Organ Recovery systems

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Technology Appraisal Project Manager

4th August 2008

Dear Mr Feinmann,

Appraisal of machine (pulsatile) perfusion versus cold (static) storage solutions for the preservation of donated kidneys – Comments on the Assessment Report for consideration by the Appraisal Committee

Thank you for the opportunity to provide comments on the Assessment Report for the above appraisal. While Organ Recovery Systems are appreciative of the work completed by PenTAG, in summarising the data on preservation of donated kidneys, we have a number of key comments. Our main observations relate to the:

1. Timing of the appraisal
2. Comparison of the PPART study and Machine Preservation Trial
3. Use of machine preservation to expand the donor pool and reduce discard rates
4. Non acceptance of delayed graft function (DGF) as a predictor of graft survival

Please note that all underlined text within this letter and accompanying table is provided on an academic in confidence basis.

1. Timing of the appraisal

We agree with the statement made on page 14 of the Assessment Report that the review of the literature *'was limited by the premature timing of the report'.* The current timelines of the appraisal have significant impact on both the degree of data available and the relevance of the final guidance to the NHS. We have previously highlighted this within our submission document.

Data availability

Scheduling the appraisal for 2007-2009 and limiting, within this timeframe, the systematic literature review to May 2008 excludes the critical results from the two key clinical studies (PPART and the Machine Preservation Trial). This exclusion severely restricts the evidence

base which can be made available to the Appraisal Committee and will result in the final guidance being out of date upon publication. A suspension of the appraisal for 6 to 12-months would avoid this issue and would result in the Committee having access to:

- 12-month results from the PPART study
- 3, 6 and 12 month data on donation after cardiac death donor (DCD) and extended criteria donor (ECD) subgroups from the Machine Preservation Trial. The preliminary results from these studies are due to be presented at the 22nd International Congress of the Transplantation Society 10th-14th August. Copies of abstracts for the:
    - 3-month data of machine perfusion versus cold storage for the preservation and transplant of kidneys from DCD
    - 6-month data of machine perfusion versus cold storage for the preservation and transplant of kidneys from ECD
    - initial cost effectiveness of machine perfusion versus cold static storage

  are attached in Appendix 1 at the end of this letter. The preliminary findings further demonstrate the benefits of machine perfusion compared with cold static storage in reducing primary non-function, reducing DGF and improving graft survival. In improving outcomes the costs of managing graft function related complications, particularly the requirement for dialysis and retransplant, are also reduced
- An economic model based on the Machine Preservation Trial. This model is being prepared by an independent group of health economists at the University of Groningen overseen by the Machine Preservation Trial's Scientific Steering Committee.
- Machine perfusion viability markers derived from a comparison of LifePort machine perfusion parameters to Machine Preservation Trial outcomes data

Relevance of Guidance to the NHS

Within the current appraisal timelines, guidance is due to be issued to the NHS in January 2009 and based on the contents of the Assessment Report will not take into account the recent Department of Health report '*Organs for Transplants: A report from the Organ Donation Taskforce*'[1] and the 14 Taskforce recommendations made within the report which have all been accepted by the Government[2].

In summary, the report recommends the establishment of a UK-wide Organ Donation Organisation under the auspices of the NHS Blood and Transplantation Authority. This organisation would be responsible for:

- Developing and managing a new national network of dedicated organ retrieval teams who would work closely with hospital critical care teams in order to retrieve safe, high quality organs for transplant across the UK. These dedicated teams would be commissioned and managed by the UK-wide Organ Donation Organisation
- The central employment of donor transplant co-ordinators.

[1] Organs for transplants: a report from the Organ Donation Taskforce: Department of Health www.dh.gov.uk/en/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/DH_082122

[2] Department of Health Media Release on the Organ Donation Task Force Report. www.gnn.gov.uk/environment/fullDetail.asp?ReleaseID=345738&NewsAreaID=2&NavigatedFromDepartment=False

- The establishment of a national organ retrieval system is an important change from current practice with potential for consequential changes in the way that organs are preserved between retrieval and transplantation with the likely provision of technologies to just one central organisation rather than to all the individual transplant units around the UK. The central organisation would then be responsible for directing the preservation technologies utilised by the national retrieval teams. The system we are looking at today may be radically different in 12-months time with a central system facilitating the sharing of kidneys preserved by machine preservation between centres.

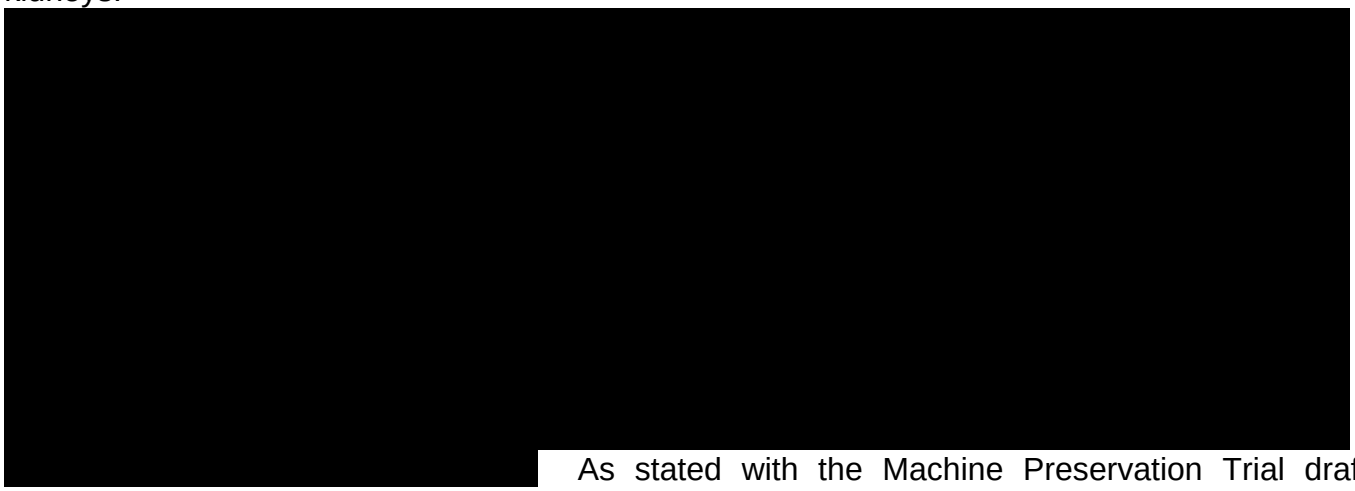
It is essential that during their deliberations the Appraisal Committee take into account the Taskforce recommendations and evaluate the preservation modality which will be most appropriate to fulfill these. In addition if there is to be a truly well integrated national system of retrieval it would make sense that NICE guidance is timed and considered in the context of the establishment of a national organ retrieval system.

Taking into account the importance of the pending evidence and changes to the current organ retrieval system we would recommend that the Institute reconsider the timing of the current appraisal and suspend the appraisal for a 6 to 12-month period in order to ensure that a more complete evidence base is available and that the resulting guidance is in line with the Taskforce recommendations.

2. Comparison of the PPART study and Machine Preservation Trial

We are concerned by the manner in which the review compares the PPART study and the Machine Preservation Trial. The two studies are different with regard to both methodology and donor populations and as a consequence the results currently available should not be compared. The current comparison introduces an unreliable level of uncertainty and leads PenTAG to disregard the positive clinical and cost effective benefits of machine preservation versus cold storage.

The results from the Machine Preservation Trial show the long term benefits of machine preservation over cold storage in a naturalistic, wide donor pool analysing 672 transplanted kidneys.



As stated with the Machine Preservation Trial draft manuscript these results are,

The smaller PPART study, analysing 90 kidneys, provides only 3-month data, and is limited to DCD donors only. DCD donors represent a small percentage of the overall donor population in the UK. Donor kidneys were kept within the region where they were retrieved. . While the PPART study shows no difference in DGF between machine preservation and cold storage it is important to remember that this finding is based on only 3-month data. In our view the 3-month time period from the PPART study should be seen as preliminary data only and the Appraisal Committee should wait for 12-month data.

In considering the DCD population alone we would highlight that, within the Machine Preservation Trial, a subgroup analysis of DCD donors is ongoing and as stated above preliminary data is due to be presented at the 22nd International Congress of the Transplantation Society 10th-14th August. Preliminary 3-month data for the DCD subgroup analysis show that machine perfusion compared with cold static storage for the preservation of DCD kidneys:

- Reduces the incidence of DGF (53.7% vs. 69.5%, p=0.027)
- Reduces the duration of DGF (9 days vs. 13 days, p=0.04)

In conclusion the authors state:
'This study demonstrates for the first time in a large controlled trial that MP of NHBD kidneys reduces the incidence, the duration and the severity of DGF and ameliorates graft function after kidney transplantation.' (see Appendix one for the full study abstract).

3. The use of machine preservation to expand the donor pool and reduce discard rates.

Throughout the Assessment Report repeated reference is made to the potential use of machine perfusion (for both BSD and DCD kidneys) within a central procurement network. We support this view and recommend that the Appraisal Committee give consideration to this and the benefits of machine preservation, within a central procurement network, during their deliberations.

We are disappointed that within the Assessment Report no reference is made to the benefits of machine preservation in terms of assessing viability. There are 2 points for consideration:

1. Whilst the debate about which specific parameter(s) should be regarded as the uniform standard(s) is ongoing, the usefulness of these as predictors of kidney viability is accepted with recognition of their increasing importance in optimising the transplant process. One element of the ongoing analysis of the Machine Preservation Trial is the determination of the most appropriate parameter(s). It is anticipated that these viability markers, which will never be possible with the old technology of cold storage, will be available within the next 6 to12-months.

From a patient perspective the more donor kidneys which are available increases their chance of receiving a transplant reducing their risk of death while on the waiting list. In addition from a cost perspective an increase in transplants will result in significant savings to the NHS with recipients no longer requiring long term dialysis.

2. A further benefit of machine preservation which has not been recognised is the combined potential for quality monitoring and improvement of kidney viability. The portable LifePort system is the only machine preservation device that provides surgeons with both the opportunity to objectively evaluate a kidneys performance *ex vivo* (via real time data indicators such as flow, pressure, temperature and vascular resistance) and safety (via detection of tampering post-lid closure and sealing). With the LifePort this is possible from recovery to transplant including the period of unattended transport.

4. Non acceptance of delayed graft function (DGF) as a predictor of graft survival

Our final main concern relates to the questioning of PenTAG of the value of DGF as an assumed predictor of long-term graft survival or patient survival.

Within the worldwide transplant community, the relationship between DGF and long-term survival is widely accepted with a number of publications providing evidence on the association between the two outcomes:

- In a study on the major effects of delayed graft function and cold ischaemic time on renal allograft survival Quiorga *et al.* (2006) demonstrated that DGF was the major factor affecting 1 year graft survival ($p<0.0005$) with effects persisting beyond 1 year.[3]

- In addition a review published by Perico *et al.* (2004) stated that DGF is important as it increases the risk of early or late graft loss[4]

- The association between DGF and graft survival was also demonstrated in the Machine Preservation Trial.
[redacted]

In addition to these main comments further detailed comments from Organ Recovery Systems are documented in the attached table.

Yours sincerely

[redacted]
Organ Recovery Systems

[redacted]
Organ Recovery Systems

[3] Quiorga I et al. Major effects of delayed graft function and cold ischaemia time on renal allograft survival. Nephrol Dial Trans 2003: 21; 1689 - 1696
[4] Perico N, et al. Delayed graft function in kidney transplantation. Lancet 2004; 364: 1814- 1827

APPENDIX ONE: Abstracts submitted for the 22nd International Congress of the Transplantation Society, 10th-14th August, Sydney

MACHINE PERFUSION VERSUS COLD STORAGE PRESERVATION IN NON-HEART-BEATING KIDNEY DONATION AND TRANSPLANTATION: FIRST RESULTS OF A MULTICENTRE TRIAL IN EUROTRANSPLANT.

F. Van Gelder[1], C. Moers[2], J.M. Smits[2], M.H.J. Maathuis[2], J. Treckmann[2], B.P.Napieralski[2], M. van Kasterop-Kutz[2], J.J. Homan van der Heide[2], E. van Heurn[2], G.R. Kirste[2], A. Rahmel[2], H.G.D. Leuvenink[2], A. Paul[2], J.Malaise[2], C. Randon[2], D. Ysebaert[2], J.P. Squiffl et[2], R.J. Ploeg[2], J. Pirenne[2]
[1]*University Hospitals Leuven, Leuven, Belgium [2] Eurotransplant MP Trial,Leiden, The Netherlands*

Rationale; Delayed Graft Function (DGF) after Kidney Transplantation causes additional morbidity and cost, and may negatively affect graft function and survival. Kidney grafts procured in Non-Heart-Beating Donors (NHBD) are exposed to both warm and cold ischemia and thus particularly vulnerable to DGF. Compared to standard Cold Storage (CS). hypothermic Machine Perfusion (MP) has been reported to provide superior preservation. This fact could be of great importance particularly for NHBD kidneys, but evidence to support this view is limited in quality and numbers.

Aim: To compare the efficacy of MP vs CS for the preservation of NHBD kidneys.

Methods: In an international prospectively randomized controlled trial we enrolled kidney pairs of 82 consecutive NHBD. All NHBDs were Maastricht category 3 (awaiting cardiac arrest/planned therapy withdrawal). One kidney was randomly assigned to MP and the contralateral kidney to conventional CS. Kidneys were allocated using the standard allocation algorithm. At time of offer, the type of preservation (MP vs CS) and perfusion parameters were not revealed. All 164 recipients were followed-up and 3 month data were analyzed.

Results: Donor age (y) was 43 (17-67). Baseline demographics were comparable between MP vs CS arms: recipient age (y) 49 (24-73) vs 52 (24-77). p=0.81; preTx dialysis duration (days) 1542 (366-6402) vs 1448 (132-3904). p=0.48; first/reTx 34/48 vs 34/48, p=0.56;% current PRA (0-5/6-84/85+) 71/11/0 vs 71/10/1, p=0.73;% of 0 HLA A,B and DR mismatches was 2.4 vs 3.7, p=0.5. Cold Ischemia Time (CIT) (h) was 15 (4.3-28.9) for MP vs 15.9 (8.6-46.6) for CS (p=0.7). Incidence of DGF was 53.7% in MP vs 69.5% in CS recipients, p=0.027. Duration of DGF (days) was 9 (1-48) in MP vs 13 (2-43) in CS kidneys, p=0.04. DGF < 7days occurred in 12/32 (27%) in the MP vs 6/51 (10.5%) in the CS arm, p= 0.028. Creatinine clearance (ml/min) at d7, d14, 1mth, and 3mth in MP vs CS was 13 vs 9, p=0.009; 23 vs 13, p=0.001; 46 vs 38, p=0.078; and 57 vs 49, p=0.19, resp. PNF rate was identical after MP and CS (2.4%). Acute rejection rate was 7.3% in MP vs 12.2% in CS kidneys; p=0.22. Graft loss (<3mth) was identical after MP and CS (3.6%). Patient survival was 98.7% in MP vs 100% in CS recipients. Logistic regression analysis showed that MP (p=0.035; Odds ratio 0.476) and CIT (p=0.009; Odds ratio 1.118) independently had an impact on DGF.

Conclusion; This study demonstrates for the first time in a large controlled trial that MP of NHBD kidneys reduces the incidence, the duration and the severity of DGF and ameliorates graft function after kidney transplantation.

MACHINE PERFUSION VERSUS COLD STORAGE IN TRANSPLANTATION OF KIDNEYS FROM OLDER DECEASED DONORS: RESULTS OF A PROSPECTIVE RANDOMIZED MULTICENTER TRIAL

A. Paul[1], C. Moers[2], J. Smits[3], H. Maathuis[2], J. Homan van der Heide[2], E. Van Heurn[4], J.P. Squiffl et[5], J. Pirenne[6], R. Ploeg[2], J. Treckmann[1]

[1]*University Hospital Essen, Germany, Clinic For General, Visceral And Transplantation Surg,* [2]*University Hospital Groningen, Netherlands,* [3]*Eurotransplant Foundation,* [4]*University Hopsital Maastricht, Netherlands,* [5]*University Hospital Brussels, Belgium,* [6]*University Hospital Leuven, Belgium*

Rationale; Delayed graft function after renal transplantation especially from older donors negatively correlates with long and short term graft function and graft survival. Retrospective studies suggest a beneficial effect of hypothermic machine perfusion (MP) on post- transplant outcome when compared to standard cold storage (CS) preservation.

Aim: Comparison of post- transplant outcome after machine perfusion vs cold storage in recipients of kidneys derived from deceased donors ¡Ý 55 years

Methods: As part of an international prospective randomized controlled trial n= 118 consecutive donation after brain death donors aged 55 years and older were included between Novermber 2005 and November 2006. In each donor one kidney was randomly assigned to MP and the contralateral kidney to conventional CS. Eurotransplant standard allocation algorithms were not affected by the trial. The accepting recipient center was blinded regarding preservation mode and perfusion parameters. Primary endpoint of the study was delayed graft function defined as necessity of dialysis in the first seven days after transplantation. Furthermore standard donor and recipient data were collected, as well as graft and patient survival, primary non function (PNF) and acute rejection episodes. All 236 recipients were prospectively followed up until six months after transplantation.

Results: Donor age was 63 yr (55-81). Baseline demographics were comparable between the MP vs the CS arm: recipient age (year) 63 (11-79) vs 61 (7-79). p=0.8; preTx dialysis duration (days) 1728 (417-5154) vs 1773 (149-3866). p=0.5;% current PRA (0-5/6-84/85+) 105/12/1 vs 109/8/1, p=0.3;% of 0 HLA A,B and DR mismatches was 8.5 vs 11, p=0.3. Cold ischemia time (CIT) (hr) was 14 (3.5-53.75) in MP vs 13 (2.5-25) in CS (p=0.6). Incidence of DGF was 22.0% in MP vs 31.4% in CS recipients, p=0.07. DGF < 7days occurred in 10/26 in the MP vs 5/37 in the CS arm, p= 0.02. PNF rate was 2.5% in MP vs 10.2% in CS kidney recipients (p=0.015) Creatinine clearance showed no differences at day 7 and 14. The rate of acute rejections was not different between the groups. When DGF occurred six month graft survival was significantly better in kidneys preserved with MP than by CS: 84% vs. 60%, p=0.026. Logistic regression analysis showed that MP (p=0.015; Odds ratio 0.432 vs CS) and CIT (p< 0.0001; Odds ratio 1.145) independently impacted on DGF.

Conclusion: Hypothermic machine perfusion of kidney grafts from older deceased donors lowers the incidence and duration of delayed graft function, strongly reduces primary non- function and improves graft survival at six months post- transplant.

COST-EFFECTIVENESS OF HYPOTHERMIC MACHINE PERFUSION VERSUS STATIC COLD STORAGE IN KIDNEY TRANSPLANTATION: FIRST RESULTS OF THE PROSPECTIVE EUROPEAN RCT

H. Groen[1], C. Moers[2], J.M. Smits[3], J. Treckmann[4], F. van Gelder[5], A. Rahmel[3], A. Paul[4], J. Pirenne[5], R.J. Ploeg[2], E. Buskens[1].

[1]Epidemiology, University Medical Center Groningen, Netherlands; [2]Surgery, University Medical Center Groningen, Netherlands; [3]Eurotransplant International Foundation, Leiden, Netherlands; [4]Abdominal and Transplant Surgery, University Hospital Essen, Germany; 5Abdominal Transplant Surgery, University Hospital Leuven, Belgium.

Introduction: Static cold storage (CS) is the most widely used organ preservation method for deceased donor kidney grafts. Retrospective analyses have indicated that preservation by hypothermic machine perfusion (MP) may lead to improved outcome after renal transplantation. We performed an economic evaluation of the use of MP versus CS with data from the recently conducted European multicenter prospective RCT. This analysis concerns the short term cost-effectiveness of MP versus CS, balancing cost of preservation versus cost of renal dysfunction and related complications after transplantation. This is the first MP related cost-effectiveness study to be based on prospectively randomized clinical data.

Methods: The clinical study involved inclusion of 336 consecutive kidney pairs from the same donor, one being randomized to MP and the contralateral organ to CS. This short-term analysis' scope comprised the clinical outcome and costs up to one year after transplantation. The primary clinical endpoint was delayed graft function (DGF). An economic evaluation was performed as a cost-effectiveness analysis with the percentage of patients with a functioning graft after one year as the clinical outcome. Costs were calculated from a hospital perspective: direct medical costs associated with hospital stay, dialysis treatment and function related complications were included, and compared preservation modality. Missing data regarding dialysis treatment following graft failure were imputed conservatively based on established clinical practice.

Results: MP significantly reduced the risk of DGF (OR 0.62; p=0.02) and also reduced the risk of graft failure (HR 0.39; p=0.03). Costs of dialysis (€760 vs. €940), graft failure or DGF (€136 vs. €193) and hospital readmission (€2,157 vs. €2,399) tended to be lower per patient with MP than with CS, but this finding was not statistically significant. Costs of preservation with MP were higher than with CS for each case (€842 vs. €167). Imputation of dialysis costs contributed considerably to average dialysis expenses, which rose to €4,354 for CS and to €2,564 for MP. Average total costs per patient after imputation were €4,896 for MP and €5,309 for CS. Bootstrap analysis (5,000 iterations) showed that the baseline probability of cost-effectiveness for MP was 71%. Further analyses including sensitivity analysis on the impact of variation of the major cost components are currently performed and prepared for presentation.

Conclusion: The clinical data show that MP has beneficial effects on renal grafts compared to CS. The first results from this cost-effectiveness analysis suggest that the additional costs of MP are more than compensated by savings due to reduced costs of graft function related complications, especially of reduced need for continued or renewed dialysis in case of DGF, primary non-function, or graft failure.

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Organ Recovery Systems: Additional Comments on the PenTAG Assessment Report - Appraisal of machine (pulsatile) perfusion versus cold (static) storage solutions for the preservation of donated kidneys

Please note all academic in confidence information is underlined

Page	Section	Comments
Executive Summary		
2	2.1 Background	For clarification on the availability of the RM3 (Water's Medical System) the final sentence in this section should be amended as follows: *'While both the LifePort Kidney Transporter (Organ Recovery Systems) and the RM3 (Water's Medical System are available in the UK only the LifePort Kidney Transporter is used. We will however also assess the RM3'*
4	2.4.1	We would draw the Appraisals Committee attention to the fact that the Machine Preservation Trial is still ongoing with 12-month outcome data being collected for two important subgroups DCD donors and ECD donors. In addition economic analysis based on the Machine Preservation Trial is also ongoing. The preliminary results from these studies are due to be presented at the 22nd International Congress of the Transplantation Society 10th-14th August. Copies of abstracts for the: o 3-month data of machine perfusion versus cold storage for the preservation and transplant of kidneys from DCD o 6-month data of machine perfusion versus cold storage for the preservation and transplant of kidneys from ECD o Initial cost effectiveness of machine perfusion versus cold static storage are attached in Appendix 1 at the end of the covering letter. The preliminary findings further demonstrate the benefits of machine perfusion compared with cold static storage in reducing primary non-function, reducing DGF and improving graft survival. In improving outcomes the costs of managing graft function related complications, particularly the requirement for dialysis and transplant, are also reduced

5	2.4.2.1	The main PenTAG concern with the Machine Preservation Trial appears to be the lack of an intention-to-treat analysis. In clinical trials of organ preservation an important and inherent characteristic is that randomisation has to be performed at a time point when many factors remain uncertain (eg would the kidney pair meet the inclusion criteria, cancellation of procedures following a donor report, multi-organ transplants etc). All these factors make ITT analysis difficult to perform. We do not believe that the lack of an ITT analysis could bias the results toward a worse outcome in the cold storage group. [redacted]
5	2.4.2.1	The Assessment Report documents that '*Only three months follow up data were available from Watson and colleagues who found no significant differences on any outcome measure (DGF, primary non-function (PNF)…..'* We would draw the Appraisal Committee's attention to the fact that this outcome is not unexpected. In our view the 3-month time period from the PPART study should be seen as preliminary data only and we would advise the Appraisal Committee to wait for 12-month data.
7	2.4.2.2	It is our view that discussion of the two studies by Guarrera and colleagues and Kazimi and colleagues is both inappropriate and misleading. Both were small retrospective hospital record reviews that had not been through a peer-review process and had only been published as abstracts and presented as posters. We would question why these studies are included when: • PenTAG themselves state that the evidence they present is *'unreliable'* • The original appraisal protocol states that reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality will be excluded. Despite statements that the results are unreliable they are discussed in detail with PenTAG making the statement *'with the exception of PNF, all outcomes favoured RM3 over the LifePort perfusion machine'.* Taking into account the poor quality data this statement is invalid and from a reader perspective distracts attention away from more relevant and reliable data.
10	2.5.1	The statement that the Water's RM3 machine is not available to the NHS is incorrect. The Water's machine is available but is not used having been superseded by LifePort in the UK transplant community.

10	2.5.1	Clarification is required as to why PenTAG did not approach the NHS for cost information on the Water's machine and why on the basis of a non-submission the Water's machine was not considered within the cost effectiveness section but was considered within the clinical effectiveness section. We would argue that the same principles should be applied to both the clinical and cost effectiveness sections and would also suggest that on the basis that the Water's system is not used in the UK and a submission was not made by the manufacturer the technology is excluded from the appraisal.
11	2.5.2.1	Due the different methodologies and donor populations the PPART study and the Machine Preservation Trial cannot be compared. [redacted] In addition preliminary 3-month data analysis for the DCD subgroup Trial show that machine perfusion compared with cold static storage for the preservation of DCD kidneys reduces the incidence of DGF (53.7% vs. 69.5%, p=0.027) and the duration of DGF (9 days vs. 13 days, p=0.04) The smaller PPART study, analysing just 90 kidneys, provides only 3-month data, and is limited to DCD donors. Kidneys were kept within the region where they were retrieved unlike the Machine Preservation Trial where donor kidneys were transported between regions opening the donor pool to a broader base of recipients. While the study shows no difference in DGF between machine preservation and cold storage, it is important to remember that this finding is only based on 3-month data and 12-month data is pending.
13	2.6	The statements in the discussion *'The evidence from the systematic review of effectiveness studies is unable to provide a definitive answer to the question on which is the best way to store kidneys from deceased donors. This is mainly because of the medium to long-term follow up data on graft survival for different types of kidney donor graft'* would not apply if the appraisal was conducted within the next 12-months when long-term data from the PPART study will be available and long-term subgroup data (based upon 12-month outcomes data for 672 kidney transplants) will be available from the Machine Preservation Trial
13	2.6	The statement *'Kidneys from BSD donors are currently not eligible for machine preservation in the NHS…'* is incorrect. Kidneys from BSD donors are eligible for machine preservation and some UK centres do preserve BSD kidneys using the LifePort system. Within the US the largest renal transplant programs (University of Wisconsin, Madison; University of Alabama, Birmingham and New York Donor Organ Network, New York City) routinely preserve BSD donor kidneys using the LifePort system.

14	2.6.1	We fully endorse the statement *'the review was limited by the premature timing of the report…*'. As stated within our covering letter the timing of the report limits the data available from both the PPART study and Machine Preservation Trial and as a consequence limits the evidence base on which the Appraisal Committee can utlilise within their decision making process. Organ Recovery Systems and the British Transplant Society made this point to NICE in their original submissions. The Assessment Report considers preservation systems within the context of the existing procurement despite the fact that the Organ Donation Taskforce had reported prior to the submission time that procurement in the UK would be changing. Organ Recovery Systems raised this point in a letter to NICE on 24th January 2008 suggesting that the appraisal is considered in the light of the new procurement system rather than the old existing system. We would strongly recommend that the appraisal is delayed for a period of 6 to 12-months in order to ensure that guidance can be developed which is based on a more complete evidence base and which address and takes into account the new organ procurement process.
15	2.6.2	We would clarify that ongoing analysis of Machine Preservation Trial includes analysis of all sources of cadaver donors including BSD, DCD and ECD donors. These data reflect the typical donor population that will be seen in any UK national organ retrieval system developed.
15	2.6.2	In the statement made by PenTAG *'whether differences in short-term graft survival (eg a one year post-transplant) reflect longer terms trends in graft survival'* we would highlight that collecting of outcome data beyond 12-months is inappropriate and within the clinical environment 12-month data is considered to be the maximum relevant time for assessing outcomes. After a period of 12-months post transplantation the recipient's outcomes are confounded by a number of other factors including co-morbidity (eg cardiovascular disease), follow up care (e.g. choice of immunosuppression) and patient lifestyle (e.g. compliance with medication and diet) hence any assessment of true outcome would be misleading.
17	2.7.2	Research priority 1 As discussed within the covering letter this research priority has already been addressed both within the published literature and more recently by the Machine Preservation Trial. Please note that the same comment applies to page 175, first bullet point.
17	2.7.2	Research priority 2

		We assume that intention-to-transplant means intention-to-treat (ITT). Within the transplantation field ITT analysis is not always possible, feasible, relevant or of value. In clinical trials of organ preservation an important and inherent characteristic is that randomisation has to be performed at a time point when many factors remain uncertain (eg would the kidney pair meet the inclusion criteria, cancellation of procedures following a donor report etc). [redacted] Please note that the same comment applies to page 175, second bullet point.
18	2.7.2	Research priority 3 We would like to make the Appraisal Committee aware that the initial results of sub group analysis which considers DCD and ECD donors will be presented at 22nd International Congress of the Transplantation Society 10th-14th August. As detailed in our covering letter a copy of the abstracts documenting the preliminary results for both DCD and ECD donors is provided, for information purposes. Summaries of the results are also provided below: • Machine perfusion vs. cold storage in transplantation of kidneys from older deceased donors: Results from a prospective randomised multicentre trial This study compared the post-transplant outcomes for machine perfused (MP) kidneys versus cold static stored (CS) kidneys from deceased donors who were aged 55 years and above. Preliminary 6-months data show that MP compared with CS reduces primary non-function (2.5% vs. 10.2%, p=0.015) DGF (22% vs. 31.4%, p=0.07) and in those recipients who do develop DGF improves graft survival (84% vs. 60%, p=0.015). The authors concluded: *'Hypothermic machine perfusion of kidney grafts from older deceased donors lowers the incidence and duration of delayed graft function, strongly reduces primary non- function and improves graft survival at six months post-transplant.'* • Machine perfusion vs. cold storage preservation in non-heart-beating kidney donation and transplantation: First results of a multicentre trial in Eurotransplant Initial 3-month data from this study comparing the efficacy of machine perfusion and cold static storage for the preservation of NHBD (DCD) kidneys shows that MP compare with CS: o Reduces the incidence of DGF (53.7% vs. 69.5%, p=0.027) o Reduces the duration of DGF (9 days vs. 13 days, p=0.04)

<table>
<tr><td></td><td></td><td>In addition logistic regression analysis showed that MP and cold ischaemic time independently have an impact on DGF. In conclusion the authors state:
‘This study demonstrates for the first time in a large controlled trial that MP of NHBD kidneys reduces the incidence, the duration and the severity of DGF and ameliorates graft function after kidney transplantation.’

Please note that the same comment applies to page 175, third bullet point.</td></tr>
<tr><td>18</td><td>2.7.2</td><td>Research Priority 6 and 7

We see no value in comparing the Water’s RM3 system with either cold storage solutions or LifePort as recommended in points 6 and 7. The Water’s system is no longer used within the NHS having become superseded by LifePort.

Please note that the same comment applies to page 175, sixth and seventh bullet points.</td></tr>
<tr><td>18</td><td>2.7.2</td><td>One aspect of the Machine Preservation Trial includes the identification of a reliable marker for predicting kidney viability. It is anticipated that this data will be available within the next 6-12 months. It should be noted that such options to assess viability will never be possible with static cold storage.</td></tr>
<tr><td colspan="3">Background</td></tr>
<tr><td>35 to 37</td><td>3.3.1.1 and 3.3.1.2</td><td>In discussing cold storage and hypothermic machine perfusion there is an inconsistency in the approach taken.

For cold storage only the benefits are presented while for machine preservation the disadvantages are listed with only inference made by the use of terms such as ‘in theory’ and ‘it is suggested that’ to the benefits of reduction of damage associated with cold ischaemic time and selection of viable grafts.

We would draw the Appraisal Committees attention to key features of both cold storage and machine preservation. For machine preservation we have focused on LifePort only on the basis that Water’s RM3 is not used within the UK.

<table>
<tr><th></th><th>CS</th><th>MP (LifePort)</th></tr>
<tr><td>Can be used for all cadaveric donor types</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Transportable</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Easy to use</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Enables elimination of metabolic waste</td><td>No</td><td>Yes</td></tr>
<tr><td>Allows for therapy during storage</td><td>No</td><td>Yes</td></tr>
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</td></tr>
</table>

		Allows organ function evaluation during preservation	No	Yes	
		Incorporates quality control measure (including constant temperature monitoring and status during transport)	No	Yes	
		Duration of unattended preservation	24 hours	24 hours	
37	3.3.1.2	The statement '*The disadvantages of machine perfusion are that it is more labour intensive and less practical in organ exchange..'* is misleading and while applying to the RM3 Water's system does not apply to LifePort. As documented later in the same section LifePort is a fully '*portable system'* which can run *'without being overseen'.* It is also important to note that the Water's RM3 system was not designed to be a portable system and was designed to be used in conjunction with cold static storage; it is not a replacement for static storage. In contrast LifePort was designed to be fully portable and is intended to be a replacement for cold static storage.			
Definition of the Decision Problem					
42	4.1.5	In addition to age and health of the recipient factors which affect the success of transplantation include the preservation method used. [redacted]			
Assessment of Clinical Effectiveness					
45	5.1.2.2	For clarification it is important to note that the Water's RM3 system was designed to be used in conjunction with cold storage unlike LifePort which is intended to be a replacement for cold static storage.			
57	5.3.1	Please note that the data for Moers and colleagues was provided on an Academic In Confidence basis not a Commercial in Confidence basis. Organ Recovery Systems will notify the Institute immediately when this restriction can be removed.			
Assessment of Cost Effectiveness					
84	6.2.4	There is a lack of transparency around which studies were considered but rejected within the cost effectiveness systematic review. In addition the current text states that four citations potentially met the review's inclusion criteria but only three references are cited. Clarification is required on the fourth reference source.			
84	6.2.4	Clarification is required as to why the 2003 Monograph by Wight and colleagues was considered with the economic part of the Report when on the basis that *'at least one comparator in every study was of an older technology and outside the scope of this report'.* (Page 49) was excluded from the review of clinical effectiveness.			

157	6.8.3	As previously highlighted we disagree with the comparison of the PPART study and Machine Preservation Trial. In considering the two studies separately and as suggested above recommend that the Committee wait for the 12-month PPART data before giving full consideration to the study results. The 12-months data from the Machine Preservation Trial clearly demonstrate the cost effectiveness of machine perfusion compared with cold storage.
Assessment of Factors Relevant to the NHS and Other Parties		
161	7.2	In addressing the statement that it *'takes more time'* to prepare a kidney for machine perfusion than cold storage we would highlight to the Appraisal Committee that the actual time taken is minimal. Following splitting and cleaning of the kidneys (which takes 15 minutes and is also required prior to cold storage) dissection of the artery and cannulation takes, on average, 5 minutes.
Discussion		
164	8.1.1	The current text which addresses the effectiveness of different kidney perfusion machines is misleading and in contrast to sections 5.3.2 and 5.3.2.1 makes no reference to the facts that the results should be *'viewed with caution'* (see page 65, section 5.3.2) and that the evidence is *'unproven'* (see page 69, section 5.3.2.1). We would also highlight that comparison of the current Water's RM3 system with LifePort is irrelevant as the Water's system is no longer used within the UK having been superseded by LifePort.
165	8.1.2.1	Clarification is required as to why the 2003 Monograph by Wight and colleagues was considered with the economic part of the Report when on the basis that *'at least one comparator in every study was of an older technology and outside the scope of this report'.* (Page 49) it has been excluded from the review of clinical effectiveness.
166	8.1.2.2	As previously stated the 3-months results from the PPART study cannot be compared with the 12-month data from the Machine Preservation Trial. The 3-month time period from the PPART study should be seen as preliminary data only and the Appraisal Committee should wait for 12-month data. At present the Machine Preservation Trial provides the most robust evidence base in regard to the benefits of machine preservation vs.cold static storage across all categories of donor kidneys.
174	8.2.2	Limitations In the second bullet the statement that the sub group analysis of the Machine Preservation Trial examined only DGF is incorrect 6 and 12-month will be available within the next 6 to12-months.