National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85) [ID456]

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The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

April 2015

Issue 1 eGFR at 12 months for Tac-PR+MMF+ST

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The change in estimated glomerular filtration rate (eGFR) is calculated for the Tac-PR+MMF+ST regimen compared with the Bas+Tac+MMF+ST regimen. There is no need to subtract mu_eGFR_Tac_Mycophenolate in the formula, as the impact of this will be cancelled out when calculating the difference with respect to baseline. At present, the benefit of this regimen is underestimated.	The formula in cell C158 of Effectiveness worksheet should be: "=$C$116-mu_eGFR_Bas+mu_eGFR_TacQD_vs_TacBID" Due to this change, the reduction in eGFR will be 2.83 versus 9.4. Worksheet: Effectiveness Cell: C158	Impact of change on costs and quality-adjusted life-years (QALYs) of Tac-PR+MMF+ST: Discounted costs decrease from £111,499 to £107,048 Discounted QALYs increase from 10.6172 to 10.7581	We confirm that this is a wiring error and the proposed amendment is appropriate. **This has been corrected. The impact is to reduce total discounted costs and increase discounted QALYs in the TAC-PR+MMF regimen.**

Issue 2 Functioning graft state

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
All patients with a functioning graft are assumed to be at the same stage of disease severity; ie, the same utility value is assigned to all. In reality, patients are in different stages of chronic kidney disease (CKD) and have different utility values. In addition, a patient's eGFR decreases with time, which means that the CKD stage might change in future. In this model, eGFR at 12 months affects graft survival. Any change in eGFR post-Year 1 has not been incorporated.	Incorporating this aspect will require a change in the model structure; ie, dividing functioning graft states as per CKD stages and considering transition from one CKD stage to another (or staying in the same).	A significant impact on costs and QALYs is expected for treatments that result in the patient staying at a lower stage of CKD for longer.	This is not a comment on the reliability of the executable model, but a suggestion to use a different model structure. **No action taken.**

Issue 3 Validation of odds ratio calculation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The calculation of odds ratios (ORs) for 'Patient death within 12 months', 'Graft loss within 12 months' and 'Acute rejection rates' makes sense intuitively but not mathematically. A treatment regimen is defined as 'Induction therapy + Maintenance therapy', and the OR for a treatment regimen is calculated by multiplying the OR of induction therapy and that of maintenance therapy. The reason for choosing a 'multiplication operator' to derive the OR of a regimen is not clear.	Request validation of the calculated ORs from any other source Worksheet: Effectiveness Cell range: C43:C58; C94:C109 and D204:D219	More robust results	The common method of chaining odds ratios is to multiply them (or, equivalently, add them in log form). Adding odds ratios would be meaningless. The point may be made that this chaining assumes independence of treatment effects, which is not proven, but this is not a comment on reliability of the model. **No action taken.**

Issue 4 Calculation of graft survival curve

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The treatment regimen OR is applied on the odds of graft loss until the start of that cycle. Ideally, this OR should be applied on the odds of graft loss in that cycle.	The treatment regimen OR should be multiplied to the odds of graft loss in that cycle; accordingly, an adjustment in the graft survival formula is needed Worksheet 'Survival curves', Cell Range: columns "AB:AQ" and "AS:BH".	Minimal impact on results (<0.1%)	The current method of calculation ensures that at each time point in {0, 0.25, 0.5, 0.75, 1} years, the odds ratio of graft loss up to that time point is as desired. The crucial point is that the odds ratio of graft loss up to 1 year should be exactly as desired, which may not be the case with the proposed method. **No action taken.**

Issue 5 Living donor costs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The cost per living donor is calculated by dividing the 'sum of total costs of LA10Z, LA11Z and LB46Z' by 'number of activities in LB46Z'. This is an issue, because the number of activities in LA11Z and LA10Z are not equal to that of activities in LB46Z and, hence, the average cost is incorrect.	Living donor cost should have been calculated as the sum of unit costs of LA10Z, LA11Z and LB46Z; ie, the formula should be: "=SUM(D371:D373)*inflate_2013" Worksheet: Costs Cell Range: D374	The living donor cost decreases to £8,484 from £8,914. Due to this change, there will be a 0.6% decrease in the cost of re-transplantation for all regimens.	We do not agree that this is incorrect. The average total cost per living kidney donation should be calculated by dividing the total costs relating to living kidney donation by the number of recipients of living kidneys. The proposed amendment would ignore the fact there are almost twice as many pre-transplantation work-ups of donors as there are actual live donations. We also note that there are, in the reference costs, more activity for kidney transplant from live donor than live donations, which suggests there may be issues of data recording. **No action taken.**

Issue 6 Dosage of tacrolimus for subsequent re-transplantation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
For subsequent re-transplantation, the dosage of tacrolimus is taken as 0.1 mg/kg/day, based on the assumption that it will be somewhat higher than the long-running dosage for first graft (0.08 with azathioprine/MMF, 0.07 with sirolimus), due to an increased risk of rejection. Whenever transplantation is performed, however, tacrolimus is administered at a higher dose initially (eg, 0.168 mg/kg/day with MMF), which is then tapered down over time. For any subsequent transplants, the initial dose of tacrolimus should, therefore, be assumed to be higher than 0.1 mg/kg/day. Not considering this underestimates the cost of immunosuppressive drugs for all regimens.	The tacrolimus dosage considered for a Tac+MMF+ST regimen for a first transplant can be assumed for subsequent transplants as well. Worksheet: Costs Cell range: D135	Considering a higher dose of tacrolimus will increase the cost of immunosuppressive therapy for subsequent transplants, which will then lead to a slight increase in discounted costs for all regimens.	It is not possible to assume a dosage schedule dependent on time since transplantation for subsequent grafts due to the Markov memoryless assumption. It should further be noted that the unit cost of transplant surgery is also likely to include 90 days maintenance immunosuppression (which has effectively been double-counted). We believe this double counting should adequately cover the higher initial dose of maintenance therapy. **No action taken.**

Issue 7 Cost calculations for ciclosporin when it is used as maintenance with MMF or EC-MPS in Cycle 1

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
For patients staying in the functioning graft stage throughout the cycle, ciclosporin should be used for 0.25 years, or around 91 days. However, when we calculate the number days for which such patients receive ciclosporin, this is around 99 days (more than the cycle length). This leads to an overestimation of the cost of ciclosporin in Cycle 1 for regimens in which it is used as maintenance with MMF or EC-MPS.	The formula in cell J3 of the Markov traces for regimens affected should be: "=c_Ciclosporin*weight*(SUM(AY3:BC3)*(Costs!$C$48*14+Costs!$C$49*28+Costs!$C$50*(365.2425/8-42))+(AZ3)*(Costs!$C$50*(84-365.2425/8)+Costs!$C$51*(365.2425/4-(12*7))))" Worksheet - CsA+MMF+ST; Bas+CsA+EC-MPS+ST, Bas+CsA+MMF+ST and rATG+CsA+MMF+ST Cell range: J3	The discounted maintenance immunosuppression cost for such regimens will decrease by around 0.07% to 0.15%.	We confirm there is a mistake in this formula and agree with the proposed amendment. **This has been corrected.**

Issue 8 Costs discounting

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
In the Markov traces, transitions have been assumed to occur mid-cycle. QALYs are discounted as if they were incurred mid-cycle, which is line with the assumption of transitions mid-cycle. Costs are discounted as if they were incurred at the beginning of the cycle, however. Costs should be discounted similar to the benefits.	The formula in cell AA3 should be: "=POWER(1+dr_costs,-(B3+0.5*cycle_length))" Should be dragged across all relevant cells in column AA Worksheet: All Markov traces sheets of all regimens Cell range: AA3:AA203	The total discounted costs of all regimens will decrease by 0.4%.	We agree there is an inconsistency between the discounting of costs and the discounting of QALYs. **This has been corrected. As expected this has reduced total discounted costs of all regimens marginally.**

Issue 9 Acute rejection, CMV infection and infection prophylaxis for subsequent transplant

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
In the model, acute rejection (AR), cytomegalovirus (CMV) infection and infection prophylaxis are limited to the first transplant only. However, these events can occur with subsequent transplants as well and this is not modelled here.	The costs associated with AR, CMV infection and infection prophylaxis for subsequent transplants should be considered by adding columns to each Markov trace. Worksheet: All Markov traces sheets of all regimens Cell range: Preferably, additional columns can be inserted between column R and column T of each Markov trace	Including these events will increase the cost of all regimens, although the QALYs are expected to remain unchanged, leading to higher incremental cost-effectiveness ratio (ICER) values.	This is not a comment on the reliability of the executable model. Assuming that AR and CMV are equally likely to occur for subsequent transplants, irrespective of the regimen for the initial graft, this is roughly equivalent to assuming a higher cost of transplant surgery, which may be a way to explore this issue if the Appraisal Committee deems it necessary. **No action taken.**

Issue 10 Tacrolimus cost in the Tac+MMF+ST regimen

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
In first cycle, tacrolimus will be used for the full cycle length by only those patients who remain in the functioning graft state. But the formula in cell J3 assumes that patient moving to the 'graft loss 1' state will also receive tacrolimus for the full cycle length. This leads to overestimation of drug costs for this regimen. In addition, there is a BD column with blank values, which can be removed from the formula.	The formula in cell J3 should be: "=c_Tacrolimus*weight*(SUM(AY3:BG3)*(Costs!C25*14+Costs!C26*28+Costs!C27*3.5)+(AZ3)*(Costs!C27*38.5+Costs!C28*7))" Worksheet: Tac+MMF+ST Cell range: J3	The total discounted cost of the Tac+MMF+ST regimen will decrease minimally by 0.004%.	We confirm this is a wiring error. **This has been corrected. There is a minimal decrease in total discounted costs for this regimen.**

Issue 11 Sirolimus cost in the Bas+Srl+MMF+ST regimen

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The dosage of sirolimus varies with treatment duration (ie, 0–3 months; 3–6 months; 6–9 months; 9–12 months; 12–48 months; 48+ months). In the Markov trace, the dose required at 48+ months has been used for treatment duration greater than two years. This leads to underestimation of sirolimus cost.	The formula in range J11:J18 should be: "=c_Rapamune*DZ18*(Costs!$C$96*(365.2425/4))" Worksheet : Bas+Srl+MMF+ST Cell range: "J11:J18"	The total discounted cost for the Bas+Srl+MMF+ST regimen increases by 0.43%.	We confirm this is a wiring error. **This has been corrected. There is an increase in total discounted costs for this regimen.**

Issue 12 Azathioprine cost in the Bas+CsA+Aza+ST regimen

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The dosage of azathioprine varies with treatment duration (ie, 0–6 months; 6–12 months; 12–36 months; 36+ months). In the Markov trace, the dosage of azathioprine applicable for 36+ months has not been linked correctly, and the dose used at 12–36 months has also been used for 36+ months.	The formula in K15 of Bas+CsA+Aza+ST worksheet should be: "=DZ15*(c_Azathioprine*weight*(Costs!$C$65*(365.2425/4)))" Should be dragged across all relevant cells in column K Worksheet: Bas+CsA+Aza+ST Cell range: "K15:K203"	This will not result in a change in costs now, because the dose of azathioprine is the same at 12–36 months and 36+ months. However, updating the formula is required to consider cases where the azathioprine dose is different for 12–36 and 36+ months.	We confirm this is a wiring error. **This has been corrected. There are no changes to costs or QALYs in the deterministic base case but may have a small effect on cost-effectiveness in probabilistic analyses due to changing correlations.**

Issue 13 Death with Functioning graft, DFWG (1st graft)

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
DWFG (1st graft) should include patients who transition from the functioning graft to the death state (ie, 1->0). However, the formula in column DV of all regimens' Markov traces also includes patients who transition from the functioning graft to the graft loss 2 state. Therefore, the value in column DV overestimates patients with DFWG (1st graft).	The formula in cell DV4 of all Markov traces should be: "=AY3" and this should be dragged across all relevant cells in column DV Worksheet: All Markov traces sheets of all regimens Cell range: "DV4:DV203"	This outcome is not linked to the total costs and QALY calculations, so it will have no impact on the costs and QALYs.	We confirm this is a wiring error. **This has been corrected, no change in costs and QALYs.**

Issue 14 Wrong labelling

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	PenTAG response
The azathioprine drug cost should be 'per mg'. It is labelled incorrectly as 'per gram', although the 'per mg' cost has been used in the calculations.	Update the label as 'Sampled price per mg' Worksheet: Drug costs Cell range: A12	This has no impact on costs and QALYs.	We confirm this is a labelling error. **This has been corrected, no change in costs and QALYs.**