

National Institute for Health and Clinical Excellence

Comment 1: the draft remit

Section	Consultees	Comments	Action
Wording	Newcastle upon Tyne NHS Hospitals Trust	There are two questions whether machine perfusion versus cold static storage has benefit in heart beating donor kidneys and non heartbeating donor kidneys.	It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors
	Organ recovery systems	The remit should be expanded to include donated kidneys from all cadaveric donors. The outcome measures and comparison technologies would be the same.	It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors
	UK transplant	Yes	Comment noted. No action required.
	British transplant society	No: the remit should consider extended criteria donors, not simply non-heart beating donors	It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors. Extended criteria donors have been identified as an additional subgroup of HB donors that should be considered in the appraisal.
	UK transplant (2)	There is much experimental work on warm machine perfusion. Since you are discussing cold machine perfusion I would rephrase the remit as: "To appraise the clinical and cost effectiveness of cold machine perfusion versus static cold storage of donated kidneys from non-heart-beating donors."	It was agreed at the scoping workshop that the remit should specify cold machine perfusion. This has been changed in the remit.
Timing Issues	Newcastle upon Tyne NHS Hospitals Trust	This appraisal should have low urgency	It was agreed at the scoping workshop that an appraisal of machine perfusion and cold static storage would provide additional value. However the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.

Summary form

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	UK transplant	There is a joint research study just starting, under the auspices of the British Transplant Society, to address these issues. Appraisal after the research study has been completed would be more logical, but this could be 12-24 months.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	British transplant society	Moderately Urgent	It was agreed at the scoping workshop that an appraisal of machine perfusion and cold static storage would provide additional value. However the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	UK transplant (2)	There is a degree of urgency due to the increased usage of kidneys from non-heart-beating donors. A demonstration of a superior technique would have important ramifications for transplantaion in the U.K. As I mention later there are two large studies ongoing that will significantly contribute to this appraisal and I believe the appraisal should wait until they report.	It was agreed at the scoping workshop that an appraisal of machine perfusion and cold static storage would provide additional value. However the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
Additional comments on the draft remit	Newcastle upon Tyne NHS Hospitals Trust	Though the case has been made for machine perfusion retrospectively in the US the conclusions are not solid because different perfusates were used - Polyak (Transplantation 2000 69 (2) 249. There are now two multicentre studies underway comparing machine perfusion and static storage (one in Europe and the other in the UK). The NICE appraisal should await the completion of these studies.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	UK transplant	This is an important question but data - particularly from the UK - are very limited. The study mentioned above is the best designed study in the world by far, and without the results from this study any appraisal will be of limited value.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	British transplant society	No	Comment noted. No action required.

Summary form

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	UK transplant (2)	It should be widened to look at the use of machine perfusion in all donor kidneys	It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Newcastle upon Tyne NHS Hospitals Trust	Page 2, 5 th Paragraph. Long term data as exists at present suggests equivalent results between NHBD and HBD - Cho NEJM 1998 338 221, Nicholson Kidney Int 2000 58 2585, Weber NEJM 2002 347, 248, though there are differences in delayed graft function.	This has been amended in the scope.
	Organ recovery systems	Currently, at least nine transplant centers in the UK are using machine preservation for NHBD kidneys.	This has been amended in the scope.
	UK transplant	Good	Commented noted. No action required.
	British transplant society	It is accurate but incomplete. An extensive analysis by Schold et al 2005 showed that machine perfusion increases utilization and decreases DGF in extended-criteria donors (eg long cold ischaemic time) rather than only in NHB donors. This has been confirmed in a recent study by Matsuoka et al 2006.	The remit has been expanded to include heart beating donors and the subgroup of extended criteria donors. A paragraph explaining extended criteria donors has been added to the scope.
	UK transplant (2)	Kidneys from non-heart-beating donors are kept locally to reduce cold ischaemic time and the associated damage. At least 6 centres currently use machine perfusion for some of their kidneys. The centre with its own locally developed system (Newcastle) now uses the Organ Recovery Systems machines.	Comment noted. No action required. This has been amended in the scope.

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The technology/ intervention	Newcastle upon Tyne NHS Hospitals Trust	1 st line - 'through' not thought. Oxygen supply is not considered important though the perfusate can be oxygenated. The organ recovery machine is not equipped with this option. "Removal of metabolic end products" is probably by neutralising acidosis by buffer which seems to be more effective than static storage. Not many units measure glutathione s transferase and those that do, do not test for the isomer as it is expensive only the total 'GST'. The enzymes are not used as a predictor of quality renal function only as to whether the organ will function enough to eliminate the need for dialysis. Therefore the fact that graft primary non function is low is sufficient. There are several units now in the UK with machine perfusion systems, some of which are participating in the trial (machine perfusion versus static storage). Our centre was the named one that used a locally developed system, we now use Organ Recovery Systems only	This has been amended in the scope.
	Organ recovery systems	In the "Technology" section, information related to mechanics of perfusion should be deleted. Pumps from the two companies have different operating platforms. Suggested wording: "In machine preservation, cold preservation solution is pumped through the organ. Machine perfusion can be used to preserve grafts from both HB and NHB donors."	This has been amended in the scope taking into consideration comments from other consultees.
	UK transplant	Yes	Comment noted. No action required.
	British transplant society	Yes	Comment noted. No action required.
	UK transplant (2)	Pumping cold preservation solution through the organ does not necessarily pump Oxygen through the organ, although this has been a feature on some of the earlier models. The ORS machine does not do this, for example, and it is this machine that is in widest use in the UK	This has been amended in the scope.
Population	Newcastle upon Tyne NHS Hospitals Trust	The preservation systems are used on the organs of the donors without the recipient being identified. The latter is the "customer". There is evidence that recipients benefit from 'marginal' NHB also.	It was agreed at the scoping workshop that the population should be defined as recipients of kidney transplants.

Summary form

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	Organ recovery systems	We recommend that recipients of cadaveric kidney transplants from heartbeating donors also be included in the evaluation. The standard comparison and outcome measures would be the same. In the United States, machine perfusion is routinely used for the preservation of kidneys from heartbeating donors with excellent outcomes.	It was agreed at the scoping workshop that the population should be expanded to include recipients of kidneys from heart beating and non heart beating donors
	UK transplant	Yes	Comment noted. No action required.
	British transplant society	See above	See response above.
	UK transplant (2)	Non-heart-beating donor kidneys stand to gain most, but all deceased donor kidneys may potentially gain from machine perfusion. Withing NHBD kidneys you should sub-divide into uncontrolled (Categories 1, 2 and 5) and controlled (3 and 4)	It was agreed at the scoping workshop that the population should be expanded to include recipients of kidneys from heart beating and non heart beating donors. Kidneys from uncontrolled and controlled NHBD have been added as subgroups that should be examined in the appraisal.
Comparators	Newcastle upon Tyne NHS Hospitals Trust	Static cold storage is often done with poorer quality perfusate. The comparator should therefore be cold storage with University of Wisconsin or equivalent solution.	It was agreed at the scoping workshop that the appraisal should be expanded to also consider the relative clinical and cost effectiveness of the different perfusion solutions used with cold static storage.
	Organ recovery systems	Yes, however, the effectiveness of machine perfusion should be evaluated in terms of its ability to replace cold static storage. This is to say that the machine preservation system should be able to go anywhere a box of ice can go. Ideally, the kidneys should be placed on the machine preservation system in the recovery theatre and then transported to the transplant center on the pump as is currently the case with cold static storage.	It was agreed at the scoping workshop that where such factors impacted on the clinical and cost effectiveness these should be included in the appraisal.
	UK transplant	Yes	Comment noted. No action required.

Summary form

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	British transplant society	Yes	Comment noted. No action required.
	UK transplant (2)	Static cold storage can use different preservation solutions, of which there are three in common use - UW (ViaSpan), Marshalls (Soltran) and EuroCollins. It is likely that not all are as good as each other, and many centres use University of Wisconsin solution (ViaSpan) for NHBD kidneys since it is perceived to be superior - this is not the same solution as the University of Wisconsin machine perfusion solution (KPS-1). The costs of the comparator solutions varies enormously, with ViaSpan UW costing £150/Litre, and Marshall's (Soltran) costing around £20 per litre. Around 8 to 10 litres of fluid are used in an organ retrieval procedure. Use of ViaSpan UW would be considered the best alternative care.	It was agreed at the scoping workshop that the appraisal should be expanded to consider the relative clinical and cost effectiveness of the different perfusion solutions used with cold static storage. Attendees agreed that ViaSpan and Soltran were most commonly used in the NHS and that these two solutions should be specified in the scope of the appraisal.
Outcomes	Newcastle upon Tyne NHS Hospitals Trust	Incidence and duration of delayed graft function	These outcomes have been included in the revised scope
	Organ recovery systems	Yes	Comment noted. No action required.
	UK transplant	Yes	Comment noted. No action required.
	British transplant society	Yes, but it might be useful to define graft and patient survival as 1 and 5 year, and to include rejection rates which may be affected by DGF	It was agreed at the scoping workshop that the survival duration did not need to be specified in the scope. Rejection rates have been included in the revised scope.

Summary form

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	UK transplant (2)	<p>You need to define incidence of delayed graft function - the commonest and most accepted definition is the need for dialysis in the first 7 days post transplant. Graft function should be defined as glomerular filtration rate (calculated using the MDRD or Nankivell equations) and not creatinine.</p> <p>Long term outcome data are important - 5 to 10 years is important to patients, most studies have endpoints at one week. Function at one year is the best surrogate of long term outcome.</p>	<p>This detail is not needed in the scope, but will be defined at the protocol stage. Serum creatinine has been removed from the draft scope.</p> <p>Long term outcome data will be collected as part of the appraisal and used to inform estimates of clinical and cost effectiveness.</p>
Economic analysis	Newcastle upon Tyne NHS Hospitals Trust	Appropriate	Comment noted. No action required.
	Organ recovery systems	No comment	Comment noted. No action required.
	UK transplant	No comment	Comment noted. No action required.
	British transplant society	No comment	Comment noted. No action required.
	UK transplant (2)	<p>Timing of the assessment of quality of life is important. A QoL questionnaire administered at 7 days will reflect the incidence of delayed graft function; a QoL at 12 months will reflect the function of the transplant at that stage and is probably more important as an economic endpoint.</p> <p>Some of the machines need careful supervision and a cool room (eg the Waters machine), while others need little supervision and can sit anywhere (ORS machine). Whether you have to pay someone to supervise the machine greatly adds to the costs of the technology. We use the ORS LifePort without a technician and without problem.</p>	<p>This detail is not needed in the scope, but is an important consideration that will be considered in the protocol and assessment report.</p> <p>It was agreed at the scoping workshop that where such factors impacted on the clinical and cost effectiveness these should be included in the appraisal.</p>

Summary form

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Other considerations	Newcastle upon Tyne NHS Hospitals Trust	If graft viability measures as are currently used are in question by NICE then grafts which are considered non viable will have to be used and this raises ethical difficulties.	It was agreed at the scoping workshop that the ability of machine perfusion to judge graft viability and to improve the viability of kidneys should be considered where it impacted on the clinical and cost effectiveness. This data will be collected from existing studies and therefore will not raise ethical issues.
	Organ recovery systems	Effectiveness of machine preservation compared to cold static storage in kidneys from heartbeating donors. Safety and ease of use of machine preservation as compared to cold static storage.	It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors It was agreed at the scoping workshop that where such factors impacted on the clinical and cost effectiveness. These should be included in the appraisal.
	UK transplant	None	Comment noted. No action required.
	British transplant society	None	Comment noted. No action required.
	UK transplant (2)	The incidence of acute rejection is higher in kidneys with delayed function, necessitating additional immunosuppressive drug treatment, renal biopsies, length of stay etc - this should be an endpoint also and needs to be taken into account when doing a cost analysis.	These factors will be taken into account when determining the cost effectiveness. Primary non function, incidence and duration of delayed graft function and rejection rates have been included in the revised scope.

Summary form

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<p>Questions for consultation</p>	<p>Newcastle upon Tyne NHS Hospitals Trust</p>	<p>The benefit for machine perfusion must be tested against similar perfusate in cold static storage.</p> <p>But also in normal heart beating kidneys some of which will be from other marginal donors.</p>	<p>It was agreed at the scoping workshop that the appraisal should be expanded to consider the relative clinical and cost effectiveness of the different perfusion solutions used with cold static storage, as well as making comparisons with machine perfusion systems.</p> <p>It was agreed at the scoping workshop that the remit should be expanded to include heart beating and non heart beating donors</p>
	<p>British transplant society</p>	<p>This remit concerns the ability of machine perfusion to improve outcome overall. However, as mentioned in the technology section, it also has the ability to select which kidneys might be suitable for transplantation: viability assessment. This is a slightly separate but equally valuable question, which should be addressed at the same time.</p>	<p>It was agreed at the scoping workshop that the ability of machine perfusion to judge graft viability and to improve the viability of kidneys should be considered where it impacted on the clinical and cost effectiveness.</p>
	<p>UK transplant (2)</p>	<p>Nil</p>	<p>Comment noted. No action required.</p>
<p>Additional comments on the draft scope.</p>	<p>British Organ Donor Society</p>	<p>My involvement is from the experience of a organ donor family. As such then the details and documents relating to Machine versus cold storage are not relevant to my knowledge and experience. However I would comment on behalf of donor families that our desire, regarding organ donation, is that the best use is made of our donated gifts. In the case of kidneys I would expect there to be more opportunity to achieve best use with the use of a machine, a dynamic process, as opposed to the cold, passive procedure to store (and transport?) kidneys.</p> <p>I believe that the machine technique should be used with all organ donations. Already a heart has been successfully transplanted that was machine maintained in a beating condition after retrieval from a donor.</p>	<p>Comments noted. Recommendations about the use of machine perfusion will be an outcome of the NICE appraisal process. No action required at the scoping stage.</p>

Summary form

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	Newcastle upon Tyne NHS Hospitals Trust	These trials are currently under way.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	Organ recovery systems	The British Transplantation Society in conjunction with UK Transplant has launched the PPART study, a prospective, randomized trial to assess the effectiveness of machine preservation in NHBD kidneys. The Coordinating Investigator for this study is Mr. Chris Watson from Cambridge. Additionally, the Machine Preservation Trial, a major, prospective, randomized trial comparing cold static storage to machine preservation in cadaveric as well as NHBD kidneys is underway. This study is being coordinated by Eurotransplant and the Coordinating Investigator is Professor Rutger Ploeg from Groningen, The Netherlands. The results from these two studies may impact the need for this technology assessment.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.
	British transplant society	None	Comment noted. No action required.
	UK transplant (2)	I welcome the appraisal of this technology, particularly with the advent of a superior machine. However the timing is not great - ORS are currently conducting the largest study ever performed in heart-beating donor kidneys in Europe and the British Transplantation Society in conjunction with UK Transplant are conducting a study targeted at non-heart-beating donors. These two studies would go a long way to answering the appraisal questions with contemporaneous and highly relevant data, which was a shortcoming in the technology review conducted by the Sheffield team. I attach the protocol for the BTS / UK Transplant study.	It was agreed that the scheduling of the appraisal will take into consideration when ongoing trials will be reporting data.

Comment 4: Regulatory issues

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Remit	Organ recovery systems	<p>The LifePort Kidney Perfusion Transporter (KTR) received Premarket notification clearance from the United States Food and Drug Administration under Section 510(k) to legally market the medical device in the United States on 31 July 2003. The medical device was voluntarily tested for the relevant safety requirements for CE Marking by TÜV and certificates were issued 15 September 2003.</p> <p>Organ Recovery Systems has implemented a Quality Management System and the National Standard Authority of Ireland (NSAI) has granted "Registered Firm" status under:</p> <p>I.S. EN ISO 9001:2000 Certificate Number 19.3547 I.S. EN ISO 13485:2003 Certificate Number MD19.3547 I.S. EN ISO 13485:2003 Certificate Number CM19.3547</p>	Comments noted. No action required.
Current or proposed marketing authorisation	Organ recovery systems	<p>LifePort Kidney Perfusion Transporter (KTR) is intended to be used for the continuous hypothermic machine perfusion of kidneys for the preservation, transportation and eventual transplantation into a recipient.</p> <p>The United States Food and Drug Administration Medical Devices Class II Premarket Notification under Section 510(k).</p> <p>The medical device has the CE (Conformité Européenne) Mark affixed on indicating that the LifePort Kidney Perfusion Transporter meets the safety standards that apply to all countries of the European Union (EU).</p> <p>The marketing authorisation is in the public domain.</p>	Comments noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Board of Community Health Councils in Wales
Royal College of Physicians of Edinburgh
Welsh Assembly Government
British Kidney Patient Association
National Kidney Federation
NHS Quality Improvement Scotland
Royal College of Nursing