HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Appraisal Consultation Document (ACD) On Machine perfusion systems and solutions for cold (static) storage of donated kidneys	
TO: NICE	**FROM: NHS Quality Improvement Scotland**

I commend the committee on this document and appreciate the deliberations undertaken in considering technologies where the quality of evidence is so poor but where the clinical issues are varied, complicated and vitally important.

Before addressing the questions asked I would like to draw attention to the fact that in Appendix B of the ACD, NHS Quality Improvement Scotland is placed in B IV "Commentator organisations (did not provide written evidence and without the right of appeal)". NHS QIS asked [redacted] to produce a written report on its behalf and this statement was available to the Appraisal Committee and the invited clinical specialists and patient advocates at the meeting on 13th August.

Specific headings

i) Yes. The relevant evidence for these technologies is sparse and I consider that all the relevant evidence was presented very clearly in the written documentation prepared prior to the Appraisal Committee meeting in August, presented and discussed at the Committee meeting and summarized in the ACD. I know of no other published reports which are relevant. There has been a presentation at the Transplantation Society meeting in Australia last month when further data from the Machine Perfusion Trial showed that in the subgroup of kidneys from non heart beating donors the kidneys which did develop delayed graft function experienced this for a shorter period of time (mean 3 days less) in the machine perfused group compared to the kidneys which were preserved with static cold storage. This data is as yet unpublished.

ii) Yes. Within the restraints of the paucity of good quality evidence I consider that the summaries of the clinical and cost effectiveness are reasonable interpretations of the available evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate.

iii) Yes. I consider that the provisional recommendations of the Appraisal Committee are sound and are a suitable basis for guidance to the NHS.

iv) No. I do not see any equality related issues that may need special consideration.

General Comment

This is a very well thought out report which takes into account the general lack of quality evidence relating to machine perfusion systems and solutions for cold storage of donated kidneys. The committee has appreciated and given heed to all the additional information and concerns expressed by the organisations and the individuals active in the clinical field and produced a document that presents the facts and makes recommendations that are safe for the viability of the kidneys within a cost awareness environment without unduly restricting responsible clinical practice.

The recommendations for further research are appropriate in that further data is awaited from the 2 RCTs relating to machine perfusion and it is important for individual transplant units to record and audit the outcomes of their preservation practice(s).
The review date in 2 years appears appropriate to allow reassessment after further evidence is available from the as yet incompletely analysed RCTs and their follow up data but may be too soon to have reported data on the impact of the implementation of the recommendations of the organ donor task force report. It is unlikely that the recommendations of the organ donor task force report will be fully implemented before about this time next year. If then we require at least a year to see what changes this produces and then to analyse the data it will not be available for consideration before the proposed August 2010 review. The task force recommendations should increase the numbers of donors and of transplants but may have little effect on the methods or quality of kidney preservation.

Appraisal Consultation Document relating to Machine Perfusion systems and cold storage of kidneys from deceased donors.

I find it surprising that this appraisal is being carried out by a committee of 20 individuals none of whom have a background in organ transplantation.

Here are my comments on the appraisal consultation document:

- Section 1, 1.1 recommends LifePort transporter or cold storage with UW or cold storage with Marshall's as the three options for storage of kidneys. I am confused by the next paragraph (1.2) which states that "*when different storage methods are considered equally appropriate, the least costly should be used*". Are they talking about methods different to the three mentioned in 1.1 or do they mean the choice between LifePort & the two different cold storage methods? I imagined that the purpose of the NICE review was to comment on the most appropriate method, rather than stating that when there are different methods *which are considered equally appropriate*, choose the cheapest.

- A fundamental shortcoming with this document is that it considers ***storage*** of kidney allografts in isolation from ***organ retrieval*** and it focuses solely on *storage of kidneys* rather than retrieval/storage/transplantation of all organs that are transplanted Organs for transplantation from deceased donors are perfused with cold preservation solution prior to retrieval. The vast majority of deceased organ donors contribute other organs in addition to kidneys for transplantation. UW solution was primarily developed as a pancreatic perfusion/preservation solution. Its superiority over Marshall's solution for pancreas and for liver perfusion and preservation has been proven beyond any doubt. No multi-organ retrieval procedure will use Marshall's as the only perfusion solution. Organ retrieval procedures where only kidneys are retrieved constitute a small proportion (certainly less than 10%, probably less than 5% of all retrievals) of all retrievals. In multi-organ retrieval UW is the standard perfusion solution in the UK. Having perfused the organs with UW, it seems illogical to then store the kidneys in Marshall's solution. I don't know how to interpret the

information in paragraph 3.5 which states that in the UK in 2000-2007 74% of deceased donor kidneys were preserved with Marshall's solution. It seems that the appraisers do not have a complete understanding of how organ retrieval is performed and have not considered the needs of other organs (primarily liver and pancreas, less commonly small bowel).

- LifePort transporter can indeed run without supervision (3.7) but in practice most transplant units who store kidneys in LifePort machines do make provision for an additional member of staff to check the machine regularly during the time that kidneys are perfused in it. This clearly adds a significant amount of extra work and cost which has not been considered in any of the analyses.
- Attachment of kidneys to the LifePort transporter requires a complete and appropriate sized patch of aorta around each renal artery. This is not always available. No published data exists but from my experience of several hundred organ retrieval procedures, I estimate that in approximately one fifth of organ retrieval procedures at least one of the kidneys can not be attached to the LifePort device because of the presence of multiple renal arteries, atherosclerotic disease of the aorta, inadequate patch size on one side…etc. This will only be evident at the end of the organ retrieval operation, after the kidneys are removed from the body. At that stage all the disposable (and expensive) consumables for the LifePort device will have been opened. Hence these costs will be incurred even if the kidney(s) can not be attached to the device. Again none of the analyses take this into account.

- Secure attachment of the renal artery to the LifePort device is a critical requirement for successful pulsatile preservation of kidneys. This can be an intricate and exacting surgical manoeuvre. If it fails, the worst possible outcome may be inadequate preservation (and discard) of the kidneys. Published data regarding discard of kidneys before transplantation is scarce (paragraph 4.3.6). Whilst discard because of inadequate cold preservation rarely occurs, if it does it must be more common in machine preserved (rather than cold stored) kidneys.

- As discussed above, the vast majority of deceased donor kidneys that are transplanted are retrieved as part of a multi-organ retrieval. Multi-organ retrievals are performed by liver transplant teams (sometimes one liver team and a separate pancreas transplant team). In Scotland all multi-organ retrievals are performed by the Edinburgh transplant team. It is uncommon for additional surgeons from the "kidney only" transplant unit to be present at the retrieval procedure (it never happens in Scotland). Hence, if LifePort devices are used, the attachment of kidneys to LifePort devices need to be performed by the liver transplant team at the end of the retrieval procedure. This inevitably delays the departure of the liver transplant team by approximately 45-60 minutes. This delay can translate into increased cold ischaemia time for the liver transplant procedure. The outcome of liver transplant operations, in particular when livers from non-heart beating donors are used, can critically depend on cold ischaemia time and in this context an additional 45-60 minutes delay can be clinically significant.

- The committee states that "*the results of the PPART study were not consistent with clinical opinion or practice for storing this type of kidney*" (paragraph 4.3.7). PPART study is the first (and the most reliable and virtually the only) prospective randomized study comparing LifePort transporter and simple cold storage for NHBD kidneys.

Until this study was conducted, there were no clinical experts nor an accepted expert clinical opinion on this issue. The results certainly did not come as a surprise to me. I agree with the final sentence of paragraph 4.3.7

- The economic modelling is based on small numbers, some assumptions are made not all of which are justified and it doesn't take into account other important aspects of the process such as potential discard rates, influence on other organs to be transplanted and other hidden costs associated with LifePort (costs of the supervision of the machines, expensive disposables opened but not used..). Importantly it also misses the fundamental point of the difference between organ perfusion during the retrieval operation and organ storage. The storage costs are part of the total cost of perfusing kidneys and other organs during the retrieval process and subsequently storing them until transplantation takes place. As stated above, this latter point is of central importance to the whole analysis, not only the economic modelling.

- Another relevant issue, mentioned in the appraisal document (4.3.2) is the need to consider NHBD and heart-beating deceased donor kidneys separately. These two types of allografts are not only different in their potential to be influenced by the storage method but they are currently subject to different rules for allocation. It is likely that in the future NHBD kidneys will be allocated nationally (similar to heart-beating donor kidneys). This will increase travelling of allografts throughout the UK and will have implications for the storage method.

- Ultimately, I agree with the conclusion of the appraisers that there is no evidence to support the use of LifePort kidney transporter system in preference to simple cold storage (4.3.11). Given the additional concerns about the LifePort system discussed above, it is debatable whether LifePort system can be considered as an alternative or whether it should only be used as part of clinical studies. My personal prejudice and preference would be the latter.

[redacted]
(This may already have been provided to you as a separate paper by [redacted]

Reviewer 1.

1. Whether you consider that all the relevant evidence has been taken into account.

As far as I can tell, all relevant information provided has been taken into account.

2. Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.

Yes

3. Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

Yes as long as acceptable to the clinical community

30 September 2008