Mr Christopher Feinmann
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Peter House
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Your ref:

Our Ref: ED/CF

26 September 2008

Dear Mr Feinmann

RE: HTA Appraisal – Appraisal Consultation Document; Machine perfusion systems and solutions for cold (static) storage of donated kidneys.

This submission is presented to NICE based on the advice and consultation with our panel of independent expert advisors.

Overall, we consider that the report produced by NICE represents a fair summary of evidence, however it should be recognised that this evidence is both limited and open to some important criticisms. In view of this, the role of machine perfusion in the preservation of deceased donor kidneys remains an open question and there is a need for more high-level evidence from randomised controlled trials before a definitive opinion can be made.

Kidney Research UK, a major dedicated funder of renal research in the UK, is unable to support large randomised clinical trials, whilst acknowledging the need for such trials to help inform the evidence base.

Do you consider that all the relevant evidence has been taken into account?
There is a paucity of published evidence and it is unfortunate that the final results of two randomised clinical trials (PPART and Machine Preservation Trial studies) are not yet available for consideration. However the early review of this NICE guidance in 2010 is welcomed and we would hope that this would take into account the evidence upon their completion and follow-up studies.

Initial results from the PPART study, taking place in the UK, involved non-heart beating donor kidneys and showed no benefit for machine perfusion over static cold storage using delayed graft function as the primary outcome measure. In contrast, the European Machine Perfusion Trial study concentrated largely on kidney from heart-beating donors and did not show a statistically significant advantage for machine perfusion over static storage, in terms of better initial graft function. Therefore the main difficulty for NICE and the transplant community is basing clinical practice on this relatively limited evidence

and unfortunately, both these trials have limitations, which have been pointed out by some of the experts giving evidence to NICE.

Some of the specific limitations of these two studies are as follows:

The PPART study is relatively small with 90 patients randomised, largely studying non-heart-beating kidneys from controlled donors (i.e. where cardiac death was predictable and thus in which warm ischaemic time can be limited to only a few minutes) More marginal donors are obtained from uncontrolled NHBDs in which cardiac death is sudden and therefore warm time suffered by these kidneys tends to be prolonged and in the region of 30-60 minutes. Therefore more evidence is needed for the effects of machine perfusion in these particular marginal kidneys. Another concern with this study is that it used a rather unusual cumulative statistical analysis, which was used to stop the trial when it was clear that there was not going to be any benefits from using machine perfusion which seems completely opposite to the usual situation where power calculations are performed and interim analysis of data is not allowed. Finally, concern over the reproducibility of the way in which the machine perfusion was used as some kidneys were perfused for very short periods and others much longer periods which makes any comparisons of outcomes more difficult.

Although the European Machine Preservation Trial study was much larger involving 600 kidneys, there are two worrying aspects to the study, as approximately half the numbers of kidneys considered for entry into the study were excluded for one reason or another which seems excessive, even unprecedented, for a clinical trial. The trial also placed kidneys with multiple vessels which were considered too difficult to store using the machine perfusion into the cold storage group, therefore making 'randomisation' questionable. It is known that kidneys with multiple vessels have a higher incidence of a poorer outcome and in particular a higher incidence of delayed graft function, therefore this is likely to have skewed the results against cold storage. We are aware that the study group are using further statistical analysis to address this issue and these results are not yet available.

Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The summary of the clinical effectiveness is a reasonable interpretation of the available evidence, however it is noted that the full data of the Machine Perfusion Trial study is not available but the DGF rates of 89% (4.1.6) are higher than anticipated, particularly when compared with the 56% rate in the PPART study for UW preservation (4.1.5).

Although detailed economic modelling was used there are some assumptions that have been made and the limited data makes accurate interpretation difficult. In sections 4.2.7

and 4.2.8 in the comparisons between Belzer UW Solution and the Lifeport the cost differences are not that different, but the findings are opposite presumably because of the marked different rates of DGF as highlighted above. Furthermore in section 4.2.10 in the comparison between Marshalls and Belzer UW preservation solutions there were slightly higher costs for the former, although numbers were much smaller and may have been from an earlier time cohort which may have affected graft survival. The document summaries have recognised that the cost effectiveness data is limited by the evidence available and as a result recommendations based on cost-effectiveness have not been made.

Do you consider the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for preparation of guidance to the NHS?
In view of the evidence available these provisional recommendations are realistic in that any of the interventions under consideration are permitted under appropriate circumstances.

Are there any equally related issues that may need special consideration?
We are not aware of any.

Other comments
Kidney Research UK seems to be excluded from Appendix B under point B. II

Yours sincerely,