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

ERRATA

This document outlines errata to the report dated March 25th 2015: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85). The majority of these errata are provided in response to consultation comments from Consultees and Commentators.

Inappropriate inclusion of non-Thymoglobulin® rabbit anti-thymocyte globulin studies

In our report we considered the two rabbit anti-thymocyte globulin (rATG) products, Thymoglobulin (anti-human thymocyte immunoglobulin) and ATG-Fresenius® (anti-human T-lymphocyte immunoglobulin), to be interchangeable. Since the terms lymphocyte immune globulin and anti-thymocyte globulin, appear to be transposable, neither we, nor our clinical experts, noted the distinction between drugs. Only Thymoglobulin is named in the final scope for this appraisal.

Sanofi (the manufacturer of Thymoglobulin) have provided arguments and some evidence that the different ATG products cannot be considered interchangeable, and we believe there is some merit to these arguments.

Therefore, we have included 4 studies which should have been excluded; three studies (Samsel 2008; Kyllonen 2007 and Sheashaa 2008)[1-3] used ATG-Fresenius and one study (Sollinger 2001)[4], which was included in the previous HTA and subsequently included by us, used both rabbit and horse ATG.

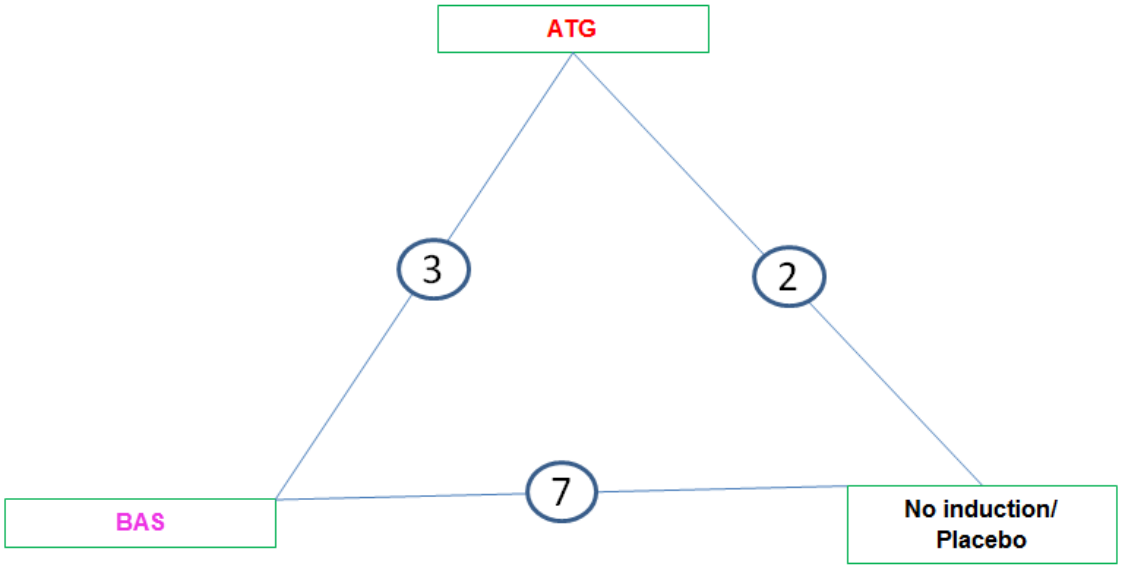
In order to establish the impact removing the non-Thymoglobulin studies, we have repeated the network meta-analysis and updated the deterministic analyses and PSA.

Updated network meta-analysis for Thymoglobulin

Induction therapy results

Network meta-analysis was performed for all induction studies reporting graft loss, mortality, BPAR and eGFR at one year follow-up. Figure 1 displays the network for included induction studies.

Figure 1. Network diagram for all included induction studies

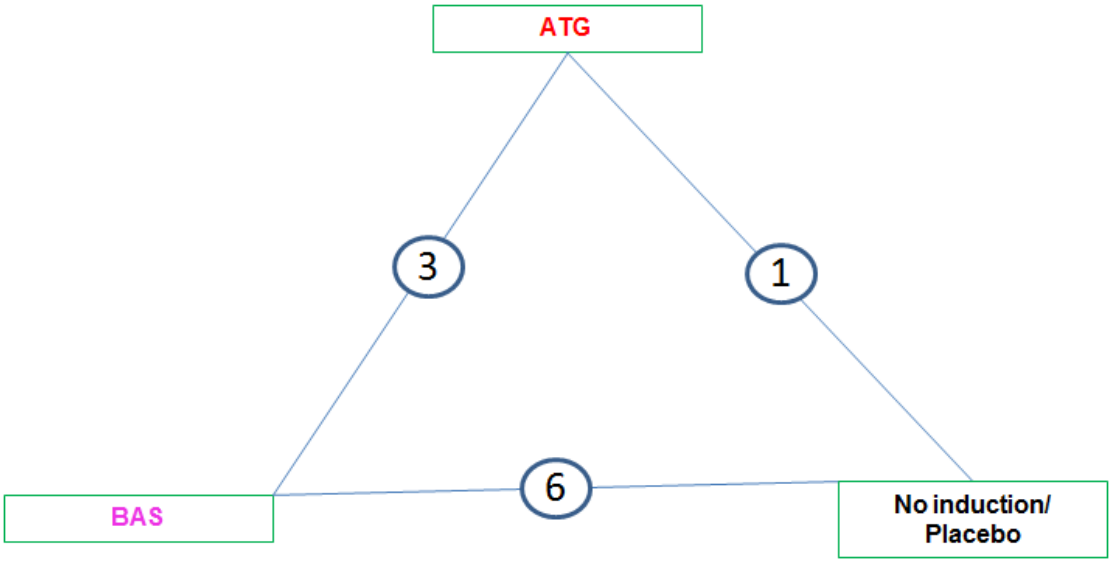


Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

Graft Loss

10 RCTs informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for graft loss (Figure 2).

Figure 2. Network diagram for induction studies reporting graft loss



Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, thus only the results of the fixed effects model are shown in Table 1.

Table 1. ORs for induction therapy from a fixed effects model (Posterior mean (95%CI))

Treatment comparison	Graft loss	Mortality	BPAR
BAS vs placebo/no treatment	0.82 (0.56, 1.18)	0.99 (0.53, 1.85)	**0.52 (0.41, 0.65)**
ATG vs placebo/no treatment	0.77 (0.39, 1.47)	0.84 (0.33, 2.07)	**0.36 (0.24, 0.54)**
ATG vs BAS	0.94 (0.50, 1.75)	0.84 (0.36, 1.96)	**0.70 (0.47, 1.03)**

Key: ATG, Antithymocyte globulin; BAS, basiliximab; BPAR, biopsy proven acute rejection.
Notes: OR < 1 favours the first treatment in the comparison; Evidence suggesting a difference between treatments highlighted in bold.

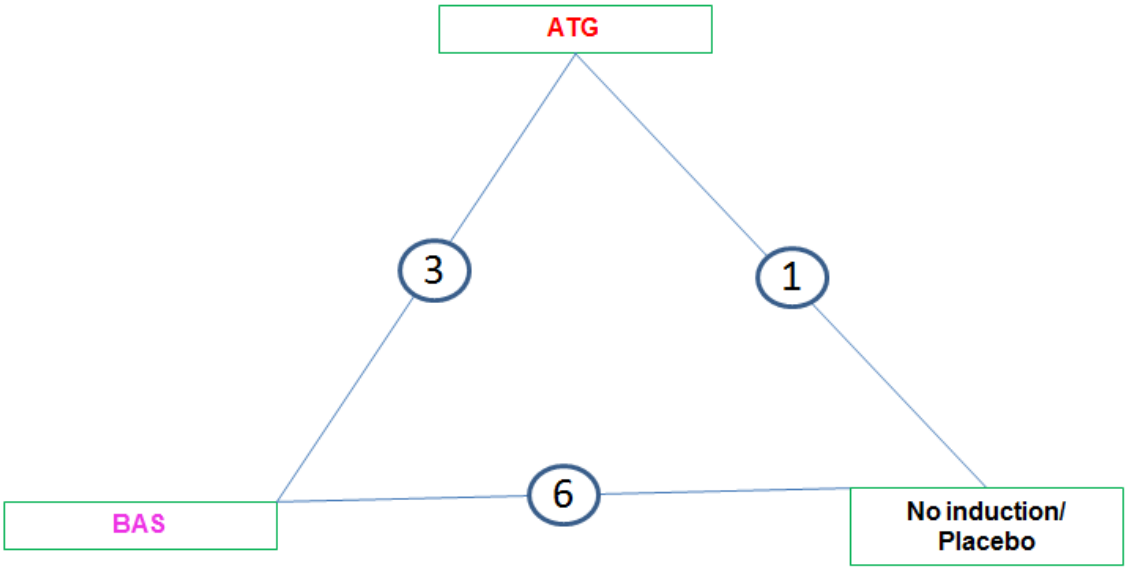
From these analyses there is little evidence to suggest that BAS and ATG are more effective than no induction/placebo in reducing graft loss as the 95% CIs include OR of one. Furthermore, there is little evidence to suggest that ATG is more effective than BAS. Of the three treatments analysed in this network, ATG was estimated as having a 57% probability

of being the most effective treatment, with BAS having a 38% probability of being the most effective treatment.Analyses suggested that there was little evidence of inconsistency within this network..

Mortality

10 RCTs informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for mortality (Figure 3).

Figure 3. Network diagram for induction studies reporting mortality



Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, thus only the results of the fixed effects model are shown in Table 1.

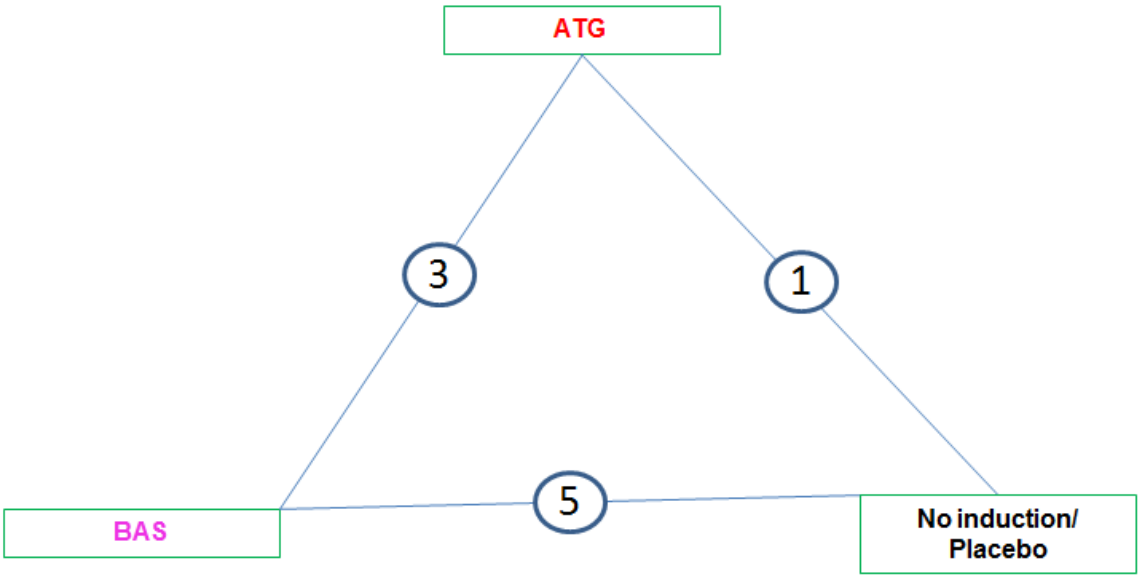
From these analyses there is little evidence to suggest that BAS and ATG are more effective than no induction/placebo in reducing mortality as the 95% CIs include OR of 1 (Table 1) and there is little evidence to suggest that ATG is more effective than BAS. Of the three treatments analysed in this network, ATG was estimated as having a 54% probability of being the most effective treatment, with BAS having a 22% probability of being the most

effective treatment. Analyses suggested that there was little evidence of inconsistency within this network.

Biopsy proven acute rejection

Nine RCTs informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for BPAR (Figure 4).

Figure 4. Network diagram for induction studies reporting BPAR



Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, and so only the results of the fixed effects model are shown in Table 1.

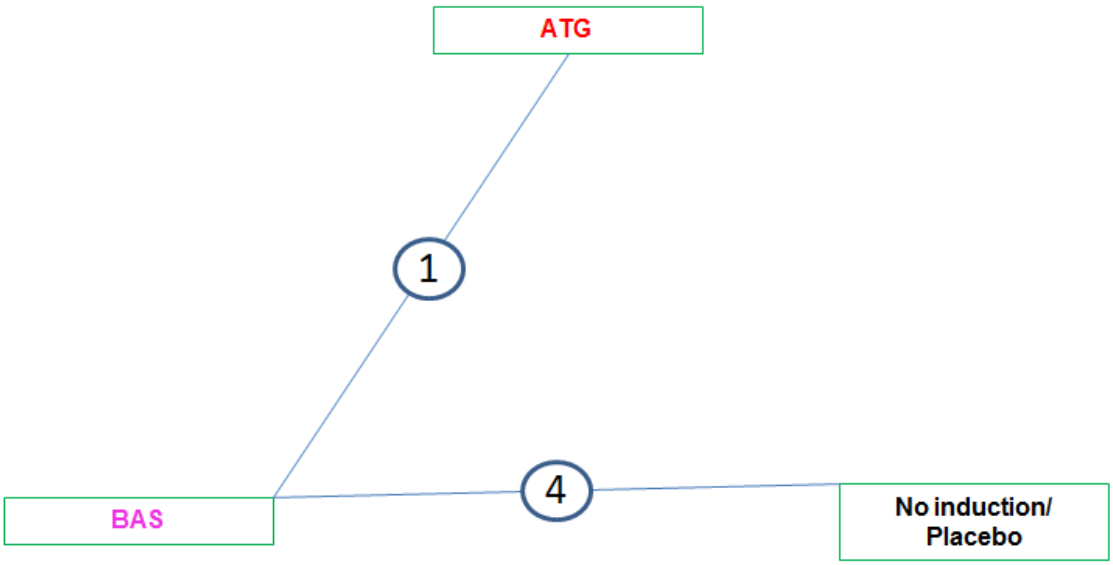
From these analyses evidence suggests that BAS and ATG are more effective than no induction/placebo in reducing BPAR but that ATG is no more effective than BAS. Of the three treatments analysed in this network, ATG was estimated as having a 96% probability of being the most effective treatment, with BAS having a 3% probability of being the most

effective treatment. Analyses suggested that there was little evidence of inconsistency within this network.

Graft function

Five RCTs informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for graft function (Figure 5).

Figure 5. Network diagram for induction studies reporting graft function



Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

The DIC suggested very little difference between the fit of the fixed and random effects model. For comparison with the above outcomes, the results of the fixed effects model are shown in Table 2.

Table 2. Mean effects for induction therapy for the outcome graft function from a fixed effects model (Posterior mean (95%CI))

	Graft function
BAS vs placebo/no treatment	**2.11 (-0.45, 4.68)**
ATG vs placebo/no treatment	-3.95 (-11.80, 3.94)
ATG vs BAS	-6.06 (-13.46, 1.37)

Key: ATG, Antithymocyte globulin; BAS, basiliximab; GRF, graft function.
Notes: Posterior mean >0 favours the first treatment in the comparison; Evidence suggesting a difference between treatments highlighted in bold

There is no evidence to suggest that BAS or ATG are more effective than placebo/no induction, and no evidence to suggest that one treatment is more effective than the other. BAS has an 89% probability of being the most effective treatment, while ATG has a 5% probability of being the most effective treatment. Analyses suggested that there was little evidence suggestion of inconsistency within this network.

Summary for network meta-analysis

Induction therapy

- There is no evidence to suggest BAS or ATG are more effective than placebo/no induction or each other in reducing the odds of graft loss, mortality, or CRC-GFR
- ATG and BAS are both estimated to be more effective than placebo/no induction, at reducing BPAR, but the evidence does not suggest a difference between the two treatments

Cumulative changes to PenTAG economic model

Here we present all changes to the reported methods and results of the PenTAG economic model as a result of errors identified since submission which are not reported elsewhere in this document.

Location	Text affected	Correction
Section 7.1.2.1 (Base case analysis), page 393, lines 12–16	• Rabbit ATG (three comparisons): Deterministic ICERs £133,000–£369,000 per QALY; Probabilistic ICERs £200,000–£1,185,000 per QALY • Ciclosporin (four comparisons): Deterministic ICERs £161,000–£256,000 per QALY (three comparisons) or dominated (one comparison); Probabilistic ICERs £204,000–£384,000 per QALY (three comparisons) or dominated (one comparison)	• Rabbit ATG (three comparisons): Dominated in deterministic and probabilistic analyses • Ciclosporin (four comparisons): Deterministic ICERs £131,000–£205,000 per QALY (three comparisons) or dominated (one comparison); Probabilistic ICERs £202,000–£303,000 per QALY (three comparisons) or dominated (one comparison)
Section 7.1.2.1 (Base case analysis), page 393, lines 21–22	• Mycophenolate sodium (one comparison): Deterministic ICER £145,000 per QALY; Dominated in probabilistic analysis	• Mycophenolate sodium (one comparison): Deterministic ICER £144,000 per QALY; Dominated in probabilistic analysis
Section 7.1.2.1 (Base case analysis), page 393, lines 24–25	• Everolimus (one comparison): Deterministic ICER £1,744,000 per QALY; Probabilistic ICER £5,425,000 per QALY	• Everolimus (one comparison): Deterministic ICER £1,532,000 per QALY; Probabilistic ICER £3,260,000 per QALY

Section 7.1.2.1 (Base case analysis), page 394, lines 1–2	• Belatacept (one comparison): Deterministic ICER £519,000 per QALY; Probabilistic ICER £546,000 per QALY	• Belatacept (one comparison): Deterministic ICER £424,000 per QALY; Probabilistic ICER £446,000 per QALY
Section 7.1.2.2 (Scenario analyses), page 394, lines 5–13	In a scenario analysis investigating the impact of structural uncertainty in the surrogate effect of acute rejection, NODAT and graft function at 12 months on graft survival it was found that if the surrogate effect was weakened (by limiting its duration), no induction and ciclosporin became cost-effective at £20,000 and £30,000 per QALY versus basiliximab induction and immediate-release tacrolimus. The duration of surrogate effect had to be limited to one year for no induction to be cost-effective versus basiliximab at £20,000 per QALY and eliminated entirely to be cost-effective at £30,000 per QALY. The duration of surrogate effect had to be limited to 3–8 years or less (depending on the comparison) for ciclosporin to be cost-effective versus immediate-relase tacrolimus at £20,000 or £30,000 per QALY.	In a scenario analysis investigating the impact of structural uncertainty in the surrogate effect of acute rejection, NODAT and graft function at 12 months on graft survival it was found that if the surrogate effect was weakened (by limiting its duration), no induction and ciclosporin became cost-effective at £20,000 and £30,000 per QALY versus basiliximab induction and immediate-release tacrolimus respectively in some combinations. When used in combination with immediate-release tacrolimus and mycophenolate mofetil, no induction became cost-effective if the duration of the surrogate effect was limited to 1–2 years. In combination with ciclosporin and mycophenolate mofetil the duration had to be further limited and in combination with ciclosporin and azathioprine no induction was not cost-effective even when the surrogate effect was eliminated entirely. The duration of surrogate effect had to be limited to 3–7 years or less (depending on the comparison) for ciclosporin to be cost-effective versus immediate-relase tacrolimus at £20,000 or £30,000 per QALY.
Section 7.1.2.2 (Scenario	When list prices were adopted	When list prices were adopted

analyses), page 394, lines 20–25	instead of average NHS acquisition costs for drug acquisition costs, ciclosporin and azathioprine became cost-effective at £20,000 to £30,000 per QALY in some combinations (when ciclosporin was used in combination with mycophenolate mofetil and when azathioprine was used in combination with tacrolimus) with immediate-release tacrolimus and mycophenolate mofetil remaining cost-effective at £20,000 to £30,000 per QALY in other comparisons.	instead of average NHS acquisition costs for drug acquisition costs, ciclosporin and azathioprine became cost-effective at £20,000 to £30,000 per QALY in some combinations, with immediate-release tacrolimus and mycophenolate mofetil remaining cost-effective at £20,000 to £30,000 per QALY in other comparisons.
Section 7.3.3.1 (Overall survival), page 405	Table 158	Table 3
Section 7.3.3.2 (Graft survival / Estimation of graft survival / Adjustments after the first year), pages 411–412	Table 161 Table 162	Table 4 Table 5
Section 7.3.3.2 (Graft survival / Estimation of graft survival / Adjustments after the first year / Acute rejection within 12 months), page 415	Table 164	Table 6
Section 7.3.4 (Effectiveness estimates), page 437	Table 182	Table 7
Section 7.3.4 (Effectiveness estimates), page 438	Table 183	Table 8
Section 7.2 (Results)	Whole section	See addendum
Appendix 9 (Additional results from the PenTAG economic model	Table 238 to Table 245	Table 9 to Table 17

Table 3: Comparison of hazard ratios for death with functioning graft from regression and calculated using Solver (updated)

Regimen	Hazard ratio for death with functioning graft	
	From regression	Using Solver
CSA+MMF	0.581	0.571
TAC+MMF	0.998	1.002
CSA+AZA	0.606	0.596
TAC+AZA	0.870	0.873
CSA+EVL	0.907	0.910
TAC+SRL	0.870	0.873
TAC-PR+MMF	1.307	1.306
BAS+CSA+MMF	0.584	0.575
BAS+TAC+MMF	0.997	1.000
BAS+CSA+AZA	0.611	0.602
BAS+SRL+MMF	1.125	1.129
BAS+BEL+MMF	0.271	0.233
BAS+CSA+MPS	0.364	0.337
rATG+CSA+MMF	0.484	0.468
rATG+TAC+MMF	0.826	0.827
rATG+CSA+AZA	0.506	0.489

Table 4: Rate parameters for graft survival after one year (updated)

Regimen	Rate parameter (λ)
CSA+MMF	0.0233
TAC+MMF	0.0201
CSA+AZA	0.0264
TAC+AZA	0.0193
CSA+EVL	0.0212
TAC+SRL	0.0244
TAC-PR+MMF	0.0202
BAS+CSA+MMF	0.0208
BAS+TAC+MMF	0.0181
BAS+CSA+AZA	0.0232
BAS+SRL+MMF	0.0196
BAS+BEL+MMF	0.0169
BAS+CSA+MPS	0.0192
rATG+CSA+MMF	0.0240
rATG+TAC+MMF	0.0210
rATG+CSA+AZA	0.0264

Table 5: 1-, 3-, 5- and 10-year graft survival for each regimen (updated)

Regimen	Graft survival (excluding death with functioning graft and primary non-function)			
	1 year	3 years	5 years	10 years
CSA+MMF	95.37%	90.71%	85.62%	73.23%
TAC+MMF	95.72%	91.66%	87.20%	76.18%
CSA+AZA	93.87%	88.69%	83.07%	69.58%
TAC+AZA	93.04%	89.26%	85.08%	74.73%
CSA+EVL	96.13%	91.84%	87.14%	75.57%
TAC+SRL	92.89%	88.13%	82.96%	70.41%
TAC-PR+MMF	94.90%	90.86%	86.41%	75.43%
BAS+CSA+MMF	96.19%	91.97%	87.34%	75.94%
BAS+TAC+MMF	96.48%	92.79%	88.73%	78.58%
BAS+CSA+AZA	94.93%	90.31%	85.27%	72.97%
BAS+SRL+MMF	94.78%	90.87%	86.57%	75.92%
BAS+BEL+MMF	96.84%	93.38%	89.54%	79.92%
BAS+CSA+MPS	96.69%	92.77%	88.45%	77.73%
rATG+CSA+MMF	96.42%	91.56%	86.27%	73.41%
rATG+TAC+MMF	96.69%	92.42%	87.73%	76.19%
rATG+CSA+AZA	95.25%	89.99%	84.30%	70.61%

Table 6: Acute rejection rates and hazard ratio for graft survival due to acute rejection for each regimen (updated)

Regimen	Acute rejection rate	Raw hazard ratio	Hazard ratio vs. baseline
CSA+MMF	23.96%	1.144	1.066
TAC+MMF	21.02%	1.126	1.049
CSA+AZA	40.05%	1.240	1.156
TAC+AZA	27.86%	1.167	1.088
CSA+EVL	23.38%	1.140	1.063
TAC+SRL	20.41%	1.122	1.046
TAC-PR+MMF	20.61%	1.124	1.047
BAS+CSA+MMF	14.10%	1.085	1.011
BAS+TAC+MMF (baseline)	12.17%	1.073	1.000
BAS+CSA+AZA	25.82%	1.155	1.076
BAS+SRL+MMF	13.19%	1.079	1.006
BAS+BEL+MMF	21.90%	1.131	1.054
BAS+CSA+MPS	19.61%	1.118	1.042
rATG+CSA+MMF	10.25%	1.062	0.989
rATG+TAC+MMF	8.80%	1.053	0.981
rATG+CSA+AZA	19.50%	1.117	1.041

Table 7: Summary of mean treatment effects from network meta-analyses (updated)

Arm	Mortality within 12 months[a] *Lower is better*	Graft loss within 12 months[a] *Lower is better*	eGFR at 12 months[b] *Higher is better*	Biopsy-proven acute rejection within 12 months[a] *Lower is better*
Induction (versus no induction)				
Basiliximab	−0.0067	−0.2021	+2.113	−0.6523
Rabbit ATG	−0.1788	−0.2687	−3.942	−1.0147
Maintenance (versus CSA+AZA)				
TAC+AZA	+0.3234	+0.1353	+9.304	−0.5484
CSA+MPA	−0.0569	−0.2971	+1.609	−0.7516
TAC+MPA	+0.4218	−0.3788	+6.531	−0.9205
BEL+MPA	−0.7630	−0.4915	+10.55	−0.2159
CSA+EVL	+0.3330	−0.4843	+4.863	−0.7835
TAC+SRL	+0.3248	+0.1587	−0.3523	−0.9574
SRL+MPA	+0.5416	+0.0321	+3.846	−0.8283

Key: MPA, mycophenolic acid = mycophenolate mofetil or mycophenolate sodium
a Presented as log odds ratios
b Presented as mean difference

Table 8: Summary of absolute effectiveness estimates for each regimen (updated)

Regimen	Mortality within 12 months (odds)	Graft loss within 12 months (odds)	Mean eGFR (ml/min/1.73 m²)	Biopsy proven acute rejection within 12 months (odds)
CSA+MMF	0.0097	0.0485	46.4	0.315
TAC+MMF	0.0154	0.0446	51.3	0.266
CSA+AZA	0.0103	0.0652	44.8	0.668
TAC+AZA	0.0140	0.0746	54.1	0.386
CSA+EVL	0.0141	0.0402	49.6	0.305
TAC+SRL	0.0140	0.0764	44.4	0.256
TAC-PR+MMF	0.0198	0.0536	51.1	0.260
BAS+CSA+MMF	0.0097	0.0396	48.5	0.164
BAS+TAC+MMF	0.0153	0.0365	53.4	0.139
BAS+CSA+AZA	0.0102	0.0533	46.9	0.348
BAS+SRL+MMF	0.0173	0.0550	50.7	0.152
BAS+BEL+MMF	0.0052	0.0326	57.4	0.280
BAS+CSA+MPS	0.0065	0.0342	52.4	0.244
rATG+CSA+MMF	0.0083	0.0371	42.4	0.114
rATG+TAC+MMF	0.0129	0.0341	47.4	0.096
rATG+CSA+AZA	0.0087	0.0499	40.8	0.242

Table 9: Disaggregated discount costs in the PenTAG model (deterministic base case) (updated)

Regimen	Induction therapy (1st graft)	Maintenance immunosuppress -ion (first graft)	Acute rejection (1st graft)	Infection prophylaxis (1st graft)	CMV infection (1st graft)	Monitoring (1st graft)	Retransplantation
CSA+MMF	£0	£15,970	£989	£761	£313	£16,112	£4,882
TAC+MMF	£0	£14,884	£867	£761	£313	£16,365	£4,392
CSA+AZA	£0	£13,519	£1,653	£755	£313	£15,622	£5,454
TAC+AZA	£0	£13,347	£1,149	£751	£313	£16,099	£4,652
CSA+EVL	£0	£96,482	£965	£762	£107	£18,891	£4,495
TAC+SRL	£0	£34,841	£842	£751	£107	£17,977	£5,309
TAC-PR+MMF	£0	£27,838	£850	£757	£313	£16,176	£4,499
BAS+CSA+MMF	£2,188	£16,558	£582	£764	£313	£16,466	£4,454
BAS+TAC+MMF	£2,188	£15,358	£502	£763	£313	£16,684	£4,010
Bas+CSA+AZA	£2,188	£14,143	£1,065	£759	£313	£16,057	£4,925
Bas+SRL+MMF	£2,188	£35,557	£544	£757	£150	£16,283	£4,439
BAS+BEL+MMF	£2,188	£140,512	£904	£767	£313	£14,426	£3,838
BAS+CSA+MPS	£2,188	£35,617	£809	£766	£313	£16,744	£4,181
rATG+CSA+MMF	£4,255	£16,026	£423	£1,692	£313	£16,200	£4,847
rATG+TAC+MMF	£4,255	£14,914	£363	£1,691	£313	£16,442	£4,388
rATG+CSA+AZA	£4,255	£13,728	£804	£1,683	£313	£15,823	£5,284

Table 10: Disaggregated discount costs in the PenTAG model (deterministic base case) (cont.) (updated)

Regimen	Immunosuppression (subsequent grafts)	Monitoring (subsequent grafts)	Dialysis	NODAT	Anaemia	Dyslipidaemia	Graft loss	Total
CSA+MMF	£2,686	£3,686	£49,145	£1,465	£865	£408	£147	£97,429
TAC+MMF	£2,403	£3,297	£44,413	£3,113	£877	£407	£133	£92,226
CSA+AZA	£3,011	£4,132	£54,264	£1,452	£842	£404	£175	£101,595
TAC+AZA	£2,567	£3,522	£46,358	£3,113	£871	£407	£169	£93,319
CSA+EVL	£2,469	£3,388	£45,572	£1,397	£877	£619	£130	£176,154
TAC+SRL	£2,908	£3,991	£52,561	£4,623	£838	£608	£183	£125,539
TAC-PR+MMF	£2,463	£3,381	£45,244	£3,592	£868	£404	£144	£106,529
BAS+CSA+MMF	£2,445	£3,355	£45,195	£1,476	£883	£410	£129	£95,219
BAS+TAC+MMF	£2,189	£3,004	£40,840	£3,134	£893	£409	£117	£90,405
Bas+CSA+AZA	£2,713	£3,723	£49,469	£1,464	£864	£407	£152	£98,244
Bas+SRL+MMF	£2,441	£3,350	£44,684	£2,518	£876	£617	£145	£114,549
BAS+BEL+MMF	£2,111	£2,897	£39,350	£658	£917	£418	£110	£209,409
BAS+CSA+MPS	£2,293	£3,146	£42,660	£1,391	£898	£414	£118	£111,540
rATG+CSA+MMF	£2,657	£3,646	£49,005	£1,467	£867	£408	£134	£101,940
rATG+TAC+MMF	£2,391	£3,282	£44,581	£3,118	£878	£408	£122	£97,146
rATG+CSA+AZA	£2,907	£3,989	£52,916	£1,456	£849	£405	£156	£104,570

Table 11: Additional clinical outcomes as calculated by the PenTAG model (deterministic base case) (updated)

Regimen	Mean undiscounted life years (life expectancy)	Undiscounted life years with functioning graft	Undiscounted life years on dialysis	Acute rejection	NODAT	Proportion receiving 2nd transplant	Proportion receiving 3rd transplant
CSA+MMF	22.397	19.070	3.326	24.0%	5.0%	23.8%	2.7%
TAC+MMF	22.421	19.407	3.014	21.0%	10.6%	21.4%	2.4%
CSA+AZA	22.102	18.471	3.631	40.1%	5.0%	26.3%	3.0%
TAC+AZA	22.430	19.342	3.088	27.9%	10.6%	22.2%	2.6%
CSA+EVL	22.509	19.404	3.105	23.4%	4.7%	22.0%	2.4%
TAC+SRL	21.886	18.395	3.491	20.4%	16.0%	25.4%	3.0%
TAC-PR+MMF	22.248	19.198	3.051	20.6%	12.3%	21.8%	2.5%
BAS+CSA+MMF	22.636	19.554	3.082	14.1%	5.0%	21.8%	2.4%
BAS+TAC+MMF	22.640	19.850	2.790	12.2%	10.6%	19.6%	2.2%
Bas+CSA+AZA	22.380	19.041	3.339	25.8%	5.0%	23.9%	2.7%
Bas+SRL+MMF	22.448	19.434	3.014	13.2%	8.6%	21.4%	2.4%
BAS+BEL+MMF	23.206	20.502	2.704	21.9%	2.2%	18.8%	2.1%
BAS+CSA+MPS	22.877	19.953	2.923	19.6%	4.7%	20.5%	2.3%
rATG+CSA+MMF	22.403	19.065	3.338	10.3%	5.0%	23.8%	2.6%
rATG+TAC+MMF	22.432	19.385	3.046	8.8%	10.6%	21.6%	2.4%
rATG+CSA+AZA	22.178	18.609	3.570	19.5%	5.0%	25.7%	2.9%

Table 12: Deterministic results when Solver is used instead of flexible regression to match mortality at 12 months (updated)

Regimen	Total discounted costs	Total discounted QALYs	Net health benefit	
			£20k/QALY	£30k/QALY
CSA+MMF	£97,441	10.9160	6.0440	7.6680
TAC+MMF	£92,222	10.8879	6.2768	7.8138
CSA+AZA	£101,607	10.7724	5.6921	7.3855
TAC+AZA	£93,315	10.8692	6.2034	7.7586
CSA+EVL	£176,148	10.9655	2.1581	5.0939
TAC+SRL	£125,534	10.6018	4.3251	6.4173
TAC-PR+MMF	£106,530	10.7920	5.4656	7.2411
BAS+CSA+MMF	£95,230	11.0261	6.2646	7.8517
BAS+TAC+MMF	£90,401	10.9875	6.4674	7.9741
Bas+CSA+AZA	£98,254	10.9042	5.9915	7.6291
Bas+SRL+MMF	£114,544	10.9005	5.1733	7.0824
BAS+BEL+MMF	£209,510	11.2998	0.8244	4.3162
BAS+CSA+MPS	£111,576	11.1417	5.5629	7.4225
rATG+CSA+MMF	£101,959	10.9304	5.8325	7.5318
rATG+TAC+MMF	£97,145	10.9045	6.0473	7.6664
rATG+CSA+AZA	£104,590	10.8205	5.5910	7.3342

Table 13: Regimens on the cost-effectiveness frontier when Solver is used instead of flexible regression to match mortality at 12 months (updated)

Regimen	Total discounted costs	Total discounted QALYs	ICER (cost per QALY)	Incremental net health benefit	
				£20k/QALY	£30k/QALY
BAS+TAC+MMF	£90,401	10.9875	—	—	—
BAS+CSA+MMF	£95,230	11.0261	£125,110	-0.2028	-0.1224
BAS+CSA+MPS	£111,576	11.1417	£141,349	-0.9045	-0.5516
BAS+BEL+MMF	£209,510	11.2998	£619,299	-5.6431	-3.6579

Table 14: Cost-effectiveness of induction agents when there is no disutility applied for NODAT (updated)

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With CSA+AZA						*vs. Basiliximab*	
No induction	£101,595	—	10.8127	—	Dominated	-0.2998	-0.2439
Rabbit ATG	£104,570	+£2,975	10.8600	+0.0472	Dominated	-0.4013	-0.2959
Basiliximab	£98,244	-£6,326	10.9450	+0.0850	—	—	—
With CSA+MMF						*vs. Basiliximab*	
No induction	£97,429	—	10.9566	—	Dominated	-0.2210	-0.1841
Rabbit ATG	£101,940	+£4,511	10.9702	+0.0136	Dominated	-0.4329	-0.3209
Basiliximab	£95,219	-£6,720	11.0671	+0.0969	—	—	—
With TAC+MMF						*vs. Basiliximab*	
No induction	£92,226	—	10.9778	—	Dominated	-0.1912	-0.1609
Rabbit ATG	£97,146	+£4,920	10.9942	+0.0165	Dominated	-0.4208	-0.3084
Basiliximab	£90,405	-£6,741	11.0779	+0.0837	—	—	—

Table 15: Cost-effectiveness of maintenance agents when there is no disutility applied for NODAT (updated)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With MMF						*vs. TAC*	
TAC-PR	£106,529	—	10.8952	—	Dominated	-0.7978	-0.5594
CSA	£97,429	-£9,100	10.9566	+0.0614	Dominated	-0.2813	-0.1946
TAC	£92,226	-£5,203	10.9778	+0.0212	—	—	—
With AZA						*vs. TAC*	
CSA	£101,595	—	10.8127	—	Dominated	-0.5601	-0.4222
TAC	£93,319	-£8,276	10.9590	+0.1463	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£114,549	—	10.9733	—	Dominated	-1.3118	-0.9094
CSA	£95,219	-£19,329	11.0671	+0.0938	Dominated	-0.2516	-0.1713
TAC	£90,405	-£4,815	11.0779	+0.0109	—	—	—
BEL	£209,409	+£119,004	11.3130	+0.2350	£506,309	-5.7152	-3.7318
With rATG+MMF						*vs. TAC*	
CSA	£101,940	—	10.9702	—	Dominated	-0.2637	-0.1838
TAC	£97,146	-£4,794	10.9942	+0.0241	—	—	—
With CSA						*vs. MMF*	
AZA	£101,595	—	10.8127	—	Dominated	-0.3522	-0.2827
MMF	£97,429	-£4,166	10.9566	+0.1439	—	—	—
EVL	£176,154	+£78,725	11.0060	+0.0494	£1,593,185	-3.8869	-2.5748
With TAC						*vs. MMF*	
SRL	£125,539	—	10.7350	—	Dominated	-1.9084	-1.3532
AZA	£93,319	-£32,220	10.9590	+0.2240	Dominated	-0.0734	-0.0552
MMF	£92,226	-£1,093	10.9778	+0.0188	—	—	—
With BAS+CSA						*vs. MMF*	

AZA	£98,244	—	10.9450	—	Dominated	-0.2733	-0.2229
MMF	£95,219	-£3,025	11.0671	+0.1221	—	—	—
MPS	£111,540	+£16,321	11.1776	+0.1106	£147,616	-0.7055	-0.4335
With rATG+CSA						*vs. MMF*	
AZA	£104,570	—	10.8600	—	Dominated	-0.2417	-0.1979
MMF	£101,940	-£2,631	10.9702	+0.1102	—	—	—

Table 16: Cost-effectiveness of induction agents when the 2007–2012 donor type distribution is used (updated)

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With CSA+AZA						*vs. Basiliximab*	
No induction	£99,452	—	10.9491	—	Dominated	-0.2958	-0.2421
Rabbit ATG	£102,558	+£3,106	10.9934	+0.0443	Dominated	-0.4068	-0.3014
Basiliximab	£96,233	-£6,325	11.0839	+0.0905	—	—	—
With CSA+MMF						*vs. Basiliximab*	
No induction	£95,517	—	11.0949	—	Dominated	-0.2166	-0.1818
Rabbit ATG	£100,114	+£4,598	11.1051	+0.0103	Dominated	-0.4363	-0.3248
Basiliximab	£93,428	-£6,686	11.2071	+0.1020	—	—	—
With TAC+MMF						*vs. Basiliximab*	
No induction	£90,413	—	11.0735	—	Dominated	-0.1853	-0.1571
Rabbit ATG	£95,394	+£4,980	11.0866	+0.0131	Dominated	-0.4212	-0.3101
Basiliximab	£88,724	-£6,670	11.1743	+0.0877	—	—	—

Table 17: Cost-effectiveness of maintenance agents when the 2007–2012 donor type distribution is used (updated)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With MMF						*vs. TAC*	
TAC-PR	£105,133	—	10.9784	—	Dominated	-0.8311	-0.5857
TAC	£90,413	-£14,720	11.0735	+0.0951	—	—	—
CSA	£95,517	+£5,103	11.0949	+0.0214	£238,659	-0.2338	-0.1487
With AZA						*vs. TAC*	
CSA	£99,452	—	10.9491	—	Dominated	-0.5164	-0.3802
TAC	£91,278	-£8,175	11.0568	+0.1077	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£113,366	—	11.0876	—	Dominated	-1.3188	-0.9081
TAC	£88,724	-£24,642	11.1743	+0.0867	—	—	—
CSA	£93,428	+£4,704	11.2071	+0.0328	£143,420	-0.2024	-0.1240
BEL	£211,416	+£117,987	11.4794	+0.2723	£433,299	-5.8295	-3.7846
With rATG+MMF						*vs. TAC*	
TAC	£95,394	—	11.0866	—	—	—	—
CSA	£100,114	+£4,721	11.1051	+0.0186	£253,976	-0.2174	-0.1388
With CSA						*vs. MMF*	
AZA	£99,452	—	10.9491	—	Dominated	-0.3426	-0.2770
MMF	£95,517	-£3,936	11.0949	+0.1458	—	—	—
EVL	£176,982	+£81,466	11.1500	+0.0551	£1,477,730	-4.0182	-2.6604
With TAC						*vs. MMF*	
SRL	£124,216	—	10.7817	—	Dominated	-1.9819	-1.4186
AZA	£91,278	-£32,938	11.0568	+0.2751	Dominated	-0.0599	-0.0455
MMF	£90,413	-£864	11.0735	+0.0167	—	—	—
With BAS+CSA						*vs. MMF*	
AZA	£96,233	—	11.0839	—	Dominated	-0.2634	-0.2167
MMF	£93,428	-£2,805	11.2071	+0.1232	—	—	—

MPS	£110,393	+£16,965	11.3211	+0.1140	£148,867	-0.7343	-0.4515
With rATG+CSA						*vs. MMF*	
AZA	£102,558	—	10.9934	—	Dominated	-0.2339	-0.1932
MMF	£100,114	-£2,444	11.1051	+0.1118	—	—	—

Errors in the PenTAG model

Novartis reliability checks

We are grateful to Novartis for conducting a thorough check of the reliability of the PenTAG model, and identifying a number of wiring and labelling errors. Very few of these errors had any significant impact on the results.

An error in the calculation of the graft function for the TAC-PR+MMF regimen was identified. In the original model eGFR was estimated as −9.4 ml/min/1.73 m² compared to BAS+TAC+MMF. Correction of only this error would result in a revised difference of −2.83 ml/min/1.73 m².

Errors were also identified in the resource use of ciclosporin (CSA+MMF, BAS+CSA+MMF, BAS+CSA+MPS and rATG+CSA+MMF regimens), resulting in a marginal overestimation of total discounted costs for these regimens.

The discounting of costs was identified as being calculated half a quarter-year cycle out relative to the discounting of QALYs. When this was corrected total discounted costs for all regimens fell by 0.4%.

Resource use for tacrolimus in the first cycle for the TAC+MMF regimen was marginally overestimated.

Resource use for sirolimus for 24–48 months after transplantation (BAS+SRL+MMF regimen) was slightly overestimated.

More details, and errors resulting in no changes to results are included in our response to the Novartis pro-forma response.

Other errors

We believe that the unit cost for belatacept administration was incorrectly estimated from NHS reference costs. Instead of using SB15Z (Deliver subsequent elements of a chemotherapy cycle), SB12Z (Deliver simple parenteral chemotherapy at first attendance) should have been used, and in the outpatient setting.

Location	Text affected	Correction
Section 7.3.6.3 (Unit costs / Drug administration), page 464, lines 3–6	We believe that the most appropriate HRG4 currencies for intravenous	We believe that the most appropriate HRG4 currencies for intravenous

	administration of basiliximab, rabbit ATG and belatacept are SB12Z (Deliver simple parenteral chemotherapy at first attendance) and SB15Z (Deliver subsequent elements of a chemotherapy cycle), which when inflated to 2014/15 prices have unit costs of £228.95 and £325.59 respectively.	administration of basiliximab and rabbit ATG are SB12Z (Deliver simple parenteral chemotherapy at first attendance) and SB15Z (Deliver subsequent elements of a chemotherapy cycle), which when inflated to 2014/15 prices have unit costs of £228.95 and £325.59 respectively. For belatacept, we believe the most appropriate HRG4 currency is SB12Z, in the outpatient setting, which when inflated to 2014/15 prices has unit cost £167.50.
Appendix 10 (Summary of parameters in PenTAG economic model), page 759, table row 4		Insert additional row: Belatacept | £167.50 | NHS Reference Costs 2013-14[406] | Normal(167.50, 11.58)

References

1. Samsel R, Pliszczyski J, Chmura A, et al. Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients--long term results. Annals of Transplantation 2008;**13**(1):32-9.

2. Kyllönen LE, Eklund BH, Pesonen EJ, et al. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. Transplantation 2007;**84**(1):75-82.

3. Sheashaa HA, Hamdy AF, Bakr MA, et al. Long-term evaluation of single bolus high dose ATG induction therapy for prophylaxis of rejection in live donor kidney transplantation. International Urology and Nephrology 2008;**40**(2):515-20.

4. Sollinger H, Kaplan B, Pescovitz MD, et al. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. Transplantation 2001;**72**(12):1915-9.