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Machine perfusion systems and cold static storage of kidneys from deceased donors

NICE technology appraisal guidance 165 Machine perfusion systems and cold static storage of kidneys from deceased donors

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1 **Guidance**

This technology appraisal covers the available methods of storing kidneys from deceased donors – that is, LifePort kidney transporter, Belzer University of Wisconsin (Belzer UW) storage solution and Marshall's hypertonic citrate solution. No cost data were available to the Committee to allow recommendations to be made for the RM3 renal preservation system.

- 1.1 Machine perfusion using the LifePort kidney transporter and cold static storage using Belzer UW storage solution or Marshall's hypertonic citrate solution are recommended as options for the storage of kidneys from deceased donors.
- 1.2 The choice of storage method should take into account clinical and logistical factors in both the retrieval teams and transplant centres. In situations where different storage methods are considered equally appropriate, then the least costly should be used.

2 **Clinical need and practice**

- 2.1 End-stage renal disease, or established renal failure, is defined as an irreversible decline in kidney function that is severe enough to be fatal without renal replacement therapy. The most common causes of chronic renal damage leading to established renal failure are diabetes mellitus, arteriosclerosis, hypertension, glomerulonephritis and microscopic vasculitis. Acute renal failure from traumatic injury or infection may also lead to established renal failure. In children, it is usually caused by congenital structural abnormalities, but may be genetic or the result of glomerulonephritis.
- 2.2 People with established renal failure can become tired and nauseated and lose their appetite, leading to weight loss. Pruritus may also occur. Signs of established renal failure include fluid

retention, pallor and raised blood pressure, which are accompanied by lowered haemoglobin levels and abnormal levels of biochemical markers. Established renal failure leads to death unless renal replacement therapy is provided, through haemodialysis, peritoneal dialysis or a kidney transplant.

2.3 In the UK in 2005 there were 41,776 adults and 748 children (younger than 18 years) on renal replacement therapy. This is a 28% increase in patient numbers since 2000. In the UK in 2005, the median age at which people started renal replacement therapy was 65 years. Survival in the 1st year after starting renal replacement therapy for all patients regardless of age was 79%. Five-year survival rates varied depending on age. In people aged 18–34 years 58% were alive 5 years after starting renal replacement therapy, and 12% in people aged 75 years or older.

2.4 Kidney transplantation, which involves implanting a kidney from a donor, is the preferred therapeutic option where it is possible. Kidneys for transplantation may come from living donors or deceased organ donors. Deceased organ donors may be certified as dead either by brainstem criteria (deceased heart-beating donors) or after cardiac arrest (non-heart-beating donors). The availability of kidneys from deceased heart-beating donors has decreased by about 20% in the last decade. Kidneys from deceased heart-beating donors are allocated nationally; kidneys from non-heart-beating donors are allocated locally.

2.5 Non-heart-beating donors are categorised according to the Maastricht criteria, and described as controlled (where cardiac death is expected, but the criteria for brainstem death are not fulfilled) or uncontrolled (where cardiac death is unexpected). Kidneys from non-heart-beating donors (particularly those categorised as uncontrolled) may have long periods of warm ischaemic time, that is, the time that the organ spends deprived of oxygen before it is cooled and retrieved. As a result, kidneys from

non-heart-beating donors can have higher rates of delayed graft function (the graft does not function immediately) or primary non-function (the graft never functions) than those from heart-beating donors. Primary non-function and early graft failure are associated with an increased risk of death in the ensuing months. Kidney function is also affected by cold ischaemic time (the duration of storage in cold conditions between retrieval and transplantation), but cooling the organ reduces the metabolic rate and thereby decreases the rate of damage to the organs compared with warm ischaemia.

- 2.6 Kidneys from 'extended criteria' deceased heart-beating donors may also be used to expand the donor pool. These are kidneys from donors who are aged over 60 years, or are over 50 years and have two or more of: a history of hypertension, a history of cerebral vascular accident, or terminal creatinine levels greater than 133 micromoles/litre. Like kidneys from non-heart-beating donors, kidneys from extended criteria donors are also associated with higher rates of delayed graft function and primary non-function than those from non-extended criteria donors.
- 2.7 Successful kidney transplantation removes the need for dialysis, but immunosuppressant drugs are needed permanently to prevent rejection of the graft. Complications of immunosuppression include increased risk of infections and malignancy, especially skin cancer and lymphoproliferative disorders. Nephrotoxicity is a particular complication of some immunosuppressive regimens. Post-transplantation diabetes mellitus is a potentially serious side-effect of treatment. Other treatment side-effects, depending on the drugs used, may include hirsutism, alopecia, tremors, mood swings or gastrointestinal intolerance.
- 2.8 In the UK in 2005, 76% of people accepted for renal replacement therapy started treatment with haemodialysis and 21% started treatment with peritoneal dialysis. Only 3% of patients received a

kidney transplant before they started dialysis. There is increasing demand for kidney transplants; the waiting list has increased by 48% since 1998. Demand for kidneys outstrips supply. In the UK in 2006, 1403 kidneys from deceased donors were transplanted (from 765 deceased kidney donors); 6384 people were awaiting transplantation. Therefore, there is a need to increase kidney donation and to make donated kidneys function in the best possible way.

3 The technologies

3.1 Kidneys need to be preserved before transplantation to allow time to match kidney to recipient, to transport and prepare the recipient and kidney, and to implant the kidney. It is important that the kidney is cooled and prepared as quickly as possible to minimise damage caused by warm ischaemia. There are two established methods of preservation: cold static storage and hypothermic machine perfusion.

Cold static storage solutions

3.2 In cold static storage, the kidney is flushed through with a sterile preservation solution and is kept on ice in a box before transplantation. Two preservation solutions are widely used in the NHS for cold storage: Marshall's hypertonic citrate (Soltran, Baxter Healthcare) and Belzer UW (Viaspan, Bristol Myers Squibb).

3.3 Marshall's hypertonic citrate solution has a marketing authorisation for use in the preservation of human kidneys before transplantation. The summary of product characteristics (SPC) states that approximately 2–3 litres of solution should be delivered to each kidney and lists no adverse events or contraindications. The cost of 1 litre of Marshall's hypertonic citrate solution is £9.60 (obtained from the Baxter Healthcare e-catalogue, 20 October 2008). It is sold in packs of ten 1-litre bags. Costs may vary in different settings because of negotiated procurement discounts.

- 3.4 Belzer UW storage solution is not classified as a device or a medicine. The manufacturer was advised by the Medicines and Healthcare Products Regulatory Agency that it is therefore not covered by relevant legislation and does not require a marketing authorisation or CE mark. The solution does have a marketing authorisation in some European Union countries and is indicated for the preservation of kidney, liver and pancreas. It is not recommended for continuous machine perfusion. The cost of 1 litre of Belzer UW storage solution is £116 (obtained from the manufacturer, 23 April 2008). It is sold in packs of six 1-litre bags. Costs may vary in different settings because of negotiated procurement discounts.
- 3.5 The submission from the British Transplantation Society indicates that in the UK from 2000 to 2007 about 74% of kidneys from deceased donors were stored with Marshall's hypertonic citrate solution and most of the remainder (23%) with Belzer UW storage solution. For the subset of kidneys from non-heart-beating donors, 42% were stored using Belzer UW storage solution and 48% with Marshall's hypertonic citrate solution.

Machine perfusion systems

- 3.6 Machine perfusion systems continuously pump cold preservation solution through the kidney. The solution provides nutrients and sometimes oxygen, carries away toxic metabolites and reduces build-up of lactic acid. In machine perfusion the kidney is attached to the machine via the renal artery. Further surgical preparation of the kidney is then required to make the seal airtight.
- 3.7 The LifePort kidney transporter (Organ Recovery Systems) is a portable machine perfusion system which can perfuse a single kidney and can run without supervision. The system requires a solution to perfuse the kidney; University of Wisconsin machine preservation solution is sold as KPS-1 by Organ Recovery Systems for use with the LifePort kidney transporter. The LifePort kidney

transporter is CE marked for the continuous hypothermic machine perfusion of kidneys for preservation, transportation and eventual transplantation into a recipient. The cost of the LifePort kidney transporter is £10,700 (obtained from the manufacturer). They are normally purchased in pairs, one for each kidney. Costs may vary in different settings because of negotiated procurement discounts.

- 3.8 The RM3 renal preservation system is a non-portable system that can perfuse two kidneys simultaneously under supervision. It is CE marked for the hypothermic pulsatile perfusion of kidneys. No further information is available.
- 3.9 There are 21 kidney transplant centres in England and Wales, eight of which use LifePort kidney transporters as well as cold static storage. These centres have non-heart-beating donor programmes. The RM3 system is not used in any centres in the UK. The submission from the British Transplantation Society indicates that in the UK from 2000 to 2007 about 2% of kidneys from deceased donors were stored using machine perfusion (excluding cases where method of storage was not reported). For the subset of kidneys from non-heart-beating donors this increased to 20% (excluding cases where method of storage was not reported). However, the data for the subset may not be accurate because only 50% of records for kidneys from non-heart-beating donors included information on how the kidney was stored.
- 3.10 Transplant arrangements limit the use of machine perfusion. Perfusion systems are the property of individual NHS trusts and have to be returned to the transplant centre that owns the machine. This means that they tend to be used only in the local transplant region, which is not compatible with the national allocation of kidneys from deceased heart-beating donors. Therefore, perfusion systems are used mainly to preserve kidneys from non-heart-beating donors, which are allocated only on a local basis. A recent

report from the Department of Health's Organ Donation Taskforce has indicated that the organisation of transplantation services may become national in the future.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group identified seven studies that compared at least two of: the RM3 renal preservation system, the LifePort kidney transporter, Belzer UW storage solution and Marshall's hypertonic citrate solution. Two of these studies, which were both retrospective record reviews, compared the two machines. Three of the studies compared the LifePort kidney transporter with Belzer UW storage solution (two ongoing randomised controlled trials and one retrospective review) and one cohort study compared the LifePort kidney transporter with Marshall's storage solution. One study compared the two different storage solutions. No studies were identified that compared the RM3 renal preservation system with either of the storage solutions.

4.1.2 Two retrospective record reviews (reported as abstracts) compared the two machine preservation systems. One study (744 kidneys transplanted) was a review over a 5-year period that included a change in practice from the use of the RM3 renal preservation system to the LifePort kidney transporter. The kidneys included in this study were from extended criteria deceased heart-beating donors (78%) or non-heart-beating donors (22%). The second study (89 kidneys transplanted) reviewed transplant records over a 22-month period and included kidneys mainly from deceased heart-beating donors (98%). Reporting in both studies was insufficient for a thorough assessment of quality. The relative risks were calculated by the Assessment Group.

- 4.1.3 In the larger study, rates of primary non-function were reported as 3% and 2% in the RM3 and LifePort groups, respectively (relative risk [RR] 1.44; 95% confidence interval [CI] 0.59 to 3.54; $p = 0.42$). Rates of delayed graft function were reported as 24% and 32% in the RM3 and LifePort groups, respectively (RR 0.76; 95% CI 0.62 to 0.94; $p < 0.01$). Patient survival and graft survival were both reported as 97% and 93% in the RM3 and LifePort groups, respectively (RR 1.05; 95% CI 1.01 to 1.08; $p < 0.01$). The smaller study reported graft survival at a different follow-up point. At 30 days this was 97% and 94% in the RM3 and LifePort groups, respectively (RR 0.97; 95% CI 0.89 to 1.06; $p = 0.49$), and at 90 days 97% and 90% (RR 0.93; 95% CI 0.83 to 1.04; $p = 0.21$).
- 4.1.4 Two ongoing randomised controlled trials and one retrospective record review compared Belzer UW storage solution with the LifePort kidney transporter. One study (the Machine Preservation Trial, 672 kidneys transplanted) included mainly kidneys from deceased heart-beating donors but also some from non-heart-beating donors. The other study (the PPART study, 90 kidneys transplanted) included only kidneys from non-heart-beating donors. The primary outcome in both studies was rate of delayed graft function. The retrospective record review (36 kidneys transplanted) included kidneys from non-heart-beating donors. The primary outcome for this study was immediate graft function.
- 4.1.5 The Machine Preservation Trial study reported a small statistically significant benefit in terms of graft survival favouring the use of machine perfusion. Further detailed results of the Machine Preservation Trial study were provided as academic-in-confidence and are not included in this document.
- 4.1.6 The PPART study reported no statistically significant differences between the LifePort kidney transporter and Belzer UW storage solution at 3-month follow-up. Rates of primary non-function were reported as 2% and 0% in the LifePort kidney transporter and

Belzer UW storage solution groups, respectively (RR 3.00; 95% CI 0.13 to 71.74; $p =$ not reported). Rates of delayed graft function were reported as 58% and 56% in the LifePort kidney transporter and Belzer UW storage solution groups, respectively (RR 1.04; 95% CI 0.73 to 1.49; $p = 0.99$). Patient survival was reported as 98% and 100% in the LifePort kidney transporter and Belzer UW storage solution groups, respectively (RR 0.98; 95% CI 0.92 to 1.04; $p = 0.32$). Rates of graft survival were reported as 96% and 100% in the LifePort kidney transporter and Belzer UW storage solution groups, respectively (RR 0.96; 95% CI 0.89 to 1.03; $p = 0.16$).

- 4.1.7 The retrospective record review reported statistically significant results favouring the use of the LifePort kidney transporter compared with Belzer UW storage solution. Delayed graft function was reported as 28% and 89% in the LifePort kidney transporter and Belzer UW storage solution groups, respectively (RR 0.31; 95% CI 0.15 to 0.67; $p < 0.001$).
- 4.1.8 One sequential cohort study (60 kidneys transplanted) compared Marshall's hypertonic citrate solution with the LifePort kidney transporter. This study included kidneys from non-heart-beating donors, where death was controlled. For the first 2 years of the study all kidneys were stored using the solution, after this point they were stored using the perfusion machine. The significance tests reported were calculated by the Assessment Group.
- 4.1.9 This study reported that no kidneys suffered from primary non-function. Rates of delayed graft function were reported as 53% and 87% in the LifePort kidney transporter and Marshall's hypertonic citrate solution groups, respectively (RR 0.64; 95% CI 0.43 to 0.93; $p = 0.012$). The rates of patient survival and graft survival were reported as the same. After 1 year of follow-up survival rates were reported as 100% and 93% in the LifePort kidney transporter and Marshall's hypertonic citrate solution groups, respectively (RR 1.07;

95% CI 0.96 to 1.20; $p = 0.24$); 2-year survival rates were 97% and 90%, respectively (RR 1.07; 95% CI 0.94 to 1.23; $p = 0.30$).

- 4.1.10 One retrospective record review (58,607 kidneys transplanted) of kidneys from deceased donors included in the Collaborative Transplant Study database included data for kidneys stored using either Belzer UW storage solution (53,560 kidneys) or Marshall's hypertonic citrate solution (5047 kidneys). This study specifically considered differences in graft survival of kidneys that had undergone different durations of cold ischaemia.
- 4.1.11 The Assessment Group's analysis of the data from the study suggests no statistically significant differences between the two solutions. The 3-year graft survival rates in kidneys that had had up to 18 hours of cold ischaemic time were 81% and 80% in the Belzer UW storage solution and Marshall's storage solution groups, respectively (RR 1.02; 95% CI 0.99 to 1.04; $p=0.13$). The 3-year graft survival rates in kidneys that had had more than 36 hours of cold ischaemic time were 75% and 73% in the Belzer UW storage solution and Marshall's storage solution groups, respectively (RR 1.03; 95% CI 0.96 to 1.11; $p = 0.45$). Comparing different durations of cold ischaemic time, the study suggests that the incidence of graft failure increases as cold ischaemic time increases.

4.2 Cost effectiveness

- 4.2.1 The manufacturers of the technologies did not submit economic analyses. The Assessment Group identified two published economic analyses, one from the UK and another from Canada, both using a healthcare system perspective. The UK study reported cost per quality-adjusted life year (QALY), while the Canadian study reported cost per delayed-graft-function event avoided. Both studies reported that machine perfusion was associated with lower costs and greater benefits than cold static storage. Both economic

analyses were completed before the most recent data from the PPART and Machine Preservation Trial studies became available.

- 4.2.2 The Assessment Group developed an economic model that made three comparisons. First, LifePort machine perfusion was compared with Belzer UW storage solution. This comparison was completed in two different populations: kidneys from non-heart-beating donors using data from the PPART study and kidneys mainly from deceased heart-beating donors using data from the Machine Preservation Trial study. Second, LifePort machine perfusion was compared with Marshall's hypertonic citrate solution using data from a cohort study. Third, Belzer UW storage solution was compared with Marshall's hypertonic citrate using data from a retrospective record review.
- 4.2.3 The Assessment Group was unable to do any cost-effectiveness analyses that included the RM3 machine perfusion system because cost data, although requested, were not made available.
- 4.2.4 The model was a Markov state transition model that included the health states immediate graft function, delayed graft function, transplant failure, explantation and a return to dialysis, and subsequent transplantation. The characteristics of the cohort modelled were chosen to be consistent with data obtained from UK Transplant and The Renal Registry. The cohort was followed up until almost all patients (97%) had died. The Assessment Group developed a standard data set for use in the model which was modified to reflect the comparisons described above.
- 4.2.5 Cost data for machine perfusion were annualised and it was assumed that perfusion machines were used for 10 years with no resale value afterwards. The estimated number of kidneys stored by each machine per year was calculated based on the total number of transplantations per year divided by the number of transplant centres. This estimate was 61 kidneys per year for

analyses using data from the Machine Preservation Trial and 16 kidneys per year for analyses using data from the PPART study. The costs for machine perfusion also included an annual maintenance contract and the costs of the perfusion kit and solution used in the machine. This resulted in a cost per kidney stored of £544 for the analyses using data from Machine Preservation Trial and £737 for the analyses using data from PPART. The costs of storing a kidney using cold static storage included the costs of the solution and the box required to store the kidney. This was calculated to be £262.53 per kidney with Belzer UW storage solution and £49.73 per kidney with Marshall's solution.

- 4.2.6 Utility data were derived from published literature. The utility of living with a transplanted kidney varied according to age and was 0.83 for people aged 18–34 years, decreasing to 0.66 for people aged 65 years and older. The reduction in utility of living with dialysis was 0.12. Therefore, a person aged 18–34 years on dialysis had a utility of 0.71 and a person aged 65 years and older had a utility of 0.54. Renal registry data were used to model patient survival on dialysis and with a transplant; this rate was also varied according to age.
- 4.2.7 Data from the PPART study were used to model the cost effectiveness of LifePort compared with Belzer UW storage solution for the preservation of kidneys from non-heart-beating donors. The results of the deterministic analyses suggested that the LifePort kidney transporter was associated with greater cost than Belzer UW storage solution (£141,319 versus £139,205) and fewer QALYs (9.13 versus 9.19). Probabilistic sensitivity analyses predicted that over a range of willingness-to-pay levels (£0–£100,000) the probability of LifePort being cost effective was about 40%.
- 4.2.8 Data from the Machine Preservation Trial study were used to model the cost effectiveness of LifePort compared with Belzer UW storage solution for the preservation of kidneys mainly from deceased

heart-beating donors. The results of the deterministic analyses suggested that Belzer UW storage solution was associated with greater cost than the LifePort kidney transporter (£142,805 versus £139,100) and fewer QALYs (9.58 versus 9.79). Probabilistic sensitivity analyses predicted that over a range of willingness-to-pay levels (£0–£100,000) the probability of LifePort being cost effective was 80%.

- 4.2.9 Data from the cohort study (described in section 4.1.8) were used to model the cost effectiveness of LifePort compared with Marshall's hypertonic citrate for the preservation of kidneys from controlled non-heart-beating donors. The results of the deterministic analyses suggested that Marshall's hypertonic citrate solution was associated with greater cost than the LifePort kidney transporter (£144,332 versus £132,953) and fewer QALYs (8.55 versus 9.54). Probabilistic sensitivity analyses predicted that over a range of willingness-to-pay levels (£0–£100,000) the probability of LifePort being cost effective was 95%.
- 4.2.10 Data from the retrospective record review (described in section 4.1.10) were used to model the cost effectiveness of Marshall's hypertonic citrate compared with Belzer UW storage solution for the preservation of kidneys from deceased donors. This study analysed kidneys by duration of cold ischaemia. The cost-effectiveness analyses were based on kidneys that had 19–24 hours of cold ischaemic time. For these kidneys graft survival at 3 years was reported as 79.5% and 77.7% in the Belzer UW storage solution and Marshall's hypertonic citrate solution groups, respectively. The results of the deterministic analyses suggested that Marshall's hypertonic citrate solution was associated with greater cost than Belzer UW storage solution (£151,826 versus £151,001) and fewer QALYs (8.57 versus 8.62). Probabilistic sensitivity analyses predicted that over a range of

willingness-to-pay levels (£0–£100,000) the probability of Marshall's storage solution being cost effective was 40%.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of machine perfusion systems and cold static storage of donated kidneys, having considered evidence on the nature of the condition and the value placed on the benefits of improvements in access to viable kidneys for transplantation by people with established renal failure, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.3.2 The Committee considered the process of retrieving donated organs and the methods for their storage. The Committee was aware that it was important to minimise the length of ischaemic time regardless of the storage method used, in order to reduce the detrimental impact of ischaemia on the donated kidney. It also recognised that kidneys could be obtained from different types of donors and that type of donor is associated with differences in rates of delayed graft function and overall graft survival. The Committee understood that minimising primary non-function and early and late graft loss was important. Unsuccessful transplantation has a significant physical and psychological effect on the recipient of the kidney and could reduce the chance of successful reimplant because of exposure to antigens. The Committee understood that kidneys from brainstem-dead (that is, deceased heart-beating) donors are allocated nationally and that kidneys from non-heart-beating donors are allocated locally. However, it was aware that transplant services may be reorganised as a result of recent recommendations to the government from the Organ Donation Taskforce. The Committee concluded that kidneys from different types of donor needed to be considered separately and that the

mechanism for allocating kidneys could influence the choice of storage method.

4.3.3 The Committee considered the different machine perfusion systems. It was aware that the RM3 is not portable and therefore does not replace cold static storage if transportation is needed. The Committee noted that although clinical effectiveness evidence comparing the RM3 with the LifePort kidney transporter was available, it had methodological limitations because it was based on retrospective record reviews rather than prospective studies. The Committee recognised that the Assessment Group had been unable to complete any cost-effectiveness analyses that included the RM3 because no cost data were made available by the manufacturer. The Committee concluded that it could only issue recommendations for storage methods whose cost is known.

4.3.4 The Committee specifically considered the use of machine perfusion to assess the viability of kidneys before implant. The Committee heard from clinical specialists that there was no clear experimental evidence to support testing the viability of the kidney using the machine, but that they considered viability testing to be potentially important. The Committee heard that clinical experience of machine perfusion systems, and knowledge of kidney function after transplantation, may enable clinicians to identify factors associated with poor viability. The Committee was aware that a retrospective analysis had been proposed as part of the Machine Preservation Trial study but had not yet been completed. The Committee concluded that although viability testing is potentially important, currently there is insufficient evidence to make this a deciding factor in choice of storage methods.

4.3.5 The Committee considered the differences in clinical effectiveness between the two cold static storage solutions. The Committee noted that the analysis by the Assessment Group suggested no statistically significant differences between the two solutions. The

Committee noted that Marshall's hypertonic citrate solution is used to store kidneys in a large proportion of centres, although choice of solution may depend on several factors. The Committee heard from clinical specialists that there are differences in viscosity between Marshall's hypertonic citrate solution and Belzer UW storage solution, which affected the choice of solution in some cases. The Committee additionally heard that for multiorgan donation that included the pancreas, Marshall's hypertonic citrate solution was not considered suitable for cooling of the organs in situ. The Committee also heard that where a longer cold ischaemic time is anticipated, clinicians consider Belzer UW storage solution to be more suitable than Marshall's hypertonic citrate solution. However, cold ischaemic times greater than 24 hours are generally avoided in the UK, unless an organ is reallocated, or national allocation means that the kidney has a long transport time. These factors are, however, difficult to predict beforehand. The Committee concluded that the clinical effectiveness evidence did not support a general preference for one storage solution over another but that both these clinical and logistical considerations need to be taken into account when choosing between storage solutions.

- 4.3.6 The Committee considered the clinical effectiveness evidence for the use of the LifePort kidney transporter for the storage of kidneys from deceased heart-beating donors. In considering the clinical effectiveness evidence, the Committee was mindful of comments from a consultee about the additional time required to attach the donated kidney to the LifePort kidney transporter, and the impact that this may have on the retrieval process for the kidneys and other organs. The Committee noted the results of the Machine Preservation Trial study. The Committee was aware that this study included mainly kidneys from deceased heart-beating donors, which does not reflect the type of kidneys for which the machines are usually used in the NHS. The Committee considered that this study suggested a small statistically significant benefit in terms of

graft survival favouring the use of machine perfusion. The Committee heard from clinical specialists that these small benefits in rates of graft survival are important, but that factors such as discard rates before implant are also important. The Committee heard clinical specialists express concern about the exclusion of a large number of kidneys from the statistical analysis in the Machine Preservation Trial study, and the effect that these exclusions may have had on results. The Committee also heard from clinical specialists that the potential advantages of machine perfusion are not necessarily considered greater for the storage of kidneys from deceased heart-beating donors because success rates with cold storage solutions are already high. The Committee concluded that machine perfusion may be marginally more clinically effective than Belzer UW storage solution for the storage of kidneys from deceased heart-beating donors. However, it was mindful of possible clinical considerations for choosing between machine perfusion and cold static storage and also the clinical specialists' comments that further evidence was required before the benefits of the LifePort kidney transporter over cold static storage can be fully demonstrated.

- 4.3.7 The Committee considered the clinical effectiveness evidence for the use of the LifePort kidney transporter for the storage of kidneys from non-heart-beating donors. The Committee noted that the PPART study had shown no statistically significant differences between the LifePort kidney transporter and cold static storage using Belzer UW storage solution. The Committee heard from clinical specialists that the results of the PPART study were not consistent with clinical opinion or practice for storing this type of kidney. The Committee also noted comments from a consultee about possible limitations in the reproducibility of the results of this study. The Committee was mindful of the preliminary nature of the data from the PPART study and considered whether the availability of longer term data would change the conclusions. The Committee

heard from clinical specialists that they did not think that the overall conclusion of the PPART study would change as more data become available. The Committee noted that the Machine Preservation Trial study reported results from a subgroup of kidneys from non-heart-beating donors in whom death was controlled. The Committee recognised that preliminary analyses suggested benefits to delayed graft function, but did not yet suggest differences in primary non-function and graft survival. The Committee was also aware that a cohort study had compared the LifePort kidney transporter and Marshall's hypertonic citrate solution for the storage of kidneys from non-heart-beating donors where cardiac death had been expected. The Committee noted that this study had shown a statistically significant difference that favoured the LifePort kidney transporter for rate of delayed graft function, but that there were methodological limitations with the design of the study. The Committee concluded that the clinical effectiveness evidence did not allow it to distinguish between the LifePort kidney transporter and cold static storage for the storage of kidneys from non-heart-beating donors.

- 4.3.8 The Committee considered the economic modelling carried out by the Assessment Group and noted the assumptions about the costs of the different storage methods. The Committee heard from clinical specialists that clinicians may use different quantities of the storage solution, varying between 2 and 8 litres per kidney. The Committee noted that the Assessment Group had assumed that two LifePort kidney transporters were required for each transplant centre, but that in clinical practice more machines may be required to ensure that a machine is readily available. The Committee also noted comments from a consultee that in some locations an extra person was employed to supervise the LifePort kidney transporter, and that consumables would be wasted if kidneys were prepared for machine perfusion and then found not to be suitable. However, the Committee was persuaded that the upfront costs of storage are

much smaller than the costs of dialysis for failed grafts used in the model and that differences in the costs of storage for different methods would have little effect on the results of cost-effectiveness analysis. The Committee concluded that while specific methods of storing kidneys may differ between centres, which would affect the cost of the technologies, this would not change the results of the cost-effectiveness analyses.

- 4.3.9 The Committee considered the cost-effectiveness evidence for the use of the different methods of kidney storage. The Committee understood that the cost-effectiveness results were driven by differences in the rate of graft survival between storage methods, because better graft survival led to fewer people on dialysis, which reduced costs and improved health-related quality of life.
- 4.3.10 The Committee noted that the results of the cost-effectiveness analyses suggested that Marshall's hypertonic citrate solution is associated with greater cost and fewer QALYs than Belzer UW storage solution. However, the Committee noted that the data suggested small differences in clinical effect between the two solutions, which led to small differences in both costs and QALYs. The Committee concluded that no robust differences in clinical effectiveness had been shown. It recommended that the cheapest solution be used if the solutions are otherwise considered equally suitable, bearing in mind the clinical considerations that might affect the choice (described in 4.3.5).
- 4.3.11 The Committee considered the cost-effectiveness evidence for the LifePort kidney transporter compared with cold static storage solutions. The Committee noted that the results of the cost-effectiveness analyses suggested that Belzer UW storage solution was associated with lower costs and more QALYs, when using data from PPART. However, using data from the Machine Preservation Trial study, the LifePort kidney transporter was associated with lower costs and more QALYs. The Committee

noted these results were also based on small differences in costs and QALYs. Taking into consideration the testimony of clinical specialists and the clinical effectiveness evidence, the Committee was not persuaded that the LifePort kidney transporter could be preferentially recommended for the storage of kidneys from deceased donors over other forms of storage. Given that the overall costs and benefits associated with kidney transplantation using either machine perfusion or cold static storage were similar, the Committee recommended that the LifePort kidney transporter be considered as an alternative to cold static storage solutions and that the choice of which to use would depend on clinical and logistical factors within both the retrieval team and transplant centres.

5 Implementation

- 5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance.

The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TA165).

- Audit support for monitoring local practice.
- A costing statement explaining the resource impact of this guidance.

6 Recommendations for further research

6.1 The PPART study is ongoing and the Machine Preservation Trial study is analysing subgroup data of kidneys from non-heart-beating donors and extended criteria donors. Both studies are collecting resource-use data.

6.2 The Committee considered that it was important for transplant centres to collect standardised and comprehensive data that follow up the outcomes for kidneys stored using different methods.

7 Related NICE guidance

There is no related guidance for these technologies.

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in August 2010. This date is to allow completion and follow up of the PPART and Machine Preservation Trial studies and to assess the implication of the implementation of the recommendations in the organ donation taskforce report.

Andrew Dillon
Chief Executive
January 2009

Appendix A: Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett (chair, first Appraisal Committee meeting)

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County Primary Care Trust

Mr Brian Buckley

Chairman, Incontact

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Mr David Chandler

Lay member

Mr Peter Clarke

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R&D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic Ltd

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, the University of Nottingham

Dr Dyfrig Hughes

Reader in Pharmacoeconomics, Centre for Economics and Policy in Health, Bangor University

Dr Peter Jackson

Consultant Physician, Royal Hallamshire Hospital

Dr Damien Longson

Consultant in Liaison Psychiatry, North Manchester General Hospital

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Katherine Payne

Health Economics Research Fellow, The University of Manchester

Dr Danielle Preedy

Lay member

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag Ltd

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens (chair, second Appraisal Committee meeting)

Professor of Public Health, Department of Public Health and Epidemiology,
University of Birmingham

Dr Cathryn Thomas

Associate Professor and General Practitioner, Department of Primary Care &
General Practice, University of Birmingham

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Zoe Garrett

Technical Lead

Janet Robertson

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group, University of Exeter.

- Bond M et al. The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors, June 2008.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Bristol-Myers Squibb (viaspan, kidney perfusion solution)
- Organ Recovery Systems (LifePort Kidney Transporter)

II Professional/specialist and patient/carer groups:

- BODY – British Organ Donor Society
- British Renal Society
- British Transplantation Society
- Renal Association
- Royal College of Nursing
- Transplants in Mind

III Other consultees

- Department of Health
- Shropshire County PCT
- Welsh Assembly Government

IV Commentator organisations (did not provide written evidence and without the right of appeal)

- AQIX Limited
- Kidney Research UK
- Department of Health, Social Services and Public Safety for Northern Ireland

- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Peninsula Technology Assessment Group, University of Exeter
- UK Transplant

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on machine perfusion and cold storage of kidneys by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Miss Laura J Buist, Director of Renal Transplantation nominated by National Health Service Quality Improvement Scotland – clinical specialist
- Mr Neville Jamieson, Consultant Surgeon and Associate Lecturer nominated by British Transplantation Society – clinical specialist
- Mr Tom Fearon, Chairman of and nominated by the British Organ Donor Society – patient expert
- Mr Ken Tupling, nominated by British Organ Donor Society – patient expert