Addendum to PenTAG report: Comments on corrections and additional analyses conducted by Novartis

Addendum to: 'Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85); a systematic review and economic model.'

1.1 Corrections to model errors, presented by Novartis

Novartis submitted additional analyses to NICE in response to the AG's report. These were derived from the company's corrections to errors in the following elements of its original analysis:

a) the unit cost of ciclosporin, the correct figure was 2.3 times that used in the original analysis
b) formula used to subtract utility loss associated with adverse events in QALYs
c) cost of acute rejection, which in the original analysis had a zero cost
d) maintenance cost of adverse events
e) transition to dialysis and further re-transplants after a first re-transplant, not allowed in the original analysis
f) the formulae used to convert yearly to monthly probabilities of acute and chronic graft rejection.

The revised figures resulting from these corrections by Novartis are presented in the upper half parts of Table 1, for the comparison of everolimus (EVL) with MMF, and Table 2, for EC-MPS relative to MMF. The AG sought to replicate these results (under the assumption that they are deterministic, as implied by the Novartis letter to NICE) by following the corrections detailed in the document 'ID456 Renal (Adult) Novartis corrections to economic model 080515' submitted by Novartis to NICE; the results are presented in the bottom of the table. There are important differences between the results obtained by AG and those reported by Novartis. First, EVL was found to have an ICER of £24,895, as opposed to the £17,182 figure reported by Novartis. Second, while EC-MPS was found to be dominant, it had larger savings and lower gains in QALYs, relative to MMF, than those reported by Novartis.

In the corrections described by Novartis, some apparent errors were identified as well as some omissions in formula definitions. In the described corrections for (d) above, acute and maintenance unit costs were incorrectly assigned to the different types of incident adverse events in the model. Also, in relation to corrections for (e) above, the formula for counting the months on dialysis ('on the original model's S column of worksheets 'Treatment' and 'Comparator') made reference to a cell that in the original model was empty and that was not defined in the new documentation supplied by Novartis (i.e. cell *'Clinical (2)'!$H$19*); the AG

used the original reference instead (i.e. the cell with the random ‘Time to re-transplantation (months)’, *'Clinical (2)'!$F$19*). Another originally empty and now undefined cell was found in the same set of corrections related to (e), in the new column created by Novartis for ‘calculation of “Transplant number” ’ (i.e. cell reference AY.); the AG used another cell instead (AW.).

The corrected figures still have the most important flaws discussed in the AG’s report. First, these analyses are based on deterministic calculations, which due to the nonlinearities in the analysis are likely to diverge from the correct ICER measure, that is, the probabilistic ICERs. There was not enough time for the AG to obtain these revised probabilistic results, due to the long time required by the model to run the required simulations. The second major issue limiting the validity of the revised results is the fact that the risk of graft failure does not vary over time and, more importantly, is entirely unrelated to any of the clinical surrogate outcomes in the model (acute rejection, graft function). This is a major shortcoming in the model, which, in its letter to NICE, Novartis has sought to address by reporting the results of new analyses (these analyses are discussed below). Third, the model is populated by data from single comparative studies and did not conduct further analyses that populated the effectiveness model parameters with the results of a systematic review of the available evidence. The results of the additional analyses by Novartis have used results from the evidence synthesis in the AG report (this is discussed below). Fourth, and related to the previous point, the analyses by Novartis are inadequate to address issues of cost-effectiveness since they do not include all relevant comparators. Further, the Novartis model does not allow one to reliably identify the most cost-effective option, because it only allows two treatment options at any one time to be compared, therefore requiring multiple runs for comparisons involving more than two immunosuppressive treatment arms. Because the Novartis model is based on an individual patient simulation, it produces different results for the same analysis each time it is run. An adequate analysis would require adding more arms to the model and testing the reliability of the new model with more than two treatment options.

In summary, the corrected analyses provided by Novartis are unlikely to provide robust evidence on which to judge the cost-effectiveness of the immunosuppressive drug therapies for kidney transplant recipients.

Table 1. Corrected results of Novartis model as submitted by the company and replicated by the AG (EVL vs. MMF)

	Discounted cost		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
Revised results provided by Novartis					
EVL	£162,014		7.60		
MMF	£141,540	£20,473	6.41	1.19	£17,182
AG's replication of Novartis revised analysis					
EVL	£160,276		7.13		
MMF	£150,318	£9,958	6.73	0.40	£24,895

Table 2. Corrected results of Novartis model as submitted by the company and replicated by the AG (EC-MPS vs. MMF)

	Discounted cost		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
Revised results provided by Novartis					
EC-MPS	£124,388		7.46		
MMF	£141,669	-£17,330	6.42	1.04	Dominant
AG's replication of Novartis revised analysis					
EC-MPS	£122,128		7.11		
MMF	£146,369	-£24,241	6.80	0.31	Dominant

1.2 Additional analyses presented by Novartis

Novartis provided the results of additional analysis adding the following elements to their revised model as discussed in section 1.1 above;

a) a utility loss associated with ageing
b) a utility loss and costs associated with incidence of NODAT in the first year post-transplant, for each comparator
c) reducing trend in average dose of maintenance immunosuppressive therapy used over time
d) revised immunosuppressive therapy drug unit costs in line with AG's values
e) revised re-transplantation costs in line with AG's costs
f) increasing proportion with age of dialysis treatment that is given as haemodialysis
g) one-year efficacy and safety parameter values from AG's network meta-analysis

In their covering letter to NICE describing these, Novartis states that their additional analyses also included an amendment to implement a variable rate of graft survival according to the AG's methods (i.e. using a Weibull survival curve that was a function of safety and efficacy outcomes at 1 year).

According to Novartis, the results of the probabilistic analysis for these scenarios indicate that EC-MPS is associated with additional costs of £28,300 and 1.04 additional QALYs (with

a resulting ICER of £27,241). EVL was associated with additional costs of £107,013 and 1.07 additional QALYs (with a resulting ICER of £100,446).

These additional results address some of the major flaws identified in the AG report, which are summarised at the end of the previous section 1.1. In particular, the results of the Novartis analysis seems to be sensitive to incorporating efficacy and safety parameter values synthesised from a systematic review of the available evidence. It is unfortunate that this evidence was produced at this stage in the process when the model underlying the additional analyses is not available for review and time is insufficient for the AG to implement the changes detailed in the company's letter to NICE.

In this regard, there are several apparent mistakes in the detailed formulae provided in the letter (ID456 Renal (adult) Novartis Additional Analyses 080515 DC) for these analyses. These include the definition of the cells for unit cost of MMF, MPS, and ciclosporin (i.e. new input cells in 'Resource Use' sheet; this appears to be a typo in the letter), the updated drug costs and dialysis calculations (in "Tx Costs" and "Comp Costs", in relation to EVL + MMF, cyclosporine + MMF, Basiliximab + ciclosporin + MPS, Basiliximab + ciclosporin + MMF).

1.2.1 Sensitivity analyses

In addition to the new results cited above, Novartis reports the results of more detailed sensitivity analyses that add individual elements of data from the AG report into their model. Although the reporting of information presented by Novartis is unclear, most of these additional analyses are based on the original model's constant risk of chronic graft rejection as opposed to the Weibull graft survival specification that was used by the AG. From the results of these analyses reported by Novartis it appears that this assumption is critical for the comparison of EC-MPS vs. MMF, so that moving from a constant to a variable (Weibull varying) risk of graft failure takes EC-MPS from being dominant to having an ICER in the range of £29,254 to £36,074, depending on whether utility values adopted by AG are applied instead of those originally used by Novartis.

Novartis argue that utility values used by the AG are less likely to be valid than their chosen values, since unlike Novartis', the AG does not account for the effect of graft function on health-related quality of life. This is a shortcoming of the analysis by the AG for which there is no clear solution (as discussed in the AG report of the cost-effectiveness literature). Although Novartis have incorporated evidence on the rate of change of renal function after year 1, which is the same for all treatment arms in their analysis, there is clearly too much

uncertainty about the medium and long term evolution of renal function to be certain of the superiority of their approach. The model by the AG has the advantage of making the model of the relationship between treatment effects on surrogate outcomes and graft failure logically consistent. Indeed, Novartis reported results of incorporating such surrogate relationship suggest that the EC-MPS may well miss the upper (£30,000) threshold of cost-effectiveness.

In conclusion, the additional evidence provided by Novartis suggests that everolimus may not be cost-effective. The additional evidence on EC-MPS is insufficient to support its cost-effectiveness. These analyses would require more detailed scrutiny than that afforded by the documentation provided and the timing of their availability if they are to properly inform NICE deliberations. In any case, a major issue casting doubt on any claim of EC-MPS being cost-effective is the omission of important comparators, which a revised model with more arms would need to accommodate for robust analysis of the NICE decision problem. Nevertheless the AG agrees that the evidence from the additional analyses provided by Novartis should supersede the results of the corrected analyses discussed in section 1.1. However, the AG has not had access to the revised model behind these additional analyses nor had the time to try to implement any of the changes described by Novartis for these additional analyses and is therefore not able to comment on the quality of their implementation by Novartis.

1.2.2 Subgroup analysis

Novartis presents results for EC-MPS as second line therapy in patients who have stopped MMF due to GI-adverse events. The company reports an ICER for EC-MPS of £34,167, when the safety and efficacy values from the AG report are used and a £12,024 when a further adjustment is made to take account for a reduced dose of MMF in this population. Alternatively results based on the assumption of no difference in effectiveness between MMF and EC-MPS in a general kidney transplant recipient population were also presented, £34,167 and £19,640, respectively. More favourable results were found with the revised Novartis model specification and parameter values.

The reporting of the methods used for these analyses is not clear, but it seems that they are based on the fixed chronic rejection rate assumption used in the original Novartis model which is discussed in section 1.2.1 above. Given the strong influence of this assumption in the previous results for the overall patient population, it is questionable that these results are sufficiently robust to support a cost-effectiveness claim of cost-effectiveness of EC-MPS for this subpopulation.