe survival data can be taken from the Weibull distribution, and are generally of the form

$$S(t) = \exp[-\eta(\alpha t)^{\beta}]$$

where $S(t)$ is the proportion surviving at time t, η is the hazard factor relating to the occurrence of DGF for an individual or population subgroup ($\eta = 2.25$ any DGF, $\eta = 1$ no DGF), α is the scale parameter of the baseline Weibull function, β is the shape parameter of the baseline Weibull function and t is the time from the start of observation.

Using the solver function in Excel to minimise the least-squares difference between the model estimates at 12-month intervals and the interval estimates, the values for α and β that give a Weibull curve which best fits the data from the Feldman study were identified. These are $\alpha = 0.001114$ and $\beta = 0.554$.

The above equation was then used to estimate the proportion of grafts surviving at different time periods.

Figure 7 shows the empirical survival plots, together with the fitted univariate Cox proportional hazards model with baseline hazard function from the Weibull distribution. The model uses the group profiles, in terms of number of patients experiencing DGF and no DGF together with the prognostic score for DGF given in *Table 5*.

Results of long-term survival model

The absolute measures of the risk of DGF of MP versus CS obtained from the meta-analysis described in Chapter 3 were applied to the model in order to obtain estimates of the long-term graft survival under DGF and no DGF. The absolute measures were calculated for HBDs and NHBDs separately. This is presented in *Figures 8* and *9*. Graft years gained are calculated from the area between the DGF and no DGF curves.

Tables 7 and *8* present the results for graft survival under DGF and no DGF together with the cumulative graft years gained, undiscounted and discounted at 1.5% per year, as a result of MP [the agreement by the National Institute for Clinical Excellence (NICE) is to follow Treasury-recommended rates of life-years discounted at 1.5% and costs at 6%].

Sensitivity analysis of long-term survival model

Error in estimating baseline survival function

In order to test the sensitivity of the results to errors in estimating the baseline survival function, random errors of the order of ±3% were introduced into each of the 12-month interval hazard estimates from Feldman and colleagues'[84] paper. The Weibull model was then refitted to obtain new baseline parameter estimates. This exercise was repeated a number of times using

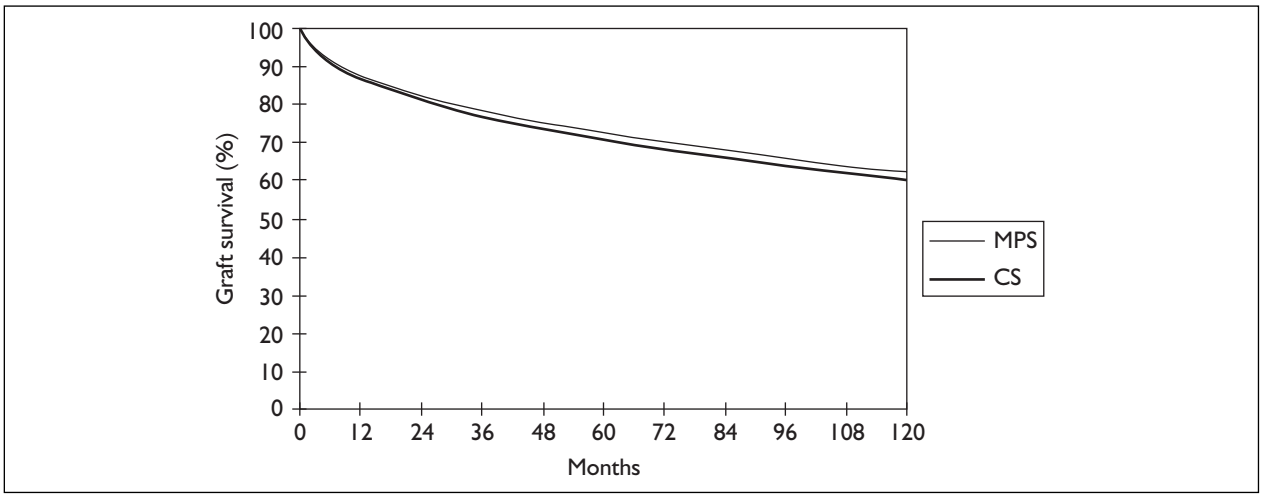

FIGURE 8 *Long-term graft survival estimated from model: HBD*

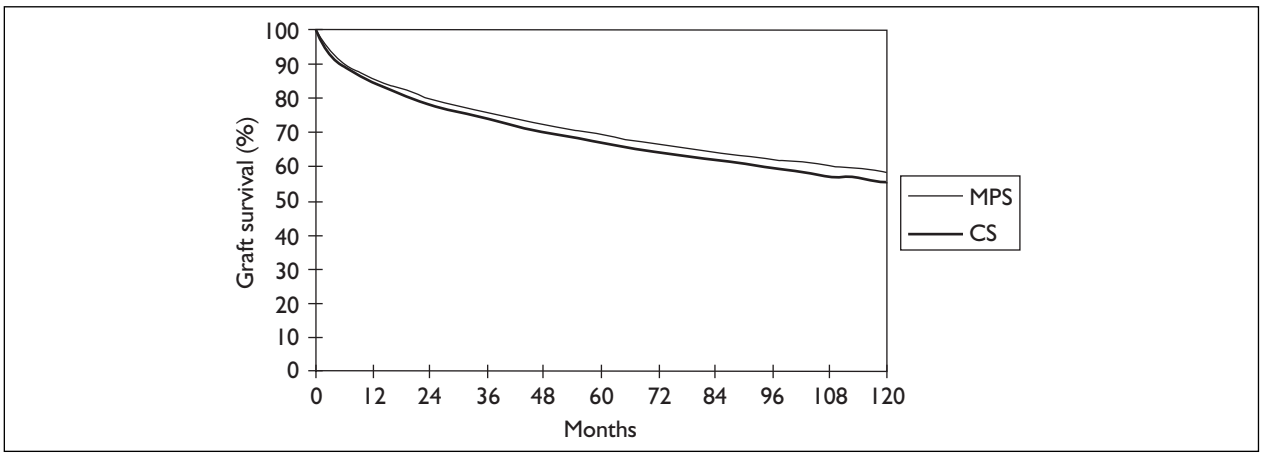

FIGURE 9 *Long-term graft survival estimated from model: NHBD*

TABLE 7 *Long-term graft survival results modelled from meta-analysis of included trials: HBD*

Years	Graft survival (%)		Difference in graft survival (%)	Graft years lost
	MP	CS		
1	88	87	1	0.01
3	79	77	1	0.03
5	73	71	2	0.06
10	62	60	2	0.14

TABLE 8 *Long-term graft survival results modelled from meta-analysis of included trials: NHBD*

Years	Graft survival (%)		Difference in graft survival (%)	Graft years lost
	MP	CS		
1	86	85	1	0.01
3	76	74	2	0.04
5	69	67	2	0.08
10	59	56	3	0.20

TABLE 9 *Sensitivity of results to error in Weibull parameters*

α	β	10-Year graft survival (%)		Graft years lost
		MP	CS	
0.000696	0.472641	63	61	0.15
0.001114	0.554193	61	59	0.15
0.001311	0.580043	60	58	0.15

different sequences of random errors. This suggests that the baseline model is insensitive to errors in estimation of the survival functions from Feldman and colleagues'[84] paper. The range of Weibull baseline parameters obtained in this exercise, together with the implications for graft loss and graft years gained is shown in *Table 9*.

Error in estimating the hazard of graft loss from DGF

The meta-analysis gave the lower and upper limits of the risk factor coefficient for DGF in MP versus

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 10 *Sensitivity of results to error in the risks from DGF*

Risk factor coefficient	10-Year graft survival (%) MP	CS	Graft years lost
0.714	63	59	0.23
0.813	61	59	0.15
0.924	60	59	0.06

CS. The implications of this uncertainty for long-term graft survival and graft years loss is presented in *Table 10*. As can be seen, the estimated benefit for MP is stable under the range of estimates for the DGF hazard provided by the meta-analysis.

Final conclusion on impact of MP versus CS on graft survival

Predicted graft survival benefit from reduction in DGF is of the order of 1–2% for HBD and 2–3% for NHBD. This is consistent with the results of the direct assessments of graft loss presented in Chapter 3. A statistically significant result would not be expected with such small trials. Considerably larger patient numbers would be required for the trials to be powered sufficiently to detect differences as small as 1–3%.

Estimation of costs

A health service perspective of costs is taken in the analysis and only direct costs are considered. Costs included in the analysis are the cost of graft loss, the short-term cost of DGF and the cost of the machine preservation system.

Cost associated with graft loss is calculated as the graft years gained, multiplied by the annual marginal cost of graft loss discounted at 6% per year. The marginal cost of graft loss has been estimated from the cost of dialysis as a result of graft loss less the cost of maintenance therapy under graft survival.

The short-term cost of DGF is estimated from the marginal cost due to DGF per day multiplied by the expected number of days with DGF. There is very little information available for the UK concerning the direct resource usage and costs associated with DGF. What economic analysis is available is largely from the USA and is not reported in sufficient detail to make a transfer to the UK health system meaningful. At the upper extreme DGF may result in an extended stay in a transplant unit; an upper limit of £695 is therefore taken as the daily cost of a stay in a renal unit. In those cases where DGF is not the primary cause of continued hospitalisation the additional cost of dialysis for these patients would be small; however, under some hospital protocols DGF will result in an increased use of expensive immunosuppressives. A lower limit of half the cost of hospitalisation has therefore been used. To reflect the lack of information in this area, a uniform distribution (uninformative prior) between these limits has been used to characterise the marginal cost of DGF per day.

TABLE 11 *Costs (£)*

Hospitalisation (renal unit) per day	695
Technician (annual salary)	20,000
Immunosuppressive maintenance therapy (annual)	4851

Numbers of days to graft function following DGF, post-transplantation, were obtained from two studies.[36,37] These were reported as 14.9 and 12.4 days under CS and 9.9 and 8 days under MP, indicating a reduction in the length of DGF as well as the incidence of DGF under MP. However, these studies are both very small and the baseline model therefore assumes no improvement in the duration of DGF under MP, although uncertainty about the relative impact is included. Costs other than MP can be seen in *Table 11*.

Cost of graft loss

Dialysis costs, adjusted for inflation to 2002, were obtained from the UK Prospective Diabetes Study Group,[85] corroborated by an earlier study undertaken by Moore.[86] Long-term dialysis is split between haemodialysis and peritoneal dialysis [continuous ambulatory peritoneal dialysis (CAPD)] based on a study undertaken in the Trent Region.[87] Costs associated with transplant maintenance were taken from a Trent Institute Guidance Note[88] and the UK medicines information service.[89]

Cost of machine preservation

The cost of machine preservation is based on the use of the Waters Corporation Medical Systems RM3 renal preservation system. This is a two-part kidney preservation system which includes the RM3 control unit for pulsatile perfusion and monitoring of one or two kidneys and a sterile, disposable, single-use cassette used to circulate a perfusate to the kidneys. The system can provide circulation of up to 1 litre of perfusate to one or two kidneys, attached either singly or *en bloc*.

TABLE 12 *Unit costs of machine perfusion (£)*

	Per transplant	Initial purchase
Maintenance	11.59	
Cassette	568.23	
Solution	163.85	
Purchase cost of machine + starter pack	234	25,762
Personnel (per transplant)	909	
Total cost per transplant – single	1887	

This machine is, as far as the authors are aware, the only commercially available preservation system available. It is currently used in three transplant centres in the UK. Machine costs were obtained from a 2002 international price list supplied by Waters Corporation.

Cost of machine preservation includes (*Table 12*):

- cost of purchase of the machine
- disposables
- maintenance
- personnel.

The machine is capable of perfusing either single kidneys or two kidneys *en bloc* at no extra cost. The number of kidneys perfused (single), number of kidneys transplanted per year, expected lifetime of the machine, maintenance costs and personnel costs are based on the experience of the Leicester General Hospital where two machines have been in use for 2 and 4 years.

The cost per kidney grafted of machine preservation was estimated from the number of transplants performed annually, the expected lifetime of the machine and the machine costs. The number of transplants performed annually, 22 in 2001, at Leicester General Hospital is comparable to the average number of kidney transplants performed by centre (23 in 2001) in the UK in 2001 provided by UK transplant (http://www.uktransplant.org.uk). The expected lifetime of the machine is based on the 'short-life medical and other equipment' lifetime of 5 years, as laid down by the standard lives of equipment NHS policy (NHS Executive, NHS Trust Capital Accounting Manual, published by the Department of Health, April 2001). Based on the experience of the Leicester General Hospital, the machine would require the employment of a dedicated technician. The personnel cost has therefore been estimated as the annual salary of a technician divided by the number of transplants per year. The cost per transplant was therefore estimated as:

- the cost of purchasing the machine with a starter pack divided by the expected number of transplants over the lifetime of the machine, plus
- the cost of transplant maintenance and disposables, plus
- personnel costs per transplant.

Utility scores

Quality of life scores were obtained from a review of the published literature.[90] A score of 0.84 was assigned to a functioning transplant and a score of 0.65 to dialysis following graft failure.

Parameter values used in the kidney preservation system model

Table 13 provides a description of the variable parameters used in the kidney preservation system model, together with the parameter value and the assumed standard error and type of distribution. Standard errors for the quality-adjusted life-year (QALY) utilities were taken from the literature.[90] Standard errors for the parameters with normal and log normal distributions were chosen to allow for a wide uncertainty in the model. Uniform distributions were assumed for those parameters where little prior knowledge is available.

Newcastle machine

The Renal and Liver Transplant Unit of the Freeman Hospital in Newcastle upon Tyne has developed its own pulsatile perfusion system.[9] This has resulted in a low-cost system that allows serial measurements of the perfusate to be taken as well as flow rates, pressure profiles and IRR.

The machine is based on existing dialysis equipment modified with sterilised inserts to create a pulsatile hyperthermic perfusion system. The machine was used in the transplantation of 65 NHBD kidneys in 1998 (Gok MA, Renal Transplant Fellow, Liver/Renal Transplant Unit, The Freeman Hospital, Newcastle upon Tyne: personal communication).

The authors recognise that not every unit would be able to make its own machine; however, the success of the Newcastle machine warrants inclusion in this analysis. The cost per transplant of using the Newcastle machine is given in *Table 14*. The cost per transplant is approximately half that of the Waters Corporation machine.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

TABLE 13 *Parameter values used in economic analysis*

Parameter description	Parameter 1	Parameter 2	Type of distribution
Annual technician cost (£)	20,000	2500	Normal
Annual maintenance (£)	5.54	0.50	Log normal
CAPD (%)	37.4	10.0	Normal
Annual cost of CAPD (£)	19,736	2000	Normal
Annual cost of haemodialysis (£)	25,756	2500	Normal
Annual cost of transplant management	8.49	0.25	Log normal
QALY functioning graft	0.84	0.05	Normal
QALY dialysis	0.65	0.075	Normal
Marginal cost of DGF (£)	300	700	Uniform
Duration of DGF CS (days), HBD	14.9	2	Normal
Duration of DGF CS (days), NHBD	12.4	2	Normal
Relative duration of DGF MPS	1	0.5	Uniform
% with DGF CS HBD	20	70	Uniform
% with DGF C NHBD	50	90	Uniform
Risk factor for all risks given DGF	0.81	0.22	Log normal
RR of DGF with MPS vs CS	–0.22	0.09	Log normal
Parameter key	**Parameter 1**	**Parameter 2**	
Normal	Mean	Standard error	
Log normal	Mean	Standard error	
Uniform	Minimum	Maximum	

MPS, Marshall's perfusion solution.

TABLE 14 *Costs of Newcastle perfusion machine (£)*

	Per transplant	Initial purchase
Non-disposable equipment costs		
Roller pump		No cost (old equipment)
Oscilloscope (Datascope 20001)		No cost (old equipment)
Heat exchange coil		No cost (old equipment)
Cooling pump ×2		134
Atraumatic clamp		200
Total	3	334
Expenditure per kidney		
Newcastle-modified UW	57	
Pressure transducer	7.7	
Tubings (inserts)	5	
Personnel	909	
Total	981.8	

Economic results

The baseline economic analysis indicates that MP has the potential both to be cost saving and to be more effective than CS. However, there is a high degree of uncertainty associated with this result and thus while the baseline analysis indicates that MP would dominate CS, the uncertainty is such that CS could dominate MP. The economic analysis has been undertaken for recipients of HBDs and NHBDs separately and the results are described below. Since the cost-effectiveness ranges from MP dominating CS to CS dominating MP, the economic results are not presented in terms of incremental cost-effectiveness between the strategies. Instead, the results are presented in terms of the cost-effectiveness acceptability and the incremental net benefit of MP compared with CS.

Results for recipients of NHBD kidneys

The cost-effectiveness plane, cost-effectiveness acceptability curve and net benefit distribution for recipients of grafts from NHBDs are shown in *Figures 10*, *11* and *12*, respectively.

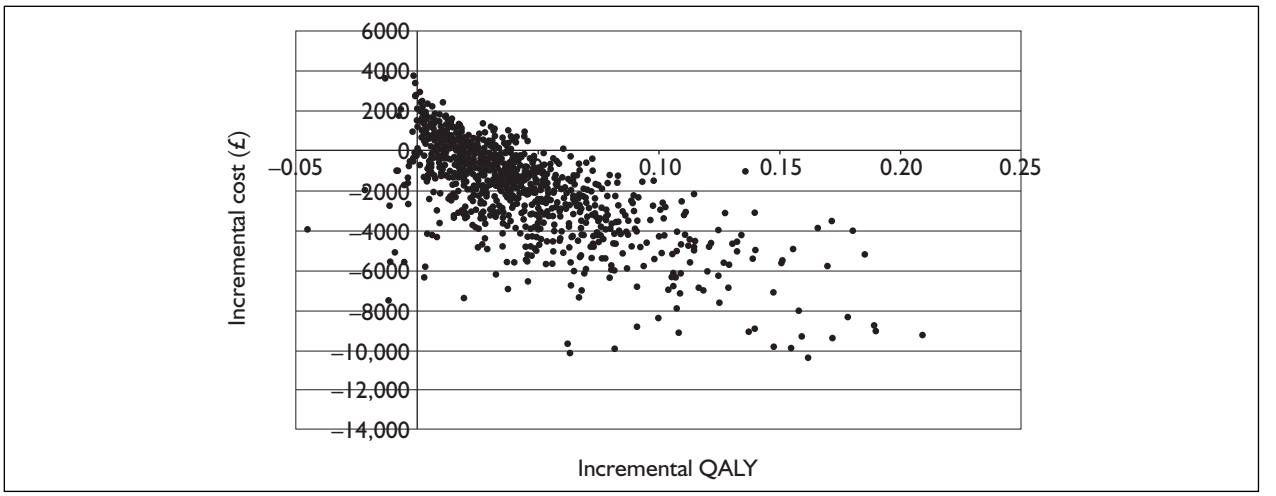

FIGURE 10 *Cost-effectiveness plane for recipients of NHBDs*

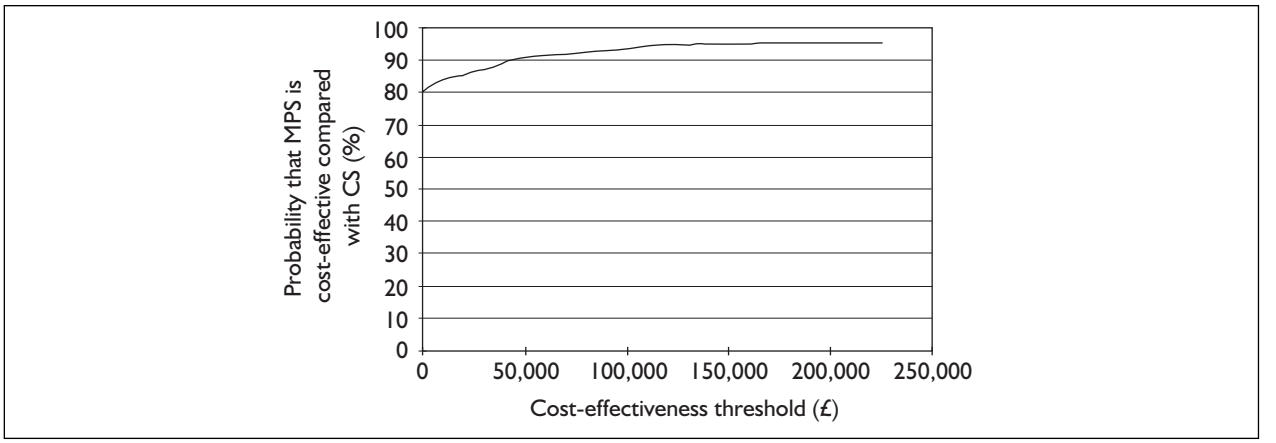

FIGURE 11 *Cost-effectiveness acceptability curve for NHBDs*

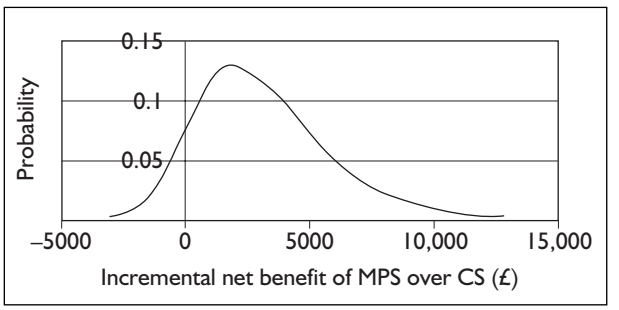

FIGURE 12 *Incremental net benefit distribution for recipients of NHBDs (threshold £20,000 per QALY)*

The linear relationship between the marginal effectiveness and marginal costs demonstrates the economic production function acting within this technology, that is, if the technology is demonstrated to be effective then cost savings also follow. The converse, however, is also true that if the effectiveness is not proven then it will result in an increase in costs. The baseline result of dominance, demonstrated here and claimed in the available published economic literature, should therefore clearly be treated with caution.

The expected health gain from MP is approximately 0.05 QALYs per transplant with a 95% confidence interval of 0 to 0.13 QALYs. The expected marginal cost per patient of MP is approximately –£1900 per transplant (i.e. cost saving), ranging between a cost saving of –£7000 and an increase of £1500.

The cost-effectiveness acceptability curve demonstrates that on the analysis presented here MP would have a probability of 80% of being the dominant strategy over CS for the transplantation of NHBD organs.

At a cost-effectiveness acceptability threshold of £20,000 per QALY, MP would have an expected net benefit of approximately £1200 per transplant recipient.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

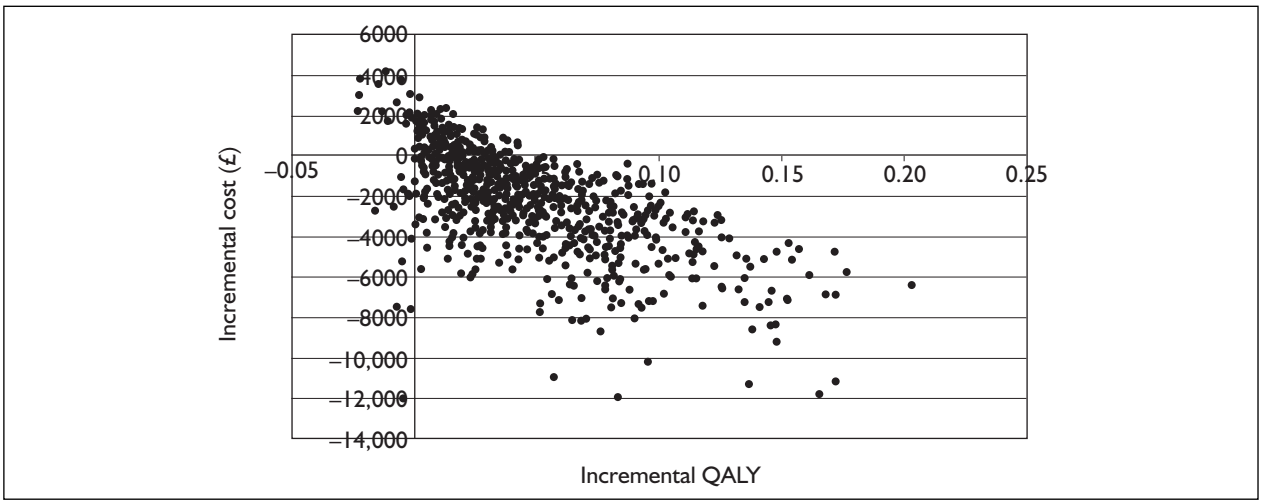

FIGURE 13 *Cost-effectiveness plane for recipients of HBDs*

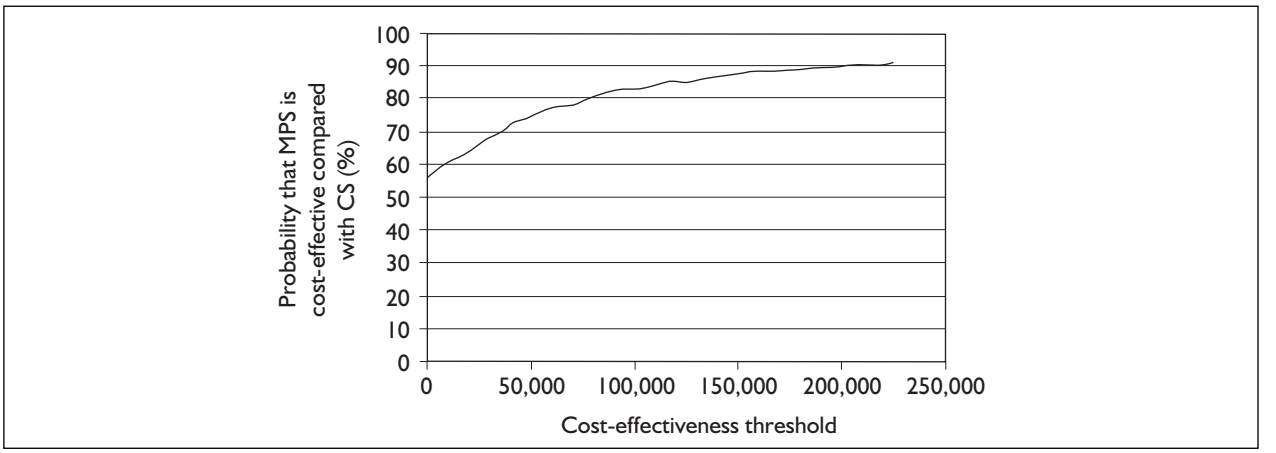

FIGURE 14 *Cost-effectiveness acceptability curve for HBDs*

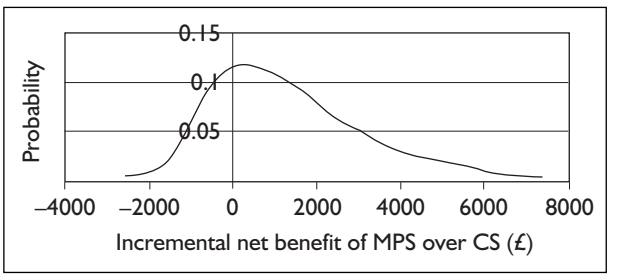

FIGURE 15 *Incremental net benefit distribution for recipients of HBDs (threshold £20,000 per QALY)*

Results for recipients of HBD kidneys

The cost-effectiveness plane, cost-effectiveness acceptability curve and net benefit distribution for recipients of grafts from HBDs are shown in *Figures 13*, *14* and *15*, respectively.

The cost-effectiveness plane demonstrates the same linear relationship between costs and effects; however, the dispersion is greater, reflecting the higher degree of economic uncertainty in the HBD transplants.

The expected health gain from MP is approximately 0.03 QALYs per transplant with a 95% confidence interval of 0 to 0.09 QALYs. The expected marginal cost per patient of MP is approximately –£600 per transplant (i.e. cost saving), ranging between a cost saving of –£4900 and an increase of £1800.

The increased economic uncertainty is perhaps better demonstrated in the cost-effectiveness acceptability curve. For HBD transplants the probability that machine preservation is cheaper and more effective is between 50 and 60%, and the probability that it is preferable at a threshold of around £20,000 is around 65%. However, there is also a 10% chance that it will cost more and be less effective. Again, the flat nature of the cost-effectiveness acceptability curve reflects the high degree of uncertainty in this technology.

TABLE 15 *Economic uncertainty analysis*

	NHBD		HBD	
Value of further information	**Per Transplant**	**England and Wales over a 5-year period**	**Per transplant**	**England and Wales over a 5-year period**
No. of transplants	1	6,500	1	1,800
Total model (£)	125	812,500	240	432,000
Annual technician cost (£)	0	0	0	0
Annual maintenance (£)	0	0	0	0
CAPD (£)	0	0	0	0
Annual cost of CAPD (£)	0	0	0	0
Annual cost of haemodialysis (£)	0	0	0	0
Annual cost of transplant management (£)	0	0	0	0
QALY functioning graft (£)	0	0	0	0
QALY dialysis (£)	0	0	0	0
Marginal cost of DGF per day (£)	0	0	0	0
Duration of DGF CS (£)	0	0	0	0
Relative duration of DGF MPS (£)	0	0	0	0
% with DGF CS (£)	0	0	73	131,420
Risk factor for all risks given DGF (£)	16	103,901	84	150,695
RR of DGF with MPS vs CS (£)	123	802,701	236	424,023

MPS, Marshall's perfusion solution.

The mean incremental net benefit in HBD transplants is similar to that in NHBD transplants at around £1200 per transplant. However, the probability of a negative net benefit is greater and the upper range for net benefit is smaller, reflecting that there is less scope for economic improvement in this population.

Uncertainty analysis

Table 15 presents the value of perfect information for the model as a whole and for each random variable within the analysis, for HBD and NHBD donor transplants. The figures are presented per transplant and scaled up for the number of transplants performed in England and Wales over a 5-year period.

The baseline analysis for both HBD and NHBD transplants indicates that economically, based on the expected net benefit, MP is the preferable option over CS. As noted above, however, this analysis has identified that CS may still dominate, that is be cheaper and more effective than MP. The value of information arises from the gain in expected net benefit from resolving this remaining uncertainty. While the value of information for each transplant is small, £125 and £240 for NHBD and HBD recipients, respectively, the large transplant population means that this is still a valid area for further research.

The value of further information associated with each random variable within the model identifies those areas where the resolution of the remaining uncertainty may change the optimal policy indicated by this analysis. Thus, while there is still a high degree of uncertainty in, for example, the marginal resource usage and costs associated with DGF, it is clear that the key uncertainties relate to the long-term effectiveness of MP. Specifically, *Table 15* indicates that the key uncertainties are the risk factor for graft loss associated with DGF, the impact of MP on DGF and, for HBD recipients, the probability of experiencing DGF under current CS techniques.

In the absence of suitable direct evidence, existing studies are all small and underpowered for graft survival, this assessment has used an indirect model to predict the potential gain that might be expected from MP. Obviously, if further research were to be undertaken, direct evidence of the impact of MP on graft survival would be preferable.

For HBD recipients the current rate of DGF achieved using CS is a key parameter. This probability of DGF, however, is to some extent not a random variable but a management variable, since transplantation centres would know the current rate of DGF achieved and could make the decision whether to use MP or not based on this knowledge. Alternatively, since the probability of

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

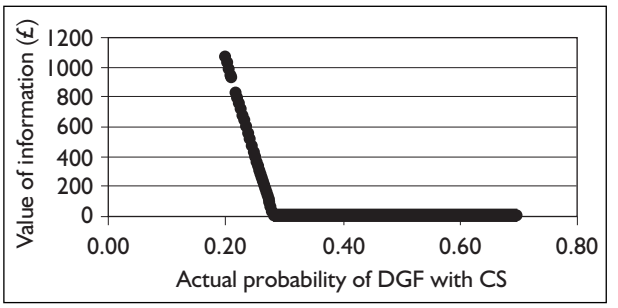

FIGURE 16 *Value of information associated with knowing the probability of DGF under current CS techniques*

DGF for an individual patient is associated with other known risk factors, MP could be focused on high-risk patients. *Figure 16* demonstrates that if DGF rates under approximately 30% can be achieved with CS then CS could be economically the preferable option over MP.

Economic conclusion

- The economic evidence is of poor quality and the generalisability of the US studies to a UK healthcare setting is low.
- Economic benefits may be hypothesised to arise from two sources, short-term impact of reducing DGF and associated resource usage and costs, and long-term impact on graft loss.
- It is unlikely that in the UK health setting complete cost recovery will be obtained from a reduction in the incidence of DGF.
- Owing to the higher incidence of DGF in NHBD transplants, there is a greater likelihood of obtaining complete cost recovery in these patients.
- The long-term evidence concerning the impact of MP on graft loss is weak.
- There is strong evidence of a link between DGF and graft survival. Quantitative models based on this evidence predict a small improvement of the order of 1% on graft survival at 1 year and 2–3% at 10 years from the reductions on DGF demonstrated with MP. This prediction is consistent with the inconclusive results obtained from the small direct studies of DGF and graft loss in MP.
- The baseline analysis indicates that MP would be expected to be cheaper and more effective than CS for both HBD and NHBD recipients. The probability that this is the case is estimated at around 80% for NHBD recipients and 50–60% for HBD recipients.
- The key economic uncertainties relate to the impact of MP on long-term graft survival. While direct evidence relating to improvements in graft survival would be preferable, the small predicted improvement indicates that a very large sample size would be required in order to detect statistically significant results. In addition to seeking better direct evidence of the impact of MP on DGF rates, further research on quantifying the predicted impact of DGF on graft survival would be warranted.

Chapter 5
Discussion

Although MP of harvested kidneys has been in practice for over 30 years, there is continuing debate as to its value. The assessment of the clinical benefit that may or may not follow from the use of MP for preservation of kidneys for transplantation is hampered by a number of factors. First among these is the relative paucity of good-quality RCTs comparing MP with CS. Further, over the 30 years during which such studies have infrequently been published, the techniques both for MP and the overall approach to transplantation have changed enormously. This is manifest in the development of the perfusion machines, the development in the perfusate (both for MP and for CS), developments in immunosuppression and development in the approach taken to tissue type matching. There is therefore considerable heterogeneity in the studies undertaken.

This systematic literature review has identified 16 studies with appropriate comparator groups that address the possible clinical benefit from MP. Although the studies are for the most part small, and of poor methodological quality, they are the best evidence available.

The studies are heterogeneous, having been published over a span of 30 years. To some extent this heterogeneity is mitigated by the fact that MP and CS will have been compared, within each study, at a similar stage of development. If there had been evidence that one technology had been evolving at a different pace to the other it might have given more cause for concern. As it is, there is no clear temporal trend in the relative risk of DGF reported in these studies.

The evidence collected suggests that MP leads to a 20% reduction in the incidence of DGF, in both HBDs and NHBDs, that in turn can be expected to lead to a reduction in the need for dialysis postoperatively, and a potential reduction in hospital length of stay. However, the published studies do not provide any direct evidence that this translates into improved graft survival, but this may well be because not enough patients have been studied. Evidence from elsewhere suggests that DGF is associated with reduced graft survival, so one would expect interventions that reduce DGF to lead to an increase in graft survival.

The economic analysis undertaken shows no overall short-term cost saving of using MP in terms of dialysis costs saved from reduced DGF. However, reductions in long-term costs, chiefly dialysis, resulting from potential reductions in graft loss could result in cost recovery and savings. The sensitivity analysis indicates that the key uncertainties relate to this long-term impact of MP.

Because the DGF rate following NHBD transplantation is substantially greater than that following HBD transplantation, the benefits from the use of MP in these patients are greater and this is clearly reflected in the economics of MP treatment.

The evidence, from human studies, that tests of kidneys on MP can effectively discriminate between those that will eventually function and those that will not is limited, and overall of poor quality. Most studies have been on preselected groups of kidneys, and have used delayed function, rather than PNF, as an outcome. In only one study[71] are adequate data provided to allow the calculation of sensitivity and specificity of a proposed test – in that case the use of α-GST concentration.

In setting a threshold for a test of viability, whether it be based on perfusate pressures and flows or on a biochemical marker, a trade-off will need to be made between the sensitivity and specificity of the test, as each of these will be influenced by the threshold chosen. The ideal test would be completely sensitive (it would identify all viable kidneys) and completely specific (it would reject all non-viable kidneys). However, this is of course practically impossible, as there will always be some kidneys below the threshold which do in fact turn out to be viable (false-negative on the test), and some above which are not (false-positive). Increasing the threshold will reduce the number of false-positives and increase the specificity of the test, but at the cost of increasing the number of false-negatives and decreasing the

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

sensitivity of the test. How the sensitivity and specificity of the test vary with varying thresholds used for the test determines the receiver operating characteristics (ROC) of the test.

In choosing the threshold to be used for the test, a judgement will need to be made as to the relative values of false-negatives and false-positives. Clearly, a false-positive test will result in a kidney being transplanted which turns out not to be viable, resulting in pain, distress and unfulfilled expectations for the patient, and costs for the NHS. On the other hand a false-negative test results in a kidney being discarded which would have been viable, and costs to the NHS resulting from a patient continuing on dialysis who would otherwise have been able to have a successful transplant. The general consensus appears to be that false-negatives are worse than false-positives (i.e. kidneys should not be wasted if at all possible, even at the cost of implanting non-viable kidneys), but we did not identify any evidence that this had been tested with patient groups. Moreover, there does not appear to be any explicit consensus as to the ratio between false-negatives and false-positives which would be an acceptable trade-off. (If there were to be consensus that the appropriate trade-off would be to have minimal numbers of false-negatives with a large number of false-positives, then the rationale for undertaking any test is called into question, as this can be achieved simply by transplanting all available organs.)

The overall aim of identifying or developing a test of viability is to permit the expansion of kidney transplantation into using more 'marginal' kidneys, be they from NHBDs, or from HBDs with adverse characteristics, such as diabetes or older age. These will inevitably include more kidneys which would be non-viable if transplanted – the aim is to identify these prior to transplantation. As these numbers increase, if the same test of viability is used, the ratio of false-positives (non-viable kidneys transplanted) to false-negatives (viable kidneys discarded) will increase. It may well be the case, therefore, that a test which is appropriate (in terms of providing an accepted trade-off of false-positives and -negatives) with the current donor pool would not be appropriate if the pool is expanded to include more marginal kidneys. It may be that this can be accommodated simply by adjusting the test sensitivity and specificity by changing the threshold of whatever marker or parameter is used.

Although the evidence overall is suggestive that MP is clinically effective in terms of reducing DGF and potentially cost-effective in the long term, it would be premature to advocate the widespread introduction of this technology into renal transplantation. What is needed are definitive studies of high methodological quality and sufficient size to determine whether or not machine preservation of kidneys for transplantation does, in fact, with current technology, lead to reduced rates of DGF, cost savings or improved graft survival. More research is also needed to determine whether or not kidney viability can accurately be determined when on perfusion.

At a time when the demand for kidneys so far exceeds supply, it is important that every means for increasing the success rate of the transplantation programme should be pursued.

Chapter 6
Conclusions

The evidence relating to the clinical effectiveness of MP as a means of preserving kidneys for transplantation is of relatively poor quality, and spans 30 years, during which time the technology has developed enormously. Nevertheless, such evidence as there is suggests that the use of these machines is associated with a 20% reduction in the incidence of DGF following transplantation, with no evidence that this effect is different in kidneys taken from HBDs and NHBDs. There is no evidence from primary research that they are associated with improvements in longer term graft survival (largely because the studies which have been reported are too small to detect improvements of the magnitude which might be expected). However, evidence from elsewhere suggests that a reduction in DGF could be expected to lead to increased graft survival.

The economics of MP potentially are very attractive, with baseline estimates suggesting improvements in effectiveness together with cost savings for both HBD and NHBD recipients. However, the remaining uncertainty is such that CS could also dominate. The potential cost savings are reliant on the predicted long-term benefits of MP for improved graft survival being realised.

The flow characteristics of the perfusate of kidneys undergoing MP may be an indicator of kidney viability, but inadequate data are available from the studies identified to calculate the sensitivity and specificity of any test based on this. The concentration of α-GST in the perfusate may be the basis of a valid test. A threshold of 2800 μg/100 g gives a sensitivity of 93% and specificity of 33% (and hence a likelihood ratio of 1.41). A key part of the development of any test or combination of tests of viability for general use would be the establishment of a consensus as to the trade-off between false-positives and false-negatives that would be acceptable. This must involve patients and their representatives.

Recommendations for research

A definitive study is needed to establish what benefits follow from the use of MP in both HBD and NHBD at the current stage in the development of transplantation technology. This study or studies need to address the various methodological flaws in the research undertaken to date. At the very least it must be adequately powered to detect a clinically important fall in the DGF rate in MP as compared with CS kidneys, and should include a detailed analysis of costs incurred. Ideally, they would also be adequately powered to detect any clinically significant change in the 1-year graft survival, but it is likely that this would make the study impossibly large.

In addition to seeking better direct evidence of the impact of MP on DGF rates, further research on quantifying the predicted impact of DGF on graft survival would be warranted. There is much evidence on this relationship available, although within the limitations of this review it has not been possible to bring all this to bear on the problem. Further analysis based on existing registry databases would be valuable in this respect.

Further research is also needed to establish whether or not a valid test (or combination of tests) of kidney viability can be developed. This should be accompanied by work with all interested parties (including patients) to establish what an appropriate trade-off between false-positive and false-negative results of such test(s) would be.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

References

1. Clark EA, Terasaki PI, Opelz G, Mickey MR. Cadaver-kidney transplant failures at one month. *N Engl J Med* 1974;**291**:1099–102.
2. Opelz G, Terasaki PI. Kidney preservation: perfusion versus cold storage – 1975. *Transplant Proc* 1976;**8**:121–5.
3. Opelz G, Terasaki PI. Advantage of cold storage over machine perfusion for preservation of cadaver kidneys. *Transplantation* 1982;**33**:64–8.
4. van der Vliet JA, Vroemen JP, Cohen B, Lansbergen Q, Kootstra G. Preservation of cadaveric kidneys. Cold storage or machine perfusion? *Arch Surg* 1983;**118**:1166–8.
5. Ploeg RJ, van Bockel JH, Langendijk PT, Groenewegen M, van der Woude FJ, Persijn GG, *et al.* Effect of preservation solution on results of cadaveric kidney transplantation. The European Multicentre Study Group. *Lancet* 1992;**340**:129–37.
6. Cho YW, Terasaki PI, Cecka JM, Gjertson DW. Transplantation of kidneys from donors whose hearts have stopped beating. *N Engl J Med* 1998; **338**:221–5.
7. Cecka JM, Terasaki PI. The UNOS scientific renal transplant registry. *Clin Transplant* 1995;1–18.
8. Stubenitsky BM, Booster MH, Nederstigt A, Kievit JK, Jacobs RW, Kootstra G. Kidney preservation in the next millennium. *Transpl Int* 1999;**12**:83–91.
9. Balupuri S, Strong A, Hoernich N, Snowden C, Mohamed M, Manas D, *et al.* Machine perfusion for kidneys: how to do it at minimal cost. *Transpl Int* 2001;**14**:103–7.
10. Szust J, Olson L, Cravero L. A comparison of OPO pulsatile machine preservation practices and results. *J Transpl Coord* 1999;**9**:97–100.
11. Jadad AR, Moore RA, Caroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
12. Southard JH, D'Alessandro AM. Pulsatile preservation versus static storage for kidney preservation. *Curr Opin Organ Transplant* 2000;**5**:237–41.
13. Veller MG, Botha JR, Britz RS, Gecelter GR, Beale PG, Margolius LP, *et al.* Renal allograft preservation: a comparison of University of Wisconsin solution and of hypothermic continuous pulsatile perfusion. *Clin Transplant* 1994;**8**:97–100.
14. Merion RM, Oh HK, Port FK, Toledo-Pereyra LH, Turcotte JG. A prospective controlled trial of cold-storage versus machine-perfusion preservation in cadaveric renal transplantation. *Transplantation* 1990;**50**:230–3.
15. Scott DF, Whiteside D, Redhead J, Atkins RC. Ice storage versus perfusion for preservation of kidneys before transplantation. *BMJ* 1974;**4**:76–7.
16. Cho SI, Bradley JW, Nabseth DC. Graft survival of perfused vs nonperfused cadaver kidneys. *Surg Forum* 1975;**26**:351–2.
17. Barber WH, Deierhoi MH, Phillips MG, Diethelm AG. Preservation by pulsatile perfusion improves early renal allograft function. *Transplant Proc* 1988;**20**:865–8.
18. Kumar MS, Samhan M, al Sabawi N, al Abdullah IH, Silva OS, White AG, *et al.* Preservation of cadaveric kidneys longer than 48 hours: comparison between Euro-Collins solution, UW solution, and machine perfusion. *Transplant Proc* 1991;**23**:2392–3.
19. Daemen JH, de Wit RJ, Bronkhorst MW, Marcar ML, Yin M, Heineman E, *et al.* Short-term outcome of kidney transplants from non-heart-beating donors after preservation by machine perfusion. *Transpl Int* 1996;**9** Suppl 1:S76–80.
20. Balupuri S, Buckley P, Snowdon C, Mustafa M, Sen B, Griffiths P, *et al.* The trouble with kidneys derived from the non heart beating donor: a single centre 10 year experience. *Transplantation* 2000;**69**:842–6.
21. Barry JM, Metcalfe JB, Farnsworth MA, Bennett WM, Hodges CV. Comparison of intracellular flushing and cold storage to machine perfusion for human kidney preservation. *J Urol* 1980;**123**:14–16.
22. Sheil AG, Drummond JM, Rogers JH, Boulas J, May J, Storey BG. A controlled clinical trial of machine perfusion of cadaveric donor renal allografts. *Lancet* 1975;**2**:287–90.
23. Mittal VK, Toledo-Pereyra LH, Kaplan M, Rosenburg JC, Allaben R. Effect of preservation method on function in the cyclosporine era. *Transplant Proc* 1985;**17**:2815–17.
24. Mittal VK, Kaplan MP, Rosenberg JC, Allaben RA, Toledo-Pereyra L. Pulsatile perfusion: better than hypothermic storage with cyclosporine as an immunosuppressant. *Dial Transplant* 1985;**14**:136–40.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

25. Light JA, Kowalski AE, Gage F, Callender CO, Sasaki TM. Immediate function and cost comparison between ice storage and pulsatile preservation in kidney recipients in one hospital. *Transplant Proc* 1995;**27**:2962–4.

26. Light JA, Gage F, Kowalski AE, Sasaki TM, Callender CO. Immediate function and cost comparison between static and pulsatile preservation in kidney recipients. *Clin Transplant* 1996;**10**:233–6.

27. Sellers MT, Gallichi, MH, Hudson SL, Young CJ, Bynon JS, Eckhoff DE, *et al.* Improved outcomes in cadaveric renal allografts with pulsatile preservation. *Clin Transplant* 2000;**14**:543–9.

28. Polyak MM, Arrington BO, Stubenbord WT, Boykin J, Brown T, Jean-Jacques MA, *et al.* The influence of pulsatile preservation on renal transplantation in the 1990s. *Transplantation* 2000;**69**:249–58.

29. Sanfilippo F, Vaughn WK, Spees EK, Lucas BP. The detrimental effects of delayed graft function in cadaver donor renal transplantation. *Transplantation* 1984;**38**:643–8.

30. Spees EK, Vaughn WK, Mendez-Picon G, Humphries AL. Preservation methods do not affect cadaver renal allograft outcome: the SEPPF prospective study 1977–1982. *Transplantat Proc* 1984;**16**:177–9.

31. van der Vliet JA, Vroemen S, Cohen B, Kootstra G. Comparison of cadaver kidney preservation methods in Eurotransplant. *Transplantat Proc* 1984;**16**:180–1.

32. Peters TG, Shaver TR, Ames JE, Santiago-Delphin EA, Jones KW, Blanton JW. Cold ischaemia and outcome in 17,937 cadaveric kidney transplants. *Transplantation* 1995;**59**:191–6.

33. Halloran P, Aprile M. A randomized prospective trial of cold storage versus pulsatile perfusion for cadaver kidney preservation. *Transplantation* 1987;**43**:827–32.

34. Jaffers GJ, Banowsky LH. The absence of a deleterious effect of mechanical kidney preservation in the era of cyclosporine. *Transplantation* 1989; **47**:734–6.

35. Mozes MF, Finch W, Reckard CR, Merkel FK, Cohen C. Comparison of cold storage and machine perfusion in the preservation of cadaver kidneys: a prospective, randomized study. *Transplant Proc* 1985;**17**:1474–7.

36. Heil JE, Canafax DM, Sutherland DE, Simmons RL, Dunning M, Najarian JS. A controlled comparison of kidney preservation by two methods: machine perfusion and cold storage. *Transplant Proc* 1987;**19**:2046.

37. Matsuno N, Sakurai E, Tamaki I, Uchiyama M, Kozaki K, Kozaki M. The effect of machine perfusion preservation versus cold storage on the function of kidneys from non-heart-beating donors. *Transplantation* 1994;**57**:293–4.

38. Alijani MR, Cutler J, DelValle CJ, Morres DN, Fawzy A, Pechan BW, *et al.* Single-donor cold storage versus machine perfusion in cadaver kidney preservation. *Transplantation* 1985;**40**:659–61.

39. Marshall VC, Ross H, Scot, DF, McInnes S, Thomson N, Atkins RC, *et al.* Preservation of cadaver of renal allografts: comparison of ice storage and machine perfusion. *Med J Aust* 1977;**2**:353–6.

40. Marshall VC, Ross H, Scott DF, McInnes S, Thomson N, Atkins RC. Preservation of cadaveric renal allografts-comparison of flushing and pumping techniques. *Proc Eur Dial Transplant Assoc* 1977;**14**:302–9.

41. Marshall VC. Renal preservation prior to transplantation. *Transplantation* 1980;**30**:165–6.

42. Matsuno N, Kozaki M, Sakurai E, Uchiyama M, Iwahori T, Kozaki K, *et al.* Effect of combination in situ cooling and machine perfusion preservation on non-heart-beating donor kidney procurement. *Transplant Proc* 1993;**25**:1516–17.

43. Matsuno N, Sakurai E, Uchiyama M, Kozaki K, Tamaki I, Kozaki M. Use of in situ cooling and machine perfusion preservation for non-heart-beating donors. *Transplant Proc* 1993;**25**:3095–6.

44. Sterling WA, Pierce JC, Hutcher NE, Lee HM, Hume DM. A comparison of hypothermic preservation with hypothermic pulsatile perfusion in paired human kidneys. *Surg Forum* 1971;**22**:229–30.

45. Beck TA. Machine versus cold storage preservation and TAN versus the energy charge as a predictor of graft function posttransplantation. *Transplant Proc* 1979;**11**:459–64.

46. Toledo-Pereyra LH. Renal hypothermic storage with a new hyperosmolar colloid solution. *Bol Assoc Med PR* 1983;**75**:347–50.

47. Rosenthal J, Herman JB, Taylo, RJ, Broznick B, Hakala TR. Comparison of pulsatile machine perfusion with cold storage for cadaver kidney preservation. *Transplantation* 1984;**37**:425–6.

48. Mendez R, Mendez RG, Koussa N, Cats S, Bogaar, TP, Khetan U. Preservation effect on oligo-anuria in the cyclosporine era: a prospective trial with 26 paired cadaveric renal allografts. *Transplant Proc* 1987;**19**:2047–50.

49. Gage F, Ali M, Alijani MR, Aquino AO, Barhyte DY, Callender CO, *et al*. Comparison of static versus pulsatile preservation of matched-paired kidneys. *Transplant Proc* 1997;**29**:3644–5.

50. Kosieradzki M, Danielewic, R, Kwiatkowski A, Polak W, Wegrowicz-Rebandel I, Walaszewski J, *et al.* Rejection rate and incidence of acute tubular necrosis after pulsatile perfusion preservation. *Transplant Proc* 1999;**31**:278–9.

51. 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. *Transplant Proc* 2001;**33**:847.

52. Baxby K, Taylor RM, Anderson M, Johnson RW, Swinney J. Assessment of cadaveric kidneys for transplantation. *Lancet* 1974;**2**:977–9.

53. Sampson D, Kauffman HM, Peters T, Walczak P. Perfusion characteristics and transplant function in machine-preserved kidneys. *Transplant Proc* 1977; **9**:1551–2.

54. Sampson D, Jun HM, Walczak P. Flow and function in machine-preserved kidneys. *Br J Surg* 1978;**65**:37–40.

55. Burleson RL, Jones DB, Yenikomshian AM, Cornwall C, DeVoe C, DeRito J. Clinical renal preservation by cryoperfusion with an albumin perfusate: renal perfusion with albumin. *Arch Surg* 1978;**113**:688–92.

56. Feinfeld DA, Levine RD, Levine SD, Fleischner G. Ligandin in perfusates from transplanted kidneys: a test for tubular necrosis. *Nephron* 1978;**21**:38–41.

57. Horpacsy G, Schroder K, Zinsmeyer J, Althaus P, May G, Mebel M. Clinical experiences in the Gambro-preservation unit: analysis of 105 human cadaver kidneys. *Acta Med Pol* 1978;**19**:59–65.

58. Horpacsy G, Scholz D, Althaus P, May G. Clinical experiences in the Gambro-preservation unit: analysis of 101 human cadaver kidneys. *Eur Surg Res* 1979;**11**:50–60.

59. Sy G, Toledo-Pereyra L, Dienst S, Oh HK. Are there any important predicting factors of renal function during hypothermic pulsatile perfusion for transplantation? *Am Surg* 1980;**46**:340–3.

60. Cho SI, Zalneraitis B, Ohmi N, Arias IM. Prediction of cadaver kidney function by ligandin analysis. *J Surg Res* 1981;**30**:361–4.

61. Tesi RJ, Elkhammas EA, Davies EA, Henry ML, Ferguson RM. Pulsatile kidney perfusion for preservation and evaluation: use of high-risk kidney donors to expand the donor pool. *Transplant Proc* 1993;**25**:3099–100.

62. Tesi RJ, Elkhammas EA, Davies EA, Henry ML, Ferguson RM. Pulsatile kidney perfusion for evaluation of high-risk kidney donors safely expands the donor pool. *Clin Transplant* 1994;**8**:134–8.

63. Daemen JH, Heineman E, Kootstra G. Viability assessment of non-heart-beating donor kidneys during machine preservation. *Transplant Proc* 1995;**27**:2906–7.

64. Matsuno N, Sakurai E, Tamaki I, Furuhashi K, Saito A, Zhang S, *et al.* Effectiveness of machine perfusion preservation as a viability determination method for kidneys procured from non-heart-beating donors. *Transplant Proc* 1994;**26**:2421–2.

65. Matsuno N, Sakurai E, Uchiyama M, Kozaki K, Miyamoto K, Kozaki M. Usefulness of machine perfusion preservation for non-heart-beating donors in kidney transplantation. *Transplant Proc* 1996;**28**:1551–2.

66. Matsuno N, Sakurai E, Uchiyama M, Kozaki K, Miyamoto K, Kozaki M, Nagao T. Role of machine perfusion preservation in kidney transplantation from non-heartbeating donors. *Clin Transplant* 1998;**12**:1–4.

67. Polyak M, Boykin J, Arrington B, Stubenbord WT, Kinkhabwala M. Pulsatile preservation characteristics predict early graft function in extended criteria donor kidneys. *Transplant Proc* 1997;**29**:3582–3.

68. Polyak MM, Arrington B, Hardy MA, Stubenbord WT, Kinkhabwala M. The state of renal preservation for transplantation in New York. *Transplant Proc* 1999;**31**:2091–3.

69. Danielewicz R, Kwiatkowski A, Polak W, Kosieradzki M, Michalak G, Wegrowicz I, *et al.* An assessment of ischemic injury of the kidney for transplantation during machine pulsatile preservation. *Transplant Proc* 1997;**29**:3580–1.

70. Kievit JK, Nederstigt AP, Oomen AP, Janssen MA, Schoot L, Kootstra G. Release of alpha-glutathione S-transferase (alpha GST) and pi-glutathione S-transferase (pi GST) from ischemic damaged kidneys into the machine perfusate – relevance to viability assessment. *Transplant Proc* 1997;**29**:3591–3.

71. Kievit JK, Oomen AP, Janssen MA, van Kreel BK, Heineman E, Kootstra G. Viability assessment of non-heart-beating donor kidneys by alpha glutathione S-transferase in the machine perfusate. *Transplant Proc* 1997;**29**:1381–3.

72. Balupuri S, Buckley P, Mohamed M, Cornell C, Mantle D, Kirby J, *et al.* Assessment of non-heart-beating donor (NHBD) kidneys for viability on machine perfusion. *Clin Chem Lab Med* 2000; **38**:1103–6.

73. Balupuri S, Buckley P, Mohamad M, Chidambaram V, Gerstenkorn C, Sen B, *et al.* Early results of a non-heartbeating donor (NHBD) programme with machine perfusion. *Transpl Int* 2000;**13** Suppl 1:S255–8.

74. Matsuno N, Kozaki K, Degawa H, Narumi Y, Suzuki N, Kikuchi K, *et al.* Importance of machine perfusion flow in kidney preservation. *Transplant Proc* 1999;**31**:2004–5.

75. Matsuno N, Kozaki K, Degawa H, Narumi Y, Suzuki N, Kikuchi K, *et al.* A useful predictor in machine perfusion preservation for kidney transplantation from non-heart-beating donors. *Transplant Proc* 2000;**32**:173–4.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

76. Kozaki K, Sakurai E, Kubota K, Iwamot, H, Hama K, Narumi Y, *et al.* Prediction of kidney nonfunction after transplantation with machine perfusion preservation. *Transplant Proc* 2000;**32**:275–6.

77. Kwiatkowski A, Danielewicz R, Kosieradzki M, Polak WP, Wszola M, Fesolowicz S, *et al.* Six-year experience in continuous hypothermic pulsatile perfusion kidney preservation. *Transplant Proc* 2001;**33**:1–2.

78. Johnson CP, Roza AM, Adams MB. Local procurement with pulsatile perfusion gives excellent results and minimizes initial cost associated with renal transplantation. *Transplant Proc* 1990;**22**:385–7.

79. Cecka JM, Terasaki P. The UNOS Scientific Renal Transplant Registry – 1990. *Clin Transplant* 1990;1–10.

80. Kato M, Mizutani K, Hattori R, Kinukawa T, Uchida K, Hoshinaga K, *et al.* In situ renal cooling for kidney transplantation from non-heart-beating donors. *Transplant Proc* 2000;**32**:1608–10.

81. Halloran PF, Aprile MA, Farewell V, Ludwin D, Smith EK, Tsai SY, *et al.* Early function as the principal correlate of graft survival. A multivariate analysis of 200 cadaveric renal transplants treated with a protocol incorporating antilymphocyte globulin and cyclosporine. *Transplantation* 1988; **46**:223–8.

82. Cole E, Naimark D, Aprile M, Wade J, Cattran D, Pei Y, *et al.* An analysis of predictors of long-term cadaveric renal allograft survival. *Clin Transplant* 1995;**9**:282–8.

83. Balupuri S, Mantle D, Mohamed M, Shenton B, Gok M, Soomro N, *et al.* Machine perfusion and viability assessment of non-heart-beating donor kidneys – a single-centre result. *Transplant Proc* 2001;**33**:1119–20.

84. Feldman HI, Gayner R, Berlin JA, Roth DA, Silibovski R, Kushner S, *et al.* Delayed function reduces renal allograft survival independent of acute rejection. *Nephrol Dial Transplant* 1996; **11**:1306–13.

85. Raikou M, Gray A, Briggs A, Stevens R, Cull C, McGuire A, *et al.* Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *BMJ* 1998;**317**:720–5.

86. Moore R. Cost effective use of immunosuppression in a world of finite health resources. International Congress and Symposium Series 217. London: Royal Society of Medicine Press; 1997.

87. Meechan D, Jones R, Payne N. Utilisation of renal replacement therapy. Trent Public Health Observatory; 2001.

88. Chilcott J, Corcoran M, Rigg K M, Burden RP. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Trent Institute for Health Services Research. Guidance Note for Purchasers: 99/07; 1999.

89. UK medicines information service. URL: http://www.ukmi.nhs.uk; 2002.

90. Hornberger JC, Best JH, Garrison LP. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. *Med Decis Making* 1997;**17**:363–72.

91. Burdick J, Rosendale JD, McBride MA, Kauffman HM, Bennett LE. National impact of pulsatile perfusion on cadaveric kidney transplantation. *Transplantation* 1997;**64**:1730–3.

92. Whittaker JR, Veith FJ, Soberman R. The fate of the renal transplant with delayed function. *Surg Gynecol Obstet* 1973;**136**:919–22.

93. Opelz G, Sasaki N, Terasaki PI. Prediction of long term kidney transplant survival rates by monitoring early graft function and clinical grades. *Transplantation* 1978;**25**:212–15.

94. Sanfilippo F, Vaughn WK, LeFor WN, Spees EK. Multivariate analysis of risk factors in cadaver donor kidney transplantation. *Transplantation* 1986;**42**:28–34.

95. Canafax DM, Torres A, Fryd DS, Heil JE, Strand MH, Ascher NL, *et al.* The effects of delayed function on recipients of cadaver renal allografts. A study of 158 patients randomized to cyclosporine or ALG-azathioprine. *Transplantation* 1986;**41**:177–81.

96. Belitsky P, MacDonald A, Gajewski J, Boudreau J, Bitter-Suermann H, Cohen A. Significance of delayed function in cyclosporine-treated cadaver kidney transplants. *Transplant Proc* 1987**;19**:2096–9.

97. Lim EC, Terasaki PI. Early graft function. *Clin Transplant* 1991;401–7.

98. Cecka JM, Cho YW, Terasaki PI. Analyses of the UNOS Scientific Renal Transplant Registry at three years – early events affecting transplant success. *Transplantation* 1992;**53**:59–64.

99. Cacciarelli T, Sumrani M, Delaney V, Hong JH. The influence of delayed renal allograft function on long term outcome in the cyclosporine era. *Clin Nephrol* 1993;**39**:335–9.

100. Yokoyama I, Uchica K, Kobayashi T, Tominaga Y, Orihara A, Takagi H. Effect of prolonged delayed graft function on long term graft outcome in cadaveric kidney transplantation. *Clin Transplant* 1994;**8**:101–6.

101. Troppmann C, Gillingham KJ, Benedetti E, Almond PS, Gruessner RWG, Najarian JS and Matas AJ. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. *Transplantation* 1995;**59**:962–8.

102. Shoskes DA, Avelino L, Barba L, Sender M. Patient death or renal graft loss within 3 years of transplantation in a county hospital: importance of poor initial graft function. *Clin Transplant* 1997;**11**:618–22.

103. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997; **63**:968–74.

104. Lehtonen SRK, Isoniemi HM, Salmela KT, Taskinen EI, von Willebrand EO and Ahonen JP. Long-term graft outcome is not necessarily affected by delayed onset of graft function and early acute rejection. *Transplantation* 1997;**64**:103–7

105. Clark EA, Opelz G, Mickey MR, Terasaki PI. Evaluation of Belzer and Collins kidney-preservation methods. *Lancet* 1973;**1**:361–4.

106. Claes G, Blohme I, Stenberg K. Kidney preservation by continuous hypothermic albumin perfusion without membrane oxygenation. *Proc Eur Dial Transplant Assoc* 1976;**12**:483–91.

107. Collins GM, Jones AC, Halasz NA. Influence of preservation method on early transplant failure. *Transplant Proc* 1977;**9**:1523–8.

108. Light JA, Annable CA, Spees EK, Jr. Oakes DD, Flye MW, Reinmuth B. Comparison of long-term kidney survival following cold storage or pulsatile preservation. *Transplant Proc* 1977;**9**:1517–19.

109. Slooff MJ, van der Wijk J, Rijkmans BG, Kootstra G. Machine perfusion versus cold storage for preservation of kidneys before transplantation. *Arch Chir Neerland* 1978;**30**:83–90.

110. Johnson HK, Fleming C, Warner H, vonSchmittou E, Tallent M, Niblack G, *et al.* The relation of graft survival to preservation method and kidney sharing. *Transplant Proc* 1977;**9**:1513–16.

111. Collins GM, Halasz NA. Clinical comparison of methods for cadaveric kidney preservation. *J Surg Res* 1978;**24**:396–400.

112. van der Vliet JA, Slooff MJH, Rijkmans BG, Kootstra G. Use of non-heart-beating donor kidneys for transplantation. *Eur Surg Res* 1981; **13**:354–60.

113. Vaughn WK, Mendez-Picon G, Humphries AL, Spees EK. Method of preservation is not a determinant of graft outcome in kidneys transplanted by Southeastern Organ Procurement Foundation Institutions. *Transplantation* 1981; **32**:490–4.

114. Manis T, Hong JH, Bronsther OL, Friedmann EA, Butt KM. Superior results with machine-perfused kidneys in cyclosporine-treated transplant recipients. *Transplant Proc* 1985;**17**:1483–4.

115. Nghiem DD, Schulak JA, Corry RJ. Cadaver kidney preservation beyond 40 hours: superiority of machine preservation over cold storage. *Transplant Proc* 1986;**18**:564–5.

116. Abouna GM, Samhan MS, Kumar MS, White AG, Silva OS. Limiting factors in successful preservation of cadaveric kidneys with ischemia time exceeding 50 hours. *Transplant Proc* 1987; **19**:2051–5.

117. Barber WH, Hudson SL, Deierhoi MH, Laskow DA, Diethelm AG. Pulsatile perfusion preservation: early posttransplant dialysis requirement predicts rapid graft loss. *Transplant Proc* 1990;**22**:446–7.

118. Barber WH, Laskow DA, Deierhoi MH, Poplawski SC, Diethelm AG. Comparison of simple hypothermic storage, pulsatile perfusion with belzer gluconate–albumin solution, and pulsatile perfusion with UW solution for renal-allograft preservation. *Transplant Proc* 1991;**23**:2394–5.

119. Zhou YC, Cecka JM. Preservation. *Clin Transplants* 1992;383–90.

120. Koyama H, Cecka JM, Terasaki P. A comparison of cadaver donor kidney storage methods: pump perfusion and cold storage solutions. *Clin Transplant* 1993;**7**:199–205.

121. Daemen JH, de Vries B, Oomen AP, DeMeester J, Kootstra G. Effect of machine perfusion preservation on delayed graft function in non-heart-beating donor kidneys – early results. *Transpl Int* 1997;**10**:317–22.

122. Daemen JH, de Vries B, Kootstra G. The effect of machine perfusion preservation on early function of non-heart-beating donor kidneys. *Transplant Proc* 1997;**29**:3489.

123. Polyak MM, Arrington BO, Kapur S, Stubenbord WT, Kinkhabwala M. Donor treatment with phentolamine mesylate improves machine preservation dynamics and early renal allograft function. *Transplantation* 2000;**69**:184–6.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Appendix 1

Search strategies used

Biological abstracts

1985–2001
SilverPlatter WebSPIRS
Search undertaken October 2001

#1 Kidney or kidneys or renal or tissue or tissues or organ
#2 Replace or replacement or allograft or transplant or replaced or transplanted or transplantation or donor or donors or donated
#3 #1 and #2
#4 preservation or preserve or preserved or procurement or procured or static or cold or cool or hypothermic or normothermic or storage or stored
#5 #3 and #4
#6 perfusion or perfused or pulsatile flow or pulsatile or non heart beating or heart beating or brain dead or nhbd
#7 #5 and #6
#8 eurocollins or belzer gluconate albumin or university of wisconsin
#9 7 and 8

CDSR and CCTR

2001, Issue 3
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken October 2001

#1 KIDNEY-TRANSPLANTATION*:ME
#2 (KIDNEY* OR RENAL) NEAR3 (TRANSPLANT* OR PRESERV* OR REPLACE* OR DONOR* OR DONATE) *:ME
#3 TISSUE-DONORS*:ME
#4 KIDNEY*:ME
#5 (KIDNEY* OR RENAL)
#6 #4 OR #5
#7 #3 AND #6
#8 #1 OR #2 OR #7
#9 TISSUE-PRESERVATION*:ME
#10 ORGAN-PROCUREMENT*:ME
#11 (STATIC OR COLD OR COOL OR HYPOTHERMIC OR NORMOTHERMIC) NEAR2 (STORAGE OR PRESERV*)
#12 #9 OR #10 OR #11
#13 #8 AND #12
#14 PERFUSION*:ME
#15 PULSATILE-FLOW*:ME
#16 NON HEART BEATING
#17 HEART BEATING
#18 BRAIN DEAD
#19 NHBD*
#20 PULSATILE*
#21 (MACHINE* OR PULSATILE) NEAR2 (PERFUSION)
#22 PERFUSATE*
#23 BELZER* GLUCONATE ALBUMIN
#24 EUROCOLLINS
#25 (UNIVERSITY) NEAR2 (WISCONSIN)
#26 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27 #13 AND #26

CINAHL

1982–2001
Ovid Biomed
Search undertaken October 2001

1. Kidney Transplantation/
2. Exp kidney/tr [Transplantation]
3. ((kidney$ or renal) adj3 (transplant$ or preserv$ or replace$ or donor$ or donate$)).mp
4. exp tissue donors/
5. exp kidney/
6. (kidney$ or renal).tw
7. or/5-6
8. 4 and 7
9. or/1-3
10. 8 or 9
11. exp tissue preservation/
12. Organ procurement/
13. ((static or cold or cool or hypothermic or normothermic) adj2 (storage or preserv$)).tw
14. or/11-13
15. 10 and 14
16. exp perfusion/
17. pulsatile flow.tw
18. non heart beating.tw
19. heart beating.tw
20. brain dead.tw

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

21. nhbd.tw
22. pulsatile.tw
23. ((machine$ or pulsatile) adj2 (perfusion).tw
24. perfusate$.tw
25. belzer$ gluconate albumin.tw
26. eurocollins.af
27. university of wisconsin.af
28. or/16-27
29. 15 and 28

Citation indexes (science and social sciences)

1981–2001
Web of Science
Search undertaken October 2001

Title=((kidney OR kidneys OR renal OR tissue OR tissues OR organ) AND (replace OR replacement OR allograft OR transplant OR transplantation OR transplanted OR donor OR donated) AND (preservation OR preserve OR preserved OR procurement OR procured OR static OR cold OR cool OR hypothermic OR normothermic OR storage OR stored) AND (perfusion OR pulsatile flow OR non heart beating OR heart beating OR brain dead OR nhbd OR pulsatile) AND (eurocollins OR belzer gluconate albumin OR university of wisconsin)); DocType=All document types; Language=All languages; Databases=SCI-EXPANDED, SSCI; Timespan=All Years

CRD Databases (NHS DARE, EED, HTA)

CRD Website – complete databases
Search undertaken October 2001

Kidney-transplantation/subject headings exploded OR tissue-preservation/ subject headings exploded OR pulsatile-flow/ subject headings exploded

Belzer gluconate albumin/all fields OR eurocollins/all fields OR university of wisconsin/all fields

EMBASE

1980–2001
SilverPlatter WebSPIRS
Search undertaken October 2001

#1 explode 'kidney-transplantation' / all subheadings
#2 (kidney* or renal) near3 (transplant* or preserv* or replace* or donor* or donate*)
#3 'kidney-donor' / all subheadings
#4 #1 or #2 or #3
#5 explode 'kidney-' / all subheadings
#6 #4 or #5
#7 'tissue-preservation' / all subheadings
#8 'cryopreservation-' / all subheadings
#9 'graft-preservation' / all subheadings
#10 'organ-preservation' / all subheadings
#11 'storage-' / all subheadings
#12 'preservation-' / all subheadings
#13 'kidney-preservation' / all subheadings
#14 'organ-transplantation' / all subheadings
#15 (static or cold or hypothermic or normothermic or cool) near2 (storage or preserv*)
#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 #6 and #16
#18 explode 'perfusion-' / all subheadings
#19 'pulsatile-flow' / all subheadings
#20 non heart beating
#21 heart beating
#22 brain dead
#23 nhbd*
#24 pulsatile
#25 machine* near2 perfusion
#26 perfusate*
#27 belzer* gluconate albumin
#28 eurocollins
#29 university of wisconsin
#30 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31 #17 and #30

EMBASE – for specific economics search

1980–2001
SilverPlatter WebSPIRS
Search undertaken January 2002

#1 (cost*) in TI
#2 (cost effectiveness) in TI
#3 (cost* benefit* analysis) in TI
#4 (economic*) in TI
#5 ((costed or costly or costing*)) in TI
#6 #1 or #2 or #3 or #4 or #5
#7 (delay*) in TI
#8 (graft*) in TI
#9 (function*) in TI
#10 (immediat*) in TI
#11 ((delay*) in TI) or ((graft*) in TI) or ((function*) in TI) or ((immediat*) in TI)

#12 (kidney*) in TI
#13 (renal*) in TI
#14 ((kidney*) in TI) or ((renal*) in TI)
#15 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 #6 and #15
#17 (cost* delay* graft* function*) in TI
#18 (economic* delay* graft* function*) in TI

HEED (Office of Health Economic Evaluations Database)

CD-ROM version
Search undertaken October 2001

Search terms

((kidney or kidneys or renal or tissue or organ) and (replace or replacement or transplant or transplantation or donor or donors or donate or donated or preservation or preserve or procurement or static or cold or cool or hypothermic or normothermic or storage or stored or perfusion or pulsatile flow or non heart beating or heart beating or brain dead or nhbd or pulsatile or eurocollins or belzer gluconate albumin or university of wisconsin))

Fields searched

- Abstract
- Article title
- Keywords
- Technology Assessed

HEED (Office of Health Economic Evaluations Database) – for specific economics search

CD-ROM version
Search undertaken January 2002

Search terms

Graft
Cost delay graft function
Kidney*
Renal*

Fields searched

- Abstract
- Article title
- Keywords
- Technology Assessed

MEDLINE

1966–2001
Ovid Biomed
Search undertaken September 2001

1. Kidney Transplantation/
2. Exp KIDNEY/tr [Transplantation]
3. ((kidney$ or renal) adj3 (transplant$ or preserv$ or replace$ or donor$ or donate$)).tw
4. exp Tissue Donors/
5. exp KIDNEY
6. (kidney$ or renal).tw
7. or/5-6
8. 4 and 7
9. or/1-3
10. 8 or 9
11. exp tissue preservation/
12. Organ Procurement/
13. ((statis or cold or hypothermic or normothermic) adj2 (storage or preserv$)).tw
14. or/11-13
15. 10 and 14
16. exp Perfusion/
17. Pulsatile Flow/
18. Non heart beating.tw
19. Heart beating.tw
20. Brain dead.tw
21. nhbd$.tw
22. pulsatile.tw
23. ((machine$ or pulsatile) adj2 (perfusion)).tw
24. perfusate$.tw
25. belzer$ gluconate albumin.tw
26. eurocollins.af
27. university of wisconsin.af
28. or/16-27
29. 15 and 28
30. limit 29 to human
31. (letter or editorial).pt
32. 30 not 31

MEDLINE – for specific economics search

1966–2001
Ovid Biomed
Search undertaken January 2002

1. cost$.ti
2. cost effectiveness.ti
3. cost$ benefit$ analysis.ti
4. economic$.ti
5. (costed or costly or costing$).ti
6. or/1-5
7. delay$.ti

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

8. graft$.ti
9. function$.ti
10. immediat$.ti
11. or/7-10
12. kidney$.ti
13. renal$.ti
14. 12 or 13
15. 6 and 11 and 14

NHS EED and CCTR – for specific economics search

2001, Issue 3
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken January 2002

#1 COST*
#2 COST EFFECTIVENESS
#3 COST* BENEFIT* ANALYSIS
#4 ECONOMIC*
#5 COSTED OR COSTLY OR COSTING*
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 DELAY*
#8 GRAFT*
#9 FUNCTION*
#10 IMMEDIAT*
#11 #7 OR #8 OR #9 OR #10
#12 KIDNEY*
#13 RENAL*
#14 #12 OR #13
#15 #6 AND #11 AND #14

Appendix 2

Methodological search filters used in Ovid MEDLINE

Economic evaluations

1. economics/
2. exp "costs and cost analysis"/
3. economic value of life/
4. exp economics, hospital/
5. exp economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. exp models, economic/
9. exp "fees and charges"/
10. exp budgets/
11. ec.fs.
12. (cost or costs or costed or costly or costing$).tw
13. (economic$ or pharmacoeconomic$ or price$ or pricing).tw
14. or/1-13

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Appendix 3

Jadad scale for assessing the quality of published research[11]

The criteria included in the Jadad scale are as follows:

1. Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?
2. Was the study described as double blind?
3. Was there a description of the withdrawals and dropouts?

Give a score of 1 point for each 'yes' or 0 points for 'no'.

Give one an additional point if the method to generate the sequence of randomisation was described and was appropriate (table of random numbers, computer-generated, etc.) Deduct one point if this method was inappropriate (patients allocated alternately, according to date of birth, hospital number, etc.)

Give one point if the study was described as double blind, but the method of blinding was appropriate (identical placebo, active placebo, dummy, etc.). Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy).

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and reasons for each withdrawal must be stated. If there were no withdrawals, it should also be stated in the article. If there is no statement on withdrawals, this item must be given no points.

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Appendix 4

Economic studies extraction table

Study	Light *et al.*, 1996[26]	Light *et al.*, 1995[25]	Johnson *et al.*, 1990[78]	Burdick *et al.*, 1997[91]
Title	Immediate function and cost comparison between static and pulsatile preservation in kidney recipients	Immediate function and cost comparison between ice storage and pulsatile preservation in kidney recipients at one hospital	Local procurement with pulsatile perfusion gives excellent results and minimises initial cost associated with renal transplantation	National impact of pulsatile perfusion on cadaveric kidney transplantation
Economic assessments should include				
Type of study	A 1-year prospective observational study of 74 patients undergoing kidney transplantation	This article reports the same study as Light *et al.*, 1996[26] with less detail	A retrospective observational study between January 1988 and March 1989 of 100 consecutive cadaveric renal allografts	A retrospective analysis of the United Network for Organ Sharing data
Methods	39 kidneys were cold stored while 35 received MP. The kidneys were not randomly allocated. Most kidneys on MPS were from marginal donors or were imported and had long ice storage times. The CS kidneys were from 'ideal donors'		18 kidneys were cold stored whilst 82 received MP. CS was used primarily in situation were imported or exported. No deliberate attempt at matching was made	The analysis included 60,827 cadaveric kidney transplants performed between 1988 and 1995. Nearly 14% of the kidneys were preserved using MP. Multivariate logistic regression analysis was used to determine the effect of preservation method on kidney function and graft survival
Outline of the economic importance of the research question	MP systems may improve immediate function rates and thereby improve patient and graft survival. They may also serve as an evaluative tool for marginal kidneys		To define procurement and preservation techniques that lead to excellent allograft survival and minimise the costs associated with renal transplantation	The increased use of marginal kidneys may result in a net benefit of the increase in the number of successful transplants
The viewpoint	Not explicitly stated, but only direct hospital resources and costs included		Not explicitly stated, but only direct hospital resources and costs included	Not explicitly stated, but only direct hospital resources and costs included

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Study	Light et *al.*, 1996[26]	Light et *al.*, 1995[25]	Johnson et *al.*, 1990[78]	Burdick et *al.*, 1997[91]
Form of evaluation	Not stated, but crude cost minimisation analysis		Not stated, but crude cost minimisation analysis	Not stated, but crude cost minimisation analysis
Effectiveness data collection	Described as a single-centre trial, but no details of design given		Not stated	
Benefit measurement and valuation	Net savings		Net savings	
Resources reported separately from price	The only resource reported is average number of hospital days		The only resource reported is average number of hospital days	None reported
Methods for estimation of quantities and price	No unit costs given		No unit costs given	No unit costs given
Currency and price date, adjustments for inflation	Not stated		Not stated	Not stated

Appendix 5

DGF studies extraction table

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Type of study	Outcomes reported	Type of analysis	Relative risk (RR) factors found significant on graft survival	Baseline survival reported	Results
Whittaker[92]	1973	New York, USA	Retrospective observational, single-centre	Graft survival	Descriptive statistics			DGF reduced graft survival at 3, 6, 12, 24 and 36 months. All statistically significant ($p < 0.001$)
Opelz[93]	1978	Los Angeles, California, USA	Retrospective observational, single-centre	Graft survival	Regression analysis			Factors found to have a statistically significant effect on graft survival were DGF 1 day ($p < 0.0001$), 1 week ($p < 0.001$), 1 month ($p < 0.0001$)
Sanfilippo[29]	1984	Virginia, USA	Prospective observational, multi-centre	Graft and patient survival	Multivariate Cox's regression analysis		No	DGF was found to have the highest weight of association with overall graft failure ($p = 0.00001$)
Sanfilippo[94]	1986	Virginia, USA	Prospective observational, multi-centre	Graft and patient survival	Multivariate Cox's regression analysis	DGF (<0.0001). RR = 1.427	No	13 factors were found to be associated with graft loss
Canafax[95]	1986	Minnesota, USA	Prospective observational, single-centre	Graft and patient survival	Descriptive statistics, actuarial methods for graft survival			DGF correlated with poorer graft survival in both treatment groups. ($p = 0.011$) 1 year
Belitsky[96]	1987	Nova Scotia, Canada	Retrospective observational, single-centre	Graft survival	Descriptive statistics			DGF of any duration is associated with significantly poorer quality of later renal function
Halloran[81]	1988	Toronto, Canada	Prospective observational, single-centre	Graft survival	Multivariate analysis, Cox's relative risk regression model	DGF ($p = 0.009$). RR = 2.858	Yes	DGF was the only risk factor for graft survival to be found significant
Cecka[79]	1990	Los Angeles, California, USA	UNOS transplant registry analysis, 1987–90	Graft survival	Descriptive statistics, actuarial methods for graft survival			Factors found to have a statistically significant effect on graft survival were race ($p < 0.001$), PRA ($p < 0.001$), sex ($p < 0.01$)

continued

Author	Year	Centre	Type of study	Outcomes reported	Type of analysis	Relative risk (RR) factors found significant on graft survival	Baseline survival reported	Results
Lim[97]	1991	Los Angeles, California, USA	UCLA transplant registry analysis, 1985–91 and UNOS transplant registry analysis, 1987–91	Graft survival	Descriptive statistics, actuarial methods for graft survival			Factors found to have a statistically significant effect on graft survival were DGF 1 day, 1 week and 1 month were all significant ($p < 0.0001$)
Cecka[98]	1992	Los Angeles, California, USA	UNOS transplant registry analysis, 1987–91	Early graft function	Univariate and multivariate models, descriptive statistics, actuarial methods for graft survival		No	DGF 1 day and 1 week were significant prognosticators of poor outcome
Cacciarelli[99]	1993	New York, USA	Retrospective observational, single-centre	Graft survival, DGF	Descriptive statistics			Dialysis dependence for more than 1 week post-transplant was associated with both a higher rate of AR and inferior 1- and 5-year graft survival
Yokoyama[100]	1994	Nagoya, Japan	Prospective observational, single-centre	CR, AR, infection, technical failure, DGF	Descriptive statistics, Kaplan–Meier survival			DGF is associated with a higher incidence of graft failure
Troppmann[101]	1995	Minnesota, USA	Prospective observational, single-centre	Graft and patient survival	Multivariate Cox's regression analysis	DGF with AR vs DGF no AR, RR = 4.2 ($p < 0.0001$).	No	DGF with AR portended poor 5-year graft survival. DGF when adjusted for AR was not associated with decreased graft survival
Cole[82]	1995	Toronto, Canada	Retrospective observational, single-centre	Graft and patient survival	Multivariate Cox's regression analysis	DGF RR = 3.197 ($p = 0.0001$)	No	DGF is the most important prognostic factor in 5-year graft survival

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Type of study	Outcomes reported	Type of analysis	Relative risk (RR) factors found significant on graft survival	Baseline survival reported	Results
Feldman[84]	1996	Pennsylvania, USA	Prospective observational, single-centre	Delayed graft function, acute rejection, graft survival	Univariate and multivarite models, Cox's proportional hazards model	Univariate: DGF, age, race, sex, previous transplantation, prior blood transfusion, PRA, AR. Multivariate: DGF, PRA, AR, race, previous transplant	Yes	DGF is strongly associated with a decrease in long-term kidney survival
Shoskes[102]	1997	California, USA	Retrospective observational, single-centre	Graft and patient survival	Descriptive statistics			The primary correlate of poor 3-year graft survival was DGF ($p < 0.05$)
Ojo[103]	1997	Michigan, USA	US renal data system analysis, 1985–92	Graft survival	Multivariate Cox's regression analysis	DGF RR = 1.53 ($p < 0.001$). DGF % AR RR = 2.54 ($p < 0.001$)	No	A significant relationship between DGF and graft survival was found
Lehtonen[104]	1997	Helsinki, Finland	Prospective observational, single-centre	Graft survival	Descriptive statistics, actuarial methods for graft survival			DGF had no effect on long-term graft survival

Appendix 6

Comparative studies not included in the analysis

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Clark[105]	1973	All USA	CS (Collins) vs MP (Belzer)	Non-randomised	Immediate function, failure within 1 month, 2 month and 1 year graft survival	146 CS 401 MP	For kidneys with cold ischaemia time <15 h, immediate function greater in CS than MP (66% vs 40%) and failure less (15% vs 31%). 2-month survival greater with CS (118/146, 81% vs 282/401, 71%), 1-year survival also reported as greater (58% vs 48%), but inconsistency in results between graph and text	Non-randomised comparison. Inconsistency in results reported. Not all kidneys accounted for in data. Some kidneys initially on MP discarded pre-transplantation. Cold ischaemic times not equal. Centre variation
Clark[1]	1974	USA and Canada	CS (Collins or Ringers) vs MP (Belzer, Waters, Stewart)	Non-randomised	1 day and 1 month function	479 CS 1206 MP	No significant difference in 1 day function. Function at 1 month better in CS (79.5%) than MP (69.4%) ($p < 0.0001$)	Pooled data from 108 transplant centres
Scott[15]	1974	Melbourne, Australia	CS mean 3.5 h (range 0.8–9.5) vs MP mean 17 h, range 8–25	Historical: 1969–Jan. 1972 CS, Feb. 1972–Dec. 1973 PP	Postoperative dialysis, graft survival at 3 months and 1 year	100:100	Postoperative dialysis in 65/100 CS, 51/100 PP. At 3 months, 69/100 functioning grafts in each group. 1-year survival 63/100 CS, 31/48 (65%) PP (only 48 followed-up for 1 year)	Nephrectomy after cardiac arrest. Mean warm ischaemic time longer for CS than MP (31 vs 22 minutes) 'Advantage of MP lies in the extra time it provides'
Cho[16]	1975	Boston, Massachusetts, USA	CS mean 3.8 h vs CS mean 2.9 h followed by MP mean 17 h	Historical: CS before July 1972, MP afterwards	Incidence of ATN, graft survival at 6 months, 1 and 2 year	81:81	No significant difference in any outcome. In CS, % ATN, 6-months, 1- and 2-year survival were 56, 76, 70, 66. In MP 42, 73, 61, 59	Primary grafts only. 'Advantages of continuous perfusion ... make it the preferred method'
Sheil[22]	1975	Sydney, Australia	CS mean 4 h vs CS mean 2 h 15 minutes followed by MP mean 14 h	Non-randomised. 'Broadly, ... kidneys at night were preserved by MP'	Immediate function, 1-month and 1-year graft survival. Causes of graft failure	83 CS, 88 MP	In CS, immediate function, 1-month and 1-year survival were 51/88 (58%), 75/88 (85%), 68%. In MP, 48/83 (58%), 67/83 (81%), 52% (not all patients followed for 1 year). Graft failure due to rejection more common in CS than MP (30% vs 16%, $p < 0.05$). Difference in 1-year survival significant at $p < 0.05$	Secondary grafts included. Mean warm ischaemic time 29 minutes for MP, 24 minutes for CS

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Opelz[2]	1975	Los Angeles, California, USA	CS (three different solutions) vs MP (two different machines)	Non-randomised, survey of 90 transplant centres	Actuarial graft survival to 1 year, 1 day function grade, effect of cold and warm ischaemia time	214 CS, 829 MP	1-year survival better for Collins CS 59% than Belzer MP 41% Waters MP 47% or Sacks CS 34% or Ringers CS ~44%. 1 day and 1 month kidney function better in CS than MP, even when warm ischaemia time >30 minutes. Non-function rates did not appear to vary with cold ischaemia time	Non-randomised. Possibility of reporting bias
Claes[106]	1976	Gothenburg, Sweden	CS mean 7 h vs MP with (mean 24 h) and without (mean 30 h) membrane oxygenation (MO)	Non-randomised	Immediate function (i.e. spontaneous fall in creatinine within 3 days)	206 CS 270 MP with MO. 20 MP without MO	Immediate function: CS 23% MP with MO 60%, MP without MO 80%	
Collins[107]	1977	San Diego, California, USA	CS (Sacks II or Collins C2) vs MP (Waters or Belzer)	Not stated	Function at 1 day, 1 month	20 CS 43 MP	Initial non-function, 1 month function in CS: 11/20 (55%), 13/20 (65%), in MP 20/43 (47%), 26/43 (60%). In CS group, of those stored for more than 24 h, 0/4 functioning at 1 month. Overall no difference between CS and MP, but CS <24 h significantly better than MP or CS >24 h	All but one were HBD
Light[108]	1977	Washington DC, USA	CS vs CS + MP	Non-randomised	ATN (defined as need for HD post-transplantation), graft survival at 1, 3, 6, 12 months	29 CS 31 CS + MP	ATN in 15/29 CS, 10/31 CS + MP. Increased frequency with longer cold ischaemia times. Overall 12 month survival 6/15 CS, 3/16 CS + MP. Duration of CS (whether or not followed by MP) appears to influence both ATN and 1-year graft survival rates. In 11 pairs where one was treated with CS, or with CS + MP, 6 CS kidneys had ATN where pair did not	Small numbers, non-randomised, long storage times. Used Sack's solution (found above to be associated with worse outcomes)

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Slooff[109]	1977	Groningen, The Netherlands	CS mean 15 h, CS + MP mean total preservation 24.6 h	Non-randomised	Initial function and graft survival	55 CS 35 MP	54 CS, 29 MP kidneys evaluable. Immediate function in 64.8% of CS, 51.7% MP. Non-function in 3.7%, 10.4%. In HBD and cold ischaemia <24 h, immediate function 71.1% vs 46.7%, but in NHBD or cold ischaemia >24 h, immediate function 33.3% vs 57.2%. 6- and 12-month graft survival better in MP than CS group (said to be non-significant)	34.5% NHBD in MP group, cf. 7.4% in CS. MP kidneys had varying periods of CS prior to MP
Johnson[110]	1977	Nashville, Tennessee, USA	CS vs MP	Non-randomised, basis of allocation not clear	Graft survival	? CS 50, MP 133	Graft survival better in CS than MP; figure suggests 1-year survival of ~65% vs 50%	Numbers of kidneys in analysis not explicit
Collins[111]	1977	San Diego, California, USA	CS vs MP (plasma or albumin perfusion)	Non-randomised, basis for allocation not clear	Immediate function, graft survival up to 2 year.	36 CS, 24 MP (plasma), 14 MP (albumin)	CS >24 h associated with significantly worse outcomes than <24 h. CS <24 h associated with improved survival at 1, 3 months ($p < 0.05$) and similar trend to 24 months (survival CS 60%, MP plasma 36%, MP albumin 44%)	Inclusion of CS >24 h would eliminate advantage of CS vs MP
Barry[21]	1980	Portland, Oregon, USA	CS (Collins C2) vs MP (MOX 100)	Historical: MP 1974–76, CS 1976–78	Dialysis at 1 week, creatinine nadir, graft function at 1 month and 2 year	40 CS 37 MP	No significant differences between CS and MP. Dialysis in first week, 1-month and 2-year survival: CS 32%, 90%, 58%, MP 30%, 73%, 45.6%. No difference between groups in results in kidneys with cold ischaemia >24 h	Mean cold ischaemia time 23 h in both groups. Crude costs of CS and MP stated
van der Vliet[112]	1981	Groningen, The Netherlands	CS (Collins) vs MP (Gambro)	Not stated	Graft survival up to 24 months	37 CS 29 MP	Data available on 60 cases. No interpretable data comparing preservation methods presented	All NHBD. Overall graft survival as good as Eurotransplant registry controls

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Vaughn[113]	1981	Richmond, Virginia (SEOPF), USA	CS mean preservation time 19.7 h vs MP mean preservation time 28 h	Not stated	ATN (= dialysis required in first week), graft and patient survival at 6, 12, 18, 24 months	347 CS 1004 MP	No significant difference in ATN in CS vs MP (40.5% vs 32.8%, $p > 0.05$). Unadjusted survival rates did not differ significantly between preservation methods (48% 12-month survival rates in both). No significant differences in graft or patient survival rates between preservation methods when HLA matching, use of anti-lymphocyte serum and pre-transplant blood transfusion controlled for	Multivariate analysis. Primary transplants only. Differences in kidney sharing patterns between CS and MP kidneys – higher proportion of CS kidneys used locally
Opelz[3]	1982	95 centres, USA	CS (Collins or Ringers) vs MP (Belzer or Waters)	Not stated	Graft survival at 1 month, 1 year	CS Collins 1926, Ringer's 400, MP Waters 3462, Belzer 1604	Results stratified by duration of warm and cold ischaemia time. Overall, CS Collins showed better 1-year graft survival than either MP group. CS Ringers equivalent to CS Collins with shorter ischaemia times. CS kidneys did better from centres with poor as well as good results. Use of MP post CS to ascertain viability did not increase 1-year survival	Argue that supposed benefits of MP demonstrated not to exist, and that it should be abandoned
van der Vliet[4]	1983	Groningen, The Netherlands (Eurotrans-plant data)	CS vs MP (Gambro, Waters or Belzer)	Not stated	Initial graft function, graft survival up to 2 year	2686 CS 75 MP	No difference in immediate function (51% vs 42%) or 2-year survival (57.3% vs 61.3%) between CS and MP	No data on duration of storage on MP
Rosenthal[47]	1984	Pittsburgh, Pennsylvania, USA	CS (Collins) vs MP (Waters). Mean preservation times 23.8 h, 24 h	Not stated	ATN (= dialysis in first week), 1-year graft survival	113 CS 86 MP	ATN in 11/113 (9.7%) CP, 9/86 (10.4%) MP. 1-year graft survival 68%, 77%. In 26 CP with preservation >24 h (mean 31), ATN in 7.7%. 40 imported kidneys had longer preservation time (mean 30.3 h) and ATN rate of 37%	HBDs only. 136 treated with cyclosporine (distribution not stated). No warm ischaemia

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Sanfilippo[29]	1984	Richmond, Virginia (SEOPF), USA	CS (various) vs MP (various)	Not stated (registry data)	DGF (= dialysis in first week), 1-year graft survival.	730 CS 455 MP (1st tx). 215 CS 96 MP (>1st tx)	First transplants, DGF, 1-year survival: 283/730 (38.8%), 384/730 (52.5%) CS; 136/455 (29.9%), 259/455 (57%) MP. Subsequent transplants: 113/215 (52.6%), 100/215 (46.7%) CS, 37/96 (38.5%), 46/96 (48.2%) MP	Registry data from June 1977 to July 1982. Analysis primarily of effect of DGF on longer term survival. Longer term survival data presented, but no denominators included
Spees[30]	1984	Richmond, Virginia (SEOPF), USA	CS (various) vs MP (various) vs CS + MP	Not stated (registry data)	DGF (= dialysis in first week), 1- and 3-year graft survival	3811 total	DGF, 1- and 3-year survival: 40.9%, 51%, 42% in CS, 35.6%, 55%, 38% in CS + MP, 28.0%, 55%, 44% in MP. Statistically significant difference in DGF ($p < 0.001$, not for graft survival)	Essentially the same database as used in Sanfilippo[29]
van der Vliet[31]	1984	Maastricht, (Eurotrans-plant), The Netherlands	CS (various) mean ischaemic time 23 h vs MP (various) mean ischaemic time 30 h	Not stated (registry data)	Immediate graft function (life sustaining, delayed, never), mean duration of HD, creatinine clearance, actuarial graft survival	2686 CS 75 MP	No statistically significant difference in graft survival or immediate graft function	First transplants only
Mittal[23,24]	1985	Michigan, USA	CS (predominantly Euro-Collins) vs MP (predominantly Waters)	Non-randomised. MP chosen when tissue typing not done at time of harvest, or with marginal donors	Immediate and 30-day function	164 CS 211 MP 206 pre-cyclo-sporine, 169 with cyclo-sporine	Results stratified into pre- and with cyclosporine. Immediate function worse in CS than MP overall 56% vs 45%, in cyclosporine patients 53% vs 75%, but no different in pre-cyclosporine patients 38% vs 43%. 30-day function no different between CS and MP overall 68% vs 75%, pre-cyclosporine 60% vs 69%, but was worse in cyclosporine-treated patients 68% vs 83% ($p < 0.025$)	Discrepancies between data in text and figure. Authors conclude that pre-cyclosporine results were equivalent despite more marginal kidneys in MP group. With cyclosporine, MP significantly better

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Manis[114]	1985	New York, USA	CS (Collins) vs MP (Waters)	Not stated (non-randomised)	Oliguria (not defined)	36 CS 50 MP 33 azathioprine treated, 53 cyclosporine treated	Azathioprine treated: oliguria in 10/16 (63%) CS, 4/17 (24%) MP. Cyclosporine treated: oliguria in 11/20 (55%) CS, 5/33 (15%) MP. Overall: oliguria in 21/36 (58%) CS, 9/50 (18%) MP. Oliguric kidneys had longer storage times	
Nghiem[115]	1986	Iowa, USA	CS (Collins) vs MP (Waters). All preserved >40 h (mean 44 37, 44.17 h)	Not stated	ATN (= dialysis in first week), creatinine levels, graft survival at 1, 3, 12 months	8 CS 41 PP	ATN higher, but graft survival equivalent, in CS vs MP. ATN, 1-, 3-, 12-month survival: 87.5, 75, 75, 62% CS vs 19.5, 92, 85, 68% MP.	No patients received cyclosporine. Authors comment that rejection more difficult to diagnose if ATN present, so advocate use of MP
Abouna[116]	1987	Kuwait	CS (Euro-Collins) vs MP. Cold ischaemia time 30–76 h	Not stated (not-randomised)	Primary non-function, post-transplant dialysis, 1-month and 2-year graft survival	47 CS 14 MP	Need for post-transplant dialysis greater ($p < 0.05$) in CS than MP, but other parameters not significantly different. DRF, PTD, 1-month and 2-year survival: 6, 51, 86, 64% in CS, 7, 74, 78, 60% in MP. Difference in need for PTD greater in kidneys with cold ischaemia >50 h (but graft survival still the same between preservation methods)	Often poor-quality kidneys. Not clear if MP was continued for the whole time in kidneys allocated to this group. Mean cold ischaemia longer in CS than MP

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Barber[117]	1988	Birmingham, Alabama, USA	CS (Euro-Collins) (immediate CyA) mean ischaemic time 16.25 h vs MP (Waters). MP group divided into immediate CyA (ischaemic time mean 26.7 h) and delayed CyA with ALG (ischaemic time mean 28.3 h)	Historical: 1986 CS, 1987 MP	Delayed renal function (dialysis in first week)	83 CS 51 MP + immediate CyA 87 MP + delayed CyA	DGF in 30/83 (36.1%) CS, 8/51 (15.6%) MP + immediate CyA, 5/87 (5.7%) MP + delayed CyA.	
Barber[117]	1990	Birmingham, Alabama, USA	CS (Euro-Collins) mean preservation 18 h vs MP mean preservation 27 h	Not stated	Early renal dysfunction (= dialysis in first week)	302 CS 176 MP	Early renal dysfunction significantly lower in MP (15%) than CS (28%) ($p < 0.002$). 1-year survival 186/274 (67.9%) in CS, 94/128 (73.4%) in MP. By multivariate analysis, preservation time an independent risk factor for graft loss in CS, not MP. Early renal dysfunction associated with lower rate of function at 1 year in MP, not CS	Authors argue that higher early renal dysfunction rate in CS obscures the influence of early rejection. These are manifest in MP group, and can be treated accordingly. Overall 1-year survival rates of CS and MP not given in paper – divided into ATN and no ATN groups

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Johnson[78]	1990	Milwaukee, Wisconsin, USA	CS (Collins or UW) vs MP (Waters)	Not stated	'Immediate function' = 20% fall in creatinine within 24 h Delayed function = not immediate. ATN = required dialysis. Patient and graft survival, no. of rejection episodes, creatinine levels, hospital stay and costs	18 CS 82 MP	Immediate function rate higher in MP than CS, but no difference in ATN (dialysis) rates. Immediate function, ATN rates 3/18 (17%), 3/18 (17%) CS, 46/82 (56%), 5/82 (6%) MP. Average hospitalisation costs US$19,872 for CS, US$15,741 for MP (p = 0.06).	Concurrent RCT of ALG vs CyA as initial treatment in MP kidneys. Numbers of kidneys rejected from MP not stated
Barber[118]	1991	Birmingham, Alabama, USA	CS (Euro-Collins) mean preservation 16 h vs MP (Waters) with Belzers gluconate – albumin solution mean preservation 27 h vs MP with UW solution (mean preservation 29 h)	Not stated	ATN (=dialysis in first week), immediate function (=diuresis and falling creatinine)	346 CS 290 MP(B) 188 MP(UW)	ATN, immediate function in 100/346 (29%), 304/346 (88%) CS, cf 79/478 (17%), 437/498 (91.4%) MP groups combined.	Majority received cyclosporine. Authors state that machine perfusion is 'highly worthwhile'

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Kumar[18]	1991	Kuwait	CS (Euro-Collins) mean preservation 57 h vs CS (UW) mean preservation 59 h vs MP mean preservation 54 h	Historical: to 1984 MP, from 1985 CS	Primary non-function, delayed function, function at 1 month, graft survival at 1 and 3 year	35 CS (EC) 21 CS (UW) 11 MP	PNF, DF, F1M, 1-, 3-year survival: 8/56 (14%), 48/56 (86%) 45/56 (80%), 72%, 53% in CS combined; 1/11 (9%), 2/11 (18%), 10/11 (91%), 55%, 42% in MP. Delayed function significantly more common in CS kidneys ($p = 0.01$), but no difference in graft survival	All preserved >48 h, all HBD imported from Europe or USA after rejection by local centres. Numbers in longer term follow-up not stated
Zhou[119]	1992	UNOS registry	CS vs MP	Not stated	1-day urine production, dialysis in first week, kidney function at discharge	1482 CS 2332 MP	1-day urine, dialysis in first week, functioning at discharge: 1397/1482 (94.3%), 267/1482 (18.0%), 1332/1482 (93.6%) in CS, 2201/2332 (94.4%), 289/2332 (12.4%), 2139/2332 (94.8%) in MS. Centres with higher volumes had higher rates of immediate function, lower rates of dialysis and higher rates of function at discharge	Data presented only from centres with >50 MP cases
Koyama[120]	1993	UNOS data 1987–91	CS vs MP	Not stated	Function at 1 week, 3 months and 1-year graft survival	19,804 CS 3118 MP	Good function at 1 week, 3 months and 1 year graft survival: 13,598/19,804 (73%), 86.2%, 79.6% in CS: 2463/3118 (84%), 86.7%, 80.0% in MP. Function at 1 week significantly better in MP than CS ($p < 0.01$). 1-year graft survival 20% greater where 1-week function good cf. poor, irrespective of preservation method. Increasing cold ischaemia associated with increased DGF, for both CS and MP, but minimal effect on overall graft survival. If analysis restricted to data from those centres with >50 MP kidneys: 1626/2117 (80%), 87.6%, 81.3% in CS: 1992/2404 (88%), 87.1%, 80.3% in MP	Same data as in Zhou.[115] 'Cyclosporine era', first transplants only. Paper also reports UCLA international registry data comparing preservation solutions. Although MP associated with significantly better 1-week function, and better 1-week function associated with better survival at 1 year, MP does **not** lead to improved graft survival at 1 year!

continued

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Veller[13]	1993	Johannesburg, South Africa.	CS (UW) vs MP (Waters)	Non-donor matched, non-random		62 CS 57 MP	ATN in 34/62 (55%) in CS, 21/57 (37%) in MP	Includes kidneys in the matched pairs study
Light[25,26]	1995, 1996	Washington DC, USA	CS (UW) mean preservation 21.4 h vs MP (Waters) mean preservation 26.2 h	'Ideal donors' had CS, 'marginal donors' had MP	Immediate function rate, days in hospital, hospital charges, rejection episodes	39 CS 35 MP	Immediate function, days in hospital, rejection episodes in first 6 months: 28/39 (71.8%), 16 days, 31 episodes in CS, 27/30 (90%) 8.6 days, 13 episodes in MP. If all MP kidneys analysed on intention to treat, IF rate would be 27/35 (77%). 2 CS kidneys lost to rejection in first 6 months, no MP kidneys. Net savings with MP 'exceeded US$20,000 per case'	Two MP kidneys not transplanted 'due to poor preservation parameters', three others excluded because of haemorrhage and cortical necrosis. All MP kidneys were from NHBD
Peters[32]	1995	SEOPF USA	CS vs MP vs CS + MP	Not stated. Registry data from 1982 to 1991	Multivariate analysis of graft survival	17,937 total	Overall preservation method not a significant predictor of graft survival. However subgroup analysis of data from 1990–1 (4137 kidneys) showed CS + MP to be significantly ($p = 0.0023$) associated with adverse outcome (risk ratio 1.33)	
Daemen[19]	1996	Maastricht, The Netherlands	CS (Euro-Collins or UW) mean preservation time 31.5 h, vs MP (Gambro-PF3B) mean preservation time 30.2 h	Historical: 1980–92 CS, 1993–4 MP	Immediate function, serum creatinine at 1, 3 months	57 CS 22 MP	No significant difference in outcomes. Immediate function, duration of delayed function, no. of dialyses, creatinine at 1, 3 months: 15/57 (26%), 17.2 days, 6.0, 338, 194 μmol in CS, 8/22 (36%), 19 days, 5.5, 325, 265 μmol in MP	All NHBD. Some (numbers not stated) kidneys on MP discarded. Higher proportion of MP kidneys treated with cyclosporine (82% vs 38%) – may have reduced early graft function

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Burdick[91]	1997	Baltimore, Maryland, USA, and UNOS	CS vs MP kidneys in multivariate logistic regression of UNOS data	Not stated	First week dialysis	60,827 kidneys in analysis	In multivariate logistic regression analysis, OR of first week dialysis was 2.13 for CS vs MP kidneys ($p < 0.0001$)	Puts forward an argument that MP in marginal kidneys is justified because of the reduced DGF
Daemen[121,122]	1997	Maastricht, The Netherlands	CS (UW) HBD vs MP (Gambro PF-3B with UW) NHBD	CS HBD 'controls' matched for a variety of characteristics to MP NHBD	Immediate function, creatinine at 1, 3, 6 months	74 CS 37 MP	Immediate function, duration of delayed function, no. of dialyses, creatinine at 1, 3, 6 months: 44/74 (59%), 14 days, 5, 185, 152, 152 μmol in CS-HBD; 12/34 (32%), 18 days, 6, 292, 217, 196 μmol in MP-NHBD	Presumably has some overlap with Daemen[19]
Sellers[27]	2000	Birmingham, Alabama, USA	CS (UW) mean ischaemic time 25 h vs CS/MP (if CS >5 h prior to MP) vs MP (if CS <5 h) mean ischaemic time 24 h	'Preferentially' use of MP, CS used occasionally 'primarily because of anatomic limitations'.	Delayed graft function (= dialysis in first week), patients with acute rejections, 6-month and overall graft survival time (by Kaplan–Meier plot)	268 CS 149 CS/MP 568 MP	DGF, acute rejection, 6-month survival: 20.2, 54 , 86% in CS, 8.8, 50, 86% in MP (DGF significantly less in MP, $p = 0.001$). Overall graft survival no different between groups. Increased warm ischaemic time associated with significantly worse graft survival ($p = 0.0004$) in CS, but not in MP kidneys	First transplants only. Induction with either Minnesota ALG or OKT3, then triple therapy including cyclosporine
Polyak[123]	2000	New York, USA	CS (UW) with phentolamine/ hydralazine/no pharmacological intervention vs MP (Waters with Belzer MPS perfusate) phentolamine/ hydralazine/no pharmacological intervention	Not stated	Delayed graft function (= dialysis in first week)	20 CS + PM 20 CS + H 20 CS 30 MP + PM 30 MP + H 30 MP	DGF rates 25, 35, 35, 10, 16.7, 16.7% ($p = 0.04$ for MP + PM vs all other groups)	Primarily a study of the effect of phentolamine mesylate

continued

Author	Year	Centre	Comparison	Basis of allocation	Outcomes reported	Numbers (kidneys)	Results	Comments
Polyak[28]	2000	New York, USA		Kidneys preserved by MP unless they had compromised vasculature or were part of combined transplant	DGF (=dialysis in first week), 1 year survival	248 CS 402 MP	DGF lower, 1-year survival higher in MP vs CS. 72/248 (29.0%), 166/192 (86.5%) in CS, 44/402 (10.9%), 309/335 (92.2%) in MP	Note CS and MP groups cannot be considered similar owing to selection protocol
Balupuri[20]	2000	Newcastle, UK	CS (phase I, 'relatively controlled cases', phase II extended recruitment to A&E Dept) vs MP	Historical: MP introduced in Aug. 1998	'Success rates' ('alive and free of dialysis' – time from tx not stated)	21 CS phase I 11 CS phase II 15 MP	Success rates: 19/21 (90.5%) CS phase I, 5/11 (45.5%) CS phase II, 12/20 (60%) in MP	All NHBD. Viability of kidneys assessed using resistance and GST analysis, and on this basis, 5 kidneys on MP not transplanted. Authors exclude these, and two patients who died, from analysis and claim a success of 12/13 (92.3%)

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Kent Woods,
Director, NHS HTA Programme & Professor of Therapeutics, University of Leicester

Professor Bruce Campbell, Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor Shah Ebrahim, Professor in Epidemiology of Ageing, University of Bristol

Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Radcliffe Hospital, Oxford

Dr Ron Zimmern, Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Kent Woods, Director, NHS HTA Programme, Department of Medicine and Therapeutics, Leicester Royal Infirmary, Robert Kilpatrick Clinical Sciences Building, Leicester

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of Ageing, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care Psychology, Academic Unit of Psychiatry and Behavioural Sciences, University of Leeds School of Medicine, Leeds

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, Oxford University, Institute of Health Sciences, Cancer Research UK Medical Statistics Group, Headington, Oxford

Professor John Bond, Professor of Health Services Research, Centre for Health Services Research, University of Newcastle, School of Health Sciences, Newcastle upon Tyne

Professor John Brazier, Director of Health Economics, Sheffield Health Economics Group, School of Health & Related Research, University of Sheffield, ScHARR Regent Court, Sheffield

Dr Andrew Briggs, Public Health Career Scientist, Health Economics Research Centre, University of Oxford, Institute of Health Sciences, Oxford

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Cloudside, Rossendale, Lancs
and
Principal Research Fellow, Clinical Therapeutics in the School of Pharmacy, Bradford University, Bradford

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, Department of Health Sciences, University of York, Research Section, Seebohm Rowntree Building, Heslington, York

Dr Andrew Farmer, Senior Lecturer in General Practice, Department of Primary Health Care, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor Fiona J Gilbert, Professor of Radiology, Department of Radiology, University of Aberdeen, Lilian Sutton Building, Foresterhill, Aberdeen

Professor Adrian Grant, Director, Health Services Research Unit, University of Aberdeen, Drew Kay Wing, Polwarth Building, Foresterhill, Aberdeen

Professor Alastair Gray, Director, Health Economics Research Centre, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor Mark Haggard, Director, MRC ESS Team, CBU Elsworth House, Addenbrooke's Hospital, Cambridge

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham, Primary Care and Clinical Sciences Building, Edgbaston, Birmingham

Professor Peter Jones, Head of Department, University Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge

Professor Sallie Lamb, Research Professor in Physiotherapy/Co-Director, Interdisciplinary Research Centre in Health, Coventry University, Coventry

Dr Donna Lamping, Senior Lecturer, Health Services Research Unit, Public Health and Policy, London School of Hygiene and Tropical Medicine, London

Professor David Neal, Professor of Surgical Oncology, Oncology Centre, Addenbrooke's Hospital, Cambridge

Professor Tim Peters, Professor of Primary Care Health Services Research, Division of Primary Health Care, University of Bristol, Cotham House, Cotham Hill, Bristol

Professor Ian Roberts, Professor of Epidemiology & Public Health, Intervention Research Unit, London School of Hygiene and Tropical Medicine, London

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital NHS Trust, Bramwell Dott Building, Edinburgh

Professor Martin Severs, Professor in Elderly Health Care, Portsmouth Institute of Medicine, Health & Social Care, St George's Building, Portsmouth

Dr Jonathan Shapiro, Senior Fellow, Health Services Management Centre, Park House, Birmingham

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

© Queen's Printer and Controller of HMSO 2003. All rights reserved.

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Dr Paul Cockcroft, Consultant Medical Microbiologist/ Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Dr Andrew Farmer, Senior Lecturer in General Practice, Institute of Health Sciences, University of Oxford

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Jane Franklyn, Professor of Medicine, University of Birmingham

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust, Devon

Mr Tony Tester, Chief Officer, South Bedfordshire Community Health Council, Luton

Dr Andrew Walker, Senior Lecturer in Health Economics, University of Glasgow

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Iain T Cameron, Professor of Obstetrics & Gynaecology, University of Southampton

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre, Bushey, Herts.

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Professor Alastair Gray, Professor of Health Economics, Institute of Health Sciences, University of Oxford

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Ken Stein, Senior Lecturer in Public Health, University of Exeter

Professor Terence Stephenson, Professor of Child Health, University of Nottingham

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry, London

Professor Dame Jenifer Wilson-Barnett, Head of Florence Nightingale School of Nursing & Midwifery, King's College, London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Professor John Bond, Head of Centre for Health Services Research, University of Newcastle upon Tyne

Mr Michael Clancy, Consultant in A & E Medicine, Southampton General Hospital

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint, West Sussex

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Professor Mark Sculpher, Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Mr Gordon Aylward, Chief Executive, Association of British Health-Care Industries, London

Ms Judith Brodie, Head of Cancer Support Service, Cancer BACUP, London

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury, Bucks

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns, Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Howard Stephen Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum, Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field, Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield, West Sussex

Ms Grace Gibbs, Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs., West Middlesex University Hospital, Isleworth, Middlesex

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs, Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Rajan Madhok, Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant, Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall, General Practitioner, The Hadleigh Practice, Castle Mullen, Dorset

Professor Alistair McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead, Surrey

Dr Andrew Mortimore, Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton, Surrey

Professor Jon Nicholl, Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Chris Price, Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge, Director, College of Health, London

Professor Sarah Stewart-Brown, Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278