Renal Transplant Clinical Reference Group, NHS England

Response to 'A Systematic Review and Economic Model' - Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

In the interests of the time available and length of the document, we have confined our responses to the executive summary

Definition of terms p25
The terms 'Cadaveric transplant' and 'Heart beating donor' are outdated terms and need to be replaced with 'Deceased donor transplant' and 'Donation after brain death donor'. Also should include a definition of the term, 'Donation after circulatory death'

Executive Summary

1.1 Para 2, line 2 'medically suitable people' rather than 'people' as currently only 20-30% of patients on dialysis are considered medically suitable to transplantation

1.1 Para 3, line 1 question the use of term 'healthy' kidney and what authors mean by this. Increasingly kidneys come from extended criteria kidney donors where there may be some disease or damage of the kidney, but where the risk/benefit ratio determine that transplantation is still the right option.

1.1 Para 4 However, whilst kidney transplantation relieves the person with ESRD from lengthy dialysis, the strict regimen of immunosuppressant medication required may produce unpleasant side effects, including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain

1.1 Para 6. Update activity date with 2014/15 figures, overall increase in transplant activity and follow up activity since 2008, and total number of patients with a functioning transplant. This data is available from the UK Transplant Registry (NHSBT) and Renal Registry.

1.1 page 29
Three service provision steps is an inadequate description of the transplant patient pathway. The recognised steps in the patient pathway are: Pre-transplant assessment of the recipient and listing; maintenance on the list, transplant episode, and transplant follow-up. Immunosuppression is part of the 'transplant episode' and 'transplant follow-up'. Alongside this pathway is the selection of the organ donor whether that be living or deceased.

1.1 Interventions p29-30
We are assume you have chosen to only assess those interventions with UK marketing authorisation at the time of compiling this report. However this is an incomplete list of interventions currently used for induction or maintenance treatment and other agents to be considered are:

- Alemtuzumab – see www.3cstudy.org/results.html
- Azathioprine – still in common use and referred to later in the executive summary; so should it not be included as an intervention?
- Corticosteroids – see comments above for azathioprine
- Envarsus - new prolonged release tacrolimus

P31 Outcome Measures
Our understanding of the current literature is that most RCTs of immunosuppressive agents will be focussed on relative short term outcomes (up to 3-4 years, although most only one year) whereas what is becoming increasingly important is longer term outcomes for the patient and graft which are not usually included within RCTs

1.1 Data synthesis p34
The list of maintenance therapies appears incomplete and this may reflect there were no studies identified for other combinations in routine use. The following observations are made:

- All combinations will more often than not also incorporate a corticosteroid; although some will be corticosteroid free.
- In clinical practice MMF or MPS can be used in all combinations where an antiproliferative is required
- Within current UK practice Everolimus and Belatacept are not routinely used; and use has only been in the context of clinical trials or on a named patient basis.
- Within the list of interventions on p29-30 a clear distinction is made between immediate release tacrolimus and prolonged release tacrolimus, yet there is no distinction between these in the list of maintenance therapies on p34. Should they not be looked at separately?

Study selection, bullet 4, page 35
Is it really valid to consider economic evaluations from other countries such as USA, Canada, Australia, and western Europe, where the funding models for healthcare are quite different?

P37 'Corticosteroids were assumed to be used in all regimens but at a tapered dose.' Can't necessarily make this assumption unless clearly specified

1.3.4.1. Need for consistency with earlier lists and assuming combinations used in clinical practice and not mentioned are because no published RCT in this area, but for completeness the following regimes should be considered as they are in widespread clinical practice:

- Regimens following no induction immunosuppression: TAC-PR + Aza
- Regimens following basiliximab induction and Regimens following rabbit ATG induction: should include all of the regimes included under those with no induction immunosuppression.

We suspect the problem will be that a number of combinations in widespread clinical use will not have been part of a clinical trial and the results of this MTA will obviously be restricted to those combinations which have been subject to a RCT. Caution will therefore need to be exercised in terms of conclusions.

1.3.4.3
There are two other issues that require to be factored in or assumptions made:

- In clinical practice there will often be a switch between immunosuppressive agents based on episodes of rejection, adverse events, graft function etc. Some of these switches will have been permitted with a trial protocol and others will have resulted in the patient being withdrawn from the study. How will these changes in immunosuppressive factors be factored in? It may be too broad an assumption to assume that patients continue on the regimen they start on, particularly in looking at long term outcomes.

- In clinical practice there has been an increasing use of generics which for the critical dose drugs e.g. ciclosporin and tacrolimus require a 90-111% equivalence. As there will be very few, if any, RCTs looking at the generic versions of MMF, tacrolimus and ciclosporin (as detailed in the list of interventions) within transplant patients, then an assumption will presumably be made that the different brands of each agent can be viewed as bioequivalents.

1.3.4.4 Costs

Drug costs do vary in practice from list price, which may add complexities to the analysis. Currently some drugs are on a national tender with significant discounts; the price of others are negotiated at a local level; whilst others are purchased at list price.

1.4.1 and 1.4.2

This section comments, '..the RCTs were of variable quality, but all appear to be flawed' and more than half the studies '...either did not report, or lacked clarity on, at least five of the ten items constituting the quality appraisal assessment.' This does raise concern regarding the validity of the conclusions of the benefits and risks in section 1.4.2 when in addition to the poor quality, the majority of studies only looked at one year data which is not a good surrogate marker for long term outcome.

1.5.2

This group does not feel qualified to comment in detail on the PenTAG economic model outside the comments that have already been made about the quality of the existing predominantly short term RCTs, current immunosuppressive regimes which have not been the subject of RCTs, and the current pricing structure of immunosuppressives in the UK.

1.6

The discussion rightly points out the many limitations to the analysis, and it is already widely known within the transplant community that there are very few long term studies that look at the right type of parameters using regimens that are in current use. As a consequence we would argue that few conclusions can be drawn from this work with regard to current service provision. We would agree that longer term clinical studies are required, but these would be challenging to set up and run.

[redacted] on behalf of Renal Transplant CRG