ADDENDUM: INDEPENDENT ECONOMIC ASSESSMENT

This addendum replaces the whole section 6 "INDEPENDENT ECONOMIC ASSESSMENT" (pages 176 – 308) in the report dated April 29th 2015 (Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal 99).

This addendum was produced in response to the following issues:

Sanofi (the manufacturer of Thymoglobulin) have provided arguments and some evidence that two rabbit anti-thymocyte globulin (rATG) products, Thymoglobulin (anti-human thymocyte immunoglobulin) and ATG-Fresenius® (anti-human T-lymphocyte immunoglobulin) cannot be considered interchangeable. In the report dated April 29th 2015, we have included evidence from four RCTs in adults which should have been excluded; three studies (Samsel et al. 2008, Kyllonen et al. 2007, and Sheashaa et al. 2008)[1-3] used ATG-Fresenius and one study (Sollinger 2001),[4] which was included in the previous assessment [5, 6] and was 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. The following corrections were made to the model:

Significant corrections (affect costs and/or QALYs)

- Revised effectiveness estimates for induction therapies following exclusion of 4 ATG studies
- Revised unit cost for drug administration of belatacept
- Resource use of sirolimus from 2-4 years corrected in BAS+SRL+MMF arm
- Discounting of costs corrected (half-cycle) in all Markov sheets

Minor corrections (no effect or negligible effect on costs, QALYs and cost-effectiveness)

- The label (A12) of cells B12:E12 has been corrected to refer to mg rather than grams

In summary, the overall conclusion of the section 6 "INDEPENDENT ECONOMIC ASSESSMENT" remained the same as the conclusions of the report dated April 29th 2015.

6 INDEPENDENT ECONOMIC ASSESSMENT

6.3 Results

Summary cost-effectiveness results are presented in the following form throughout, with regimens sorted in order of ascending effectiveness (total discounted QALYs):

- Total costs
- Incremental costs versus previous regimen
- Total QALYs
- Incremental QALYs versus previous regimen
- ICER (versus the previous regimen on the cost-effectiveness frontier unless the regimen is dominated or extended dominated)
- Incremental net health benefit at £20,000 and £30,000 per QALY versus the referent regimen (the regimen on the cost-effectiveness frontier with the lowest total QALYs)

For probabilistic cost-effectiveness results the following are also presented:

- The probability that each regimen is cost-effective (i.e., gives the greatest net health benefit of all regimens being compared) at £20,000 and £30,000 per QALY

6.3.1 Based on child/adolescent RCTs

6.3.1.1 Trompeter et al. 2002

In the deterministic analysis based on Trompeter et al. 2002 we found that immediate-release tacrolimus dominated ciclosporin whether restricting attention to the reported duration of the trial (four years) or additionally extrapolating to a maximum time horizon of fifty years using the Markov decision model (Table 108).

Table 108. Cost-effectiveness results based on Trompeter et al. 2002 (deterministic analysis)

Regimen	TAC+AZA	CSA+AZA
Trial duration (4 years)		
Discounted costs	£17,731	£25,550
Discounted QALYs	3.3290	3.2530
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	0.4669	—
INHB at £30k/QALY	0.3366	—
Extrapolation (46 years)		
Discounted costs	£159,214	£195,939
Discounted QALYs	13.3895	12.9169
Combined (50 years)		
Discounted costs	£176,946	£221,489
Discounted QALYs	16.7185	16.1698
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	2.7758	—
INHB at £30k/QALY	2.0334	—

During the trial period costs were predicted to be lower in the TAC arm due to significant savings in dialysis costs (£5,897 savings), as well as in the costs of immunosuppression and acute rejection (£638 and £1,508 savings respectively), offset in part by increased costs of adverse events (£225 greater). Table 109 gives further details.

Table 109. Predicted costs during trial duration of Trompeter et al. 2002 (deterministic analysis)

Regimen	TAC+AZA	CSA+AZA
Undiscounted costs		
Immunosuppression	£5,965	£6,652
Acute rejection	£1,232	£2,756
Adverse events	£1,158	£921
Dialysis	£10,710	£17,167
Total	**£19,065**	**£27,496**
Discounted costs		
Immunosuppression	£5,650	£6,288
Acute rejection	£1,219	£2,728
Adverse events	£1,082	£857

Costs were also predicted to be lower in the TAC arm during the extrapolation period, mainly due to savings in dialysis (Table 110).

Table 110. Extrapolated discounted costs following Trompeter et al. 2002 (deterministic analysis)

Regimen	TAC+AZA	CSA+AZA
Maintenance immunosuppression (initial graft)	£8,277	£5,914
Monitoring (initial graft)	£5,145	£3,096
Dialysis	£105,979	£136,719
Retransplantation	£14,703	£18,717
Maintenance immunosuppression (subsequent grafts)	£8,684	£11,220
Monitoring (subsequent grafts)	£13,122	£16,973
Other costs	£3,304	£3,299
Total	**£159,214**	**£195,939**

Discounted QALYs were predicted to be greater in the TAC arm in both the trial duration and extrapolation periods, due in part to extended life expectancy (3.92 and 39.51 years with four and 50 year time horizons respectively versus 3.85 and 38.68 years for CSA). Increased graft survival also contributed to QALY gains for TAC versus CSA.

Probabilistic analysis

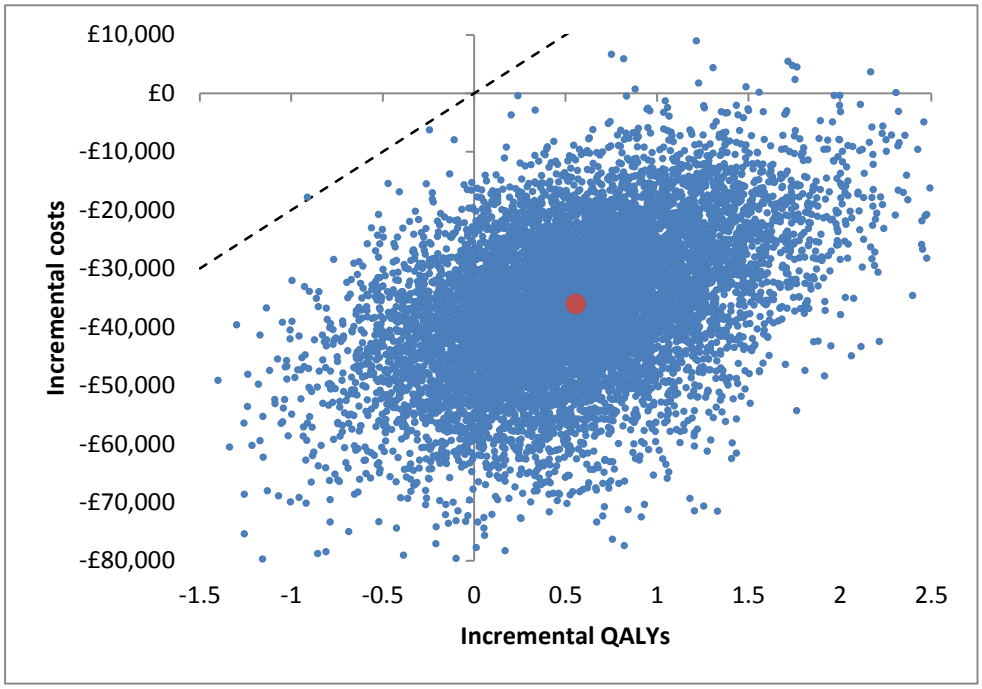
When the average costs and QALYs from the probabilistic analysis are considered, as in the deterministic analysis immediate-release tacrolimus is dominant over ciclosporin (Table 111). Costs are predicted to be lower with immediate-release tacrolimus, particularly those of dialysis, and QALYs are predicted to be greater

Table 111. Cost-effectiveness results based on Trompeter et al. 2002 (probabilistic analysis)

Regimen	TAC+AZA	CSA+AZA
Trial duration (4 years)		
Discounted costs	£17,979	£25,749
Discounted QALYs	3.3267	3.2512
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	0.4640	—
INHB at £30k/QALY	0.3345	—
Extrapolation (46 years)		
Discounted costs	£156,878	£192,962
Discounted QALYs	13.3755	12.8957
Combined (50 years)		
Discounted costs	£174,857	£218,711
Discounted QALYs	16.7022	16.1469
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	2.7480	—
INHB at £30k/QALY	2.0171	—

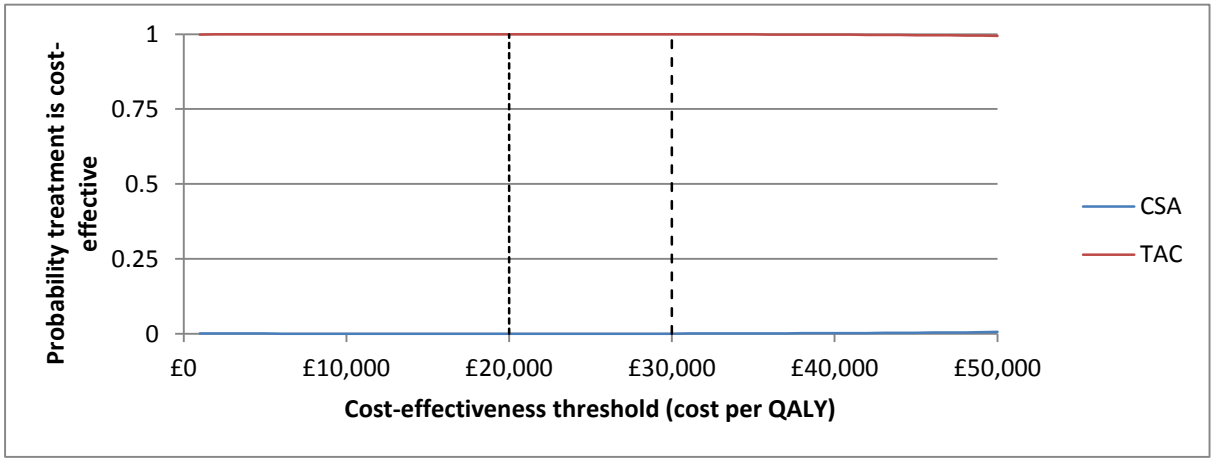
As shown in the scatter cloud (Figure 27), the vast majority of probabilistic simulations predict that immediate-release tacrolimus is cost-saving versus ciclosporin, and a significant number also predict that immediate-release tacrolimus results in greater QALYs. Immediate-release tacrolimus is predicted to be cost-effective at £20,000 per QALY in 100.0% of simulations and at £30,000 per QALY in 100.0% of simulations (Figure 28).

Figure 27. Probabilistic sensitivity analysis scatter cloud for Trompeter et al. 2002 (TAC versus CSA)



Note: Dashed line indicates £20,000 per QALY threshold – points to South-East of this line indicate that TAC is cost-effective versus CSA at £20,000 per QALY; red dot indicates mean incremental costs and QALYs

Figure 28. Cost-effectiveness acceptability curves for Trompeter et al. 2002



Scenario analyses

Below average weight for KTRs

Assuming that body weight in the extrapolation period follows the 9th centile for age (rather than the median) results in marginally reduced costs of maintenance immunosuppression in both arms.

Immediate-release tacrolimus remains dominant over ciclosporin. The incremental net health benefit for immediate-release tacrolimus versus ciclosporin is marginally increased at £20,000 and £30,000 per QALY (2.7773 and 2.0344 respectively).

Surrogate relationship between acute rejection and graft survival removed

When the surrogate relationship between acute rejection and graft survival is removed (leaving eGFR at 12 months as the dominant determinant of graft survival), immediate-release tacrolimus continues to dominate ciclosporin in the deterministic analysis.

Trial duration outcomes are not affected (since the surrogate relationship is only used for extrapolation). The effect of removing the surrogate relationship is to increase the extrapolated graft survival in both arms, but more so for the ciclosporin arm. This consequently leads to reduced total costs and increased QALYs in both arms.

The incremental net health benefit for immediate-release tacrolimus versus ciclosporin is reduced but remains positive at £20,000 and £30,000 per QALY (2.6762 and 1.9665 respectively).

6.3.1.2 Grenda et al. 2006

In the deterministic analysis based on Grenda et al. 2006 we found that induction with basiliximab was more effective and less costly than no induction, whether looking at just the trial duration (two years) or extrapolating to a 50 year time horizon. Basiliximab dominated no induction with a two year or 50 year time horizon (Table 112).

Table 112. Cost-effectiveness results based on Grenda et al. 2006 (deterministic analysis)

Regimen	TAC+AZA	BAS+TAC+AZA
Trial duration (2 years)		
Discounted costs	£13,757	£13,631
Discounted QALYs	1.7319	1.7436
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.0179
INHB at £30k/QALY	—	0.0159
Extrapolation (48 years)		
Discounted costs	£127,256	£121,684
Discounted QALYs	15.7609	15.9309
Combined (50 years)		
Discounted costs	£141,012	£135,315
Discounted QALYs	17.4928	17.6745
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.4665
INHB at £30k/QALY	—	0.3716

The additional £2,481 cost of induction in the basiliximab arm (and the £269 additional cost of adverse events) in the trial duration are marginally outweighed by savings (£2,776 from dialysis and £99 from acute rejection costs), as shown in Table 113.

Table 113. Predicted costs during trial duration of Grenda et al. 2006 (deterministic analysis)

Regimen	TAC+AZA	BAS+TAC+AZA
Undiscounted costs		
Immunosuppression	£2,266	£4,758
Acute rejection	£531	£428
Adverse events	£242	£515
Total	£11,264	£8,361
Discounted costs	**£14,304**	**£14,063**
Immunosuppression		
Acute rejection	£2,220	£4,702
Adverse events	£525	£426
Total	£240	£508

Cost savings are also realised in the extrapolation period by reducing future expenditure on dialysis and subsequent grafts, partially offset by increased cumulative immunosuppression costs for the initial graft and increased costs associated with NODAT (Table 114).

Table 114. Extrapolated discounted costs following Grenda et al. 2006 (deterministic analysis)

Regimen	TAC+AZA	BAS+TAC+AZA
Maintenance immunosuppression (initial graft)	£13,334	£14,021
Monitoring (initial graft)	£9,167	£9,630
Dialysis	£75,689	£69,730
Retransplantation	£10,567	£9,799
Maintenance immunosuppression (subsequent grafts)	£6,121	£5,640
Monitoring (subsequent grafts)	£9,279	£8,538
NODAT	£424	£1,611
Other costs	£2,676	£2,715
Total	**£127,256**	**£121,684**

Basiliximab was predicted to give greater QALYs in the trial duration, due to better graft survival (overall survival was very similar in both arms). In the extrapolation basiliximab was predicted to give greater QALYs and greater life expectancy

Probabilistic analysis

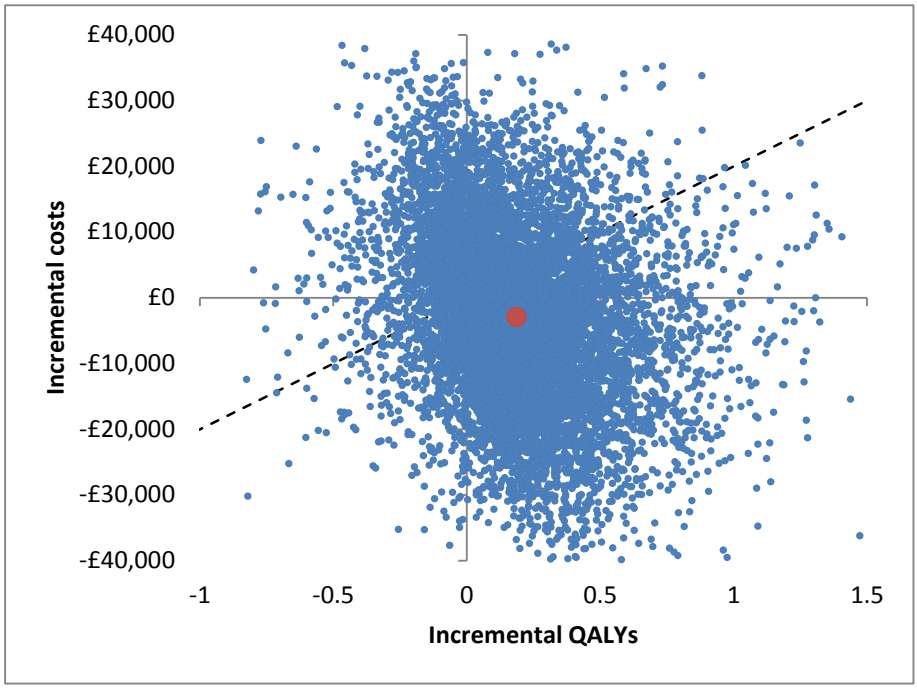
When the average costs and QALYs from the probabilistic analysis are considered, as in the deterministic analysis basiliximab is dominant over no induction (Table 115).

Table 115. Cost-effectiveness results based on Grenda et al. 2006 (probabilistic analysis)

Regimen	TAC+AZA	BAS+TAC+AZA
Trial duration (2 years)		
Discounted costs	£13,751	£13,636
Discounted QALYs	1.7302	1.7419
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.0174
INHB at £30k/QALY	—	0.0155
Extrapolation (48 years)		
Discounted costs	£129,696	£124,073
Discounted QALYs	15.6259	15.8008
Combined (50 years)		
Discounted costs	£143,447	£137,708
Discounted QALYs	17.3562	17.5427
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.4734
INHB at £30k/QALY	—	0.3778

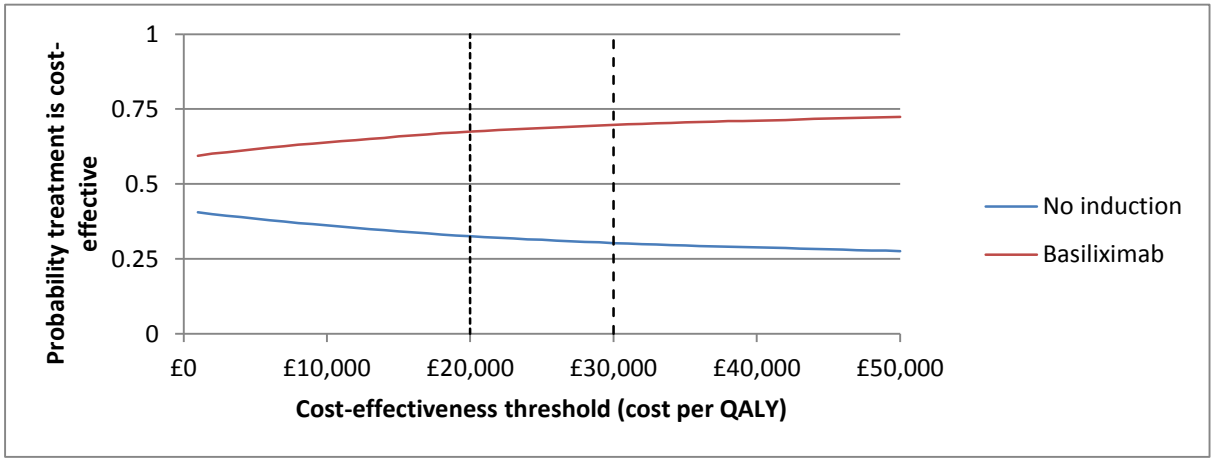
As shown in the scatter cloud (Figure 29), the majority of probabilistic simulations predict that basiliximab results in greater QALYs than no induction, and 59% of simulations predicting cost savings with basiliximab. Basiliximab is predicted to be cost-effective at £20,000 per QALY in 67.4% of simulations and at £30,000 per QALY in 69.7% of simulations (Figure 30).

Figure 29. Probabilistic sensitivity analysis scatter cloud for Grenda et al. 2006 (basiliximab versus no induction)



Note: Dashed line indicates £20,000 per QALY threshold – points to South-East of this line indicate that basiliximab is cost-effective versus no induction at £20,000 per QALY; red dot indicates mean incremental costs and QALYs

Figure 30. Cost-effectiveness acceptability curves for Grenda et al. 2006



Scenario analyses

Below average weight for KTRs

Assuming that body weight follows the 9th centile for age (as opposed to the median) results in reduced costs of immunosuppression in both arms.

Basiliximab remains dominant over no induction in the deterministic analysis. The incremental net health benefit for basiliximab versus no induction increases slightly at £20,000 and £30,000 per QALY (0.4725 and 0.3755 respectively).

Surrogate relationship between acute rejection and graft survival removed

Removing the surrogate relationship between acute rejection and graft survival marginally increases graft survival in both arms, reducing costs and increasing QALYs.

Basiliximab remains dominant over no induction in the deterministic analysis. The incremental net health benefit for basiliximab versus no induction decreases slightly at £20,000 and £30,000 per QALY (0.4446 and 0.3559 respectively).

6.3.1.3 Offner et al. 2008

Contrary to analyses based on Grenda et al. 2006, analyses based on Offner et al. 2008 suggest that basiliximab is more costly and less effective than no induction, whether with a time horizon of one year (trial duration) or 50 years (Table 116).

Table 116. Cost-effectiveness results based on Offner et al. 2008 (deterministic analysis)

Regimen	BAS+CSA+MMF	CSA+MMF
Trial duration (2 years)		
Discounted costs	£5,408	£3,297
Discounted QALYs	0.8839	0.8992
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.1208	—
INHB at £30k/QALY	−0.0857	—
Extrapolation (48 years)		
Discounted costs	£129,804	£123,387
Discounted QALYs	16.9461	17.4765
Combined (50 years)		
Discounted costs	£135,212	£126,684
Discounted QALYs	17.8300	18.3757
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.9721	—
INHB at £30k/QALY	−0.8299	—

During the trial duration basiliximab was predicted to result in lower acute rejection costs (saving of £387) but also increased costs of immunosuppression, adverse events and dialysis (increases of £2,203, £19 and £276 respectively), as shown in Table 117.

Table 117. Predicted costs during trial duration of Offner et al. 2008 (deterministic analysis)

Regimen	BAS+CSA+MMF	CSA+MMF
Undiscounted costs		
Immunosuppression	£3,795	£1,591
Acute rejection	£462	£851
Adverse events	£500	£481
Dialysis	£683	£401
Total	**£5,441**	**£3,323**
Discounted costs		
Immunosuppression	£3,778	£1,575
Acute rejection	£461	£849
Adverse events	£500	£481
Dialysis	£669	£393
Total	**£5,408**	**£3,297**

When extrapolated beyond the trial duration, basiliximab was expected to result in greater costs of dialysis and costs associated with retransplantation (Table 118).

Table 118. Extrapolated discounted costs following Offner et al. 2008 (deterministic analysis)

Regimen	BAS+CSA+MMF	CSA+MMF
Maintenance immunosuppression (initial graft)	£15,715	£16,481
Monitoring (initial graft)	£9,807	£10,606
Dialysis	£73,825	£68,017
Retransplantation	£11,706	£10,770
Maintenance immunosuppression (subsequent grafts)	£6,003	£5,522
Monitoring (subsequent grafts)	£9,933	£9,093
Other costs	£2,815	£2,899
Total	**£129,804**	**£123,387**

In the trial duration basiliximab is predicted to give worse graft survival and overall survival, resulting in less QALYs. When extrapolated to 50 years basiliximab is still expected to give less QALYs, and reduced life expectancy (40.6 years compared to 41.8 for no induction).

Probabilistic analysis

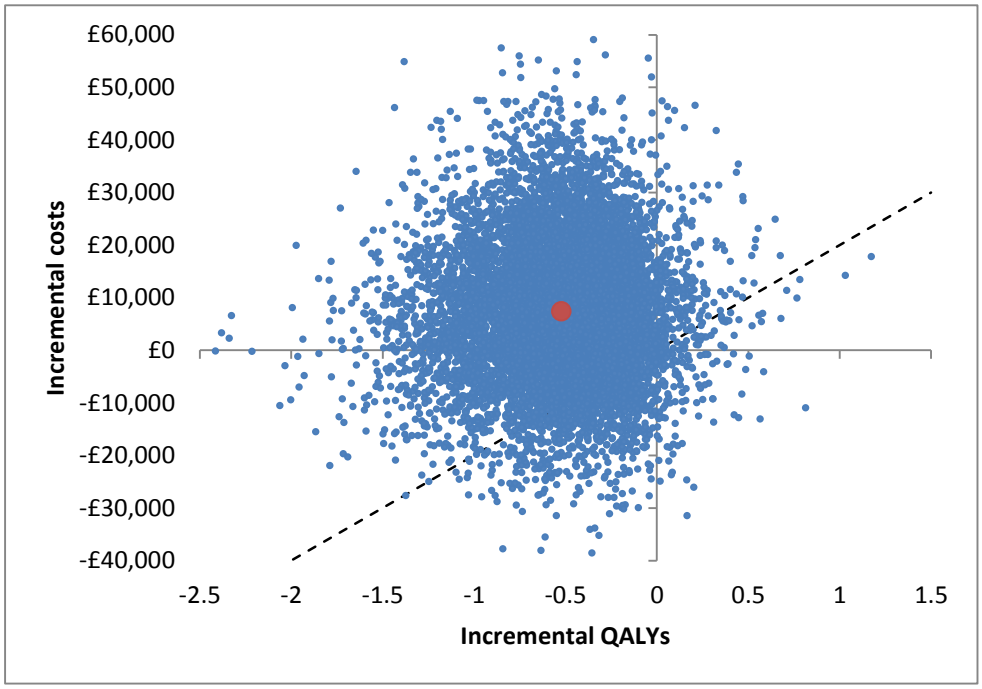
Results from the probabilistic analysis are consistent with the deterministic analysis; basiliximab is still expected to be dominated by no induction (Table 119).

Table 119. Cost-effectiveness results based on Offner et al. 2008 (probabilistic analysis)

Regimen	BAS+CSA+MMF	CSA+MMF
Trial duration (2 years)		
Discounted costs	£5,423	£3,301
Discounted QALYs	0.8789	0.8941
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.1212	—
INHB at £30k/QALY	−0.0859	—
Extrapolation (48 years)		
Discounted costs	£130,442	£124,886
Discounted QALYs	16.8328	17.3400
Combined (50 years)		
Discounted costs	£135,865	£128,187
Discounted QALYs	17.7117	18.2341
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.9062	—
INHB at £30k/QALY	−0.7783	—

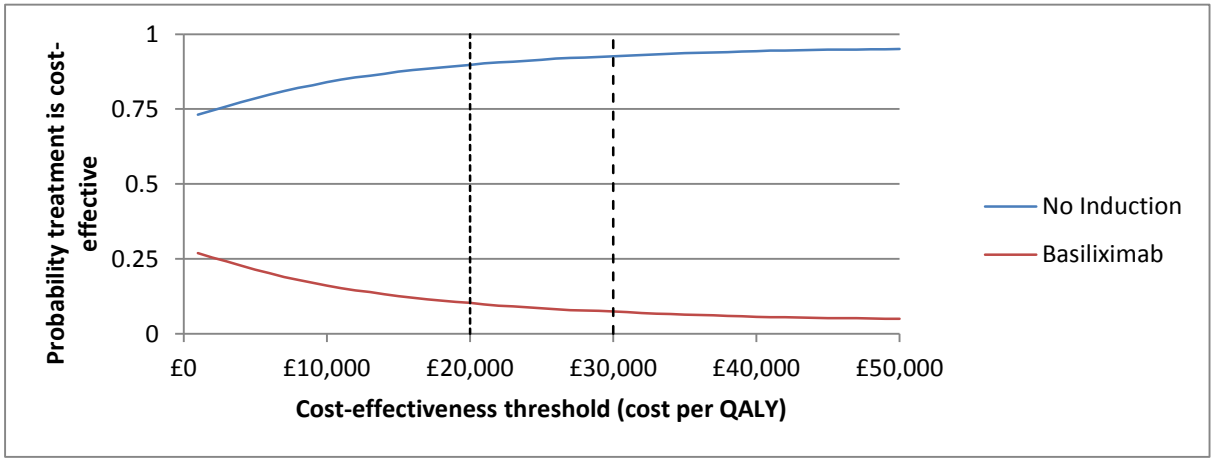
As shown in the scatter cloud (Figure 31), basiliximab is predicted to result in QALY loss in a significant majority of simulations, it is also predicted to increase costs in the majority of simulations. Basiliximab is predicted to be cost-effective in 10.3% and 7.4% of simulations at £20,000 and £30,000 per QALY respectively (Figure 32).

Figure 31. Probabilistic sensitivity analysis scatter cloud for Offner et al. 2008 (basiliximab versus no induction)



Note: Dashed line indicates £20,000 per QALY threshold – points to South-East of this line indicate that basiliximab is cost-effective versus no induction at £20,000 per QALY; red dot indicates mean incremental costs and QALYs

Figure 32. Cost-effectiveness acceptability curves for Offner et al. 2008



Scenario analyses

Below average weight for KTRs

Assuming that body weight follows the 9th centile for age (as opposed to the median) results in reduced costs of immunosuppression in both arms.

Basiliximab remains dominated by no induction in the deterministic analysis. The incremental net health benefit for basiliximab versus no induction decreases slightly at £20,000 and £30,000 per QALY (−0.9743 and −0.8314 respectively).

Surrogate relationship between acute rejection and graft survival removed

Removing the surrogate relationship between acute rejection and graft survival marginally decreases graft survival in the basiliximab arm, increasing costs and reducing QALYs, while increasing graft survival in the no induction arm.

Basiliximab remains dominated by no induction in the deterministic analysis. The incremental net health benefit for basiliximab versus no induction decreases at £20,000 and £30,000 per QALY (−1.1409 and −0.9474 respectively).

6.3.1.4 Summary of results from analyses based on child/adolescent RCTs

The analysis based on Trompeter et al. 2002 suggested that immediate-release tacrolimus would be cost-effective versus ciclosporin at £20,000 or £30,000 per QALY as it was more effective and cost-saving both in the trial duration and when extrapolated.

The analyses based on Grenda et al. 2006 and Offner et al. 2008 produced contradictory results for the cost-effectiveness of basiliximab versus no induction. The analyses based on Grenda et al. 2006 suggested that basiliximab would result in reduced costs and increased QALYs (i.e., basiliximab was dominant) while the analyses based on Offner et al. 2008 suggested that basiliximab would result in increased costs and decreased QALYs (i.e., basiliximab was dominated). These results were robust to scenario analyses.

6.3.2 Using effectiveness estimates from adult studies

Further results for these analyses are given in Appendix 10.

6.3.2.1 Deterministic results

Induction agents

Basiliximab and rabbit ATG were both simultaneously compared to no induction with four different maintenance combinations (CSA+MMF, TAC+MMF, CSA+AZA and TAC+AZA).

Basiliximab was found to be less costly and more effective (and therefore dominant) over no induction and rabbit ATG in all comparisons (Table 120). Rabbit ATG was also found to be more costly and effective than no induction (i.e., no induction dominated rabbit ATG).

The differences in QALYs from rabbit ATG to no induction and from no induction to basiliximab are explained by increased life expectancy overall and by more projected time with functioning graft and less projected time dependent on dialysis (Table 121). Graft life expectancy for the first graft was greater for basiliximab than for rabbit ATG and no induction. The gains in graft survival for the first graft do not fully translate to gains in projected time with functioning graft or life expectancy because when a graft is lost later in life there is less time to achieve retransplantation and the mortality rate while on dialysis is greater.

Table 120. Summary of cost-effectiveness results for induction agents when adult RCTs are used to estimate effectiveness

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*	
Rabbit ATG	£216,114	—	17.9721	—	Dominated	-1.0123	-0.7278
No induction	£210,097	-£6,017	18.0031	+0.0310	Dominated	-0.6804	-0.4962
Basiliximab	£199,042	-£11,055	18.1308	+0.1277	—	—	—
With CSA+MMF						*vs. Basiliximab*	
Rabbit ATG	£209,097	—	18.0702	—	Dominated	-1.0887	-0.7846
No induction	£199,910	-£9,188	18.1269	+0.0567	Dominated	-0.5726	-0.4217
Basiliximab	£190,856	-£9,053	18.2468	+0.1200	—	—	—
With TAC+AZA						*vs. Basiliximab*	
Rabbit ATG	£183,191	—	18.2468	—	Dominated	-1.1228	-0.8082
No induction	£174,989	-£8,202	18.2970	+0.0502	Dominated	-0.6625	-0.4846
Basiliximab	£164,316	-£10,673	18.4259	+0.1288	—	—	—
With TAC+MMF						*vs. Basiliximab*	
Rabbit ATG	£189,637	—	18.1763	—	Dominated	-1.1560	-0.8317
No induction	£179,719	-£9,918	18.2398	+0.0635	Dominated	-0.5966	-0.4377
Basiliximab	£170,182	-£9,537	18.3596	+0.1198	—	—	—

Table 121. Projections of expected life years for induction agents when adult RCTs are used to estimate effectiveness

Induction agent	Graft life expectancy (1st graft; years)		Life expectancy (years)		Projected years with functioning graft		Projected years receiving dialysis	
	Total	Incremental	Total	Incremental	Total	Incremental	Total	Incremental
With CSA+AZA								
Rabbit ATG	14.421	—	43.136	—	33.557	—	9.578	—
No induction	15.098	+0.677	43.175	+0.039	33.784	+0.226	9.391	-0.187
Basiliximab	17.229	+2.131	43.378	+0.203	34.490	+0.706	8.888	-0.503
With CSA+MMF								
Rabbit ATG	15.983	—	43.294	—	34.059	—	9.236	—
No induction	17.110	+1.126	43.374	+0.080	34.445	+0.386	8.929	-0.306
Basiliximab	19.171	+2.062	43.566	+0.191	35.159	+0.714	8.407	-0.523
With TAC+AZA								
Rabbit ATG	20.068	—	43.582	—	35.474	—	8.109	—
No induction	21.263	+1.194	43.649	+0.067	35.925	+0.451	7.724	-0.385
Basiliximab	23.597	+2.334	43.858	+0.209	36.785	+0.860	7.073	-0.651
With TAC+MMF								
Rabbit ATG	18.881	—	43.467	—	34.994	—	8.473	—
No induction	20.304	+1.423	43.553	+0.086	35.502	+0.508	8.051	-0.422
Basiliximab	22.449	+2.145	43.746	+0.193	36.286	+0.784	7.460	-0.591

Maintenance agents

Table 122 shows the summary of cost-effectiveness results for maintenance agents. It shows that immediate-release tacrolimus is dominant over ciclosporin, prolonged-release tacrolimus and sirolimus, but is less effective and less costly than belatacept. Because the ICER of belatacept versus immediate-release tacrolimus is over £500,000 per QALY, only immediate-release tacrolimus is cost-effective in these comparisons at £20,000 and £30,000 per QALY.

Table 122 also shows that when considering azathioprine, mycophenolate mofetil, mycophenolate sodium, everolimus and sirolimus, the results are less simple. Sirolimus is dominated by mycophenolate mofetil and azathioprine, but everolimus and mycophenolate sodium are both the most effective and most costly treatments in their comparisons. The ICER for everolimus is over £600,000 per QALY and therefore everolimus is not predicted to be cost-effective at £20,000 or £30,000 per QALY, while the ICER for mycophenolate sodium is slightly over £50,000 per QALY. The cost-effectiveness of mycophenolate mofetil appears to be dependent on the concomitant treatments: when mycophenolate mofetil is used in combination with ciclosporin it is dominant over azathioprine (and cost-effective at £20,000 and £30,000 per QALY), while when it is used in combination with immediate-release tacrolimus azathioprine is dominant (and mycophenolate mofetil is therefore not cost-effective at £20,000 or £30,000 per QALY).

Table 123 gives further details in terms of projected life years (overall and in certain health states).

Table 122. Summary of cost-effectiveness results for maintenance agents when adult RCTs are used to estimate effectiveness

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*	
CSA	£199,910	—	18.1269	—	Dominated	-1.1224	-0.7859
TAC-PR	£196,165	-£3,744	18.1854	+0.0586	Dominated	-0.8767	-0.6026
TAC	£179,719	-£16,446	18.2398	+0.0544	—	—	—
With AZA						*vs. TAC*	
CSA	£210,097	—	18.0031	—	Dominated	-2.0494	-1.4642
TAC	£174,989	-£35,108	18.2970	+0.2940	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£198,631	—	18.2423	—	Dominated	-1.5397	-1.0655
CSA	£190,856	-£7,775	18.2468	+0.0045	Dominated	-1.1464	-0.8019
TAC	£170,182	-£20,674	18.3596	+0.1127	—	—	—
BEL	£293,175	+£122,993	18.5901	+0.2306	£533,449	-5.9191	-3.8692
With BAS+AZA						*vs. TAC*	
CSA	£199,042	—	18.1308	—	Dominated	-2.0314	-1.4526
TAC	£164,316	-£34,726	18.4259	+0.2951	—	—	—
With rATG+MMF						*vs. TAC*	
CSA	£209,097	—	18.0702	—	Dominated	-1.0791	-0.7548
TAC	£189,637	-£19,460	18.1763	+0.1061	—	—	—
With rATG+AZA						*vs. TAC*	
CSA	£216,114	—	17.9721	—	Dominated	-1.9209	-1.3722
TAC	£183,191	-£32,923	18.2468	+0.2748	—	—	—

Table 122. Summary of cost-effectiveness results for maintenance agents (cont.)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With CSA						*vs. MMF*	
AZA	£210,097	—	18.0031	—	Dominated	-0.6332	-0.4634
MMF	£199,910	-£10,188	18.1269	+0.1238	—	—	—
EVL	£259,327	+£59,417	18.2209	+0.0940	£632,246	-2.8769	-1.8866
With TAC						*vs. AZA*	
SRL	£222,300	—	17.9553	—	Dominated	-2.7073	-1.9187
MMF	£179,719	-£42,581	18.2398	+0.2844	Dominated	-0.2938	-0.2149
AZA	£174,989	-£4,730	18.2970	+0.0572	—	—	—
With BAS+CSA						*vs. MMF*	
AZA	£199,042	—	18.1308	—	Dominated	-0.5254	-0.3889
MMF	£190,856	-£8,186	18.2468	+0.1161	—	—	—
MPS	£198,303	+£7,447	18.3907	+0.1438	£51,770	-0.2285	-0.1044
With BAS+TAC						*vs. AZA*	
MMF	£170,182	—	18.3596	—	Dominated	-0.3596	-0.2618
AZA	£164,316	-£5,866	18.4259	+0.0663	—	—	—
With rATG+CSA						*vs. MMF*	
AZA	£216,114	—	17.9721	—	Dominated	-0.4490	-0.3321
MMF	£209,097	-£7,017	18.0702	+0.0982	—	—	—
With rATG+TAC						*vs. AZA*	
MMF	£189,637	—	18.1763	—	Dominated	-0.3928	-0.2853
AZA	£183,191	-£6,446	18.2468	+0.0705	—	—	—

Table 123. Projections of expected life years for maintenance agents when adult RCTs are used to estimate effectiveness

Maintenance agent	Graft life expectancy (1st graft; years)		Life expectancy (years)		Projected years with functioning graft		Projected years receiving dialysis	
	Total	Incremental	Total	Incremental	Total	Incremental	Total	Incremental
With MMF								
CSA	17.110	—	43.374	—	34.445	—	8.929	—
TAC-PR	20.038	+2.929	43.452	+0.077	35.370	+0.925	8.082	-0.848
TAC	20.304	+0.266	43.553	+0.102	35.502	+0.132	8.051	-0.031
With AZA								
CSA	15.098	—	43.175	—	33.784	—	9.391	—
TAC	21.263	+6.164	43.649	+0.474	35.925	+2.141	7.724	-1.667
With BAS+MMF								
SRL	20.376	—	43.534	—	35.533	—	8.001	—
CSA	19.171	-1.204	43.566	+0.032	35.159	-0.374	8.407	+0.406
TAC	22.449	+3.277	43.746	+0.180	36.286	+1.127	7.460	-0.947
BEL	24.625	+2.176	44.125	+0.379	37.236	+0.950	6.889	-0.571
With BAS+AZA								
CSA	17.229	—	43.378	—	34.490	—	8.888	—
TAC	23.597	+6.367	43.858	+0.480	36.785	+2.295	7.073	-1.815
With rATG+MMF								
CSA	15.983	—	43.294	—	34.059	—	9.236	—
TAC	18.881	+2.898	43.467	+0.173	34.994	+0.935	8.473	-0.763
With rATG+AZA								
CSA	14.421	—	43.136	—	33.557	—	9.578	—
TAC	20.068	+5.647	43.582	+0.447	35.474	+1.916	8.109	-1.470

Table 123. Projections of expected life years for maintenance agents when adult RCTs are used to estimate effectiveness (cont.)

Maintenance agent	Graft life expectancy (1st graft; years)		Life expectancy (years)		Projected years with functioning graft		Projected years receiving dialysis	
	Total	Incremental	Total	Incremental	Total	Incremental	Total	Incremental
With CSA								
AZA	15.098	—	43.175	—	33.784	—	9.391	—
MMF	17.110	+2.011	43.374	+0.200	34.445	+0.661	8.929	-0.462
EVL	19.183	+2.074	43.499	+0.124	35.118	+0.673	8.380	-0.549
With TAC								
SRL	15.862	—	43.139	—	33.979	—	9.160	—
MMF	20.304	+4.442	43.553	+0.415	35.502	+1.524	8.051	-1.109
AZA	21.263	+0.959	43.649	+0.096	35.925	+0.423	7.724	-0.327
With BAS+CSA								
AZA	17.229	—	43.378	—	34.490	—	8.888	—
MMF	19.171	+1.942	43.566	+0.188	35.159	+0.669	8.407	-0.481
MPS	21.364	+2.193	43.810	+0.244	35.983	+0.824	7.827	-0.579
With BAS+TAC								
MMF	22.449	—	43.746	—	36.286	—	7.460	—
AZA	23.597	+1.148	43.858	+0.111	36.785	+0.498	7.073	-0.387
With rATG+CSA								
AZA	14.421	—	43.136	—	33.557	—	9.578	—
MMF	15.983	+1.562	43.294	+0.159	34.059	+0.501	9.236	-0.343
With rATG+TAC								
MMF	18.881	—	43.467	—	34.994	—	8.473	—
AZA	20.068	+1.187	43.582	+0.115	35.474	+0.480	8.109	-0.365

Immediate-release tacrolimus

Immediate-release tacrolimus was compared to ciclosporin (six comparisons), prolonged-release tacrolimus (one comparison), sirolimus (one comparison), and belatacept (one comparison).

Immediate-release tacrolimus was found to be less costly and more effective than all comparators except belatacept in all comparisons. Belatacept was predicted to be more costly and more effective than immediate-release tacrolimus with an ICER over £500,000 per QALY.

As demonstrated in Table 123 (page 24), immediate-release tacrolimus is predicted to result in prolonged survival of the initial graft by 3.2–6.4 years versus ciclosporin, as well as to prolong overall survival by 0.2–0.5 years. Immediate-release tacrolimus is predicted to give greater graft and overall survival than ciclosporin, prolonged-release tacrolimus and sirolimus, but reduced graft and overall survival compared to belatacept.

Prolonged-release tacrolimus

Prolonged-release tacrolimus was compared to ciclosporin and immediate-release tacrolimus, in combination with mycophenolate mofetil and corticosteroids.

Prolonged-release tacrolimus was predicted to be less costly and more effective than ciclosporin but was also predicted to be more costly and less effective than immediate-release tacrolimus and was therefore dominated and not cost-effective at any cost-effectiveness threshold.

Belatacept

Belatacept was compared to ciclosporin, immediate-release tacrolimus and sirolimus, in combination with basiliximab induction, mycophenolate mofetil and corticosteroids.

Belatacept was predicted to be more costly and more effective than all comparators. Since ciclosporin and sirolimus were predicted to be dominated by immediate-release tacrolimus the relevant comparator for belatacept is immediate-release tacrolimus. The ICER of belatacept was predicted to be over £500,000 per QALY.

Mycophenolate mofetil

Mycophenolate mofetil was compared to azathioprine (six comparisons), mycophenolate sodium (one comparison), sirolimus (one comparison) and everolimus (one comparison).

When used in combination with ciclosporin (three comparisons), mycophenolate mofetil was predicted to be less costly and more effective than azathioprine. However, when used in combination with immediate-release tacrolimus (three comparisons), mycophenolate mofetil was predicted to be more costly and less effective than azathioprine. To summarise, mycophenolate mofetil was **dominant** when used in combination with ciclosporin but was **dominated** when used in combination with immediate-release tacrolimus.

When compared to everolimus in combination with ciclosporin and corticosteroids, mycophenolate mofetil was predicted to be less costly and less effective, with the ICER of everolimus predicted to be over £600,000 per QALY.

When compared to sirolimus in combination with tacrolimus and corticosteroids, mycophenolate mofetil was predicted to be less costly and more effective than sirolimus, but was itself dominated by azathioprine in this comparison.

When compared to mycophenolate sodium in combination with basiliximab induction, ciclosporin and corticosteroids, mycophenolate mofetil was predicted to be less costly and less effective, with the ICER of mycophenolate sodium predicted to be over £50,000 per QALY.

At a cost-effectiveness threshold between £20,000 and £30,000 per QALY mycophenolate mofetil is predicted to be cost-effective in regimens containing ciclosporin, but not in regimens containing immediate-release tacrolimus.

Mycophenolate sodium

Mycophenolate sodium was compared to azathioprine and mycophenolate mofetil in combination with basiliximab induction, ciclosporin and corticosteroids. It was found to dominate azathioprine and was predicted to be more costly and more effective than mycophenolate mofetil with an ICER of over £50,000 per QALY.

Sirolimus

Sirolimus was compared to ciclosporin, immediate-release tacrolimus and belatacept, in combination with basiliximab induction, mycophenolate mofetil and corticosteroids, and was

also compared to azathioprine and mycophenolate mofetil, in combination with immediate-release tacrolimus and corticosteroids.

When compared to ciclosporin, immediate-release tacrolimus and belatacept, sirolimus was predicted to be dominated by ciclosporin and immediate-release tacrolimus.

When compared to azathioprine and mycophenolate mofetil, sirolimus was predicted to be dominated by azathioprine and mycophenolate mofetil.

Everolimus

Everolimus was compared to azathioprine and mycophenolate mofetil in combination with ciclosporin and corticosteroids. Everolimus was predicted to be more costly and more effective than azathioprine and mycophenolate, with the appropriate ICER of everolimus (versus mycophenolate mofetil) predicted to be over £600,000 per QALY.

Regimens

When all 18 regimens were simultaneously compared, all regimens were predicted to be dominated by BAS+TAC+AZA, except for BAS+BEL+MMF, which was predicted to have an ICER of over £700,000 per QALY.

Table 1. Summary cost-effectiveness results of regimens not dominated

Regimen	Discounted total costs	Discounted total QALYs	ICER (cost per QALY)	INHB at £20k/QALY	INHB at £30k/QALY
BAS+TAC+AZA	£164,316	18.4259	—	—	—
BAS+BEL+MMF	£293,175	18.5901	£784,515	−6.2787	−4.1310

Summary

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY basiliximab was predicted to be cost-effective when compared to no induction and to rabbit ATG.

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY immediate-release tacrolimus was predicted to be cost-effective when compared to ciclosporin, prolonged-release tacrolimus, sirolimus and belatacept.

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY, azathioprine was predicted to be cost-effective (versus mycophenolate mofetil and sirolimus) when used in

combination with tacrolimus while mycophenolate mofetil was predicted to be cost-effective (versus azathioprine, mycophenolate sodium and everolimus) when used in combination with ciclosporin.

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY, the only regimen predicted to be cost-effective when compared to all other regimens was BAS+TAC+AZA, which dominated all other regimens except BAS+BEL+MMF (which was more costly and more effective with an ICER of over £700,000 per QALY).

6.3.2.2 Probabilistic results

Probabilistic results were obtained after running 10,000 iterations. As demonstrated in Figure 33 (which compares the discounted costs for each regimen) there is good agreement between deterministic and probabilistic total discounted costs, with no significant non-linearities observed. Figure 34 suggests that total discounted QALYs overall are slightly lower when estimated in probabilistic analyses. Two regimens appear to have dropped more QALYs than the others in the probabilistic analyses – these are TAC-PR+MMF and BAS+TAC+MMF.

Figure 33. Comparison of deterministic and probabilistic total discounted costs

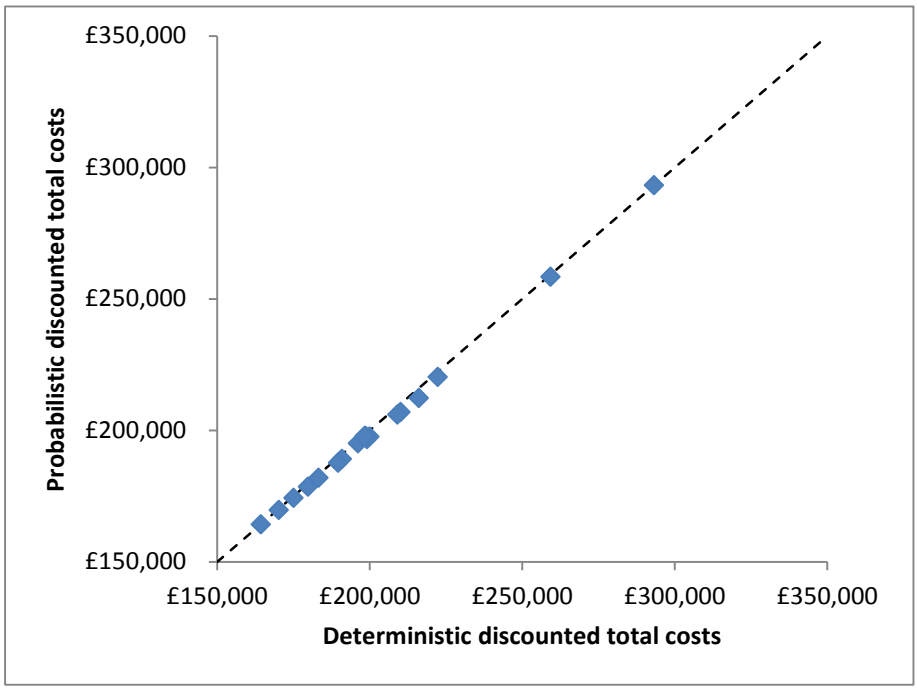
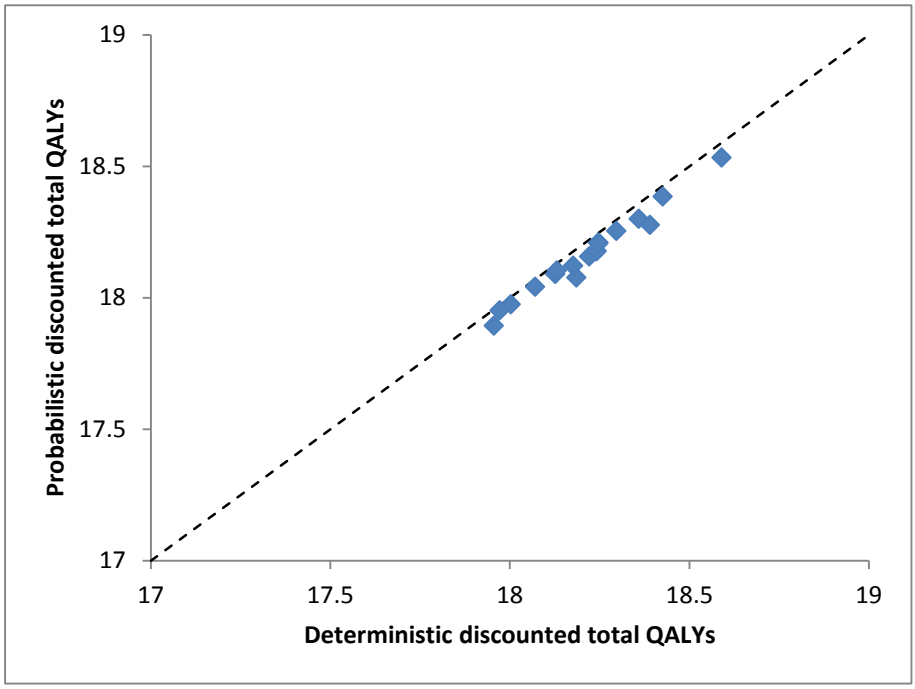


Figure 34. Comparison of deterministic and probabilistic total discounted QALYs



Induction agents

Summary cost-effectiveness results are shown in Table 125. In all four comparisons basiliximab is expected to dominate no induction, which is in turn expected to dominate rabbit ATG. The same pattern was observed in deterministic analyses.

There is limited uncertainty predicted in the cost-effectiveness results as a result of parameter uncertainty. The probability of basiliximab being cost-effective at £20,000 to £30,000 per QALY is predicted to range from 91.4% to 91.9%. It is predicted that it is possible (though much less likely) that rabbit ATG could be cost-effective at £20,000 to £30,000 per QALY. It is predicted to be very unlikely that no induction could be cost-effective.

Table 125. Summary cost-effectiveness results for induction agents (probabilistic analyses)

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
With CSA+AZA						*vs. Basiliximab*			
Rabbit ATG	£212,166	—	17.9509	—	Dominated	-0.9361	-0.6747	8.1%	8.2%
No induction	£206,855	-£5,310	17.9751	+0.0242	Dominated	-0.6463	-0.4735	0.5%	0.4%
Basiliximab	£196,484	-£10,371	18.1029	+0.1278	—	—	—	91.4%	91.4%
With CSA+MMF						*vs. Basiliximab*			
Rabbit ATG	£205,769	—	18.0414	—	Dominated	-1.0072	-0.7275	6.8%	7.0%
No induction	£197,421	-£8,347	18.0896	+0.0482	Dominated	-0.5416	-0.4011	1.5%	1.3%
Basiliximab	£188,991	-£8,430	18.2097	+0.1201	—	—	—	91.8%	91.8%
With TAC+AZA						*vs. Basiliximab*			
Rabbit ATG	£181,824	—	18.2064	—	Dominated	-1.0652	-0.7696	7.4%	7.7%
No induction	£174,153	-£7,671	18.2538	+0.0473	Dominated	-0.6343	-0.4666	0.7%	0.6%
Basiliximab	£164,088	-£10,065	18.3848	+0.1311	—	—	—	91.9%	91.7%
With TAC+MMF						*vs. Basiliximab*			
Rabbit ATG	£187,494	—	18.1220	—	Dominated	-1.0751	-0.7760	6.7%	6.9%
No induction	£178,415	-£9,079	18.1765	+0.0545	Dominated	-0.5667	-0.4188	1.4%	1.3%
Basiliximab	£169,546	-£8,870	18.2997	+0.1232	—	—	—	91.9%	91.9%

Maintenance agents

Table 126 shows the summary cost-effectiveness results for maintenance agents in the probabilistic analysis.

As in the deterministic analysis it is predicted that immediate-release tacrolimus dominates ciclosporin (as well as prolonged-release tacrolimus and sirolimus), but is less costly and less effective than belatacept (ICER £530,421 per QALY).

Also matching the results of the deterministic analysis it is again predicted that mycophenolate mofetil is cost-effective when used in combination with ciclosporin, but not when used in combination with immediate-release tacrolimus.

Mycophenolate sodium is still not predicted to be cost-effective, and in fact its estimated ICER is £130,080 per QALY in the probabilistic analysis compared to £51,770 per QALY in the deterministic analysis.

Sirolimus is still not predicted to be cost-effective. As in the deterministic analyses, sirolimus is dominated by ciclosporin and immediate-release tacrolimus when used in combination with basiliximab and mycophenolate mofetil, and is dominated by mycophenolate mofetil and azathioprine when used in combination with immediate-release tacrolimus.

Everolimus is still not predicted to be cost-effective. It is predicted to be more expensive and more expensive than mycophenolate mofetil and azathioprine when in combination with ciclosporin with an ICER over £900,000 per QALY (compared to an ICER of over £600,000 per QALY in the deterministic analysis).

Table 126. Summary cost-effectiveness results for maintenance agents (probabilistic analyses)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
With MMF						*vs. TAC*			
CSA	£197,421	—	18.0896	—	Dominated	-1.0372	-0.7204	0.5%	0.8%
TAC-PR	£194,861	-£2,560	18.0765	-0.0130	Dominated	-0.9222	-0.6481	0.1%	0.3%
TAC	£178,415	-£16,446	18.1765	+0.0999	—	—	—	99.4%	98.9%
With AZA						*vs. TAC*			
CSA	£206,855	—	17.9751	—	Dominated	-1.9138	-1.3688	0.0%	0.0%
TAC	£174,153	-£32,702	18.2538	+0.2787	—	—	—	100.0%	100.0%
With BAS+MMF						*vs. TAC*			
SRL	£197,730	—	18.1774	—	Dominated	-1.5315	-1.0617	0.0%	0.0%
CSA	£188,991	-£8,739	18.2097	+0.0323	Dominated	-1.0623	-0.7382	0.4%	0.6%
TAC	£169,546	-£19,445	18.2997	+0.0900	—	—	—	99.6%	99.3%
BEL	£293,117	+£123,571	18.5326	+0.2330	£530,421	-5.9456	-3.8861	0.0%	0.0%
With BAS+AZA						*vs. TAC*			
CSA	£196,484	—	18.1029	—	Dominated	-1.9018	-1.3618	0.0%	0.0%
TAC	£164,088	-£32,396	18.3848	+0.2820	—	—	—	100.0%	100.0%
With rATG+MMF						*vs. TAC*			
CSA	£205,769	—	18.0414	—	Dominated	-0.9943	-0.6897	0.4%	0.7%
TAC	£187,494	-£18,275	18.1220	+0.0806	—	—	—	99.6%	99.3%
With rATG+AZA						*vs. TAC*			
CSA	£212,166	—	17.9509	—	Dominated	-1.7727	-1.2670	0.0%	0.0%
TAC	£181,824	-£30,342	18.2064	+0.2556	—	—	—	100.0%	100.0%

Table 126. Summary cost-effectiveness results for maintenance agents (probabilistic analyses) (cont.)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
With CSA						*vs. MMF*			
AZA	£206,855	—	17.9751	—	Dominated	-0.5862	-0.4290	0.1%	0.1%
MMF	£197,421	-£9,434	18.0896	+0.1145	—	—	—	99.9%	99.9%
EVL	£258,260	+£60,839	18.1562	+0.0666	£912,988	-2.9753	-1.9613	0.0%	0.0%
With TAC						*vs. AZA*			
SRL	£220,087	—	17.8930	—	Dominated	-2.6574	-1.8918	0.0%	0.0%
MMF	£178,415	-£41,672	18.1765	+0.2834	Dominated	-0.2904	-0.2194	25.9%	25.1%
AZA	£174,153	-£4,262	18.2538	+0.0773	—	—	—	74.1%	74.9%
With BAS+CSA						*vs. MMF*			
AZA	£196,484	—	18.1029	—	Dominated	-0.4815	-0.3566	0.2%	0.2%
MMF	£188,991	-£7,493	18.2097	+0.1068	—	—	—	74.0%	69.8%
MPS	£197,722	+£8,730	18.2768	+0.0671	£130,080	-0.3694	-0.2239	25.9%	30.1%
With BAS+TAC						*vs. AZA*			
MMF	£169,546	—	18.2997	—	Dominated	-0.3581	-0.2671	20.4%	19.9%
AZA	£164,088	-£5,458	18.3848	+0.0852	—	—	—	79.6%	80.1%
With rATG+CSA						*vs. MMF*			
AZA	£212,166	—	17.9509	—	Dominated	-0.4104	-0.3038	0.4%	0.3%
MMF	£205,769	-£6,397	18.0414	+0.0905	—	—	—	99.6%	99.7%
With rATG+TAC						*vs. AZA*			
MMF	£187,494	—	18.1220	—	Dominated	-0.3680	-0.2735	18.3%	18.0%
AZA	£181,824	-£5,670	18.2064	+0.0845	—	—	—	81.7%	82.0%

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QA
With CSA						*vs. MMF*			
AZA	£209,016	—	17.9481	—	Dominated	-0.5472	-0.4292	0.1%	0.
MMF	£199,539	-£9,477	18.0614	+0.1133	—	—	—	99.9%	99.
EVL	£259,701	+£60,162	18.1244	+0.0630	£954,838	-2.9451	-1.9424	0.0%	0.
With TAC						*vs. AZA*			
SRL	£221,807	—	17.8558	—	Dominated	-2.6408	-1.8824	0.0%	0.
MMF	£180,529	-£41,278	18.1350	+0.2792	Dominated	-0.2977	-0.2273	24.9%	23.
AZA	£176,305	-£4,224	18.2215	+0.0865	—	—	—	75.1%	76.
With BAS+CSA						*vs. MMF*			
AZA	£197,127	—	18.1019	—	Dominated	-0.4830	-0.3575	0.2%	0.
MMF	£189,597	-£7,530	18.2083	+0.1065	—	—	—	75.0%	71.
MPS	£198,660	+£9,063	18.2739	+0.0656	£138,196	-0.3876	-0.2365	24.8%	28.
With BAS+TAC						*vs. AZA*			
MMF	£170,179	—	18.2944	—	Dominated	-0.3602	-0.2696	20.0%	19.
AZA	£164,746	-£5,433	18.3829	+0.0885	—	—	—	80.0%	80.
With rATG+CSA						*vs. MMF*			
AZA	£201,211	—	18.0837	—	Dominated	-0.4273	-0.3173	0.4%	0.
MMF	£194,609	-£6,602	18.1809	+0.0972	—	—	—	99.6%	99.
With rATG+TAC						*vs. AZA*			
MMF	£175,703	—	18.2763	—	Dominated	-0.3816	-0.2823	17.9%	17.
AZA	£169,739	-£5,963	18.3598	+0.0835	—	—	—	82.1%	82.

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Cost-effectiveness acceptability curves

Cost-effectiveness acceptability curves show, for each regimen, the probability that regimen is cost-effective at various thresholds. In this context, the probability of a regimen being cost-effective is the proportion of PSA iterations in which the regimen gives the greatest net health benefit.

No cross-overs are observed in the cost-effectiveness acceptability curves and it was verified that in all cases the regimen with the greatest probability of being cost-effective at each threshold also gave the greatest expected net health benefit.

Induction agents

Figure 35. Cost-effectiveness acceptability curves for induction agents in combination with ciclosporin and azathioprine

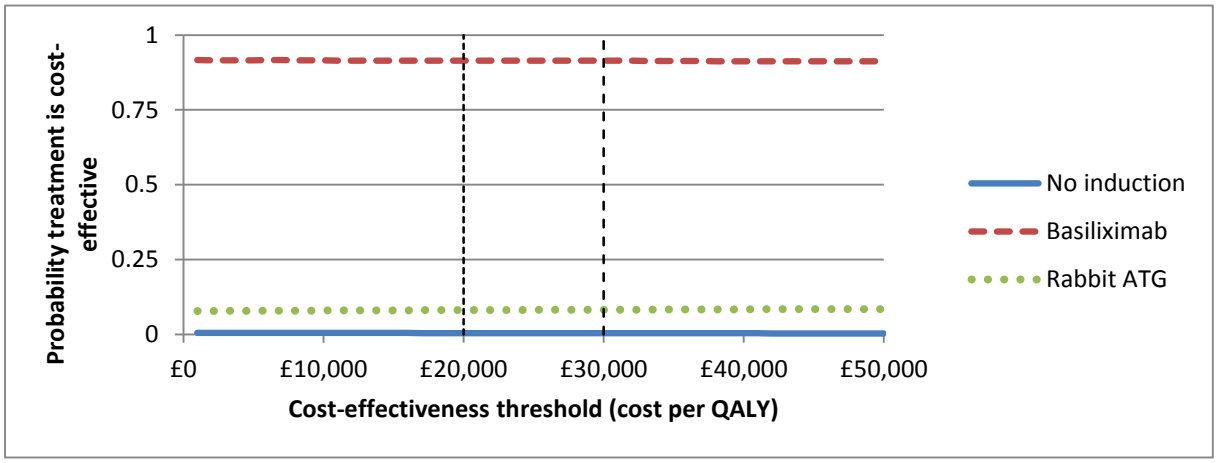


Figure 36. Cost-effectiveness acceptability curves for induction agents in combination with ciclosporin and mycophenolate mofetil

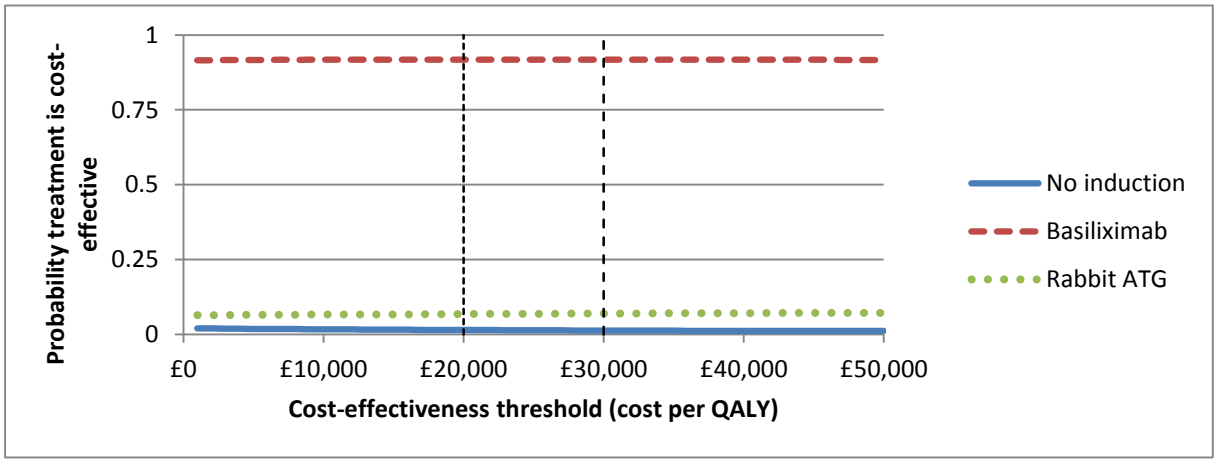


Figure 37. Cost-effectiveness acceptability curves for induction agents in combination with immediate-release tacrolimus and azathioprine

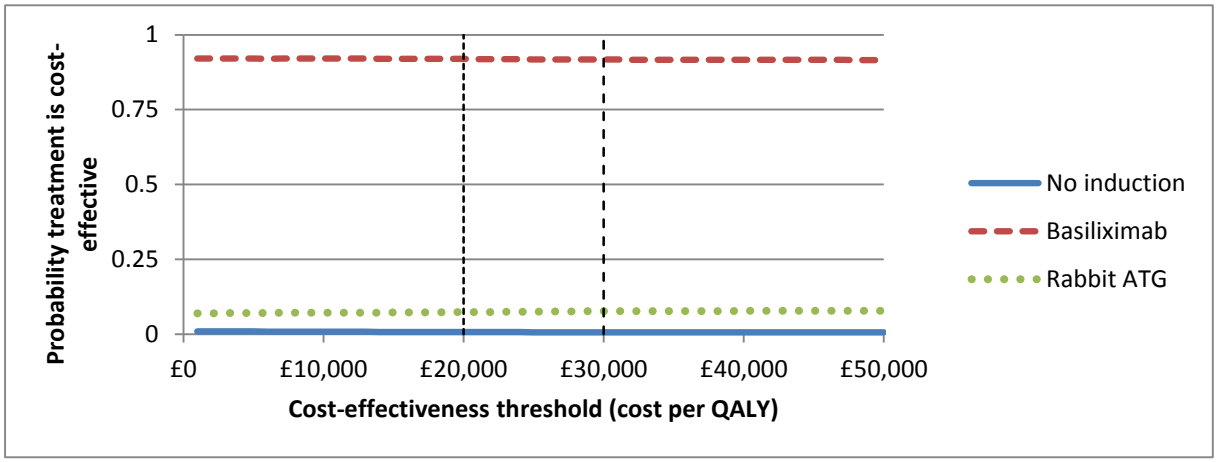
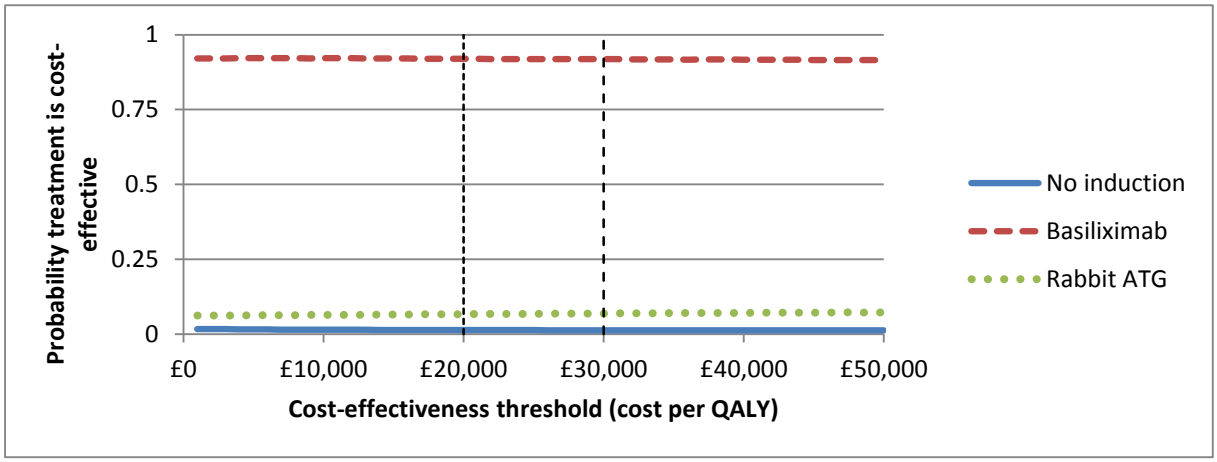


Figure 38. Cost-effectiveness acceptability curves for induction agents in combination with immediate-release tacrolimus and mycophenolate mofetil



Maintenance agents

Figure 39. Cost-effectiveness acceptability curves for maintenance agents in combination with mycophenolate mofetil

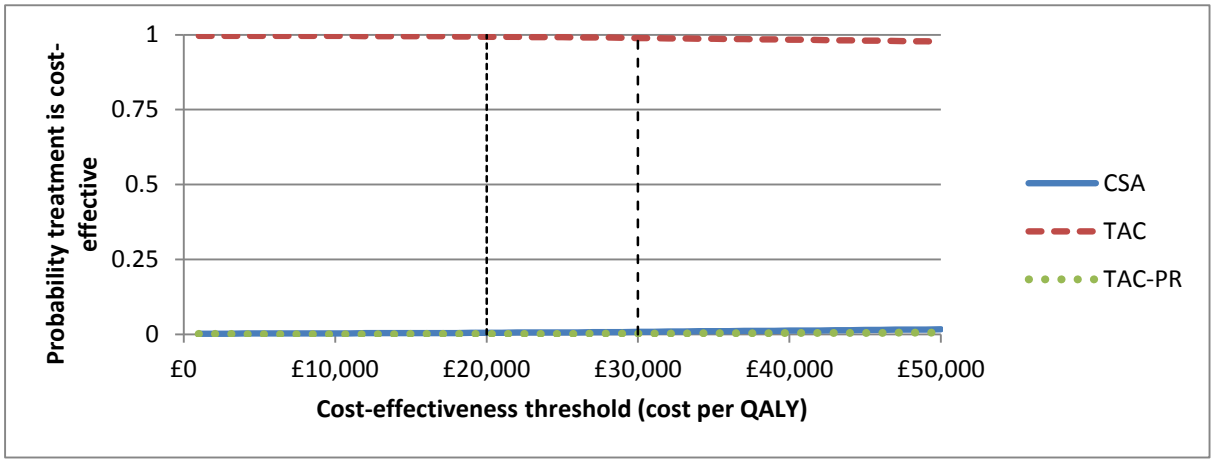


Figure 40. Cost-effectiveness acceptability curves for maintenance agents in combination with azathioprine

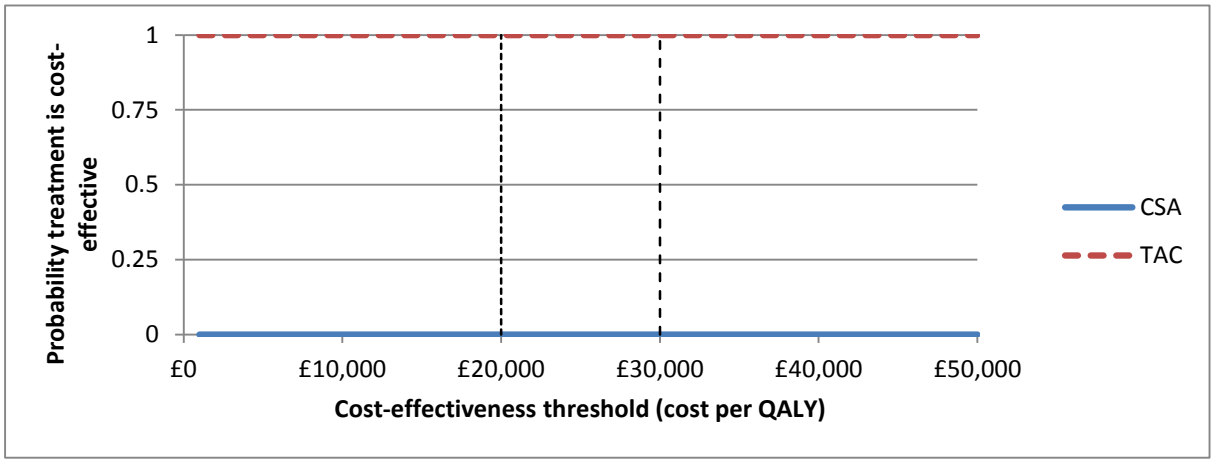


Figure 41. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and mycophenolate mofetil

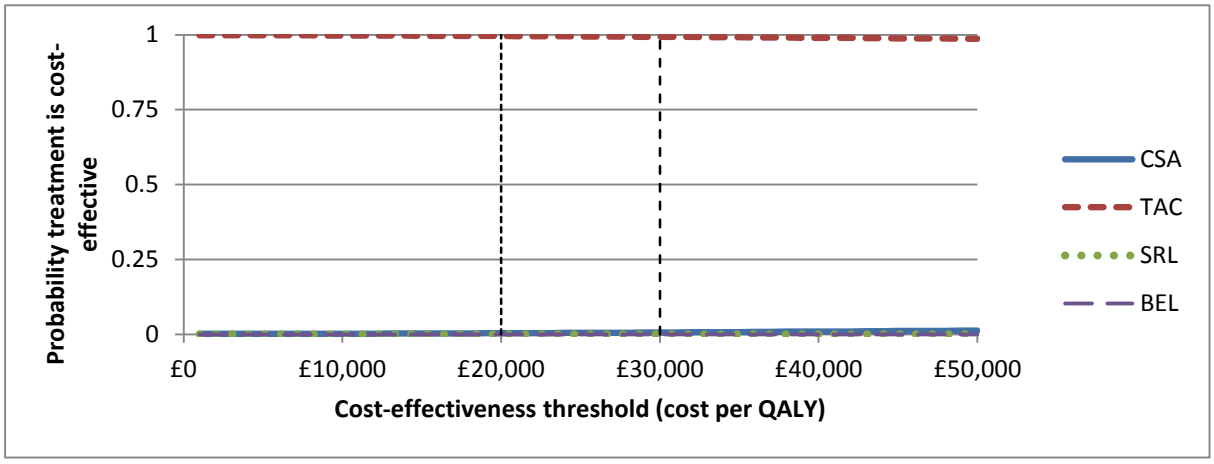


Figure 42. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and azathioprine

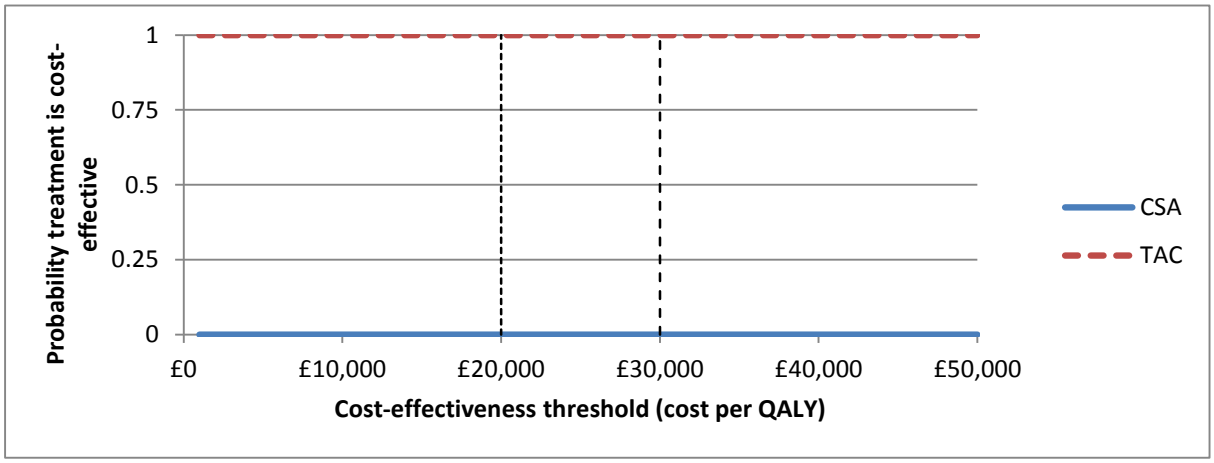


Figure 43. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and mycophenolate mofetil

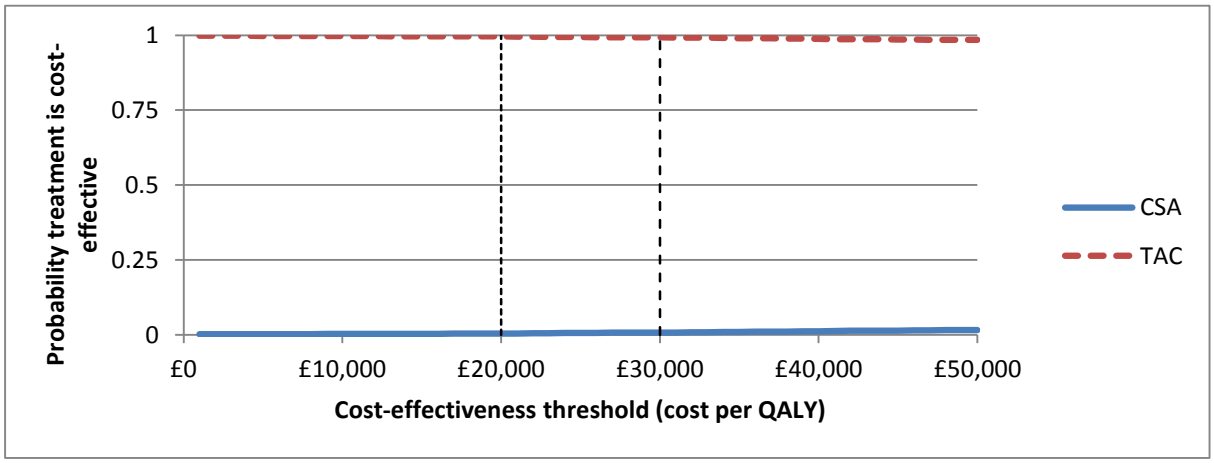


Figure 44. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and azathioprine

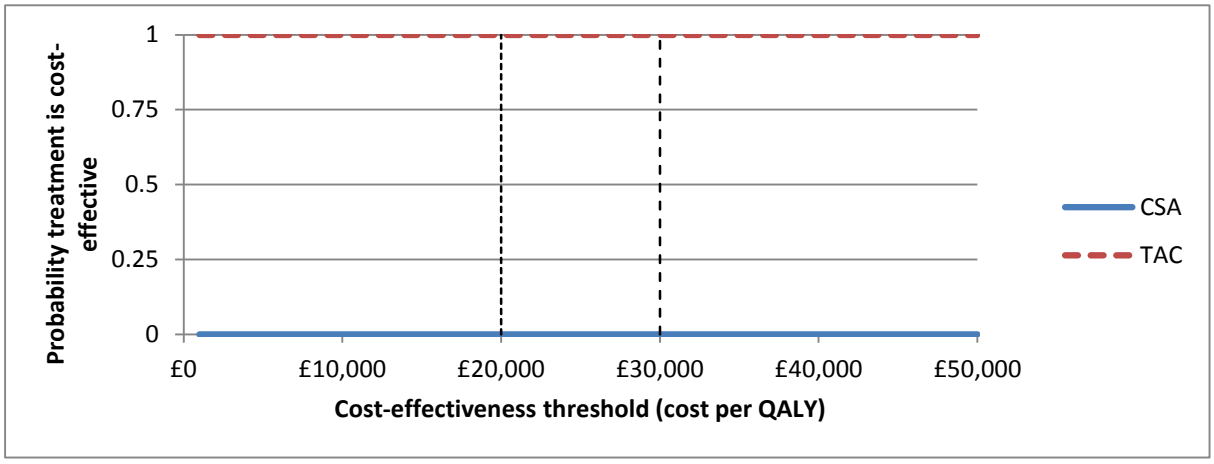


Figure 45. Cost-effectiveness acceptability curves for maintenance agents in combination with ciclosporin

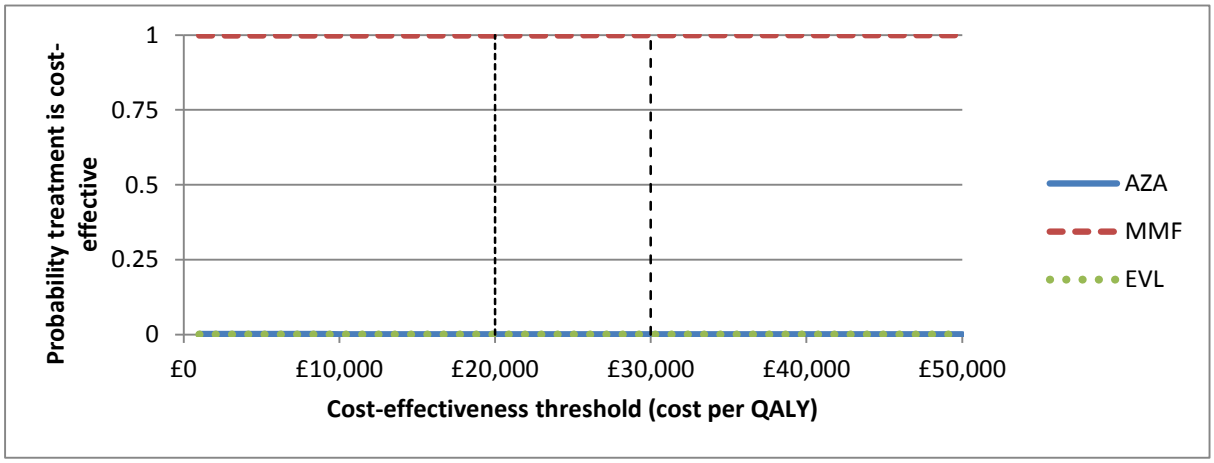


Figure 46. Cost-effectiveness acceptability curves for maintenance agents in combination with immediate-release tacrolimus

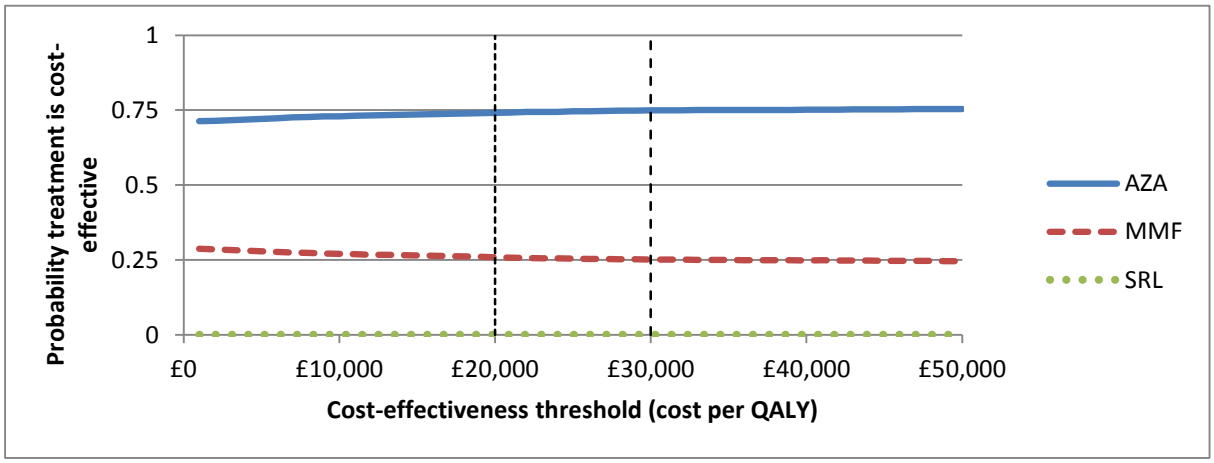


Figure 47. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and ciclosporin

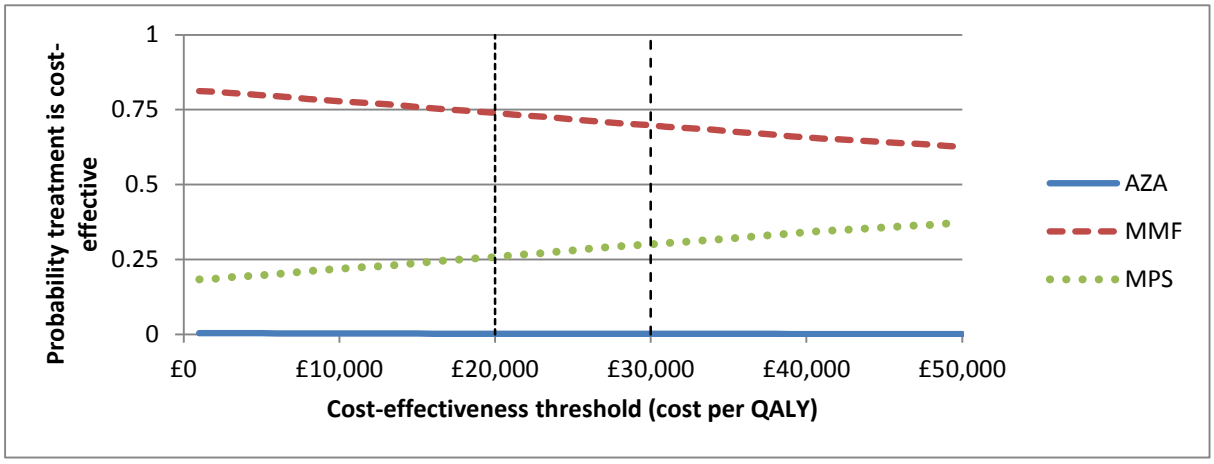


Figure 48. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and immediate-release tacrolimus

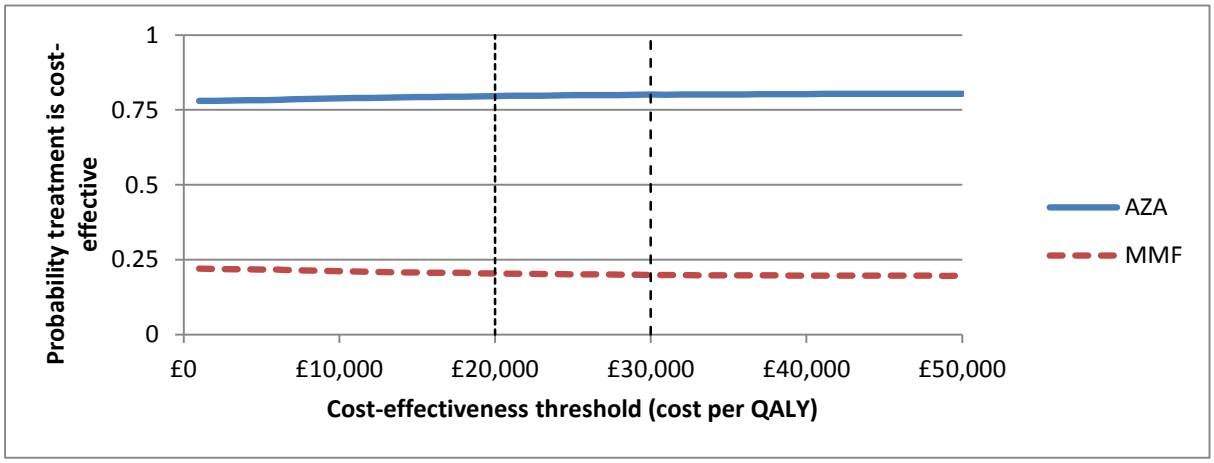


Figure 49. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and ciclosporin

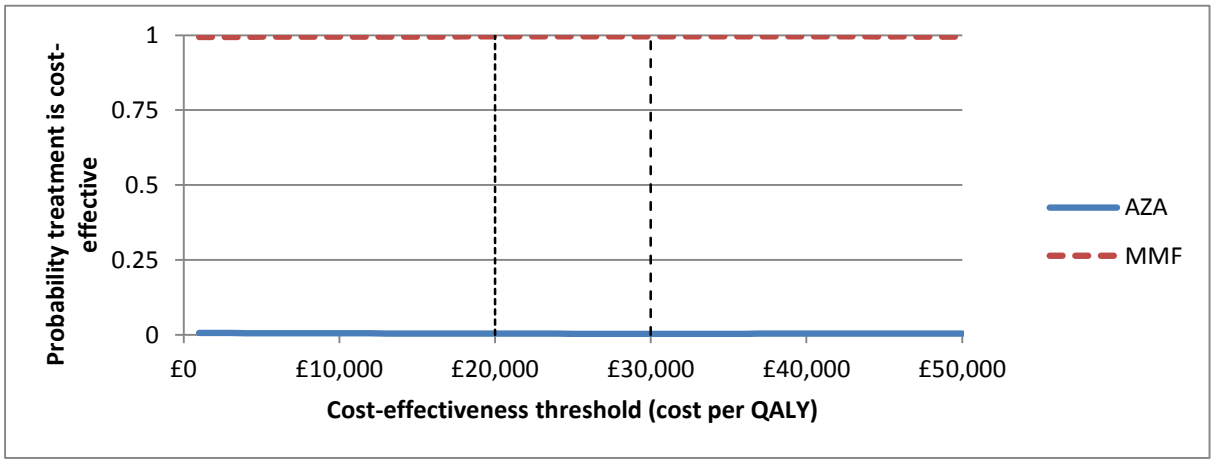
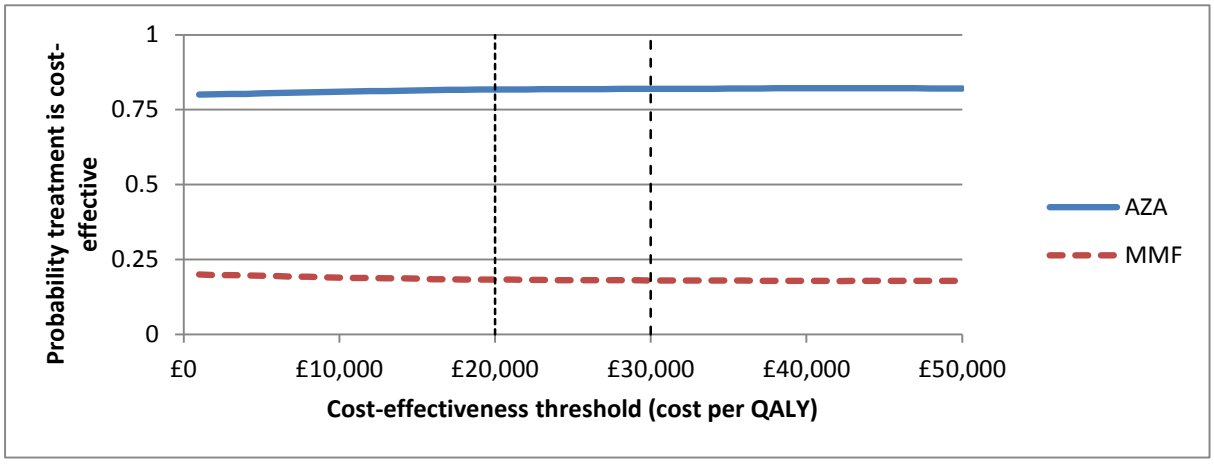


Figure 50. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and immediate-release tacrolimus



6.3.2.3 Scenario analyses

Below average weight for KTRs

When body weight was assumed to follow the 9th centile for age (rather than the median) the immunosuppression costs of most arms decreased. QALYs were unaffected.

The incremental net health benefits at £20,000 per QALY did not change sign (i.e., no agents previously not cost-effective became cost-effective or vice versa). At £30,000 per QALY the incremental net health benefit for mycophenolate sodium became positive, suggesting that in this scenario mycophenolate sodium is cost-effective at £30,000 per QALY (but not at £20,000 per QALY). The ICER for mycophenolate sodium in this scenario is £27,006 per QALY.

Surrogate relationship between acute rejection and graft survival removed

When the surrogate relationship between acute rejection and graft survival was removed, the result was increased graft survival for all regimens except BAS+CSA+MMF, BAS+TAC+MMF, BAS+SRL+MMF, rATG+CSA+MMF, rATG+TAC+MMF and rATG+TAC+AZA (for which graft survival was decreased). Increased graft survival usually results in reduced overall costs and increased QALYs, and this was observed across regimens as expected.

No incremental net health benefits changed sign at £20,000 or £30,000 per QALY, although the ICER for mycophenolate sodium drops to £33,157 per QALY.

6.3.2.4 Subgroup analyses

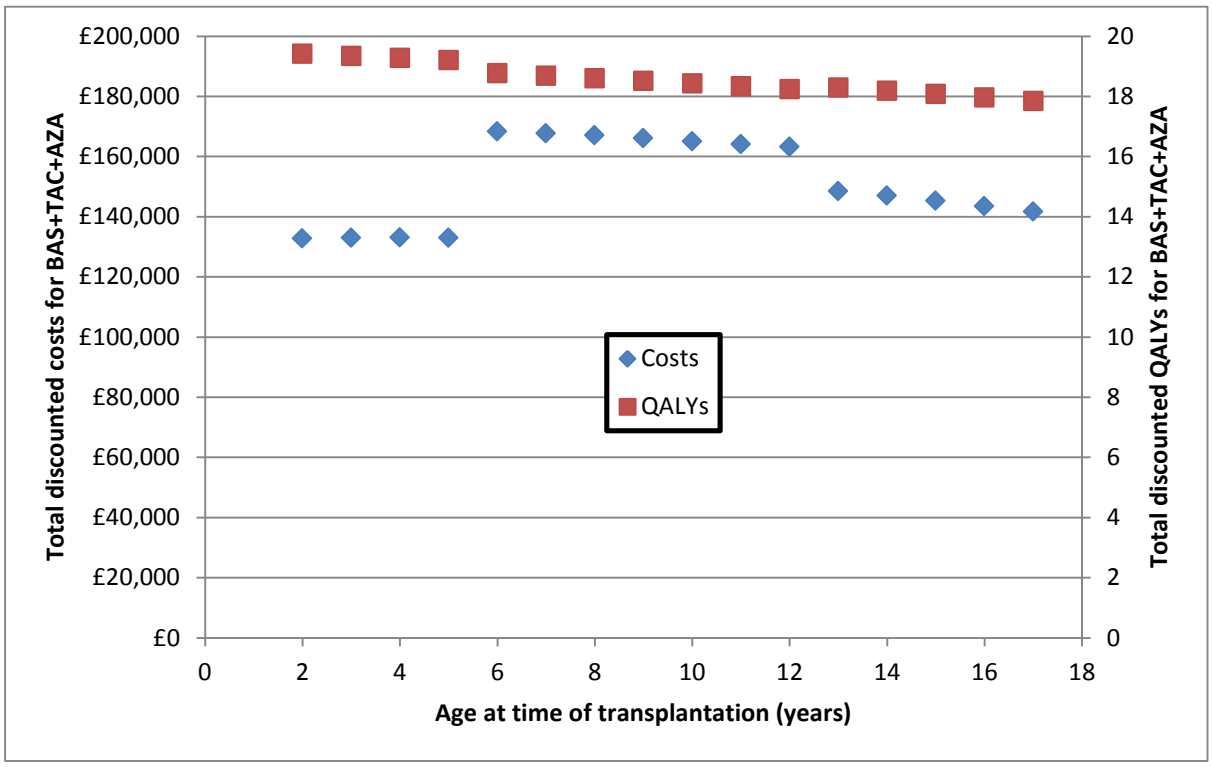
The only subgroup analyses which were conducted were based on the age of KTRs. The age at time of transplantation was varied from 2 years to 17 years.

For most regimens discontinuities in total discounted costs were observed at age 6 and age 13, which are explained by the hazard ratios for graft survival according to age, taken from Muscheites et al. 2009,[7] in which graft survival was predicted to be worse for children aged 6–12 at the time of transplantation than for younger children or older adolescents. Reduced graft survival results in greater total costs as more recipients lose their grafts earlier and require dialysis.

For all regimens the total discounted QALYs decreased with increasing age, except at age 13 where discounted QALYs were greater than for age 12 (due to the changing hazard ratio for graft survival indicated above). The cause of decreasing total discounted QALYs is likely to be greater exposure to higher rates of death with functioning graft.

The total discounted costs and QALYs are shown for basiliximab, immediate-release tacrolimus and azathioprine in Figure 51.

Figure 51. Total discounted costs and QALYs for regimen of basiliximab, immediate-release tacrolimus and azathioprine as age at transplantation is varied



Across the age range, BAS+TAC+AZA was the most cost-effective regimen at £20,000 and £30,000 per QALY (Figure 52 and Figure 53).

Figure 52. Rank of net health benefit at £20,000 per QALY for all regimens as the age at time of transplantation is varied

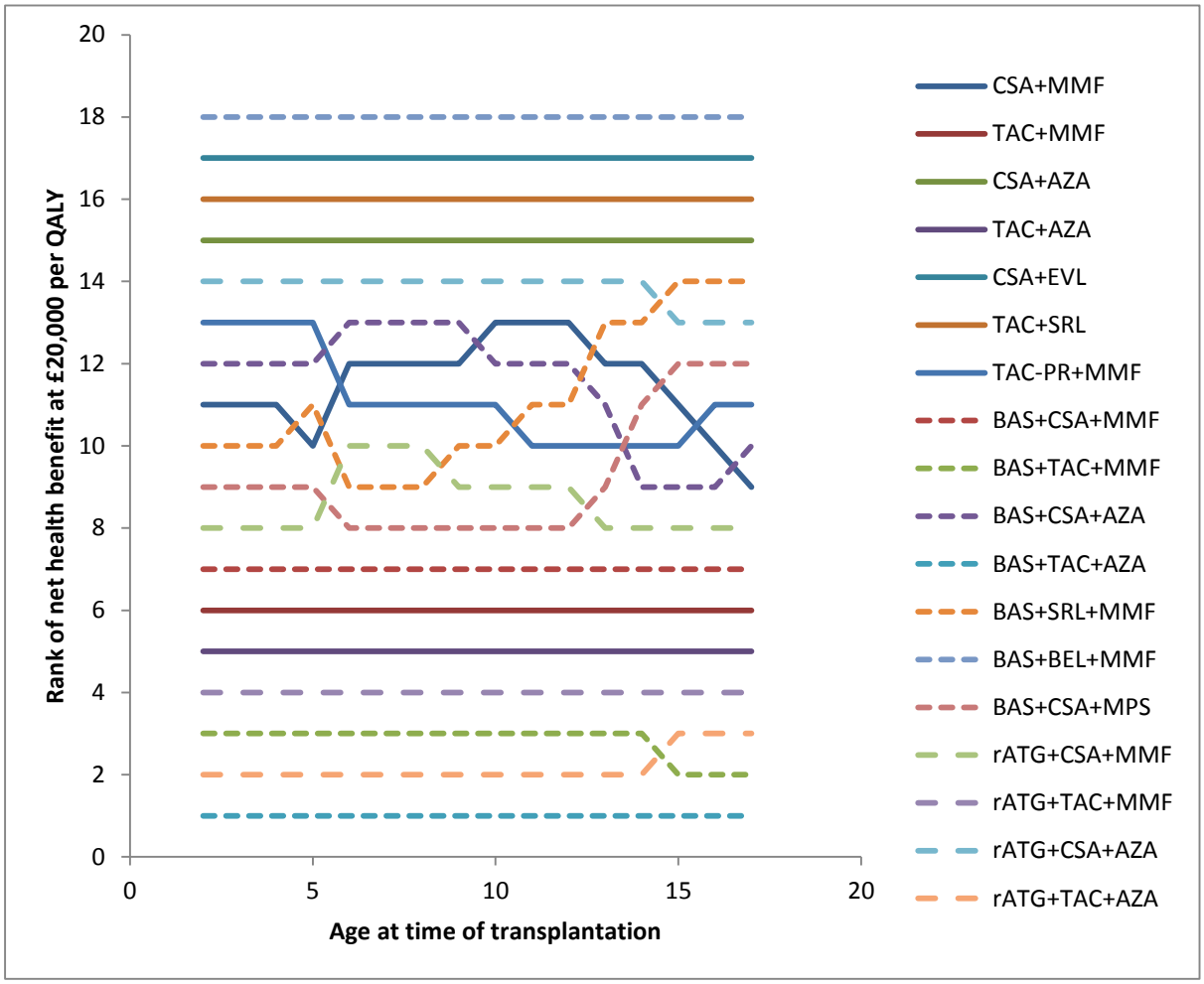
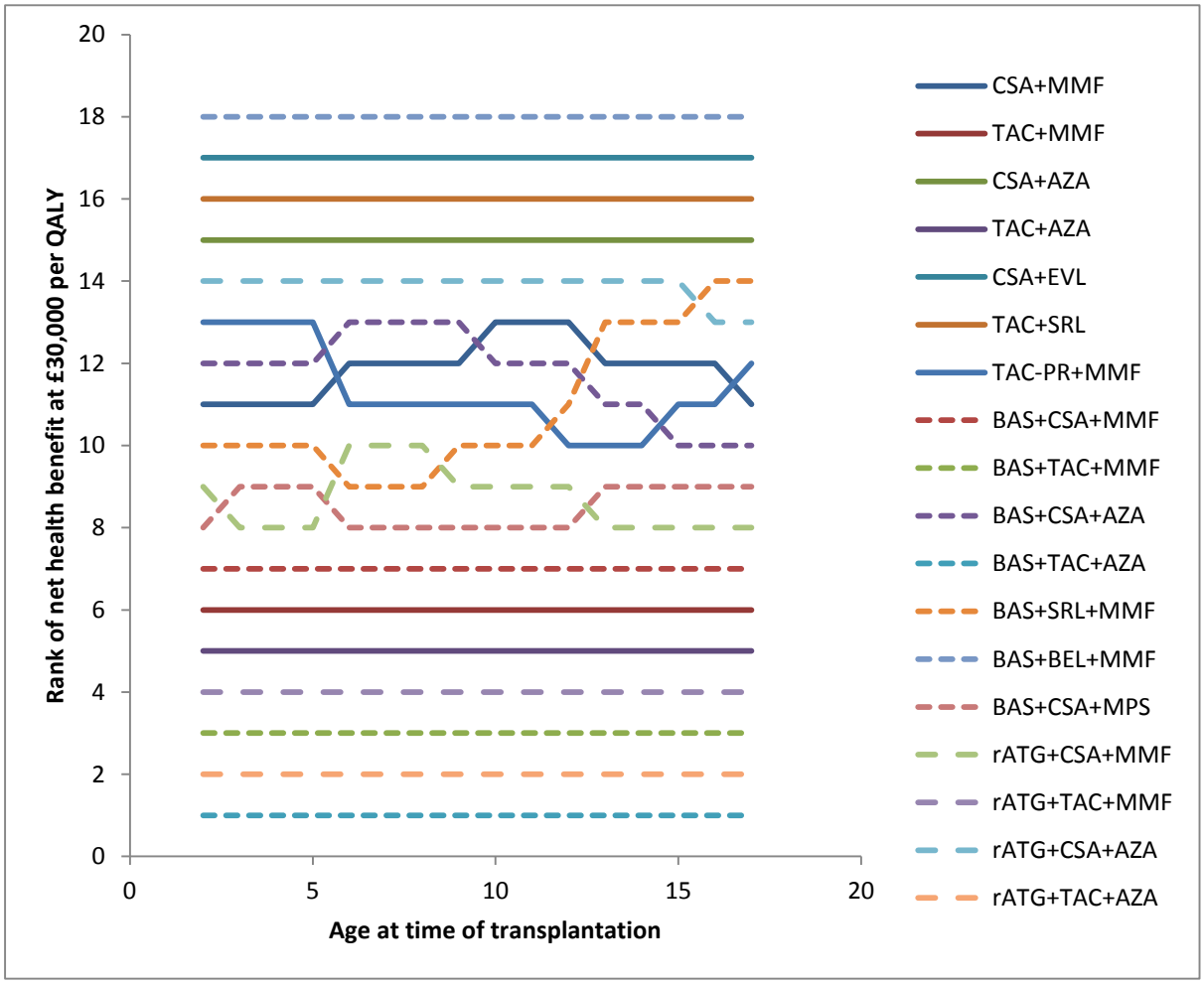


Figure 53. Rank of net health benefit at £30,000 per QALY for all regimens as the age at time of transplantation is varied



When the weighted average total discounted costs and QALYs (weighted by number of KTRs at each age) are calculated, BAS+TAC+AZA is the cost-effective regimen at £20,000 and £30,000 per QALY (Table 127).

Table 127. Net health benefit of regimens when averaged across age range

Regimen	Net health benefit	
	£20,000 per QALY	£30,000 per QALY
CSA+MMF	9.08	12.11
TAC+MMF	9.99	12.74
CSA+AZA	8.32	11.55
TAC+AZA	10.25	12.93

CSA+EVL	5.60	9.81
TAC+SRL	7.50	10.99
TAC-PR+MMF	9.10	12.13
BAS+CSA+MMF	9.59	12.49
BAS+TAC+MMF	10.65	13.23
BAS+CSA+AZA	9.08	12.11
BAS+TAC+AZA	10.95	13.45
BAS+SRL+MMF	9.02	12.10
BAS+BEL+MMF	2.33	7.76
BAS+CSA+MPS	9.23	12.29
rATG+CSA+MMF	9.28	12.28
rATG+TAC+MMF	10.34	13.02
rATG+CSA+AZA	8.83	11.94
rATG+TAC+AZA	10.69	13.27

6.3.2.5 Summary of results from analyses based on extrapolating effectiveness estimates from adults

Basiliximab was predicted to be cost-effective at £20,000 to £30,000 per QALY.

Rabbit ATG and no induction were not predicted to be cost-effective at £20,000 to £30,000 per QALY versus basiliximab.

Immediate-release tacrolimus was predicted to be cost-effective at £20,000 to £30,000 per QALY.

Prolonged-release tacrolimus, sirolimus, belatacept and ciclosporin were not predicted to be cost-effective at £20,000 to £30,000 per QALY versus immediate-release tacrolimus and each other.

Mycophenolate mofetil was predicted to be cost-effective at £20,000 to £30,000 per QALY when used in combination with ciclosporin, but not when used in combination with immediate-release tacrolimus.

Azathioprine was predicted to be cost-effective at £20,000 to £30,000 per QALY when used in combination with immediate-release tacrolimus, but not when used in combination with ciclosporin.

Mycophenolate sodium was not predicted to be cost-effective at £20,000 to £30,000 per QALY versus mycophenolate mofetil and azathioprine, but was cost-effective at £30,000 per QALY in a scenario analysis in which body weight followed the 9th centile rather than median weight for age.

Sirolimus and everolimus were not predicted to be cost-effective at £20,000 to £30,000 per QALY versus mycophenolate mofetil and azathioprine.

6.3.3 Summary of results from PenTAG economic assessment

Basiliximab was predicted to be cost-effective at £20,000 to £30,000 per QALY versus no induction in one analysis based on an RCT in children and adolescents (Grenda et al. 2006), but was not predicted to be cost-effective in an analysis based on another RCT in children and adolescents (Offner et al. 2008). Basiliximab was predicted to be cost-effective at £20,000 to £30,000 per QALY versus no induction and rabbit ATG in analyses based on extrapolating effectiveness estimates from the adult population.

Rabbit ATG was not predicted to be cost-effective at £20,000 to £30,000 versus basiliximab in analyses based on extrapolating effectiveness estimates from the adult population.

Immediate-release tacrolimus was predicted to be cost-effective at £20,000 to £30,000 per QALY versus ciclosporin in an analysis based on an RCT in children and adolescents (Trompeter et al. 2002), and was also predicted to be cost-effective versus ciclosporin, prolonged-release tacrolimus, sirolimus and belatacept in analyses based on extrapolating effectiveness estimates from the adult population.

Mycophenolate mofetil was predicted to be cost-effective at £20,000 to £30,000 per QALY when used in combination with ciclosporin in analyses based on extrapolating effectiveness estimates from the adult population, but was not predicted to be cost-effective when used in combination with immediate-release tacrolimus.

Prolonged-release tacrolimus, sirolimus, belatacept, mycophenolate sodium and everolimus were not predicted to be cost-effective at £20,000 to £30,000 per QALY versus immediate-release tacrolimus in analyses based on extrapolating effectiveness estimates from the adult population.

REFERENCES

1. Samsel R, Pliszczynski J, Chmura A, Korczak G, Z W, Cieciura T, et al. Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients--long term results. Annals of Transplantation [Internet]. 2008; 13(1):[32-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/384/CN-00638384/frame.html.

2. Kyllönen LE, Eklund BH, Pesonen EJ, Salmela KT. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. Transplantation [Internet]. 2007; 84(1):[75-82 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/081/CN-00707081/frame.html.

3. Sheashaa HA, Bakr MA, Ismail AM, Sobh MA, Ghoneim MA. Basiliximab reduces the incidence of acute cellular rejection in live-related-donor kidney transplantation: a three-year prospective randomized trial. Journal of Nephrology. 2003;16:393-8.

4. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. Transplantation. 1995;60(3):225-32.

5. Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: A systematic review and modelling study. Health Technology Assessment. 2005;9:i-179.

6. Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, et al. A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. Health Technology Assessment. 2006;10:iii-65.

7. Muscheites J, Wigger M, Drueckler E, Klaassen I, John U, Wygoda S, et al. Estimated one-yr glomerular filtration rate is an excellent predictor of long-term graft survival in pediatric first kidney transplants. Pediatr Transplant. 2009;13(3):365-70.