The Response of the British Transplantation Society

to the PenTAG Health Technology Appraisal

of Machine perfusion systems and solutions for cold (static) storage of donated kidneys

Summary

1. The BTS welcomes an appraisal of preservation technologies for kidney transplantation.
2. The BTS is concerned that this appraisal has taken place before the two key trials of this technology have finished follow up and completed their economic analysis.
3. Throughout the report there was a lack of appreciation that DCD donors and BSD donors have suffered different physiological insults at the time of death which means that extrapolation of results in DCD donors to BSD donor kidneys and vice versa is unsound. The BTS believes that it is inappropriate to extrapolate results from preservation studies in DCD kidneys to BSD kidneys and vice versa.
4. The BTS questions the validity of any interpolation of long term results of preservation technologies based purely on the numbers enrolled into the two principle trials as has been undertaken in the PenTAG cost effectiveness analysis.
5. The BTS is concerned regarding the reanalysis of some published data, which has been done apparently without reference to the original authors.
6. The BTS is concerned that delayed graft function has not been accepted as an important influence on long term survival in BSD kidneys.
7. The BTS is concerned that the effects of prolonged ischaemic times have not been taken into account in the analysis.
8. There were a number of factual inaccuracies in the document which lead to uncertainty regarding the validity of the analyses.

Authors

Declarations

[redacted] was gave advice to PenTAG and was the Principle Investigator of the PPART study.

The PPART study was a product of the British Transplantation Society Clinical Research Group

[redacted] was an investigator in the PPART study.

This response is written in two parts. In the first section we identify our main concerns with the appraisal. In the last section we identify errors, mistakes and unsafe assumptions made in the report.

1. The BTS welcomes a NICE appraisal of kidney preservation for transplantation.

As set out in our submission to NICE the British Transplantation Society (BTS) welcomes the appraisal of preservation technologies for kidney transplantation, and welcomed the extension of this appraisal from consideration of kidneys donated after Cardiac Death (DCD) to also appraise preservation of kidneys donated following brain stem death (BSD).

2. Timing of the appraisal report

Until the undertaking of the European Machine Perfusion Study (MPS) and the UK PPART study there had been no large properly powered studies evaluating machine perfusion, something that the PenTAG report acknowledges. It is therefore of concern to the BTS that evaluation of the technologies is proceeding without first waiting for the outcome of these two studies to be properly evaluated and published.

3. Extrapolation of studies on DCD donor kidneys to BSD donor kidneys

In comparing preservation technologies the results of studies on DCD and BSD donors have been combined. Hence the effects of machine perfusion in the PPART study are compared with the European MPS study.

A DCD donor kidney suffers a period of warm ischaemia following death (the asystolic period) which may extend from 10 minutes to 60 minutes, in addition to any period of poor perfusion during the agonal phase of dying. BSD donors suffer a brain injury that results in death of the brain stem and the heart continues to beat up to the moment of cold perfusion. There is no warm period prior to organ removal so the organs are in a better condition at the time of storage – the intracellular ATP stores are replete and there is no lactic acidosis, for example. Hence the organs are very different at the time of storage, and will respond differently to storage. This is seen by the high rate of DGF in kidneys from DCD donors.

To group donors of both sorts together in an analysis is to miss this point, a point that NICE previously acknowledged in its original proposal to conduct an appraisal of only DCD kidneys.

Data are available for the DCD donors in the European MPS study, and were presented in March in London at the 4th International Meeting on Transplantation from Non-Heart-Beating Donors and in April at the British Transplantation Society Annual Congress. It is not clear to the BTS why these data weren't analysed separately. Likewise the BSD donor kidneys from the European MPS study should have been analysed separately – if they weren't available to PenTAG at the time of their report then the report should be delayed until the data are available.

The BTS believes that it is inappropriate to extrapolate results from preservation studies in DCD kidneys to BSD kidneys and vice versa.

4. Interpolation of recent trials with registry data for economic analysis

In the cost effectiveness analysis PenTAG used data from UK Transplant to predict long term outcomes of kidneys in the two principle studies, PPART and the European MPS. This approach is fundamentally flawed since it presupposes that the preservation method has no influence on long term outcome. The data from UK Transplant would be based on kidneys variably stored in Marshall's solution (Soltran) and the University of Wisconsin solution (ViaSpan); very few would have been machine perfused (see BTS submission to NICE). Since both studies will provide more long term data it is unclear why it was necessary to "make up the results" rather than wait.

The BTS believe that the cost utility analysis is fundamentally flawed.

5. Reanalysis of published data.

The BTS is concerned regarding the reanalysis of some of the data, which has been done apparently without reference to the original authors. Of particular note is the registry analysis from the Collaborative Transplant Study contrasting graft survival in kidneys using different preservation solutions for different cold ischaemic times[1]. The authors are independent investigators of high repute. To reanalyse their data without discussion with them appears to be presumptive, and to then infer that their analysis was incorrect and by inference that their paper unsound would appear to accuse the authors of research misconduct. It would seem appropriate that the authors were contacted and allowed to justify their data, particularly since they have a far greater pedigree in transplantation research than PenTAG. Furthermore since the paper by Opelz and Döhler is the only evidence upon which the most appropriate preservation fluid for longer ischemic times can be judged it is imperative that the data is clarified.

The BTS believe in principle that authors should have been contacted and allowed to respond where their data has been questioned.

6. Delayed graft function is a risk factor for poor graft survival in BSD donor kidneys

There are many published data, in addition to data from the European MPS, which show that delayed graft function is a predictor of poor graft outcome in BSD kidneys. The association of DGF and poor outcome in DCD kidneys is not as convincing, which is probably a consequence from the different physiological injury in DCD kidneys that is responsible for DGF.

7. Lack of consideration of applicability of different preservation technologies for different storage periods.

The BTS were concerned that a conclusion about technologies had been made with consideration to the extremes of cold ischaemia. In our original submission we noted that one quarter of all deceased donor kidney transplants in the UK between 2000 and

[1] Opelz and Döhler. Transplantation 2007; 83: 247-253.

2007 had an ischaemic time of 22 hours or longer. There is no discussion of the role of different technologies in the preservation of kidneys with such ischaemic times.

8. Factual inaccuracies

There are a number factual inaccuracies in the report, some of which are detailed in the next section of this response.

Errors, mistakes and unsafe assumptions identified in the report

1. Page ii. Expert Advisory Group
   Mr David Talbot was not a co-investigator of the PPART study. He was involved with development of the original protocol but took no part in the study.

2. Page xiv. Anastomosis
   This should read Anastomosis Period, often called the second warm ischaemic time, which occurs when the kidney is being implanted into the recipient.

3. Page xiv. Graft survival
   Conventionally represents the proportion of transplant recipients with a functioning kidney after a given time period.

4. Page xiv. Extended criteria donor.
   This was specifically defined by NICE using the UNOS definitions. This should be the definition used here.

5. Page xiv. Cold ischaemic time.
   That part of the preservation period when the kidney has been cooled down and is not perfused by blood.

6. Page 7. RM3 vs LifePort
   No discussion is made comparing the safety of storing kidneys with the two machines. The LifePort is engineered to be independent of supervision, such that if mechanical failure occurs the default position is that the kidney gets stored as if undergoing static cold storage. The RM3 needs supervision because should mechanical failure occur the kidneys warm up and suffer irreversible warm ischaemic damage.

7. Page 8. ViaSpan vs Marshall's
   The BTS are not clear why one product is referred to by its trade name while the other is not.

   The BTS would like to challenge the re-analysis of the data from Opelz and Döhler in the belief that ViaSpan is superior to Soltran for longer periods of cold storage.

8. Page 8. Last paragraph and Page 79 last paragraph.
   The British Transplant Society should read British Transplantation Society.

9. Page 9. Machine perfusion
   PenTAG modelled that Transplant centres would need to purchase two machines. This will not suffice. Transplants come along like buses, nothing for ages and then a flurry. There needs to be capacity for peaks of donation. It is therefore likely that sufficient capacity for at least four kidneys would be necessary, plus an allowance for transport of the machine from the recipient centre to the retrieval team, something that would take several days.

10. Page 13. 2.6, discussion, 1st paragraph.
PenTAG state that kidneys from BSD donors are "currently not eligible for machine preservation". This is not so. Where a kidney is removed and it is known that it will be transplanted locally then that kidney may be machine preserved at the centre's discretion.

11. Page 15. Generalisability , paragraph 1.
PenTAG state that the European Machine preservation trial compared LifePort to ViaSpan. It did not. The protocol also allowed HTK (Custodiol) solution to be used[2].

12. Page 17. Research Priority 2. Intention to Transplant analysis
It is not clear what is meant here. Is this not an intention to treat analysis

13. Page 18. UK Transplant data completion rates
I noted with surprise that PenTAG stated that data parameters were only 58% complete in the UK Transplant data set. PenTAG should specify which parameters they mean here. UK Transplant has in excess of 97% data completion for graft and patient survival, sensitisation, HLA types of donor and recipient to mention but a few. Which parameters were missing?

14. Page 19. Paragraph 2.
The reduction in numbers of BSD donors does not reflect a reduction in fatal road accidents, which is a popular misconception. The reference quoted is from 2002, so is unlikely to represent the last decade as inferred in the text. One likely factor responsible for a reduction in BSD donors is a change in neurosurgical practice, such that where once a potential donor would suffer intracranial hypertension be diagnosed brain stem dead they are now offered decompressive craniectomy to reduce the intracranial hypertension; they instead become DCD donors.

15. Page 22. Figure 1.
This figure is in the BTS submission, but there it is attributed to UK Transplant at the request of Mrs Johnson.

16. Page 22. extended criteria donors
The report mentions a number of different definitions of an extended criteria donor. The criteria include death from a cerebrovascular accident, not a history of cerebrovascular accident. The appropriate reference for this would be the work of Port et al[3] upon whose work the UNOS definitions were based, rather than use of a secondary reference. It would have been more appropriate to consult with UK Transplant to derive a set of "extended donor" criteria relevant to the UK donor population than to use those derived in the USA.

17. Page 31. Figure 5.
It is not clear how the incidence of primary non function seems to increase with time, and appears to result in a 5% graft loss at 28 days. If a kidney never functions it never

---

[2] Machine Preservation Trial Protocol, Ploeg RJ. Dated 25th October 2005.

[3] Port et al. Transplantation 2002;74(9):1281

functions. Graft loss from PNF in the UK is less than 1% for BSD donor kidneys, although is higher in DCD donor kidneys.

18. Page 35. 3.3.1. The core of the kidney.
    It is important to cool the entire kidney, particularly the glomerulae which reside in the cortex, not medulla. "Core cooling" refers to perfusion of a kidney with cold solution in order to cool the entirety of the kidney, rather than topically cooling where only the outside of the kidney is cooled. PenTAG have misinterpreted the phrase.

19. Page 38, top paragraph. 3.3.2. DCD kidneys discarded due to lack of a matched recipient.
    DCD kidneys are not discarded "due to lack of a [local] matched recipient". They may be offered nationally. Kidneys are too valuable a resource for one centre to discard without reference to the pool.

20. Page 42. 4.1.4. Graft rejection rates
    Convention takes this to mean the proportion of kidneys that suffer at least one episode of acute allograft rejection. This is the definition used in all the trials, and **not** the one described by PenTAG.

21. Page 46. 5.1.2.3. Extended criteria donors
    PenTAG quote diabetes as a comorbidity making the donor and "extended criteria donor". This is not in the definition given by NICE or used by UNOS, although the presence of donor diabetes does result in adverse outcomes. However PenTAG need to adopt one definition and stick to it throughout. Which definition did they use in their analyses?

22. Page 64. Paragraph 2. ".. However Watson and colleagues found less DGF with ViaSpan."
    The difference in DGF was not significantly different, so should **not** be considered to be different. (See comment to section 8.1.1).

23. Page 73. Pedotti et al. . "It was not reported what ± meant"
    It is surprising that PenTAG did not contact the authors of the studies in question to find out.

24. Page 80. 5.4. Safety. Marshall's use when the Liver is removed
    This is not quite what we said. In the BTS submission to NICE we pointed out that were Marshall's (Soltran) was used when the liver was removed for transplantation the liver would need to be flushed through with UW (ViaSpan) before the liver was cold stored. This would reduce any cost saving. When the pancreas and/or intestine were removed for transplantation then UW should be used.

    Note that the society is the British Transplantation Society not British Transplant Society.

25. Page 96. Modelling
    Not all patients who lose a graft return to the transplant waiting list. UK Transplant could supply these data. Few patients return to the list after failure of a second transplant.

26. Page 104, Table 26 and page 116, Table 33: Numbers read from a bar chart.
If the data in Tables 26 and 33 were important for modelling why were they read from a bar chart instead of contacting the Renal Registry who could have given the actual data?

27. Page 115. Table 32. Graft survival data
As identified in the BTS summary, the use of registry data comprising kidneys not preserved with machines or solely with UW to provide long term outcome data is to presuppose there is no difference in long term outcome, which is exactly what the trials are there to determine. Such assumptions must be considered flawed.

28. Page 117. 6.5.5.3 Retransplantation following graft failure.
Kidney allocation in the UK is based on a complex algorithm which includes tissue type matching and length of time on the waiting list as its two principle determinants, but does include a factor for age matching and favours young recipients. Recognising that primary non-function is not the fault of the recipient, patients who lose their grafts within the first 6 months keep their waiting list points and are therefore likely to be allocated a second kidney relatively quickly.

29. Page 131. 6.6.1.2 LifePort vs Marshall's Soltran
The study cited here has so many differences between treatment arms, in particular in the use of induction agents (and by inference exposure to calcineurin inhibitor therapy) and the non-randomised sequential nature of the patients studied, there are serious reservations about attempting any cost appraisal based upon it.

30. Page 163. 7.2. Paragraph 1. Avoidance of unnecessary surgery.
PenTAG correctly state that the kidney needs to undergo "benchwork" prior to placement on the LifePort machine. However static cold stored kidneys also need to undergo benchwork before implantation. This should never be undertaken when the patient is anaesthetised for the reasons they state. Hence there is no difference whether or not the LifePort is used. Use of machine preservation does carry a risk of damaging the renal artery when placing the kidney on the machine, something that is of much more importance.

31. Page 163. 8.1.1 "Non significant result slightly in favour..."
Results that are not significantly different in appropriately powered, randomised clinical trials are just that: NOT SIGNIFICANT. To infer a difference is to imply a lack of appreciation of this basic principle of clinical research, a worrying trait in an organisation undertaking a Health Technology Appraisal.

32. Page 175. 8.4 The effects of HLA matching and cold ischaemia.
HLA matching and cold ischaemia have independent effects on the outcome of a transplant kidney. From Figure 1 of the PenTAG report it can be seen that there is a difference of around 10% in the outcome at one year of kidneys with CITs of <20 hours compared to >34 hours. This is the same as the difference between kidneys that are well matched and those that are poorly matched for HLA in the UK. Cold ischaemia is another variable affecting graft survival, one which can be address by better preservation and better infrastructure. It is the appreciation of this that has led to the resurgence of interest in organ preservation, including the evaluation of machines.

33. Page 182. Reference 51.
We assume this refers to the protocol for the PPART study. However the title is inaccurate, and the protocol date is wrong. None of the other references cited in the document have been checked for accuracy.