Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal 99)

A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Acute rejection	Process by which the graft recipient's immune system attempts to destroy the graft, usually within the first three months of transplanation
Cadaveric transplant	A transplant kidney removed from someone who has died.
Calcineurin inhibitor	Ciclosporin or tacrolimus
Cytomegalovirus	A virus that normally causes only a mild 'flu-like' illness. In people with a kidney transplant, CMV can cause a more serious illness, affecting the lungs, liver and blood.
Donor	A person who donates an organ to another person (the recipient).
Glomerular filtration rate	Flow rate of filtered fluid through the kidney, measured directly by injecting a harmless chemical (e.g. inulin) into the blood, and then measuring how much of the chemical is filtered in a given unit of time.
Graft function	A measure of the efficiency of the graft by various markers e.g. glomerular filtration rate and serum creatinine levels.
Graft loss	Absence of kidney function occurring any time after transplantation requiring chronic dialysis and/or retransplantation (excluding loss due to death)
Haemodialysis	Removal of waste products by passing blood out of the body, through a filtering system (dialyser) and then back to the body.
1-Haplotype identical	HLA antigens are inherited as a set called a 'haplotype' from one or both parents. 1-Haplotype identical is not a 'perfect' HLA match; a 2-halotype identical is a perfect HLA match.
Heart-beating donor	A donor kidney where the heart is still beating in the donor after brain death has occurred. Most, but not all, cadaveric transplants
Living related transplant	A kidney donated by a living relative of the recipient. A well matched living related transplant is likely to last longer than either a living unrelated transplant or a cadaveric transplant.
Living unrelated	A kidney transplant from a living person who is biologically unrelated to

transplant	the recipient
Mycophenolic acid	Mycophenolate mofetil or mycophenolate sodium.
Nephritis	A general term for inflammation of the kidneys. Also used as an abbreviation for glomerulonephritis.
Peritoneal dialysis	Removal of waste products using the peritoneum as a filter, Dialysis fluid is pumped into the peritoneal cavity and waste products and excess fluid are moved from the blood into the dialysis fluid which is then drained from the cavity.
Recipient	In the context of transplantation, a person who receives an organ from another person (the donor).
Rejection	The process whereby a patient's immune system recognises a transplant kidney as foreign and tries to destroy it. Rejection can be acute or chronic.
Renal replacement therapy	Dialysis or kidney transplantation.

List of abbreviations

AE	adverse events
ANCA	antineutrophil cytoplasmic autoantibody
AMR	antibody-mediated rejection
AR	acute rejection
ATG	anti-human thymocyte/antithymocyte (immune)globulin
AZA	azathioprine
BAS	basiliximab
BKVN	BK virus nephropathy
BNF	British National Formulary
BPAR	biopsy-proven acute rejection
CAN	chronic allograft nephropathy
CCS	corticosteroids
CI	confidence interval
CNI	calcineurin inhibitor
CMV	cytomegalovirus
CSA	ciclosporin
CVD	cardiovascular disease
DAC	daclizumab
DARE	Database of Abstracts of Review of Effects
DBD	donation after brain death
DCD	donation after circulatory death

DGF	delayed graft function
EBV	Epstein–Barr virus
ECD	expanded criteria donor
EQ-5D	EuroQoL instrument
ESRD	end-stage renal disease
ESRF	end-stage renal failure
FSGS	focal segmental glomerulosclerosis
GBM	glomerular basement membrane
GFR	glomerular filtration rate
GI	gastrointestinal
HLA	human leucocyte antigen
HR	hazard ratio
HUS	haemolytic-uremic syndrome
ICER	incremental cost-effectiveness ratio
IF/TA	interstitial fibrosis/tubular atrophy
IgA	immunoglobulin A
ITT	intention-to-treat
IV	intravenous
KM	kaplan-meier
KT	kidney transplant
KTR	kidney transplant recipient
MPA	mycophenolic acid
MMF	mycophenolate mofetil

MPGN	membranoproliferative glomerulonephritis
MPS	mycophenolate sodium
NAPRTCS	North American Paediatric Renal Transplant Cooperative Study
NHS EEDS	National Health Service Economic Evaluation Database
NODAT	new-onset diabetes after transplantation
OHE HEED	Office of Health Economics Health Economic Evaluation Database
PBO	placebo
PCR	polymerase chain reaction
PNF	primary non-function
PTLD	post-transplant lymphoproliferative disease
QALY	quality-adjusted life-year
r-ATG	rabbit anti-human thymocyte immunoglobulin
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SD	standard deviation
SDS	standard deviation score
TAC	tacrolimus
TAC PR	tacrolimus prolonged release
TCMR	T-cell-mediated rejection
TMA	thrombotic microangiopathy
UNOS	United Network of Organ Sharing
WMD	weighted mean difference

EXECUTIVE SUMMARY

1.1 Background

Chronic kidney disease in childhood leads to lifelong health complications, often resulting in the need of a kidney transplant. A long-term progression of irreversible decline in kidney function to end stage renal disease will require renal replacement therapy for a child or adolescent to survive. Renal replacement therapy will consist of either a kidney transplant or dialysis (haemodialysis or peritoneal dialysis). The preferred option for a child/adolescent with end stage renal disease is kidney transplantation.

Kidney transplantation is the transfer of a healthy kidney from a donor to a recipient. Kidneys for transplantation may be obtained via living donation (related or unrelated), donation after brain death, or donation after circulatory death. When considering a kidney transplant, children and adolescents represent a distinct group, and can differ from adults in several aspects. There are however, adolescents aged between 16 and 18 years old, who may receive their medical care in adult nephrology centres.

Between April 2013 and March 2014, 125 kidney transplant operations were performed on children and adolescents in the UK. The number of kidney transplants performed on children and adolescents from 2004 to 2014 has remained relatively constant (ranging from 106-143 transplants per year over the 10 years). Survival following a kidney transplant at five years (April 2009 to March 2013) was 99% (95% CI 96 to 100).

Following kidney transplantation, major clinical concerns in children and adolescents are acute kidney rejection, graft loss and growth. Acute kidney rejection occurs when the immune response attempts to destroy the graft as the graft is deemed foreign tissue. Therefore, immunosuppressive therapy is implemented to reduce the risk of kidney rejection and prolong survival of the graft.

There are three main service provision steps that are followed in the management of kidney transplant: organ procurement, provision of immunosuppressive therapy, and short and long term follow-up following transplantation. Immunosuppressive therapy can be divided into induction and maintenance regimes. Induction drugs are powerful antirejection drugs that are taken at the time of transplantation, and soon after, when the risk of rejection is highest. Maintenance drugs are less powerful antirejection drugs that are used as both initial and long term maintenance therapy.

Interventions

This technology assessment report considers nine pharmaceutical interventions. Two are used as induction therapy and seven are used as a part of maintenance therapy.

The two interventions considered for induction therapy are:

- **basiliximab** (Simulect® [Novartis Pharmaceuticals]) which is a monoclonal antibody acting as an interleukin-2 receptor antagonist;
- **rabbit anti-human thymocyte immunoglobulin** (rATG; Thymoglobuline® [Sanofi]) which is a gamma immune globulin, generated by immunising rabbits with human thymocytes;

Both have UK marketing authorisation for prevention of graft rejection in renal transplantation.

The interventions considered for maintenance therapy all have UK marketing authorisation for immunosuppressive treatment in kidney transplantation and are as follows:

- **immediate-realease tacrolimus** (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]);
- **prolonged-release tacrolimus** (Advagraf® [Astellas Pharma]);

both of which are calcineurin inhibitors;

- **belatacept** (Nulojix® [Bristol-Myers Squibb]) which is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T-cells;
- **mycophenolate mofetil** which is a prodrug of mycophenolic acid and acts as an antiproliferative agent (Arzip® [Zentiva], CellCept® [Roche Products], Myfenax® [Teva]; generic mycophenolate mofetil is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt);
- **mycophenolate sodium** is an enteric-coated formulation of mycophenolic acid (Myfortic®, [Novartis Pharmaceuticals]);
- **sirolimus** (Rapamune® [Pfizer]) which is a non-calcineurin inhibiting immunosuppressant and acts as an antiproliferative;

- **everolimus** (Certican® [Novartis Pharmaceuticals]) which is a proliferation signal inhibitor and is an analogue of sirolimus.

Comparators

The comparators of interest for induction therapies were regimens without monoclonal or polyclonal antibodies or one of the other interventions under consideration.

For maintenance therapies the comparators were a calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids or a regimen including one of the other interventions under consideration.

Population

Children and adolescents 0-18 years (inclusive) undergoing kidney transplantation only and receiving immunosuppressive therapy are included in this review. Children and adolescents receiving multi-organ transplants and those who have received transplants and immunosuppression previously are excluded.

Outcome measures

Studies were included in the systematic review if they reported data on one or more of the following outcomes:

- Mortality
- Graft-related outcomes:
    - Graft survival
    - Graft function
    - Time to and incidence of biopsy proven acute rejection
    - Severity of acute rejection according to Banff classification
- Growth
- Adverse events (AEs)
- Health-related quality of life (HRQoL)

Study design

The clinical effectiveness review included randomised controlled trials (RCTs) and systematic reviews which included non-randomised studies evaluating the interventions of interest in children and adolescents.

1.2 Objectives

The aim of this assessment is to review and update the evidence for the clinical and cost-effectiveness of immunosuppressive therapies in children and adolescent undergoing renal transplantation. This was achieved by conducting a systematic review of clinical effectiveness studies and a model based economic evaluation of induction and maintenance immunosuppressive regimens to inform an update of the current NICE guidance (TA99). In addition, we conducted a systematic review of relevant economic evaluations and a summary and critique of an economic analysis submitted by Astellas (manufacturers of Advagraf®, Prograf® and Modigraf®).

1.3 Methods

1.3.1 Clinical effectiveness systematic review

Identification of studies

Bibliographic literature searching was conducted on April 14th 2014 and updated January 7th 2015. The searches for individual effectiveness studies (RCTs and controlled clinical trials) took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a study design limited to randomised control trials [RCT] or controlled trials). Literature searches were not restricted to child or young adult populations so as to preserve the sensitivity of the searches and identify RCTs where mixed populations may have been recruited, but outcomes were reported according to age. In order to update the previous assessment by Yao et al. 2006 the searches were date limited (2002-current). The following databases were searched: Medline and Medline In-Process (OVID), Embase (OVID), CENTRAL (Wiley) and Web of Science (ISI – including conference proceedings). In addition, the following trials registries were hand searched in January 2015: Current Controlled Trials; ClinicalTrials.gov; FDA website; EMA website (European Public Assessment Reports [EPARs]).

Separate searches were undertaken to identify systematic reviews (SRs) of RCTs and non-randomised controlled studies. These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a pragmatic limit to systematic reviews). The search was run from database inception in the following databases: Medline and Medline In-Process (OVID), Embase (OVID), CDSR, DARE and HTA (The Cochrane Library via Wiley) and HMIC (OVID).

Study selection

Studies retrieved from the searches were selected for inclusion according to the inclusion/exclusion criteria. Initially, titles and abstracts returned by the search strategy were screened. The screening was distributed across a team of five researchers (TJ-H, LC, MHa, MB and HC). Update searches were screened by two reviewers (MHa and JV-C). Disagreements were resolved by discussion, with involvement of a third reviewer (TJ-H or MHa). Full texts of identified studies were obtained and screened in the same way.

Data extraction

Information from new studies (not informing the current NICE guidance TA99) was extracted and tabulated. All included studies (studies informing the current NICE guidance TA99 and newly identified studies) were quality appraised. If several publications were identified for one study, the data was extracted from the most recent publication and supplemented with information from other publications.

Data synthesis

Data were tabulated and discussed in a narrative review. Where data permitted the results of individual studies were pooled and meta-analysis was conducted.

1.3.2 Cost-effectiveness systematic review

Identification of studies

Bibliographic literature searching was conducted on April 8th 2014. The searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a costs or economic literature search filter). The search was date limited 2002-current in line with the previous assessment and the searches were

updated on January 15th 2015. The search was not limited by language and it was not limited to human only studies.

The following databases were searched: Medline (OVID), Embase (OVID), NHS EEDs (via Wiley), Web of Science (ISI – including conference proceedings), HEED (Wiley) and Econlit (Ebsco Host).

Study selection

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review, with the following exceptions:

- Non-randomised studies were included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses were included. (Economic evaluations which only report average cost-effectiveness ratios were only be included if the incremental ratios could be easily calculated from the published data.)
- Studies that measure only costs but not health benefits were excluded except for stand alone cost analyses from the perspective of the UK NHS.
- Only economic evaluations from UK, USA, Canada, Australia, and western Europe were included as these settings may include data generalizable to the UK.

Titles and abstracts were screened by two reviewers (RMM and LC), with disagreements resolved by discussion. Full texts were retrieved for references and were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of systematic review articles not judged eligible for inclusion were examined by one reviewer (LC) to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as full texts from database searches.

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers et al. (2005). Where studies were based on decision models they were further quality assessed using the checklist developed by Philips et al. (2004; 2006).

Data extraction and synthesis

Economic studies were extracted, summarised and synthesised using tabulated data and narrative synthesis.

1.3.3 Appraisal of company submissions

The appraisal of company submissions primarily focused on their model-based economic analyses. Their systematic reviews and related searching were primarily assessed in order to identify if any includable RCTs missed by our own searches. None were found.

1.3.4 PenTAG economic model

A new economic model was developed to address the decision problem in a cost–utility analysis. A discrete-time state transition model (semi-Markov) was employed in which transition probabilities were dependent on age and time since initial transplantation. A cycle length of a quarter year was used and transitions were assumed to occur mid-cycle. A time horizon of 50 years was adopted. Costs were included from an NHS and personal social services perspective. Health effects were measured in quality-adjusted life years (QALYs) and were calculated by assuming health state-specific utility decrements from a baseline utility which was age-dependent and derived from the Health Survey for England (2012). Costs and QALYs were discounted at 3.5% per annum and costs were inflated as necessary to 2014/15 prices.

1.3.4.1 Interventions and comparators

The following induction agents were included:

- Basiliximab (BAS)
- Rabbit ATG (rATG)

Regimens not including induction by monoclonal or polyclonal antibodies were also included.

The following maintenance agents were included:

- Immediate-release tacrolimus (TAC)
- Prolonged-release tacrolimus (TAC-PR)
- Mycophenolate mofetil (MMF)

- Mycophenolate sodium (MPS)
- Sirolimus (SRL)
- Everolimus (EVL)
- Belatacept (BEL)

Regimens including ciclosporin (CSA) and/or azathioprine (AZA) were also included. Corticosteroids were assumed to be used in all regimens but at a tapered dose.

Eighteen regimens were modelled in total.

Regimens without induction using monoclonal or polyclonal antibodies

- CSA+MMF
- TAC+MMF
- CSA+AZA
- TAC+AZA
- CSA+EVL
- TAC+SRL
- TAC-PR+MMF

Regimens with basiliximab induction

- BAS+CSA+MMF
- BAS+TAC+MMF
- BAS+CSA+AZA
- BAS+TAC+AZA
- BAS+SRL+MMF
- BAS+BEL+MMF

- BAS+CSA+MPS

Regimens with rabbit ATG induction

- rATG+CSA+MMF
- rATG+TAC+MMF
- rATG+CSA+AZA
- rATG+TAC+AZA

1.3.4.2 Model structure

Kidney transplant recipients were assumed to be in one of three health states at any time: FUNCTIONING GRAFT, GRAFT LOSS or DEATH. In the FUNCTIONING GRAFT state, kidney transplant recipients were not dependent on dialysis, whereas in the GRAFT LOSS state, kidney transplant recipients were dialysis-dependent. In addition to these health states, for each regimen the incidence of acute rejection, cytomegalovirus (CMV) infection, dyslipidaemia and new-onset diabetes after transplantation (NODAT) were estimated, with corresponding costs (one off for acute rejection and CMV infection; ongoing for dyslipidaemia and NODAT). New-onset diabetes after transplantation was also associated with a utility decrement. The incidence of acute rejection and NODAT were also used as surrogate determinants of graft survival and the rate of death with functioning graft (NODAT only).

Up to three retransplantations were modelled, which could take place from the GRAFT LOSS state. Pre-emptive retransplantation was also modelled for the initial graft, allowing retransplantation from the first FUNCTIONING GRAFT state. Kidney transplant recipients would transition to the next FUNCTIONING GRAFT state if retransplantation was successful or to the next GRAFT LOSS state if it was unsuccessful.

Transitions out of the FUNCTIONING GRAFT state correspond to the clinical outcome of graft loss and are either death with functioning graft or graft loss excluding death with functioning graft (i.e., dependence on dialysis or pre-emptive retransplantation). The baseline rates of these transitions from the FUNCTIONING GRAFT state were calculated from the UK Transplant Registry standard dataset (which contains data on all UK solid organ transplants between 1995 and 2012). The rate of mortality in the GRAFT LOSS state was based on UK data published in the UK Renal Registry annual reports.

Baseline death-censored graft survival was taken directly for the first year from Kaplan–Meier analysis of the UK Transplant Registry standard dataset, and from the first year onwards a Weibull curve was fitted to the same dataset.

Due to the paucity of RCT evidence in children and adolescents (only basiliximab and immediate-release tacrolimus were evaluated in RCTs included in our systematic review), two separate types of analysis were conducted.

In the first type of analysis, attention was restricted to comparisons in RCTs in children and adolescents. Decision trees were constructed to represent the duration of trial follow-up, at the end of which kidney transplant recipients would be distributed in the FUNCTIONING GRAFT, GRAFT LOSS and DEATH STATES based on the results of the trial, and extrapolation would take place according to the rates of acute rejection and NODAT and the eGFR at 12 months. With this type of analysis, minimal evidence from adults was used, but cost-effectiveness could only be estimated for basiliximab and immediate-release tacrolimus.

In the second type of analysis, clinical effectiveness estimates from RCTs in the adult population were extrapolated to the child and adolescent population, i.e., it was assumed that the odds ratios of mortality, graft loss and acute rejection, and the mean difference in eGFR, would be the same for children and adolescents as for adults. With this type of analysis, cost-effectiveness was estimated for all interventions.

Analyses based on RCT evidence in children and adolescents

As described above, decision trees were constructed to represent the duration of trial follow-up, at the end of which kidney transplant recipients would be distributed in the FUNCTIONING GRAFT, GRAFT LOSS and DEATH STATES based on the results of the trial, and extrapolation would take place according to the rates of acute rejection and NODAT and the eGFR at 12 months. The same surrogate relationships were used for graft survival and death with functioning graft, although these relationships were only used for extrapolation after the trial duration (which ranged from one to four years).

Analyses based on RCT evidence in adult population

Network meta-analyses and head-to-head comparisons of RCTs in the adult population were used to estimate the odds ratios for each regimen of death, graft loss and acute rejection (all in the first 12 months) and the mean difference in eGFR at 12 months versus the baseline (taken to be BAS+TAC+AZA). These were applied to baseline estimates in children and adolescents to estimate the regimen-specific mortality, graft loss, acute rejection and graft

function. Mortality and graft loss at 12 months were used to drive patient survival and the rate of death with functioning graft during the first 12 months, while acute rejection and graft function at 12 months were used (along with the rate of NODAT) to predict graft survival after 12 months for each regimen. The rate of NODAT was additionally used to estimate the rate of death with functioning graft after the first 12 months.

The incidences of NODAT, CMV infection and dyslipidaemia were estimated by applying odds ratios derived from network meta-analyses of RCTs in the adult population to baseline estimates for children and adolescents.

1.3.4.3 Costs

Drug acquisition costs were average NHS acquisition costs where these could be estimated (from the Commercial Medicines Unit eMit database) or list prices (BNF 68) otherwise.

Drug administration costs included intravenous administration for basiliximab, rabbit ATG and belatacept (estimated from NHS Reference Costs 2013-14), and therapeutic drug monitoring for tacrolimus, sirolimus, everolimus and ciclosporin (estimated from a price list for NHS patients from University Hospital of Wales).

Costs of procedures and dialysis were estimated from NHS Reference Costs 2013-14 where available or from UK sources otherwise. Where reference costs were broken down into costs for under 19s and adults these were used appropriately.

1.3.4.4 Utility weights

Utility weights were estimated as utility decrements from baseline age-related general health, and for the functioning graft and dialysis (graft loss) states were based on a systematic review and meta-analysis of empirical studies that had reported EQ-5D (pooled estimates of 0.81 for functioning graft, 0.56 for haemodialysis, 0.58 for peritoneal dialysis). A disutility of -0.06 associated with new onset diabetes was also applied.

1.3.4.5 Uncertainty analyses

Probabilistic sensitivity analyses were conducted for the analyses based on RCT evidence in adults and for the analyses based on RCT evidence in children and adolescents.

Scenario analyses were also conducted to explore the impact of removing the surrogate relationship between acute rejection and graft survival (but keeping the surrogate

relationships from graft function and NODAT to graft survival), and to explore the possibility that kidney transplant recipients might have significantly below average weight for their age (thus affecting doses).

1.4 Clinical effectiveness results

1.4.1 Number and quality of studies

Three RCTs are included in the clinical effectiveness systematic review presented in this report; one new RCT, Offner et al. (2008), and two RCTs from the previous assessment Grenda et al. (2006), and Trompeter et al. (2002).

Four non-randomised controlled trials (non-RCTs) are included in our review. All of these were also included in the previous assessment by Yao et al. (2006). No new non-randomised studies were identified in our searches.

1.4.2 Summary of benefits and risks

1.4.2.1 Induction therapy

Two RCTs of induction therapy (reported in four publications and one abstract) evaluating **BAS** in children and adolescents were identified in the review; Offner et al. (2008), and Grenda et al. (2006). No RCTs were identified that evaluated **r-ATG** in children and adolescents.

No non-RCTs in the child and adolescents population evaluated induction therapies.

We found no significant difference in **survival**, **graft loss**, **graft function**, and **incidences of BPAR** and **time to BPAR** between BAS and placebo/no induction. Grenda et al. (2006), found more severe BPAR (Grade IIA) in placebo compared with BAS (OR=0.05; favours BAS; 95% CI 0.003 to 0.87).

The results of the current review are similar to the previous HTA.

1.4.2.2 Maintenance therapy

RCT evidence

One RCT of maintenance therapy (reported in three publications) evaluating **TAC** (compared with CSA) in children and adolescents was identified; Trompeter et al. (2002).No RCTs were identified that evaluated **TAC-PR**, **MMF**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

From the RCTs, we found no significant difference in **survival**, **graft loss** between TAC and CSA. However, a significantly higher **graft function** (mean eGFR of 71.5 (SD 22.9) ml/min/1.73m^2 in TAC vs mean eGFR of 53.0 (21.6) ml/min/1.73m^2 in CSA; t-test = 4.03, p<0.01 at four years follow-up), and less **BPAR** (OR=0.41,favours TAC, 95%CI: 0.16 to1.00 at six months follow-up) was found in TAC compared with AZA at up to four years follow-up.

The results of the current review for **survival, graft function,** and **BPAR** are similar to the previous HTA. However, the RCT child and adolescent evidence identified in the previous HTA review concluded that TAC lowered **graft loss** at two and four years follow-up. The difference in these results is because we excluded graft loss due to death from all analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related. After the removal of graft loss due to death from the analyses, the evidence from the RCT suggested a borderline (statistically non-significant) lower graft loss with TAC compared with CSA (OR=0.41, 95%CI: 0.16 to 1.00, and OR=0.43, 95%CI: 0.18 to 1.01 at two and four years follow-up respectively).

Non-RCTs evidence

Three non-RCTs evaluating **MMF** (compared with AZA) in children and adolescents were identified; Antoniadis, et al. (1998), Staskewitz, et al. (2001), Benfield et al. (2005). One non-RCT compared **TAC+AZA** with **CSA+MMF**; Garcia et al. (2002). No non-RCTs were identified that evaluated **TAC-PR**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

We found no statistically significant difference in **survival** between MMF and AZA in the non-RCTs. Similarly, no statistically significant difference in **BPAR** between MMF and AZA in the non-RCTs was identified. A significantly lower **graft loss** was found in MMF compared with AZA at one to five years follow-up in one of the two non-RCTs; Staskewitz, et al. (2001) reports OR=0.24 at five years follow-up (favours MMF; 95%CI: 0.09 to 0.63). However, this was not confirmed by the other non-RCT at one year follow-up; Antoniadis et al. (1998). In

addition, we found no statistically significant difference in **survival**, **graft loss, BPAR, graft function,** and **delayed graft function** between TAC+AZA and CSA+MMF in Garcia et al. (2002).

1.4.2.3 Adverse events

Induction

More infections were found in children treated with BAS compared with those treated with placebo (OR=2.23, favours placebo; 95%CI 1.03 - 4.68) in one of the two included RCTs (Offner et al. 2008). In addition, Grenda et al. (2006) found that toxic nephropathy and abdominal pain was higher in the BAS arm compared with no induction (p=0.03 and p=0.02 respectively). The previous HTA only reported no statistically significant differences between BAS and placebo for post-transplant diabetes mellitus found in Grenda et al. (2004).

Maintenance therapy

In the RCT by Trompeter et al. (2002) no statistically significant differences between TAC and CSA for a range of AE (any infections, urinary tract infections, bacterial infections, viral infections, PTLD, solid tumour, hypertension, any AE, and NODAT) wer identified. This is similar to the conclusions of the previous HTA. In addition, there were no statistically significant differences between MMF and AZA for urinary tract infection, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhea were identified in the non-randomised evidence. Similarly, no statistically significant differences between TAC+AZA and CSA+MMF in CMV infections and NODAT were identified in the non-randomised evidence.

1.5 Cost-effectiveness results

1.5.1 Review of cost-effectiveness evidence

Only one previous cost-effectiveness study of immunosuppressive regimens in children and adolescents by Yao et al. (2006) was identified. It was conducted by the technology assessment group at the University of Birmingham as part of the previous NICE technology appraisal process. The study evaluated the cost-effectiveness of adding basiliximab induction to CNI maintenance therapy with tacrolimus or ciclosporin combined with azathioprine and steroids. The study also compared ciclosporin with tacrolimus when given

in combination with azathioprine and steroids, and separately, MMF versus azathioprine as part of the triple therapy containing ciclosporin and steroids.

The analysis was conducted using a Markov model of a cohort with starting age ranging between 3-13 years and a 10-year horizon. The study found that basiliximab induction resulted in higher costs and more QALYs than the alternative of no induction in both the tacrolimus and ciclosporin containing regimens. Tacrolimus was found to have a base case ICER (incremental cost per QALY) of £145,000 relative to ciclosporin, whilst MMF had an ICER of £195,000 relative to azathioprine when given as part of ciclosporin-containing triple therapy. Although some of the methodological details were not provided in the study report, the sensitivity analysis showed that these results were subject to a high degree of uncertainty. In particular, when the costs of dialysis were increased to reflect high possible levels of staff requirements of dialysis treatment in children and adolescents and the estimated treatment effects on acute rejection based on data from adults were used, the ICER for the comparison of tacrolimus vs. ciclosporin triple therapy reduced to £35,000 per QUALY. This uncertainty, and the fact that the underlying model used in this analysis only accounted for BPAR as the surrogate measure of effectiveness (ignoring the role of renal function) suggest that new evidence on the cost-effectiveness of immunosuppressive regimens in children and adolescents is warranted.

1.5.2 PenTAG economic model

1.5.2.1 Analyses based on RCT evidence in children and adolescents

Base case analysis

Based on Grenda et al. (2006) basiliximab was predicted to be cost-effective at £20,000 to £30,000 per QALY versus no induction when used in combination with immediate-release tacrolimus and azathioprine (basiliximab was dominant).

Based on Offner et al. (2008) basiliximab was not predicted to be cost-effective at £20,000 to £30,000 per QALY versus no induction when used in combination with ciclosporin and mycophenolate mofetil (basiliximab was dominated).

Based on Trompeter et al. (2002) immediate-release tacrolimus was predicted to be cost-effective at £20,000 to £30,000 per QALY versus ciclosporin when used in combination with azathioprine (immediate-release tacrolimus was dominant).

Scenario analyses analysis

Results were robust to removal of the surrogate relationship between acute rejection and graft survival and/or to assuming weight would follow the 9th centile for age instead of the median.

1.5.2.2 Analyses based on RCT evidence in adults

Base case

In the base case deterministic and probabilistic analyses, the following agents were predicted to be cost-effective at £20,000 to £30,000 per QALY:

- Basiliximab
- Immediate-release tacrolimus
- Mycophenolate mofetil (only when used in combination with ciclosporin)
- Azathioprine (only when used in combination with tacrolimus)

Relevant ICERs cannot be presented for these agents because they dominated other agents or were less costly and less effective than other agents with ICERs significantly above £30,000 per QALY.

When all regimens were simultaneously compared, only BAS+TAC+AZA was cost-effective at £20,000 to £30,000 per QALY.

Deterministic and probabilistic cost-effectiveness results for other agents were:

- No induction (four comparisons), rabbit ATG (four comparisons), ciclosporin (six comparisons), prolonged-release tacrolimus (one comparison), and sirolimus (two comparisons): Dominated in deterministic and probabilistic analyses
- Mycophenolate sodium (one comparison): Deterministic ICER £52,000 per QALY; Probabilistic ICER £138,000 per QALY
- Everolimus (one comparison): Deterministic ICER £661,000 per QALY; Probabilistic ICER £955,000 per QALY
- Belatacept (one comparison): Deterministic ICER £667,000 per QALY; Probabilistic ICER £661,000 per QALY

Scenario analyses

Removal of surrogate relationship between acute rejection and graft survival

Basiliximab continued to be the only induction agent predicted to be cost-effective at £20,000 to £30,000 per QALY.

Immediate-release tacrolimus continued to be predicted to be cost-effective at £20,000 to £30,000 per QALY, as did mycophenolate mofetil (in combination with ciclosporin) and azathioprine (in combination with immediate-release tacrolimus). Mycophenolate sodium approached cost-effectiveness at £30,000 per QALY (ICER £33,000 per QALY).

Weight assumed to follow 9th centile for age instead of median

Basiliximab continued to be the only induction agent predicted to be cost-effective at £20,000 to £30,000 per QALY.

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

Mycophenolate mofetil (when used in combination with ciclosporin and no induction or with ciclosporin and rabbit ATG induction) continued to be predicted to be cost-effective at £20,000 to £30,000 per QALY, but when used with basiliximab induction, mycophenolate sodium was predicted to be cost-effective at £30,000 per QALY (ICER £27,000 per QALY) and mycophenolate mofetil was predicted to be cost-effective at £20,000 per QALY.

1.5.3 Company submissions

The only cost-effectiveness analysis submitted by pharmacuetical companies was that of Astellas, the sponsor of two immediate-release tacrolimus formulations (Prograf and Modigraf) and prolonged-release tacrolimus (Advagraf). It compared tacrolimus immediate-release (Prograf) with tacrolimus oral solutions (specials), sirolimus with MMF (CNI avoidance regimen), sirolimus with ciclosporin (CNI minimisation regimen), everolimus, and belatacept. Although Tacrolimus IR was found to have an ICER relative to sirolimus CNI minimisation of £1,600,000 the company concluded that sirolimus is unlikely to be used routinely for recipients of kidney transplants in general. Since tacrolimus dominated all other regimens it was deemed to be cost-effective. In a separate analysis, immediate-release tacrolimus (Prograf) was compared with prolonged-release tacrolimus (Advagraf), by modelling the effects of the different adherence profiles between the two regimens on biopsy

proven acute rejection and, independently, on graft survival. Advagraf was found to result in lower costs and more QALYs than Prograf and was therefore recommended as the cost-effective treatment option.

Although these analyses were set out to meet the specification of the NICE reference case, they are subject to limitations that question the validity of the results and conclusions derived from them. The most important problem is that the model uses efficacy data from RCTs conducted in adult patients. The triple regimen of ciclosporin + MMF + steroids was an important omission from the list of comparators and for which no reason was given in the submission. The unit cost values adopted for the analysis reflect drug list prices as opposed to prices actually paid by hospitals at a discount, as evidenced from eMIT data. Also the drug dosages used for regimens other than MMF and everolimus in the cost analysis were derived from those specified by national prescribing guidelines for adults (BNF). In addition, by truncating the analysis at age 18, the sensitivity analysis conducted by Astellas based on starting age become meaningless. The model ignored important recent evidence about renal graft function as an important outcome for both costs and health related quality of life. Further, the Markov model structure used by Astellas was based on annual cycles and assumed that within the first year after transplantation some patients would experience graft failure and re-transplantation. Although some patients may experience this in reality, the way the model implemented this effectively assumed that all such patients would experience failure and re-transplantation on day one. This suggests that the cycle length chosen by Astellas inadequately reflected the patient experience that they sought to model. These limitations cast more uncertainty on the results than seems justified by the available data and knowledge of the disease, and suggest more evidence addressing some of those limitations would benefit NICE recommendations in this area.

1.5.4 Comparison of the PenTAG, Astellas and previous assessment group's model-based analyses

We attempted to compare and explain the main differences in cost, effectiveness and cost-effectiveness estimates between the three models. In the case of the Astellas analyses this was hampered by the substantial number of important differences in modelling assumptions (such as the much shorter time horizon – 10 years, and reliance on data from different trials and different outcome measures from those trials to drive effectiveness differences).

For comparing IR-tacrolimus with PR-tacrolimus, the PenTAG and Astellas analyses arrive at opposite conclusions (the Astellas analysis in favour of PR tacrolimus). This is primarily due reliance on BPAR at 12 months post-transplant as the main surrogate outcome driving QALY

differences, different unit cost sources, and using outcome data from different trials to those on which the PenTAG analysis is based. The other analysis by Astellas, comparing a larger range of maintenance therapies (but omitting ciclosporin), showed that sirolimus would be the most cost-effective treatment (although their report does not highlight this) whereas the PenTAG analysis shows IR-tacrolimus to be the most cost-effective. However, there is considerable uncertainty and the Astellas analysis is based on very small differences in estimated QALYs.

It was virtually impossible to compare our model-based analyses with those by Yao et al (2006) which informed NICE's current guidance on these drugs for children and adolescents (TA99). This is because the Yao et al. (2006) model is not fully described in a single report, the model itself is not available, and even the results were only reported at the level of incremental costs and QALYs (i.e. no separately reported total costs and QALYs by model comparator). Their cost-effectiveness results also reflect differential discounting of future QALYs (1.5% per year) and costs (6%), and a limited 10 year time horizon. Despite these major differences, the findings in favour of the use of basiliximab as an induction therapy were similar between the Yao et al. (2006) and current PenTAG analyses. In contrast, based on more adult RCT evidence and a 50 year time horizon, the PenTAG analysis found that tacrolimus (with azathioprine) was more effective and less costly than ciclosporin, and that MMF (with ciclosporin) was more effective and less costly than azathioprine.

1.6 Discussion

1.6.1 Strengths and limitations of the systematic review of studies of effectiveness

The systematic review was conducted by an independent research team using the latest evidence. In addition, the literature searches were not restricted to child/adolescent populations so as to preserve the sensitivity of the searches and enable identifing RCTs where mixed populations may have been recruited, but outcomes were reported according to age. However, there are some important sources of uncertainty that may impact on the conclusions:

- The number of included RCTs is low; child/adolescent-specific evidence was identified only for basiliximab and immediate-release tacrolimus. No RCT evidence from children or adolescents was identified for rabbit ATG, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept.

- Databases were searched to identify systematic reviews of non-RCTs. However, individual non-RCTs were not searched for directly. It is likely that some non-RCT comparative evidence was missed. In addition, results from non-randomised studies may differ from RCT evidence. It can be argued that large, prospective and comprehensive case series may achieve high external validity, but we did not search for such studies.

- There is a possibility of spuriously positive tests for statistical significance arising from conducting multiple tests; we did not formally make adjustments for multiple testing. In addition, due to a small number of included studies publication bias were not assessed.

- For all included studies, less than half of the items constituting the quality appraisal assessment were adequately addressed in the research articles.

- No studies reporting on quality of life, adherence, or growth were identified.

- No RCTs were found to support the subgroup analyses specified in the review protocol.

In addition, this report highlights some methodological issues. Some of the newer immunosuppressive drugs, such as everolimus and sirolimus, would normally be given to children and adolescents after an initial maintenance therapy that consists of more conventional drugs. This makes it challenging to compare the clinical effectiveness of such regimens as only children and adolescents who are well maintained on their initial maintenance therapy would be given such drugs.

1.6.2 Generalisability of the findings

The systematic reviews of clinical and cost-effectiveness were conducted by an independent, experienced research team using the latest evidence and working to a pre-specified protocol (PROSPERO CRD42014013544). This technology assessment builds on existing secondary research and economic evaluations. The independent economic evaluations are, where possible, in line with the NICE reference case. Costs are those relevant to the NHS and are based on recent estimates. Principal issues of generalisability concern the estimates of effectiveness:

- Some of the RCT evidence in children and adolescents is quite old (patient recruitment in one RCT dates back to December 1996).

- All the RCT evidence in children and adolescents is from multiple centres in Europe.

- Analyses comparing all interventions rely on effectiveness estimates from the adult population (which may or may not generalise to children and adolescents).

1.7 Conclusions

There is limited high-quality evidence for the effectiveness of immunosuppressive agents in children and adolescents: only three randomised controlled trials were included in our systematic review.

An RCT comparing immediate-release tacrolimus to ciclosporin demonstrated that immediate-release tacrolimus resulted in statistically significant improvements in graft function and acute rejection. No other outcomes in that RCT or the other RCTs were statistically significant.

Cost-effectiveness estimates based on extrapolating effectiveness estimates from the adult population suggest that at a cost-effectiveness threshold of £20,000 to £30,000 per QALY, basiliximab and immediate-release tacrolimus are cost-effective in all considered combinations, while mycophenolate mofetil is cost-effective only if used in combination with ciclosporin.

Cost-effectiveness estimates based on effectiveness estimates in children and adolescents are only available for basiliximab and immediate-release tacrolimus. For immediate-release tacrolimus the economic analysis suggests that immediate-release tacrolimus is cost-effective (versus ciclosporin, in combination with azathioprine) at £20,000 to £30,000 per QALY. For basiliximab, the analysis based on one RCT found basiliximab to be dominant, while the analysis based on the other RCT found basiliximab to be dominated.

1.7.1 Implications for service provision

Basiliximab, immediate-release tacrolimus, mycophenolate mofetil and azathioprine are all used regularly in the NHS.

It is not clear whether changes to induction agents used in the NHS would significantly affect costs.

It is likely that, if immediate-release tacrolimus were to be replaced by prolonged-release tacrolimus, sirolimus, belatacept or ciclosporin, this would result in increased costs.

It is possible that replacing mycophenolate mofetil by azathioprine when in combination with immediate-release tacrolimus will result in reduced costs, while it is likely that replacing these with sirolimus, everolimus or mycophenolate sodium would increase costs.

1.7.2 Recommendations for research

High-quality primary research should be conducted into the effectiveness of immunosuppressive agents for kidney transplantation in children and adolescents.

Potentially, the UK Renal Registry could form the basis for a prospective study. This may require collection of additional information above the current data collected. Such a study could also include health-related quality of life measurements, preferably using a generic instrument validated in the paediatric population, measurements of growth, and measurements of growth.

In addition, a systematic review of non-RCTs (not limited to search for systematic reviews of non-RCTs) to map all available child and adolescents evidence in this topic may be recommended.

2 BACKGROUND

The aim of this assessment is to review and update the evidence of the clinical effectiveness and cost-effectiveness of immunosuppressive regimens for renal transplantation in children and adolescents (TA99).

Two therapy stages are assessed: induction therapy (regimens including basiliximab or rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (regimens including immediate-release tacrolimus, prolonged-released tacrolimus, belatacept, mycophenoate mofetil, mycophenolate sodium, sirolimus and everolimus, alone or in combination).

The systematic review and economic evaluation developed to support current NICE guidance TA99, published by Yao et al. in 2006.[1] We will incorporate relevant evidence presented in this previous report and report new evidence from 2002 to the present.

2.1 Description of health problem

2.1.1 End stage renal disease

Chronic kidney disease in childhood leads to lifelong health complications, often resulting in the need of a kidney transplant.[2] In 2013, 891 children and adolescents under 18 years were receiving treatment at paediatric nephrology centres for ESRD.[3] End stage renal disease (ESRD) is a long-term irreversible decline in kidney function, for which renal replacement therapy (RRT) is required if the individual is to survive. End stage renal disease is often the result of an acute kidney injury (AKI) or primarily a progression from chronic kidney disease (CKD), which describes abnormal kidney function and/or structure. Whilst RRT can take a number of forms (kidney transplantation, haemodialysis and peritoneal dialysis), the preferred option for people with ESRD is kidney transplantation, rather than dialysis. This is due to improved duration and quality of life with transplantation compared with dialysis.[4]

2.1.2 Transplantation

Kidney transplantation is the transfer of a healthy kidney from a donor to a recipient. Kidneys for transplantation may be obtained via living donation (related or unrelated), donation after brain death (DBD; deceased heart-beating people who are maintained on a ventilator in an intensive care unit, with death diagnosed using brain stem tests) or donation after circulatory death (DCD; non-heart-beating donors who cannot be diagnosed as brainstem dead but whose death is verified by the absence of a heart beat [cardiac arrest]).

Children and adolescents represent a distinct group of transplant recipients, and can differ from adults in several important aspects, including: the cause of established renal failure, the complexity of the surgical procedure, the metabolism and pharmacokinetic properties of immunosuppressants, the developing immune system and immune response following organ transplantation, the measures of success of the transplant procedure, the number and the degree of comorbid conditions, the susceptibility to post-transplant complications, and the degree of adherence to treatment.[5, 6] The metabolism of many immunosuppressive medications substantially differs in young children compared with adults, and drug metabolism changes as children grow and develop.

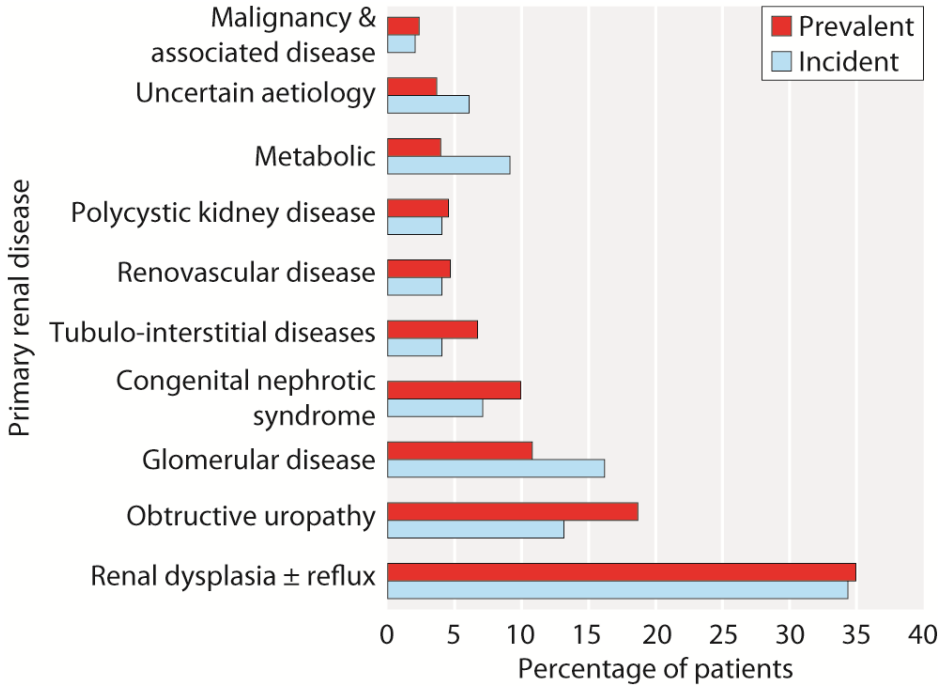
Following kidney transplantation, major clinical concerns for children and adolescents are acute kidney rejection, graft loss, and diminished growth. Acute kidney rejection occurs when the immune response of the graft recipient attempts to destroy the graft as the graft is deemed foreign tissue.[4] Therefore, immunosuppressive therapy is implemented to reduce the risk of kidney rejection and prolong survival of the graft. Prior to renal transplantation, growth retardation in children and adolescents with CKD may already be an issue due to a combination of inadequate nutritional intake, acidosis, renal osteodystrophy, and alterations to the growth hormone, insulin-like growth factor.[7] However, post-transplant, the steroidal therapy often included in immunosuppression regimens can affect longitudinal growth and calcium/phosphorous metabolism.[8, 9]

2.1.3 Aetiology, pathology and prognosis

2.1.3.1 Aetiology

In children, ESRD is usually due to innate structural abnormalities or genetic causes or is acquired in childhood through glomerulonephritis.[10] Figure 1 displays the causative diagnoses for children and adolescents (<16 years old) with primary renal disease in 2013.

Figure 1. Causative diagnoses for children and adolescents; primary renal disease percentage in incident and prevalent children and adolescents with established renal failure patients <16 years old in 2013



Source: UK Renal Registry 17th Annual Report [3] Fig. 4.3.p 99.

2.1.3.2 Pathology

Table 1displays the distribution of the UK primary renal diagnosis for ESRF over time, reported from 1999–2003, 2004–2008 and 2008–2013 in children and adolescents 16 and under. Renal dysplasia, which is abnormal tissue development in the kidney, is the primary renal disease diagnosis in approximately a third of all children and adolescents with ESRD.

When chronic renal failure occurs, children and adolescents may experience malaise, nausea, loss of appetite, change in mental alertness, bone pain, headaches, stunted growth, change (high or no) urine outputs, urinary incontinence, pale skin, bad breath, poor muscle tone, tissue swelling and hearing deficit. Treatment of chronic renal failure depends on the degree of kidney function that remains and the age of the child/adolescent. Treatment may include: dialysis, kidney transplantation, diet restrictions, diuretic therapy and medications (to help with growth and prevent bone density losses)[11].

Table 1. Number and percentage of children and adolescents under 16 years for whom a primary renal diagnosis had been reported as a cause of ERF, by 5-year time period and observed change in proportion of children and adolescents in each diagnostic group

	1999-2003		2004-2008		2009-2013		1999-2013
Primary renal diagnosis	N	%	N	%	N	%	% change
Renal dysplasia+reflux	157	29.1	191	33.7	182	33.7	4.6
Obstructive uropathy	80	14.8	75	13.3	97	18	3.1
Glomerular disease	130	24.1	112	19.8	83	15.4	−8.7
Tubulo-interstitial diseases	42	7.8	46	8.1	41	7.6	−0.2
Congenital nephrotic syndrome	27	5	33	5.8	35	6.5	1.5
Metabolic	29	5.4	25	4.4	31	5.7	0.4
Uncertain aetiology	12	2.2	32	5.7	29	5.4	3.1
Renovascular disease	23	4.3	19	3.4	19	3.5	−0.7
Polycystic kidney disease	16	3	19	3.4	19	3.5	0.6
Malignancy & associated disease	10	1.9	9	1.6	4	0.7	−1.1
Drug nephrotoxicity	14	2.6	5	0.9	0	0	−2.6

Note: Six children in 1999–2003, nine in 2004–2008 and twenty in 2009–2013 with no primary renal diagnosis recorded are excluded from this table
Source: UK Renal Registry 17th Annual Report [3] Table. 4.13.p 102 .

Acute rejection

In patients who survive transplantation, acute rejection may occur when the immune response of the host attempts to destroy the graft as the graft is identified as foreign tissue.[4] Acute rejection is treated by modifying the immunosuppressive regimen (increasing doses or switching treatments). Untreated acute rejection will ultimately result in destruction of the

graft. However, high levels of immunosuppression may also increase the risk of other infections and malignancy.[4] Acute rejection is primarily measured following a biopsy and graded according to Banff criteria (grade I to III, where grade III indicates the most severe). The gradings are[12]:

- Banff grade I: Tubulo-interstitial inflammation only
- Banff grade IA: Interstitial inflammation moderate-severe and/or tubulitis moderate
- Banff grade IB: Tubulitis severe
- Banff grade II: Intimal arteritis
- Banff grade IIA: Intimal arteritis mild-moderate
- Banff grade IIB: Intimal arteritis severe
- Banff grade III: Transmural arteritis and/or fibrinoid necrosis

While the incidence of acute rejection following a transplant is included in this appraisal, its treatment is outside the scope. In addition to acute rejection affecting the survival of the graft, other reasons which may instigate graft loss include; blood clots, narrowing of an artery, fluid retention around the kidney, side effects of other medications and recurrent kidney disease.[13]

It is important to note that failing to stay on the immunosuppression regime prescribed following a kidney transplant will also significantly increase the risk of acute rejection and/or graft loss.[14] If the kidney is lost, ultimately the patient will need to return/start on dialysis where quality of life is reduced and overall costs are higher.[4]

Graft function

Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. GFR is expressed in terms of volume filtered per unit time (some times this is also expressed per average surface area [1.73m^2]). There are various methods used to calculate eGFR from serum creatinine levels, age, sex and race (e.g. Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault, Nankivell). Different methods are used for children and adolescents (e. g. Schwartz and Counahan-Barrat equations). Levels of eGFR represent the level of kidney function, Table 1 presents the NICE cut off values for classification of CKD (NICE guidelines CG182).[15] These values are apply to children above the age of two, up to (and including) adulthood.[16]

Table 2. Glomerular filtration rate categories

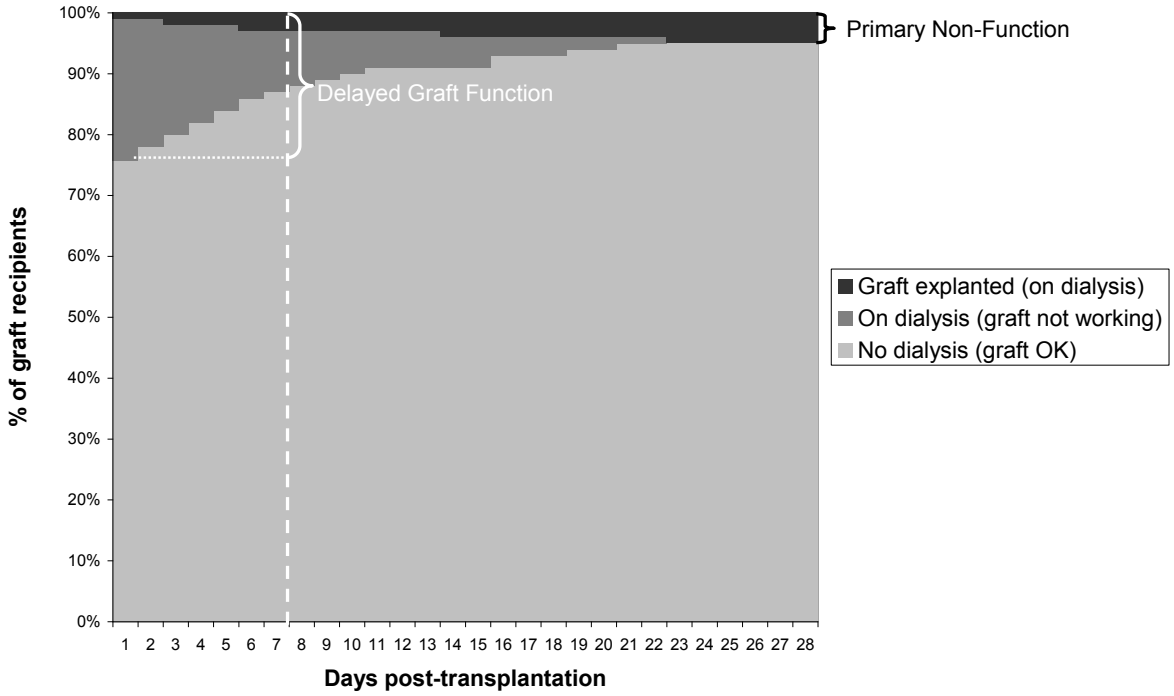
GFR	GFR	Terms

category	(ml/min/1.73m^2)	
1	> 90	Normal or high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severely decreased
4	12-29	Severely decreased
5	<15	Kidney failure

Key: GFR, Glomerular filtration rate.
Source:NICE guidelines CG182.[15]

The eGFR and level of serum creatinine following a transplant can guide postoperative care as indicators ofacute rejection, recurrence of original kindey disease or development of de novo kidney disease.

Figure 2. Hypothetical graph to explain graft function, delayed graft function and primary non- functioning graft



Source: NICE TA165 [17]

Some children and adolescents may experience delayed graft function (DGF) after transplantation Figure 2 shows a hypothetical graph to explain the relationship between normaly functioning grafts, DGF and primary non-functioning grafts (PNF). At seven days post-transplant some of the children and adolescents who need to dialyse and whose grafts

are therefore classified as DGF will have grafts that never function. When this has been established these grafts are classified as PNF.

Growth

Normal growth is often affected in children and adolescents with ESRD; short stature is diagnosed if the height standard deviation score (SDS) is below 2.5 of the target height.[18] There are three main factors that may impact post-transplant growth:

- Age at transplantation. Following a transplant, post-transplantation catch-up growth is not uncommon. However, it is unlikely to be sufficient to compensate for the pretransplant accrued deficit.[19] Data from the North American Pediatric Renal Trials and collaborative Studies (NAPRTCS) indicated that children under six years of age exhibit catch-up growth whereas children older than six years at the time of transplantation exhibited limited to-no catch-up growth.

- Allograft function. An increase in 1.0 mg/dl increase in serum creatinine level (indicating a decrease in kidney function) has been associated with a decrease in 0.17 SDS.[20]

- Corticosteroid dose. For example, reducing steroids to every other day[21] or to withdraw or avoid steroids[22] have been associated with improved growth. Similarly, Grenda et al[23] indicated an increase in 0.13 SDS in a group of primarily prepubertal children who withdrew from steroids on day five compared to those that tapered to 10 mg/m².

UK data are not available on growth changes following kidney transplant in children and adolescents, however, data from the NAPRTCS are available. The NAPRTCS 2010 annual report indicates that at transplantation, the mean height deficits for all children and adolescents is -1.75 SDS (-1.78 for boys and -1.70 for girls). For children and adolescents who have reached their adult height (n=2867) following kidney transplant, the average SDS is -1.40, with 25% having a SDS of -2.2 or worse and 10% are over 3.24 SD below the population average.[24] In addition, German data reported by Nissel et al [25] who followed 37 children for a mean duration of 8.5 years to monitor their growth found that those children who received their transplant before the start of puberty attained an adult height that was on average 5.2 cm (boys) and 13.0 cm (girls) lower than predicted whilst those who received their transplant after the onset of puberty had a final adult height that was on average 12.6 cm (both boys and girls) lower than the target.

2.1.3.3 Prognosis

Data collected for survival rates of children and adolescents under 16 years starting RRT between 1999 and 2012 were collected from UK paediatric centres.[3] The median follow-up time was 3.5 years (ranging from one day to 15 years). There were a total of 99 deaths reported. Table 3 shows the survival hazard ratios (following adjustment for age at start of RRT, sex and RRT modality) and highlights that children starting RRT under two years of age, as compared to 12-16 year olds starting RRT, had a worse survival outcome with a hazard ratio of 5.0.

Various factors may influence survival following a kidney transplant. A study of 1189 child/adolescent kidney transplants in England between April 2001 and March 2012 found that 33 children and adolescents did not survive.[26] The most common causes of these 33 deaths were: renal (n=8; classified as ESRD, renal dysplasia, and disorder of kidney/ureter), infections (n=6) and malignancy (n=5).[26] The age of recipient was not found to significantly impact patient survival: age 0-1 (100% survival), age 2-5 (96% survival), age 6-12 (97.5% survival), age 13-18 (97.4% survival).[26]

Table 3. Survival hazard ratio during childhood and adolescence for renal replacement therapy patients

	Hazard ratio	Confidence interval	p-value
Age			
0-<2 years	5	2.8-8.8	<0.0001
2-<4 years	2.9	1.4-5.7	0.003
4-<8years	2.2	1.3-4	0.006
8-<12 years	1.4	0.7-2.9	0.400
12-<16 years	1.0	-	-
Sex			
Female	1.2	0.7-1.9	0.5
Male	1.0	-	-
Modality			
Dialysis	7.1	4.7-10.7	<0.0001
Transplant	1.0	-	-

Key: Modality, renal replacement therapy modality.
Note: survival hazard ratios are adjusted for age at start of RRT, gender and renal replacement therapy modality; results are presented for children under 16 years old because data for the 16–18 year old patients were incomplete.
Source: UK Renal Registry 17th Annual Report[3]; table 4.16, p104.

2.1.4 Important prognostic factors

A number of important factors have been identified within the research literature which may influence overall survival and graft survival. These factors are summarised below:

- Age – both the age of the recipient and the age of the donor will influence the survival of the transplant. The number of kidney transplants performed is much smaller in infants and small children compared to older children. This has been attributed to some centres keeping a child on dialysis until they reach an arbitrary age where they are deemed suitable for a transplant.[27]

- Recipient ethnicity – black patients tend to have worse graft function, shorter graft survival and higher rates of chronic allograft nephropathy than compared with white patients.[28] Racial differences have also been indicated in American children with poorer

outcomes in black children following a kidney transplant when compared to white or Hispanic children.[29]

- Waiting time to transplant – the longer a person is on dialysis waiting for a kidney transplant, the poorer their outcomes post transplantation.[30]

- Cold ischaemia time – the shorter this time (20 hrs or under), the better the immediate and long term outcomes.[31]

- Donor type – receiving a donated kidney from a live donor will probably result in better outcomes in comparison to receiving a kidney from a deceased donor.[28] Similarly, receiving a kidney from extended criteria donors (donors who may for example be older, have a history of diabetes or hypertension, or have an increased risk of passing on an infection or malignancy) will have inferior graft survival rates and increased incidences of acute rejection when compared to receiving a standard donated kidney.[32]

- Immunological risk, to include HLA and blood group incompatibility - where the number of mismatches from the donor to the recipient are higher, there is an increased likelihood of acute rejection and graft loss[28]

- Comorbidities for example diabetes, cancer and cardio vascular disease – the higher a patient scores on the Charlson Comorbidity Index (CCI) the lower the patient and graft survival is likely to be. Acute rejection is not significantly correlated to the CCI.[33]

2.1.5 Incidence and/or prevalence

In 2013, 891 children and young people under 18 years were receiving treatment for ESRD at UK paediatric nephrology centres of which, 80.2% had a functioning kidney transplant, 11.7% were receiving haemodialysis and 8.1% were receiving peritoneal dialysis.[3] When comparing RRT data from the most recent 5-year period (2009–2013) with the two previous periods (1999–2003 and 2004–2008), a sustained increase in the number of younger children (aged zero to < eight years when starting RRT) can be seen, whilst the number of older children (eight to <16 years when starting RRT) has decreased. Consequently, the total number of children starting RRT has remained relatively consistent; 546 children between 1999–2003, 575 children between 2004–2008, and 560 children between 2008–2013.[3]

Table 4 presents the number of children and adolescents commencing RRT in 2013 with data presented by age and by sex.

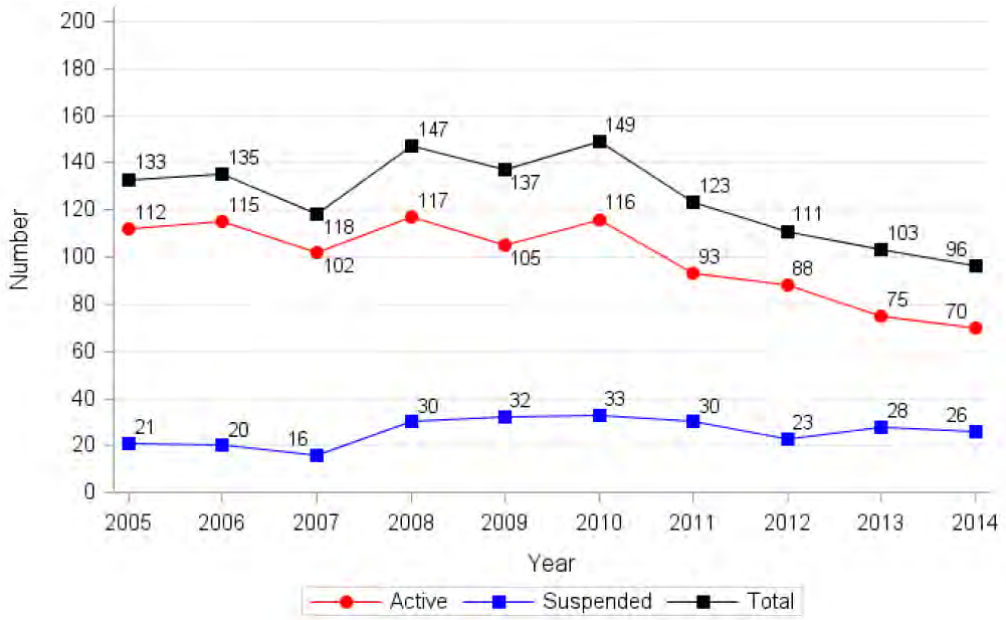
Table 4. The 2013 UK incidence of established renal failure by age group and sex

Age group	All patients	Male	Female	M:F ratio
	N (pmarp)	N (pmarp)	N (pmarp)	
0-<2 years	19 (11.8)	13 (15.7)	6 (7.6)	2.1
2-<4 years	17 (10.6)	11 (13.4)	6 (7.6)	1.7
4-<8years	14 (4.5)	4 (2.5)	10 (6.6)	0.4
8-<12 years	31 (11.0)	20 (13.9)	11 (8.0)	1.7
12-<16 years	31 (10.7)	12 (8.1)	19 (13.4)	0.6
Under 16 years	***112 (9.3)***	***60 (9.7)***	***52 (8.8)***	***1.1***

Key: F, female; M, male; N, number of patients; pmarp, per million age related population.
Note: Results are presented for children under 16 years old because data for the 16–18 year old patients were incomplete;
Source: UK Renal Registry 17th Annual Report [3]; table 4.7, p 100.

While the number of children and adolescents starting RRT has not changed significantly, the number of children and adolescents actively waiting for a kidney transplant has fallen from 112 in 2005 to 70 children and adolescents in 2014. Figure 3 displays the number of children and adolescents on the transplant list both active and suspended over time from 2005 to March 2014 (where suspension from the list may occur if the transplant cannot go ahead e.g. further medical problems making the operation unsafe).

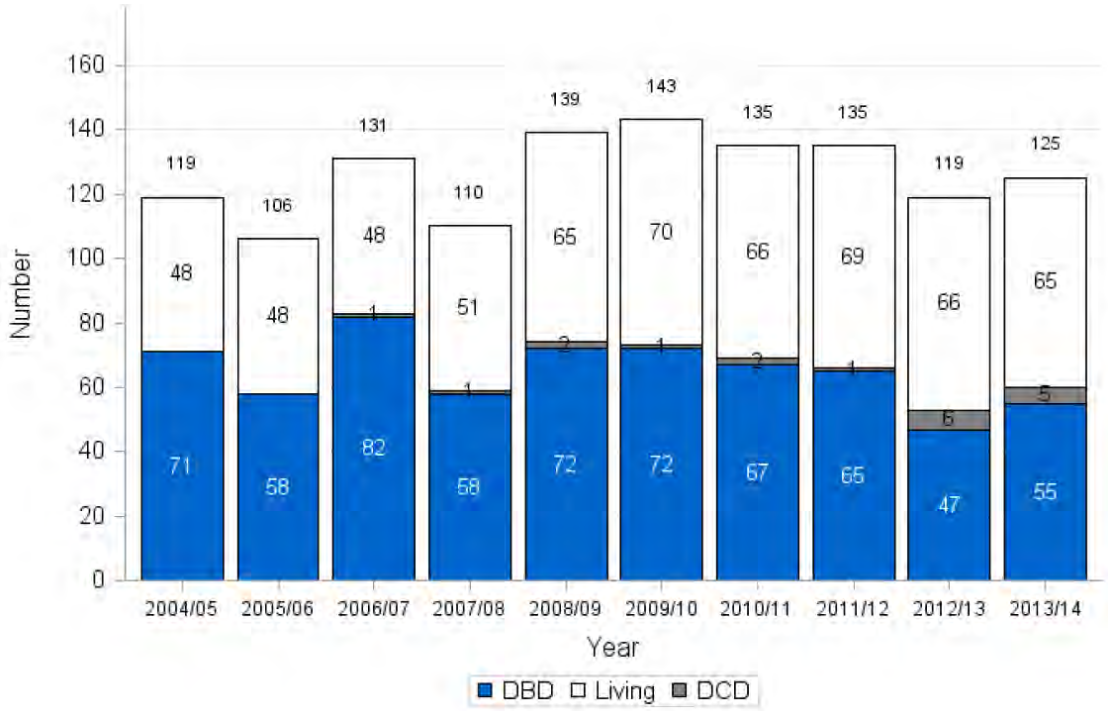
Figure 3. Children and adolescents on the kidney only transplant waiting list at March 2013



Source: Annual Report on Kidney Transplantation [31]

One hundred and twenty five kidney transplant operations were performed on children and adolescents in the UK between April 2013 and March 2014.[31] The total number of transplants in children and adolescents and the graft type (living, DBD and DCD) performed each year from 2004–2014 are displayed in Figure 4. In children and adolescents, most donated kidneys are from living and DBD donors, with very few kidneys being form DCD donors.

Figure 4. Kidney only transplants in children and adolescents 2004 - 2014



Key: DBD, donation after brain death; DCD, donation after circulatory death
Source: Annual Report on Kidney Transplantation [31]

Overall survival is reported in children and adolescents following kidney transplants from deceased and living donors is similar at both one and five years follow-up [31], however, graft survival at five years is improved where the donors are living; see Table 5 for more details.

Table 5. Kidney graft and overall survival in children and adolescents in the UK

	Kidney Graft Survival		Patient Survival	
	One Year[a] % (95% CI)	Five Years[b] % (95% CI)	One Year[a] % (95% CI)	Five Years[b] % (95% CI)
Deceased Donors	93 (93-98)	84 (79-88)	99 (97-100)	99 (96-100)
Living Donors	95 (92-97)	94 (89-96)	99 (97-100)	99 (96-100)

Key: a, Includes transplants performed between 1 April 2009- 31 March 2013. b, Includes transplants performed between 1 April 2005 – 31 March 2009
Source: Annual Report on Kidney Transplantation [31]

Data on incidence and prevalence of acute rejection in children and adolescents are not available for the UK. They are, however, likely to be similar to those reported in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which indicates that

for transplants occurring between 1987 and 2010 the prevalence in children and adolescents of at least one episode of acute rejection following a kidney transplant is 46% (41% in live donors and 51% in deceased donors).[24]

2.1.6 Impact of kidney transplantation

2.1.6.1 Significance for patients

Living with ESRD may substantially challenge the well-being of children and adolescents. Not only will the disease impact physical health, mental and social health may also be affected due to increased hospital visits and the child/adolescent inability to take part in the same activities as their peers.[34] However, having a kidney transplant will improve the symptoms associated with ESRD and dialysis and reduce the time spent in hospital.[35] The median wait time for a child/adolescent requiring a kidney transplant in the UK is 342 versus days.[31]

Kidney transplantation requires a life long regimen of immunosuppressive medication. Immunosuppressants may produce unpleasant side effects (including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain).[36] Nevertheless, favourable social and professional outcomes have been observed from a long-term follow-up (15.6 ± 3 years) of people who had a kidney transplant as a child (aged 10 ± 5 years).[37] Adherence to post-transplant immunosuppressive regimens is important for favourable clinical outcomes in children and adolescents [38] and has been suggested as a core strategy to improve clinical outcomes.[39] In addition, failing to follow treatment may result in an increase in medical costs.[40]

Acute rejection is common in the first year after kidney transplantation and treatment of acute rejection involves a more intensive drug treatment than standard maintenance regimens, which in turn increases the possibility of adverse events. Should a graft be lost, the child/adolescent will face another wait for transplantation (if appropriate) and will need to undergo dialysis whilst waiting for transplantation (although a pre-emtive transplantation may be available), or need to undergo dialysis for life where transplantation is not possible.

The impact on a child/adolescent returning or starting to dialysis (of the psychological burden of graft failure and going back to a previous treatment) is little researched, but necessarily includes the impact of being on dialysis per se: dialysis is time-consuming and may affect education, normal family life and require changes in diet and fluid intake. Common side effects of dialysis (either hemodialysis or peritoneal dialysis) include fatigue, low blood

pressure, invasive staphloccoccal infections, muscle cramps, itchy skin, peritonitis, hernia and weight gain.[41]

Finally, growth retardation in children and adolescents with ESRD is thought to be a combination of inadequate nutritional intake, acidosis, renal osteodystrophy, and alterations to the growth hormone, insulin-like growth factor.[7] Ensuring optimal growth or optimisation of final height is a major concern for children and adolescents with ESRD, as short stature may impact upon social development, self-esteem, QOL, increased hospitalisations, behavioural and cognitive disorders, lower level of education and a lower level of employment in adulthood.[19, 42-44]

Unfortunatelly, data relating specifically to quality of life is currently only available in the adult population, where there are clear quality of life improvements from having a functioning kidney transplant compared with being on dialysis.[45-51]

2.1.6.2 Significance for the NHS

Treatment for ESRD is considered resource intensive for the NHS, since current costs have been estimated to use 1-2% of the total NHS budget to treat 0.05% of the population (both adult and child/adolescent).[52] Data from the Department of Health estimated that in 2008/09 the total expenditure on 'renal problems' in England was £1.3bn, representing 1.4% of the NHS expenditure. An economic evaluation of treatments for ESRD by de Wit et al.1998 showed that transplantation is the most cost-effective form of RRT with increased quality of life and independence for an individual.[53]

There are no apparent reasons why RRT demand may dramatically increase in children and adolescents. However, it is projected that an increasingly overweight population will increase the demand for RRT, with a consequent increase in pressure on services from renal units and other healthcare providers dealing with co-morbidities. Increased resources may be needed for: dialysis, surgery, pathology, immunology, tissue typing, histopathology, radiology, pharmacy and hospital beds. Demand is likely to be particularly significant in areas where there are large South Asian, African and African Caribbean communities and in areas of social deprivation, where people are more susceptible to kidney disease.[3]

2.1.7 Measurement of disease

The outcome of kidney transplants (and of the success of immunosuppressive regimens) can be measured in a variety of ways. These include:

Short-term

- Immediate graft function: The graft works immediately following transplantation removing the need for further dialysis.
- Delayed graft function (DGF): The graft does not work immediately and dialysis is required during the first week post-transplant. Dialysis has to continue until graft function recovers sufficiently to make it unnecessary. This period may last up to twelve weeks in some cases.
- Primary non-function (PNF): The graft never works after transplantation.

Long-term

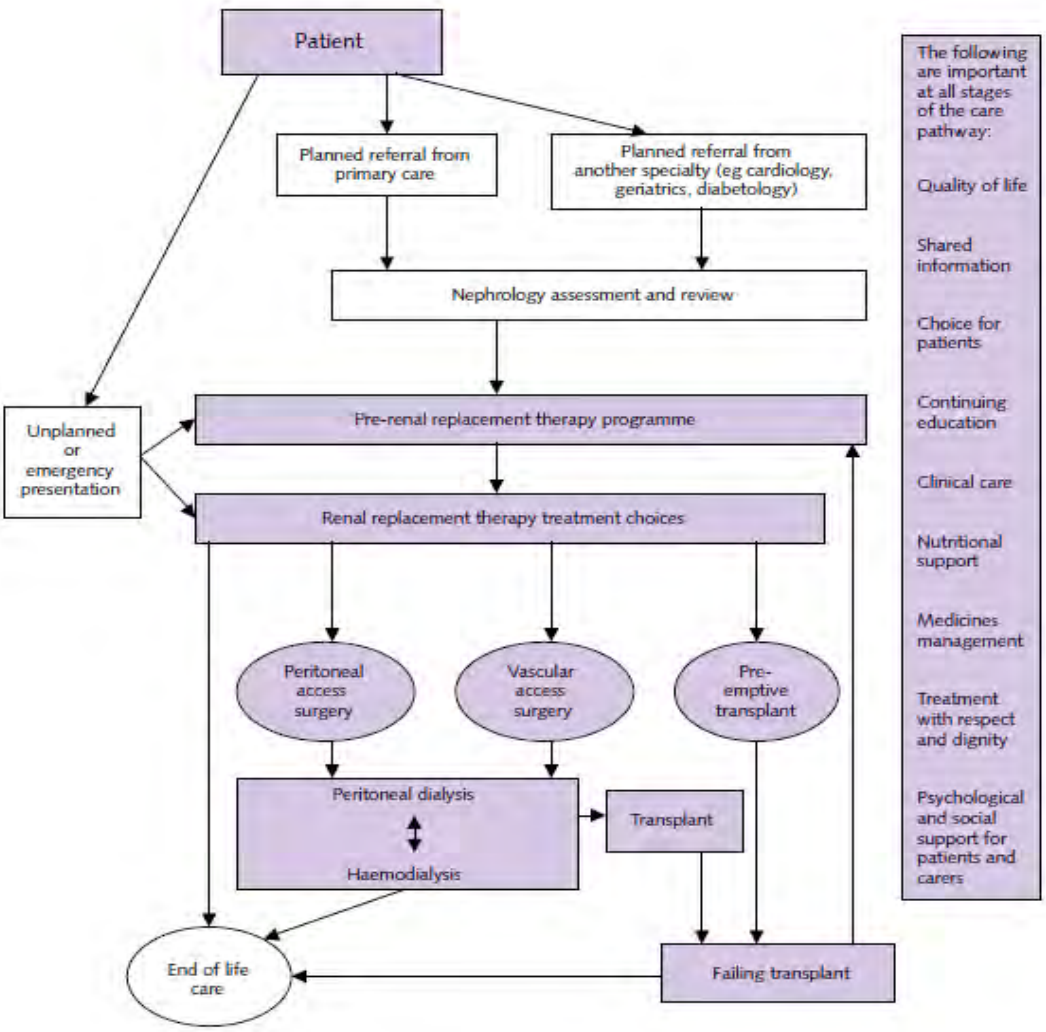
- Rejection rates: The percentage of grafts that are rejected by the recipients' bodies, these can be acute or chronic.
- Graft survival: The length of time that a graft functions in the recipient.
- Graft function: A measure of the efficiency of the graft by various markers e.g. glomerular filtration rate and serum creatinine levels.
- Patient survival: How long the recipient survives.
- Quality of life: How a person's well-being is affected by the transplant.

2.2 Current service provision

2.2.1 Management of end-stage kidney disease

End-stage renal disease is primarily managed by RRT. The patient pathway leading to RRT for those with ESRD can be seen in **Figure 5**. Once a child/adolescent has been diagnosed with ESRD, the RRT options are: a transplant (from a living or deceased donor) or dialysis (haemodialysis and peritoneal dialysis). If suitable, the option of a pre-emptive kidney transplant (when transplantation is performed without the child/adolescent spending any time on dialysis) is also available.

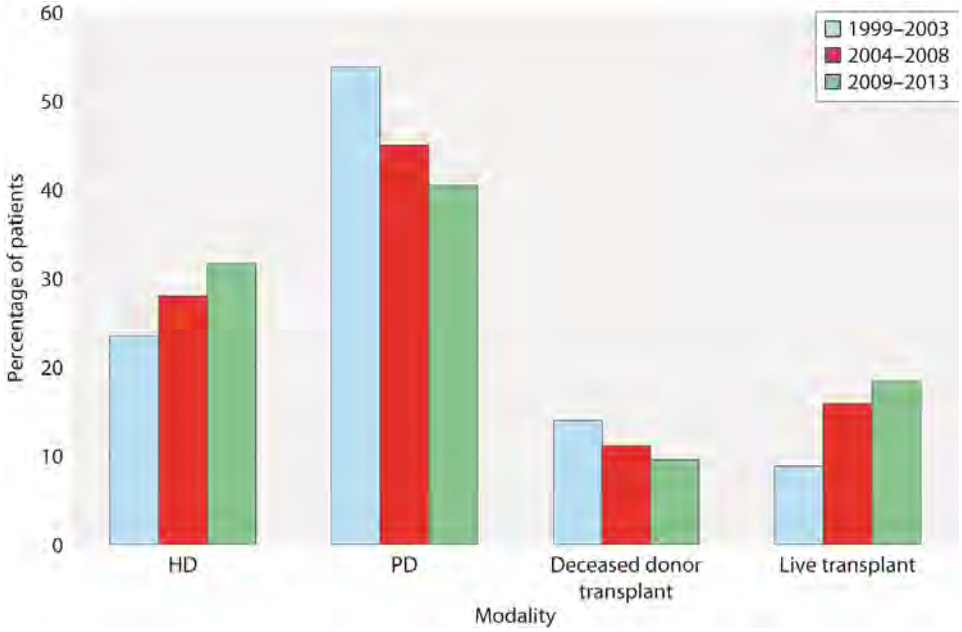
Figure 5. The care pathway for renal replacement therapy



Source: The National Service Framework for Renal Services – Part 1: Dialysis and Transplantation[54]

The form of treatment modality at the start of RRT has changed from 1999–2013 (**Figure 6**). The primary changes are an increase in the number of kidney transplants from living donors and a simultaneous decrease in donations from deceased donors. In addition, an increase in haemodialysis and a concurrent decrease in peritoneal dialysis are seen (**Figure 6**).

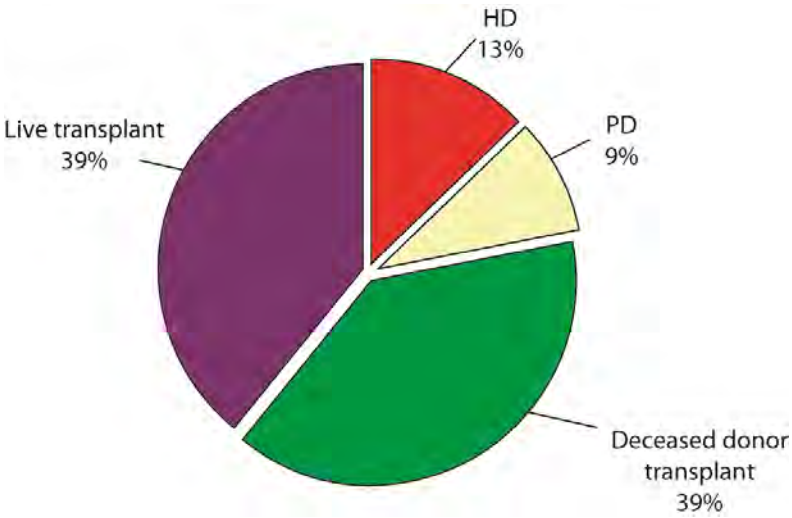
Figure 6. Type of treatment at start of RRT for incident children and adolescents <16 years old by 5-year time period



Key: HD, haemodialysis; PD, peritoneal dialysis.
Source: UK Renal Registry 17th Annual Report [3]; Fig. 4.4.p 102.

The 2013 data suggest that most children and adolescents receive a kidney transplant (78%) and that the proportion of living and deceased kidney donations is equal; 50% and 50% respectively (**Figure 7**).

Figure 7. RRT treatment used by prevalent children and adolescents <16 years old in 2013



Key: HD, haemodialysis; PD, peritoneal dialysis.
Source: UK Renal Registry 17th Annual Report [3]; Fig. 4.1.p 98

2.2.1.1 Management of kidney transplants

If transplantation is the chosen method for RRT for a child/adolescent with ESRD then there are three main service provision steps required for the management of the transplant.

The first of these is organ procurement which includes the identification and management of potential donors, and assessment of donor suitability. HLA antigens are carried on cells within the body enabling the body to distinguish between its 'self' or to recognise 'nonself' that should be attacked. The closer the HLA matching, the less vigorously the body will attack the foreign transplant, consequently the chances of graft survival are improved. HLA mismatch refers to the number of mismatches between the donor and the recipient at the A, B and DR loci, with a maximum of two mismatches at each loci.[31] Therefore, a match would have a score of zero and a complete mismatch would have a score of six. However, it should be noted that with the improvements in immunosuppressants, the significance of HLA matching has diminished.[55]

The second step is the provision of immunosuppressive therapy. Immunosuppressants are the drugs taken around the time of, and following, an organ transplant. They are aimed at reducing the body's ability to reject the transplant, and thus at increasing patient and graft survival and preventing acute and/or chronic rejection (whilst minimising associated toxicity, infection and malignancy). Immunosuppressants are required in some form for all kidney transplant recipients, except potentially where the donor is an identical twin.

The final service provision step is short and long-term follow-up following transplantation. This step involves looking for indications of any kidney graft dysfunction and other complications. Complications fall into four categories

- Medical follow-ups to include rejections, nephrotoxicity of calcineruin inhibitors and recurrence of the native kidney diseases
- Anatomic complications of surgery to include renal artery thrombosis, renal artery stenosis, urine leaks from disruption of the anastomosis, ureteral stenosis and obstruction and lymphocele
- Other complications include, infection, malignancy, new onset of diabetes, liver disease, hypertension, cardiovascular disease
- Ensuring growth is not impeded and maximal 'catch up' growth is achieved. The 2010 NAPRTCS report suggests that the average final adult height of a renal transplant

recipient has increased significantly from -1.93 standard deviations score (SDS) between 1987 to 1991 to -0.94 SDS between 2002 and 2010.[24]

If the kidney loses its function, many of the physiological changes that occur mimic those seen with progressive renal diseases from other causes. Therefore, these symptoms should be managed in a similar way to the non-transplant population. Although, it should be noted, that the loss of a kidney transplant carries increased susceptibility to bruising and infection compared to pre-transplant kidney failure.[56]

Once the kidney is confirmed to have been lost, the graft may or may not need to be surgically removed. The decision as to whether the graft is removed is often made on a case-by-case basis taking into consideration all perceived benefits and risks. The immunosuppression regime can then be tapered and withdrawn whilst the patient returns to dialysis and waits for a new kidney to become available.

2.2.2 Current service cost

Overall costs of CKD to the NHS in England was estimated as £1.45 billion in 2009–10, with more than half of total estimated expenditure for RRT.[57] Costs of RRT can be divided into costs associated with the transplantation and costs associated with dialysis. Transplantation costs can include the cost of work up for transplantation (assessing recipient suitability), maintaining and coordinating the waiting list, obtaining donor kidneys (harvesting, storage and transport for deceased donors; nephrectomy procedure for living donors), cross-matching for donor-recipient compatibility, the transplantation procedure, induction immunosuppression, hospital inpatient stay following procedure, initial and long-term maintenance immunosuppression, prophylaxis and monitoring for infections, monitoring of graft function and general health, adjustment of immunosuppressant dosages, treatment of acute rejection, and treatment of associated adverse events. Should the kidney be lost, the costs of restarting dialysis (dialysis costs, the cost of treatment for adverse events attributable to dialysis, and the cost of dialysis access surgery) would be incurred.

Data from the NHS Reference Costs 2013/14 indicated that the cost kidney transplantation in under 19s is on average £20,576. [58] Paediatric nephrology outpatient clinics are on average £249, and the cost of haemodialysis and peritoneal dialysis is on average £79,807 and £41,382 respectively. [58]

2.2.3 Variation in services

There are currently 13 paediatric renal centres in the UK, nine who offer dialysis and perform transplantations (Birmingham, Bristol, Glasgow, Leeds, London [Guys and Great Ormond Street], Nottingham, Belfast and Manchester) and four that offer renal care but not transplantations (Cardiff, Liverpool, Newcastle and Southampton).

After kidney transplantation, recipients are prescribed an immunosuppression regime consisting of both induction and maintenance therapy. Following this, they are offered check-up appointments with their clinic (consultant nephrologist) to monitor general health, kidney function, immunosuppressive drugs, infections (prophylaxis and treatment), and to address any, social or psychological concerns. The Renal Association Guidelines suggest the following frequency of clinic appointments[59]:

- Two-three times weekly for the first month after transplantation.
- One-two times weekly for months two-three after transplantation.
- Every one-two weeks for months four-six after transplantation.
- Every four-six weeks for months six-12 after transplantation.
- Three-six monthly thereafter.
- Detailed annual post-operative reviews.

Clinician estimations of average frequency of outpatient visits have been reported as 34.3, 6.3 and 4.7 visits respectively for the first, second and third years posttransplant, with UK database figures suggesting 39.7, 11.0 and 9.2 visits respectively for the first, second and third years posttransplant.[60]

Service provision (clinic appointments or other services) is likely to increase if acute rejection occurs (possibly requiring hospital admission and escalating treatment), and where there is declining graft function (which might necessitate more regular clinic visits, blood tests and other investigations and changes to treatment regimens). Patients may also present to their GP or A&E with adverse events related to kidney transplantation or immunosuppressive regimen and this may be followed by an additional referral to the consultant nephrologist or other appropriate specialist (e.g., renal dietician), followed by management as required (e.g., additional prescribing and monitoring).

In addition to these services, The Renal Association Guidelines also recommend that recipients of a transplant should have the following [59]:

- Online access to their results via the "Renal Patient View" service
- Open access to the renal transplant outpatient service
- An established point of contact for enquiries
- Access to patient information(which should be available in both written and electronic formats)

2.2.4 Current NICE guidance

Current NICE guidance on "Immunosuppressive therapy for renal transplantation in children and adolescents" (NICE technology appraisal guidance, TA99) have the following recommendations for induction and maintenance therapy:

Induction therapy:

Basiliximab or daclizumab, used as part of a ciclosporin-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in children and adolescents undergoing renal transplantation, irrespective of immunological risk. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used, unless it is contraindicated.[61] The marketing authorisation for daclizumab has been withdrawn at the request of the manufacturer.

Maintenance therapy:

Tacrolimus is recommended as an alternative option to ciclosporin when a CNI is indicated as part of an initial or a maintenance immunosuppressive regimen for renal transplantation in children and adolescents. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for the individual patient.[61]

Mycophenolate mofetil is recommended as an option as part of an immunosuppressive regimen for child and adolescent renal transplant recipients only when:

- there is proven intolerance to CNIs, particularly nephrotoxicity which could lead to risk of chronic allograft dysfunction, or

- there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a CNI until the period of high risk has passed.[61]

The use of mycophenolate mofetil in corticosteroid reduction or withdrawal strategies for child and adolescent renal transplant recipients is recommended only within the context of randomised clinical trials.[61]

Mycophenolate sodium is currently not recommended for use as part of an immunosuppressive regimen in child or adolescent renal transplant recipients.[61]

Sirolimus is not recommended for children or adolescents undergoing renal transplantation except when proven intolerance to CNIs (including nephrotoxicity) necessitates the complete withdrawal of these treatments.[61]

As a consequence of following this guidance, some medicines may be prescribed outside the terms of their UK marketing authorisation. Healthcare professionals prescribing these medicines should ensure that children and adolescents receiving renal transplants and/or their legal guardians are aware of this, and that they consent to the use of these medicines in these circumstances.[61]

2.3 Description of technology under assessment

2.3.1 Summary of Intervention

This technology assessment report considers nine pharmaceutical interventions. Two are used as induction therapy and seven are used as a part of maintenance therapy in renal transplantation. The two interventions considered for induction therapy are basiliximab and rabbit anti-human thymocyte immunoglobulin. The seven interventions considered for maintenance therapy are immediate and prolonged-release tacrolimus, mycophenoate mofetil, mycophenolate sodium, belatacept, sirolimus, and everolimus.

Induction therapy

Basiliximab (Simulect® [Novartis Pharmaceuticals]) is a monoclonal antibody which acts as an interleukin-2 receptor antagonist. It has a UK marketing authorisation for prophylaxis of acute rejection in allogeneic renal transplantation in children (one-17 years). The summary of product characteristics states it is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing

ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.[6]

Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline® [Sanofi]) is a gamma immune globulin. It has a UK marketing authorisation for the prevention of graft rejection in renal transplantation. The summary of product characteristics states it is usually used in combination with other immunosuppressive drugs. It is administered intravenously. The UK marketing authorisation is not restricted to adults only.[6]

Maintenance therapy

Tacrolimus is a calcineurin inhibitor which is available in an immediate-release formulation (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]). All of these formulations of tacrolimus have UK marketing authorisations for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisations include adults and children.[6] Modigraf® [Astellas Pharma]; is available in a granule form which can be suspended in liquid and maybe more suitable for those who struggle swallowing pills.

Tacrolimus is also available in a **prolonged-release formulation** (Advagraf® [Astellas Pharma]). It has a UK marketing authorisation for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisation is restricted to adults. The Commission on Human Medicines advises that all oral tacrolimus (including both short release and prolonged–release tacrolimus) medicines in the UK should be prescribed and dispensed by brand name only.[6]

Belatacept (Nulojix® [Bristol-Myers Squibb]) is designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept has a UK marketing authorisation for prophylaxis of graft rejection in adults receiving a renal transplant, in combination with corticosteroids and a mycophenolic acid. The summary of product characteristics recommends that an interleukin-2 receptor antagonist for induction therapy is added to this belatacept-based regimen. The summary of product characteristics states that the safety and efficacy of belatacept in children and adolescents zero to 18 years of age have not yet been established. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[6]

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid which acts as an antiproliferative agent (Arzip® [Zentiva], CellCept® [Roche Products], Myfenax® [Teva]; generic mycophenolate mofetil is manufactured by Accord Healthcare, Actavis, Arrow

Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt). It has a UK marketing authorisation for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. The UK marketing authorisation is not restricted to adults (dosage recommendations for children aged 2-18 years are included in the summary of product characteristics).[6]

Mycophenolate sodium (MPS) is an enteric coated formulation of mycophenolic acid (Myfortic® [Novartis Pharmaceuticals]). This formulation has the same UK marketing authorisation as mycophenolate mofetil, however, this is restricted to adults. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[6]

Sirolimus (Rapamune® [Pfizer]) is an antiproliferative with a non-calcineurin inhibiting action. It has a UK marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with ciclosporin and corticosteroids for two to three months. It may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[6]

Everolimus (Certican ® [Novartis Pharmaceuticals]) is a proliferation signal inhibitor and is an analogue of sirolimus. Everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation in children and adolescents.[6]

2.3.2 Current usage in the NHS

There is a variation in the use of induction and maintenance therapy in the UK. Table 6 provides an overview of immunosuppression regimens for low risk first renal transplants (e.g. blood group and HLA compatible) in the ten paediatric transplant centres in the UK. Four out of the ten centres use BAS as a part of induction therapy. Apart from the use of antibody induction, all centres use a single dose of methylprednisolone at the time of transplantation. The table also illustrates the difference in the use of the two proliferative agents (MMF and AZA), the agreement in the use of CNI across all centres (TAC; usually Adoport), and the use of steroids as a part of maintenance therapy. The current NICE guidelines are followed by using TAC+AZA+CCS ± BAS regimens. However, the use of MMF is not limited to proven intolerance to CNIs, or to a very high risk of nephrotoxicity necessitating a temporary minimisation or avoidance of CNI (see section 2.2.4 for more details).

Table 6. The use of immunosuppressive agents in paediatric centres in the UK

Hospital	Antibody used for induction therapy	Maintenance therapy
Birmingham Children's Hospital	Basiliximab	TWIST protocol: TAC+MMF+CCS
Bristol Children's Hospital	None[a]	Triple therapy: TAC+AZA+CCS
Glasgow, Yorkhill	Basiliximab	TWIST protocol: TAC+MMF+CCS
Leeds, Paediatric Unit[b]	None[c]	Triple therapy: TAC+AZA+CCS
London, Evelina Children's Hospital	Basiliximab	Triple therapy: TAC+AZA+CCS[e]
London, Great Ormond Street	None	Triple therapy: TAC+AZA+CCS
Newcastle Great North Childrens Hospital	None	Triple therapy: TAC+AZA+CCS
Nottingham Children's Unit	None[f]	Triple therapy: TAC+AZA+CCS[g]
Royal Belfast Hospital for Sick Children	None[c]	Triple therapy: TAC+MMF+CCS[h]
Royal Manchester's Children's Hospital	Basiliximab	TWIST protocol: TAC+MMF+CCS

Key: AZA, azathioprine; BAS, basiliximab; MMF, mycophenolate mofetil; CCS, steroids; TAC, tacrolimus.
Notes: TWIST protocol is based on a European study of an early steroid withdrawal study; The TWIST Study[62] with two doses of antibody (day zero and day four) and only five doses of steroids (day zero − day four), TAC, and MMF; a, basiliximab is used for second and subsequent transplants where the previous transplant was lost as a result of acute rejection; b, 16-18 year old patients follow adult protocol of antibody+TAC+MMF+CCS; c, basiliximab is used if high level of panel reactive antibodies; d, MMF for second transplantation or post rejection; e, early CCS withdrawal in certain cases (eg risk of diabetes etc); f, basiliximab for high risk patients; g, low thresholds for MMF switching; h,children who have bony problems (e.g. slipped upper femoral epiphysis) or obesity (Bardet Biedl) basiliximab with rapid steroid withdrawal is used.
Source: personal communication with Consultant Nephrologists Dr Jan Dudley and Dr Stephen Marks.

2.3.3 Anticipated costs associated with intervention

The cost of the intervention (immunosuppressive regimen) is determined primarily by the choice and combination of the drugs and their respective dosages. Indicative costs for different immunosuppressive agents are given in Table 7. Caution should be exercised in interpreting these since dosages are commonly titrated and may differ from those indicated.

In addition, drug administration costs are also incurred for some maintenance agents: ciclosporin, tacrolimus, sirolimus and everolimus are routinely titrated using therapeutic drug monitoring, which are estimated to cost approximately £26 per test (testing frequency is reduced as patients become stabilised in dosage); belatacept requires intravenous infusion, entailing catheterisation and nursing time. The cost of this is difficult to estimate but estimates range from £154[63] to £320.[54]

Table 7. Overview of costs and dose for different immunosuppressive agents

Compound	Unit cost	Recommended dose	Estimated weekly cost for 31.5 kg body weight, surface area 1.1 m^2 (10 yr old male)[e]
Azathioprine	Hospital pharmacy: 0.1p per mg[a] Community pharmacy: 0.1p per mg[c]	1-3 mg/kg per day, adjusted according to response[2]	Hospital pharmacy: 22.05p to 66.15p Community pharmacy: 22.05p to 66.15p
Basiliximab	7586.9p per mg (10mg vial) and 4211.9p per mg (20mg vial)[b]	Child over 1 year, body-weight under 35kg 10mg within 2 hours before transplant surgery and 10 mg 4 days after surgery. Child body-weight over 35 kg 20 mg within 2 hours before transplant surgery and 20 mg 4 days after surgery[b]	Child under 35 kg: £1517.38p (induction period only) Child over 35 kg: £842.38 (induction period)
Belatacept	141.8p per mg[b]	**Not licensed for use in children[2]** Adult dose 5 mg/kg per 4 weeks	£55.83 (adult, weight-based dose)
Ciclosporin	Hospital pharmacy: 1.65p per mg[a] Community pharmacy: 2.55p per mg[b]	8 to 12 mg/kg/day[f]	Hospital pharmacy: £29.10 - £43.66 Community pharmacy: £44.98 - £67.473
Corticosteroids	Hospital pharmacy: 0.3p per mg[a] Community pharmacy: 0.9p per mg[c]	Methylprednisolone: 10-20 mg/kg or 400-600 mg/m^2 (max 1 g) once daily for 3 days[2] Prednisolone: Consult local treatment protocols for details[2] An example: 60mg/m^2/day during first week, eventually weaned down to <10mg/m^2/alternate days	Hospital pharmacy: £2.83 – £5.67 Community pharmacy: £8.49 – £17.01
Everolimus	990.0p per mg[4]	**Not licensed for use in children[2]** Adult dose of 1.5 mg per day[g]	£103.95 (adult non-weight based dose)
Immediate-release tacrolimus	Hospital pharmacy: 52.0p per mg[a] Community pharmacy: 118.6p per mg[b,c]	150µg/kg twice daily, adjusted according to whole blood concentration[2]	Hospital pharmacy: £34.40 Community pharmacy: £78.45

Mycophenolate mofetil	Hospital pharmacy: 0.0377p per g[a] Community pharmacy: 0.0404p per g[c]	300 mg/m^2 twice daily (max 2 g) if in addition with tacrolimus and corticosteroids[2] 600mg/m^2 twice daily (max 2 g) if in addition with ciclosporin and corticosteroids[2]	Hospital pharmacy:£1.74 Community pharmacy: £1.86 Hospital pharmacy: £3.48 Community pharmacy: £3.73
Mycophenolate sodium	0.5p per mg[b]	**Not licensed for use in children[2]** Adult dose 1,440 mg per day[2]	£50.4 (adult non-weight based dose)
Prolonged-release tacrolimus	106.8p per mg[b]	**Not licensed for use in children[2]** Adult dose 0.2 mg/kg per day	£47.10 (adult weight based dose)
Rabbit antithymocyte immunoglobulin	635.08p per mg[b]	**Not licensed for use in children[2]** 1.5 mg/kg/day administered by IV infusion for 7 to 14 days[h]	£2100.52 (induction period only)
Sirolimus	288.3p per mg[b,c]	**Not licensed for use in children[2]** Adult dose: 2 mg per day[b]	£40.36 (adult non-weight based dose)

Notes: Costs are estimated based on units of mg or g, which may not be appropriate if fine dosing is not possible, or if fine dosing products are substantially more expensive per unit; in particular for belatacept it assumes that perfect vial sharing is employed (in which one vial may be used by more than one patient to eliminate wastage). a; Commercial Medicines Unit. Drug and pharmaceutical electronic market information (eMit), 2014; b, BNF 68; c, NHS Business Services Authority, NHS Drug Tariff for England and Wales (2015); d, Novartis submission; e, Weight to age taken from Astellas submission and weight to surface area taken from http://www.ouh.nhs.uk/oxparc/professionals/documents/Body-surfaceareaCCLGChart1.pdf; f, http://www.drugs.com/dosage/cyclosporine.html ; g, MHRA SPC; h, http://www.drugs.com/dosage/anti-thymocyte-globulin-rabbit.html#Usual_Pediatric_Dose_for_Renal_Transplant.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

The purpose of this assessment is to answer the following question:

What is the clinical effectiveness and cost-effectiveness of the following immunosuppressive therapies in renal transplantation in children and adolescents?

- Basiliximab and rabbit anti-human thymocyte immunoglobulin as an induction therapy, and
- immediate-release tacrolimus, prolonged-release tacrolimus, mycophenoate mofetil, mycophenolate sodium, belatacept, sirolimus, and everolimus as a maintenance therapy;
- Including a review of TA99.

The project was undertaken based on a published scope,[6] and in accordance with a protocol.[64]

3.1.1 Interventions

A total of nine interventions are considered, two for induction therapy and seven for initial and long-term maintenance therapy.

The two induction treatments are:

- Basiliximab (Simulect® [Novartis])
- Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline® [Sanofi])

The seven maintenance treatments are:

- Tacrolimus prolonged-release formulation (Advagraf® [Astellas Pharma]
- Tacrolimus immediate-release formulations (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma])

- Belatacept (Nulojix® [Bristol-Myers Squibb])
- Mycophenolate mofetil (Arzip® [Zentiva], CellCept® [Roche], Myfenax® [Teva]; generic mycophenolate mofetil manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt)
- Mycophenolate sodium (Myfortic® [Novartis])
- Sirolimus (Rapamune® [Pfizer])
- Everolimus (Certican® [Novartis]).

These treatments are described in the Background section 2.3.1. Several of the drugs being assessed are used in the NHS outside the terms of their UK marketing authorisation, for example in children and adolescents, or in high-risk people, or in unlicensed drug combinations. Specifically **everolimus, prolonged-release tacrolimus, belatacept, mycophenolate sodium** and **sirolimus** are not currently licensed for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.

Under an exceptional directive from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. Accordingly, the review will include controlled studies that used drugs outside the terms of their marketing authorisations.

3.1.2 Populations including subgroups

The population being assessed are children and adolescents 0-18 years (inclusive) undergoing kidney transplantation. Patients receiving multi-organ transplants and those who have received transplants and immunosuppression previously will be excluded.

If data allows, the following subgroups will be considered:

- Different age groups;
- Level of immunological risk (including human leukocyte antigen compatibility
- and blood group compatibility);
- People at high risk of rejection within the first six months;
- People who have had a re-transplant within two years;
- Previous acute rejection;
- People at high risk of complications from immunosuppression (including newonset

diabetes).

3.1.3 Relevant comparators

For induction therapy, the treatments are to be compared with each other as data permits, or with other regimens that do not include monoclonal or polyclonal antibodies. For maintenance therapy each treatment or regimen (combination of treatments) is to be compared with the other treatments or regimens as data permits, or with a calcinueirin inhibitor with or without an antiproliferative agent and/or corticosteroids.

3.1.4 Outcomes

The health related outcomes to be included in this technology assessment are:

- Patient survival
- Graft survival
- Graft function
- Time to and incidence of acute rejection (AR)
- Severity of AR
- Growth
- Adverse effects (AE) of treatment
- Health-related quality of life (HRQL)

3.1.5 Key issues

A number of factors may influence the survival and function of transplanted kidney and the survival of the recipient.

The viability of the kidney may depend on the type of donor (living-related, living-unrelated, DBD, DCD or ECD), the age of the donor, whether they had comorbidities such as diabetes, and the length of cold ischaemia. Furthermore, the age, sex, ethnicity and health of the recipient, and the length of time the recipient is on dialysis prior to transplantation, may affect the outcome of transplantation. These issues have beed discussed in more detail in Background section 2.1.4 (page 55).

3.2 Overall aims and objectives of assessment

This assessment will review and update the evidence for the clinical and cost-effectiveness of immunosuppressive therapies in children and adolescents renal transplantation. This will be done by conducting a systematic review of clinical effectiveness studies and a model-based economic evaluation of induction and maintenance immunosuppressive regimens to update the current guidance (TA99).[61] We have incorporated relevant evidence presented in this previous report and report new evidence from 2002 to the present. This will include a new decision analytic model of kidney transplantation outcomes to investigate which regimen is the most cost-effective option.

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

4.1 Methods for reviewing effectiveness

This systematic review was commissioned by the National Institute for Health and Care Excellence (NICE) to update the previous guidance (TA99)[61] The systematic review and economic evaluation developed to support current NICE guidance TA99, was published by Yao et al. in 2006.[1] The differences between the remit of the previous review and the protocol of the current one are discussed in Section 4.2.3.

There was one departure from the protocol [64]: the age of population eligibility criterion was changed from <18 years (a common definition of children and adolescents) to ≤18 years (the age inclusion criterion applied by the three eligible RCTs).

The aim was to systematically review the effectiveness of immunosuppressive therapies in child and adolescent (≤18 years) renal transplantation; that is to determine their effect on patient survival, graft survival, graft function, time to and incidence of acute rejection, severity of acute rejection and quality of life, growth, and their impact on adverse events.

4.1.1 Identification of studies

Bibliographic literature database searching was conducted on April 14th 2014 and updated on January 7th 2015. The searches for individual effectiveness studies (RCTs and controlled clinical trials) took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a study design limit to randomised control trials [RCT] or controlled trials). In order to update the previous assessment,[1] the searches were date limited (2002-current). These searches were not limited by language and not limited to human only studies because such a limit may have blocked retrieval of includable studies for Rabbit ATG (line 8 of the Medline search). The following databases were searched: Medline and Medline In-Process (OVID), Embase (OVID), CENTRAL (Wiley) and Web of Science (ISI – including conference proceedings). In addition, the following trials registries were hand searched in January 2015: Current Controlled Trials; ClinicalTrials.gov; FDA website; EMA website (European Public Assessment Reports [EPARs]).

Separate searches were undertaken to identify systematic reviews (SRs) of RCTs and non-randomised studies. These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a

pragmatic limit to systematic reviews). The same population and intervention search terms were used as in the individual studies search. A pragmatic, methodological search filter was used to limit by study design. No other limits (e.g. language) were applied to this search. The search was run from database inception in the following databases: Medline and Medline In-Process (OVID), Embase (OVID), CDSR, DARE and HTA (The Cochrane Library via Wiley) and HMIC (OVID).

The search strategies are recorded in Appendix 1.

The database search results were exported to, and de-duplicated using Endnote (X5). De-duplication was also performed manually.

Furthermore, the following websites were searched for background information:

Renal societies (UK)

- British Renal Society (www.britishrenal.org/)
- Renal Association (www.renal.org/)
- UK Renal Registry (www.renalreg.com/)
- Kidney Research UK (www.kidneyresearchuk.org/)
- British Kidney Patient Association (www.britishkidney-pa.co.uk/)
- National Kidney Federation (www.kidney.org.uk/)

Renal societies (international)

- American Society of Nephrology (www.asn-online.org/)
- American Association of Kidney Patients (www.aakp.org/)
- National Kidney Foundation (US; www.kidney.org/)
- Canadian Society of Nephrology (www.csnscn.ca/)
- Kidney Foundation of Canada (www.kidney.ca/)
- Australian and New Zealand Society of Nephrology (www.nephrology.edu.au/)
- Kidney Health Australia (www.kidney.org.au/)

- Kidney Society Auckland (www.kidneysociety.co.nz/)

Previous HTA review

Studies included in the previous HTA review (Yao et al. 2006)[1] were screened using the inclusion criteria for the PenTAG review (section 4.1.2).

Reference lists

Reference lists of included guidelines, systematic reviews, company submissions, and clinical trials were scrutinised in order to identify additional studies.

Ongoing trials

Searches for ongoing trials were also undertaken. Terms for the intervention and condition of interest were used to search the following trial registers for ongoing trials: ClinicalTrials.gov and Controlled Trials (ISRCTN). Trials that did not relate to immunosuppressive therapies for kidney transplantation in children and adolescents were removed by hand-sorting. All searches for onging trials were carried out in January 2015. The search strategies can be found in Appendix 1.

Adult RCT evidence

In addition, as specified in the review protocol, all child/adolescents RCTs and non-RCTs evidence included in this review was compared with adult evidence identified from parallel HTA 09/46/01 appraisal.[*]

4.1.2 Inclusion and exclusion criteria

Studies retrieved from the literature searches were selected for inclusion according to the inclusion/exclusion criteria specified below. Studies only available as abstracts were included provided sufficient methodological details were reported to allow critical appraisal of study quality; we also contacted authors for additional data.

Study design

The clinical effectiveness review included:

- Eligible studies: RCTs in children and adolescents (≤18 years), RCTs of adults and children/adolescents in which a subgroup analysis of children and adolescents is

[*] This parallel Health Technology Assessment was conducted by PenTAG to inform the ongoing technology appraisal of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85; NICE appraisal ID 456). The NIHR Evaluation, Trials and Studies Coordinating Centre reference for the adult report is 09/46/01. After the first Appraisal Committee meeting, the adult report will be uploaded to the NICE website as part of the Committee papers: http://www.nice.org.uk/guidance/indevelopment/gid-tag348/documents

reported, and non-randomised controlled studies (comparative quasi-experimental and observational studies were considred).

- Search strategy: Databases were searched to identify RCTs, systematic reviews of RCTs, and systematic reviews of non-randomised controlled studies. Individual non-randomised controlled studies were identified via the bibliographies of systematic reviews (i.e. individual non-randomised controlled studies were not searched for directly).

For the purpose of this review, a systematic review was defined as one that has:

- A focused research question.
- Explicit search criteria that are available to review, either in the document or on application.
- Explicit inclusion/exclusion criteria, defining the population(s), intervention(s), comparator(s), and outcome(s) of interest.
- A critical appraisal of included studies, including consideration of internal and external validity of the research.
- A synthesis of the included evidence, whether narrative or quantitative.

Interventions

Studies evaluating the use of the following immunosuppressive therapies for renal transplantation were included.

Induction therapy:

- Basiliximab (Simulect® [Novartis])

- Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline® [Sanofi])

Maintenance therapy:

- Tacrolimus prolonged-release formulation (Advagraf® [Astellas Pharma]

- Tacrolimus immediate-release formulations (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma])

- Belatacept (Nulojix® [Bristol-Myers Squibb])

- Mycophenolate mofetil (Arzip® [Zentiva], CellCept® [Roche], Myfenax® [Teva]; generic mycophenolate mofetil manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt)

- Mycophenolate sodium (Myfortic® [Novartis])

- Sirolimus (Rapamune® [Pfizer])

- Everolimus (Certican® [Novartis]).

All treatments are described in detail in section 1.3.1 (page 69).

In addition (as evidence allows), adherence to treatment and the use of treatments in conjunction with either corticosteroid or CNI reduction or withdrawal strategies is considered. To achieve this, only studies that meet the inclusion criteria are examined. As such, studies where the intervention is identical in both study arms, but dose reduction or withdrawal of corticosteroids or CNIs occurs in one arm, were excluded.

Comparator

Studies using the following comparators were included:

Induction therapy

- Regimens without monoclonal or polyclonal antibodies; for example, regimens that include methylprednisolone or placebo

- Interventions should also be compared with each other

Maintenance therapy

- A calcineurin inhibitor (CNI) with or without an antiproliferative agent and/or corticosteroids (CCS)

- Interventions should also be compared with each other

In addition, where appropriate, the interventions will be appraised as part of combination regimens.

Population

The population is children and adolescents ≤18 years of age undergoing kidney transplantation. The kidney donor may be living-related, living-unrelated or deceased. Patients receiving multi-organ transplants and those who have received transplants and immunosuppression previously will be excluded.

Outcomes

The outcome measures to be considered are:

- Patient survival
- Graft survival
- Graft function

- Time to and incidence of acute rejection (AR)
- Severity of AR
- Growth
- Adverse effects (AE) of treatment
- Health-related quality of life (HRQL)

4.1.3 Screening

First, titles and abstracts returned by the search strategy were screened for inclusion. The screening was distributed across a team of five researchers (TJ-H, LC, MHa, MB and HC). Update searches were screened by two reviewers (MHa and JV-C). Disagreements were resolved by discussion, with involvement of a third reviewer (TJ-H or MHa) if necessary. Full texts of identified studies were obtained and screened in the same way. Studies reported only as abstracts were included provided sufficient methodological details were reported to allow critical appraisal of study quality. In addition, studies included in the review conducted by Yao et al. 2006[1] were screened for inclusion.

As specified in the review protocol, the searches for systematic reviews were separately screened to identify SRs of non-randomised studies, and these in turn were screened to identify non-randomised studies for inclusion in the review.

4.1.4 Data extraction

Information from new studies (not included in TA99) was extracted and tabulated; information included details of the study's design and methodology, baseline characteristics of participants, and results including HRQL and any AEs if reported (Appendix 2). All included studies (including those in TA99) were quality appraised.

If we identified several publications for one study, we evaluated the effectiveness data from the most recent publication and amended this with information from other publications. For quality appraisal purposes, all publications relating to a study were assessed together.

4.1.5 Critical appraisal strategy

Randomised control trials

Four reviewers (LC, MHa, HC and TJ-H) independently assessed quality of all studies included in the clinical effectiveness review. The internal and external validity of RCTs was assessed according to criteria based on CRD guidance[65] (Table 8).

Table 8. Critical appraisal checklist for randomised control studies

Treatment allocation	1. Was the assignment to the treatment groups really random? 2. Was treatment allocation concealed?
Similarity of groups	3. Were the groups similar at baseline in terms of prognostic factors?
Implementation of masking	4. Were the care providers blinded to the treatment allocation? 5. Were the outcome assessors blinded to the treatment allocation? 6. Were the participants blinded to the treatment allocation?
Outcomes	7. Were all a priori outcomes reported? 8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes? 9. Did the analyses include an ITT analysis?
Generalisability	10. Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?

Key: ITT, intention-to-treat; NHS, National Health Service.
Notes: Criteria were based on CRD guidance.[65]

Non-Randomised control trials

There is no agreed recommended appraisal tool for the assessment of non-randomised studies.[66] The CRD handbook suggests considering the study design, risk of bias, other issues related to study quality, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalisability.[65] Therefore the internal and external validity of non-RCTs was assessed according to criteria based on CRD guidance[65] (Table 9).

Table 9. Critical appraisal checklist for non-randomised control studies

Treatment allocation	1. Was the method of allocation reported? 2. Is the allocation to groups or to the study a source of selection bias?
Similarity of groups	3. Were the groups similar at baseline in terms of prognostic factors?
Implementation of masking	4. Were the care providers blinded to the treatment allocation? 5. Were the outcome assessors blinded to the treatment allocation? 6. Were the participants blinded to the treatment allocation?
Outcomes	7. Was follow-up long enough for outcomes to occur? 8. Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes? 9. Were statistical analyses adjusted to remove to account for any between group differences?
Generalisability	10. Was the group(s) representative of NHS renal transplant patients?

Key: NHS, National Health Service.
Notes: Criteria were based on CRD guidance.[65]

4.1.6 Methods of data synthesis

Data were tabulated and discussed in a narrative review. The subgroups defined in section 3.1.2 (page 77) were considered in the analyses.

Meta-analyses

Where data permitted the results of individual studies comparing the same regimens were pooled using the methods described below.

A random-effects model was assumed for all meta-analyses (MA). For binary data, odds ratio (OR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling.[67] For continuous data (e.g. graft function), mean differences were calculated if the outcome was measured on the same scale in all trials. Publication bias was assessed using funnel plots; the Harbord test was used for binary outcomes (OR, logSE) and the Egger test for continuous data (Table 8). All analyses were performed in Stata 13.[68]

For studies with more than one intervention arm (that were separately compared with the same control arm), the number of events and the total sample size in the control arm were divided equally across the comparisons, and when pooling mean differences the total sample size in the control arm was adjusted and divided equally across the comparisons. However, if only one experimental arm was eligible for the analysis all participants and events assigned to the control arm were included. If the number of events was zero in one of the studies arms, a value of 0.5 was added to all study arms to allow for statistical analyses.

4.2 Results of the systematic review

4.2.1 Quantity and quality of research available

The current review summarises both randomised and non-randomised controlled evidence. The assessment of effectiveness is reported separately for induction and maintenance regimens.

Randomised control trials

Our searches returned 5,079 unique titles and abstracts, with 784 papers retrieved for detailed consideration. To ensure the inclusion of trials with mixed child/adolescent and adult populations that reported separate resuts for children and adolescents, the searches and title and abstract screening were not limited to children and adolescents. Update searches conducted on 7th January 2015 returned 416 unique titles and abstracts. Fourty papers were retrieved for detailed consideration.

Of the 824 full text papers retrieved, 793 were excluded, (a list of these records with reasons for their exclusion can be found in Appendix 3; Table 133). Although RCTs in mixed populations were identified none included subgroup analysis by age – providing separate results for children/adolescents and adults – and were therefore excluded from the review (a list of these records can be found in Appendix 3; Table 134). Three RCTs (published in seven papers and one abstract) met the inclusion criteria.

Only one abstract (Jungraithmayr et al. 2009)[69] was included in the review. This abstract included new data related to Offner et al. 2008[70] and sufficient methodological information to inform the quality appraisal. In addition, there were 23 articles that were SRs; all eligible SRs were tabulated (Appendix 4; Table 135).

The process is illustrated in detail in Figure 8.

In summary, three RCTs (published in seven papers and one abstract) were found eligible and are included in this review (Table 10).

Table 10. Summary table of included randomised controlled studies

Study, year	N[a]	Agent (n)	Control (n)	Outcomes	Multiple publications
		Induction therapy			
Offner et al. 2008[70]	192	**BAS**+CSA+MMF+CCS (100)	**PBO**+CSA+MMF+CCS (92)	Mortality, graft loss, graft function, BPAR, AE	Höcker et al. 2008;[71] Jungraithmayr et al. 2009;[69]
Grenda et al. 2006[72]	192	**BAS**+TAC+AZA+CCS (99)	**NI**+TAC+AZA+CCS (93)	Mortality, graft loss, graft function, BPAR, AE	Webb et al. 2009[73]
		Maintenance therapy			
Trompeter et al. 2002[74]	196	**TAC**+AZA+CCS (103)	**CSA**+AZA+CCS (93)	Mortality, graft loss, graft function, BPAR, AE	Filler et al. 2002;[75] Filler et al. 2005[76]

Key: AZA, azathioprine; BAS, basiliximab; BPAR, biopsy proven acute rejection; CSA, ciclosporin; MMF, mycophenolate mofetil; NI; no induction; PBO, placebo; CCS, steroids; TAC, tacrolimus.
Notes: a, Intention-to-treat population.

Non-randomised trials

The SRs were used to identify non-randomised trials (non-RCTs). We screened the titles and abstracts of 226 unique references identified by the PenTAG systematic review searches (including 43 records from update searches), and retrieved 38 papers for detailed consideration. All eligible SRs were tabulated (Appendix 4; Table 135).

In total, four non-RCTs met the inclusion criteria and were considered eligible for inclusion (see Table 11 for more details). All of these were included in the previous HTA by Yao et al. 2006,[1] so no new non-RCTs were identified. However, in 2007 one of the four non-RCT studies (Staskewitz et al 2001[77]) published five years follow-up data (Jungraithmayr et al. 2007[78]) that were not included in the previous HTA.

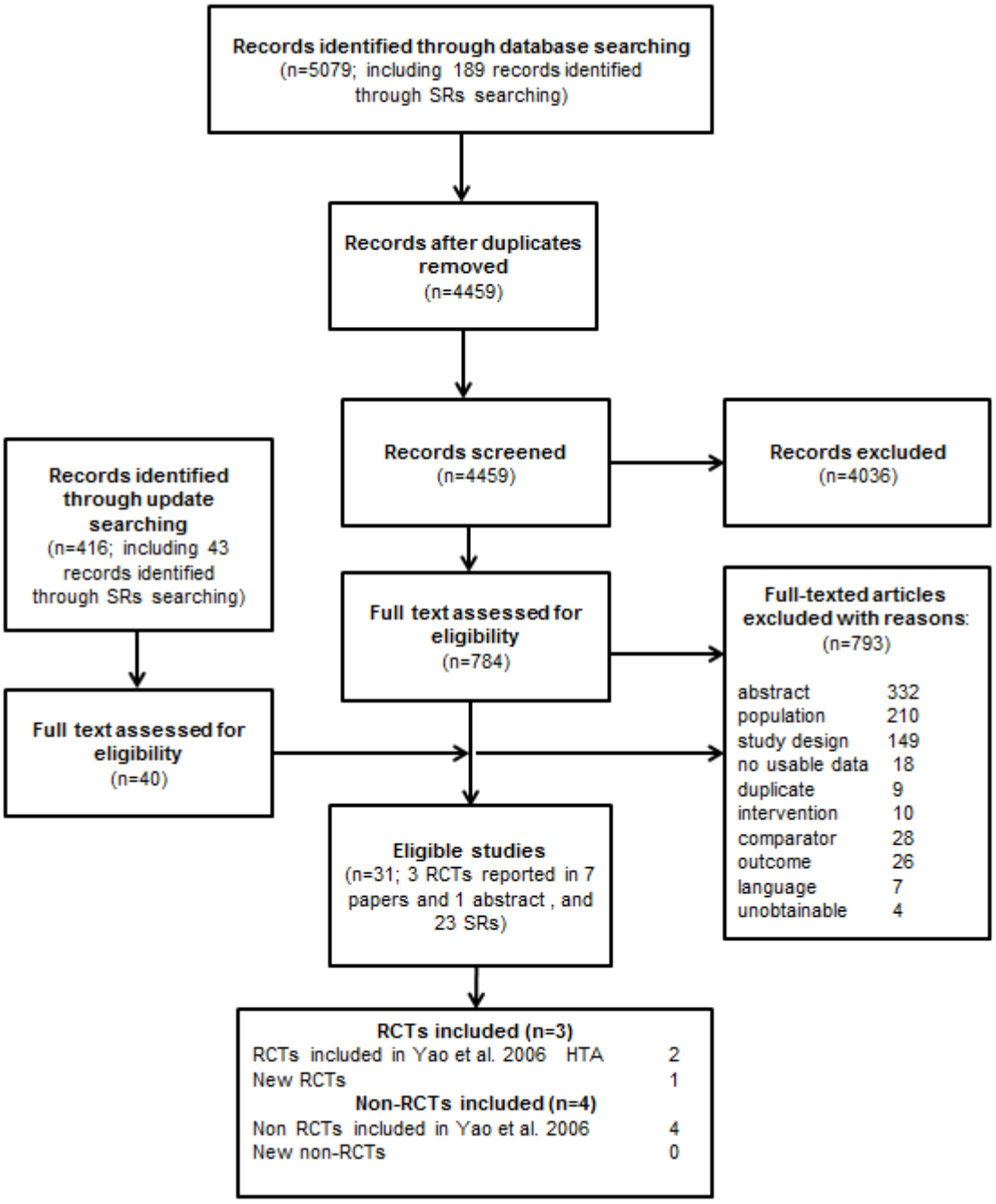
Table 11. Summary table of included non-randomised studies

Study, year	N[a]	Treatment (n)	Outcomes	Multiple publications
		Induction and maintenance therapy		
Garcia et al. 2002[79]	24	**BAS**+**TAC**+**AZA**+CCS *vs* **BAS**+**CSA**+**MMF**+CCS	Mortality, graft loss, graft function, BPAR, AE	NA
		Maintenance therapy		
Antoniadis et al. 1998[80]	14	CSA+ **MMF**+CCS *vs* CSA+**AZA**+CCS[b]	Graft function, BPAR,AE	NA
Benfield et al. 1999[c 81]	67	(OKT3 or CSA)+**MMF** + CCS *vs* (OKT3 or CSA)+ **AZA**+CCS	Mortality, graft loss, graft function, BPAR	NA
Staskewitz et al 2001[77]	139[d]	CSA+**MMF**+CCS[e] *vs* CSA+**AZA**+CCS	Mortality, graft loss, graft function, BPAR, AE	Jungraithmayr et al. 2003;[82] Jungraithmayr et al. 2007[78]

Key: ALG, anti-lymphocyte globulin; AE, adverse events; AZA, azathioprine; BAS, basiliximab; BPAR, biopsy proven acute rejection; MMF, mycophenolate mofetil; CCS, steroids; TAC, tacrolimus.

Notes: a, Intention-to-treat population; b, Methylprednisolone induction in all participants; c, This was randomised trial of OKT3 vs CSA at the time of transplantation. First 31 participants were given AZA and subsequent 36 participants were given MMF. In addition participants were randomly assigned to receive Sandimun or Neoral CSA preparations. Only a subgroup of participants was considered in this review.; d, Staskiewitz et al. 2001 reported results for 65 MMF and 54 AZA participants, however the following two publications (Jungraithmayr et al. 2003 and Jungraithmayr et al. 2007) reports on 85 MMF and 54 AZA participants; e, participants received Prednisone/ methylprednisolone induction in this arm, no induction reported for the historical control arm (CSA+AZA+CCS).

Figure 8. Clinical effectiveness; flow chart



Key: HTA, Health Technology Assessment; n, number of papers; RCT, randomised control trial; SR, systematic review.

4.2.2 Ongoing studies

Eleven ongoing trials were considered relevant to this review and were investigated further. An overview of the 11 trials with reasons for inclusion/exclusion in PenTAG review is provided in Appendix 5 (Table 136). Only one of these ongoing trials was identified as eligible for inclusion; study A2314. The methods and design of this trial were reported as

conference abstracts (Gupta et al. 2013, Langer et al. 2013, Tonshoff et al. 2012 and Tonshoff et al. 2013).[83-86] This international trial investigates the efficacy, tolerability and safety of early introduction of everolimus, reduced calcineurin inhibitors and early steroid elimination compared to standard CNI, mycophenolate mofetil and steroid regimen in paediatric renal transplant recipients and is sponsored by Novartis. The estimated date of completion is December 2016, so it was not included in this review. The search of ongoing studies in trial registries did not identify any additional RCTs for inclusion in the PenTAG systematic review.

4.2.3 The previous assessment report

The assessment report published as Yao et al. 2006[1] informed the current NICE guidance TA99. The aim of the previous HTA was to establish the clinical effectiveness (harms and benefits) and cost-effectiveness of four of the newer immunosuppressive drugs for renal transplantation, namely **basiliximab**, **daclizumab**, **tacrolimus** and **mycophenolate** (**mofetil** and **sodium**), and of **sirolimus** in children and adolescents.

The previous HTA review adopted the following approach of three evidence levels:

- Level-1 evidence: findings from RCTs carried out in children and adolescents with kidney transplants. This could include RCTs undertaken solely in children and adolescents, or RCTs where a subgroup analysis in children and adolescents was reported.
- Level-2 evidence: where level-1 evidence was not available, use of findings from RCTs undertaken in adults with kidney transplants.
- Level-3 evidence: findings from non-randomised comparative evidence collected in children and adolescents with kidney transplants. Level-3 evidence was used to complement and check the consistency of level-2 evidence (where level-1 evidence was not available).

The current PenTAG systematic review aims to establish the clinical-effectiveness and cost-effectiveness of immunosuppressive regimens including **basiliximab** and r**abbit anti-human thymocyte immunoglobulin** as an induction therapy in renal transplantation in children and adolescents, and of immunosuppressive regimens including **immediate-release tacrolimus**, **prolonged-release tacrolimus**, **mycophenoate mofetil**, **mycophenolate sodium**, **belatacept**, **sirolimus**, and **everolimus** as a maintenance therapy in renal transplantation in children and adolescents (including review of TA99).

The current PenTAG review included:

- Randomised controlled trials in children and adolescents (≤18 years), and RCTs of adults and children and adolescents in which a subgroup analysis of children and adolescents is reported.
- Systematic reviews which include non-randomised studies evaluating the interventions of interest in children and adolescents (≤18 years).

In addition, the penTAG review compares results in children and adolescents with those from the parallel HTA 09/46/01 appraisal "Immunosuppressive therapy for kidney transplantation in adults".

In the sections below we summarise the evidence included in TA99 and highlight the differences between the PenTAG review and the previous review.

Randomised control trials

Children and adolescents

The previous TA99 included three paediatric RCTs; the unpublished Wyeth 0468E1-217-US study, Trompeter at al .2002, and an abstract by Grenda et al. 2004 (Table 12).[74, 87] The Wyeth submission 0468E1-217-US study compared an addition of SRL to a CNI maintenance therapy ([CSA or TAC] + CCS), with a triple maintenance therapy ([CSA or TAC] + [MMF or AZA] + CCS) in children and adolescents (≤20 years old) who experienced 1 or more episodes of acute rejection or chronic rejection after kidney transplantation. Because of the trial design (a breakdown of the numbers [and results] in each treatment combination is unknow) and population characteristics (age and time from transplantation) this study is not eligible to be included in the current review. The other two paediatric RCTs included in Yao et al. 2006[1] are included in the PenTAG review.[74, 87] Additional publications of Grenda te al. 2004 were identified in our searches (the previous HTA included only 6 months follow-up data; see Table 12 for more details). We identified one new RCT (Offner et al. 2008)[70] that was not included in Yao et al. 2006.[1]

Table 12. Previous HTA review; included children and adolescents randomised control trials

No	Study ID	Multiple ID	Treatments	Published	Included in PenTAG (reason)
1	Grenda et a. 2004[87]	Fijusawa/Astellas 2005	BAS vs PBO	Abstract only; full trial provided in Fujusawa/Astellas submission.	Yes, trial was published as **Grenda et al. 2006**;[72] and **Webb et al. 2009**.[73]
2	Trompeter et al. 2002[74]	Filler et al. 2002;[75] Filler et al. 2005.[76]	TAC vs CSA	Yes.	Yes.
3	Wyeth submission 2005	0468E1-217-US, NCT00005113 (study was terminated)	Addition of SRL	No; full trial provided in Fujusawa/Astellas submission.	No (population, design).

Key: BAS, basiliximab; CSA, ciclosporin; ID, identification; No, number; PBO, placebo; SRL, sirolimus; TAC, tacrolimus.

Non-randomised studies

An overview of the nine non-randomised studies included in the Yao et al. 2006[1] with reasons for inclusion/exclusion in the currrent review is provided in Table 13. Five studies were excluded from the PenTAG (Table 13):

- Duzova et al. 2003[88] (compared BAS and no induction) administered triple therapy of (CSA or TAC) + (AZA or MMF)+CCS, however, a breakdown of the numbers (and results) in each combination was not reported, n addition, the mean recipient age was 14.9 3.6 years (range 7–21 years);
- Pape et al. 2002[89] recruited a child with a combined kidney-liver transplantation;
- Swiatecka-Urban et al. 2001[90] included children, adolescents, and adults (inclusion criteria age: < 21 years);
- Neu et al. 2003[91] included children, adolescents, and adults (inclusion criteria age: >2 and < 21 years) and the use of induction therapy varied in the the study;
- Steffen et al. 2003[92] was published as an abstract only, and did not include enough information to allow criticall appraisal.

Table 13. Previous HTA review; included children and adolescents non-randomised studies

No	ID	Multiple ID	N[a]	Treatments	Included in PenTAG (reason)
			Induction therapy		
1	Duzova et al. 2003[88]	NA	43	**BAS**+(CSA or TAC)+(AZA or MMF)+CCS *vs* (CSA or TAC)+(AZA or MMF)+CCS	No (design & population)
2	Pape et al. 2002[89]	NA	77	**BAS**+CsA+CCS *vs* CSA+CS	No (population)[b]
3	Swiatecka-Urban et al. 2001[90]	NA	32	**BAS**+TAC+CCS *vs* TAC+CCS[c]	No (population)
			Maintenance therapy		
4	Garcia et al. 2002[79]	NA	24	BAS+**TAC**+**AZA**+CCS *vs* BAS+**CSA**+**MMF**+CCS	Yes
5	Neu et al. 2003[91]	NA	986	**TAC**+MMF+CCS *vs* **CSA**+MMF+CS	No (population)
6	Antoniadis et al. 1998[80]	NA	14	CSA+**MMF**+CCS *vs* CSA+**AZA**+CS[d]	Yes
7	Steffen et al. 2003[92]	NA			No (abstract)
8	Staskewitz et al 2001[77]	Jungraithmayr et al. 2003[82]	120	CSA+**MMF**+CCS[e] *vs* CSA+**AZA**+CCS	Yes
9	Benfield et al. 1999[f81]	NA	678	(OKT3 or CSA)+**MMF**+CCS *vs* (OKT3 or CSA)+**AZA**+CCS	Yes

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; ID, identification; No, number; MMF, mycophenolate mofetil; CCS, steroids; OKT3, Orthoclone OKT3; TAC, tacrolimus.

Notes: a, an intention to treat population; b, one child had a combined kidney-liver transplantation; c, a single AZA dose perioperatively in 7/8 participants in the non BAS; d,Methylprednisolone induction in all participants; e, participants received Prednisone/ methylprednisolone induction in this arm, no induction reported for the historical control arm (CSA+AZA+CCS); f, this was randomised trial of OKT3 vs CSA at the time of transplantation. First 31 participants were given AZA and subsequent 36 participants were given MMF. In addition participants were randomly assigned to receive Sandimun or Neoral CSA preparations.

In summary, four non-randomised studies were included in the PenTAG review; all were also included in the previous HTA review by Yao et al. 2006.[1] No new non-randomised studies were identified in PenTAG systematic review searches.

Adults

The previous TA99 included evidence from 25 adult RCTs. In comparision, the updated HTA 09/46/01 appraisal "Immunosuppressive therapy for kidney transplantation in adults" included 89 trials; 14 induction studies, 73 maintenance studies, and two studies of both induction and maintenance treatment. An overview of the 25 adult RCTs included in Yao et al. 2006[1] with

reasons for inclusion/exclusion in the parallel HTA 09/46/01 review is provided in Appendix 6 (Table 137).

Where relevant, the adult evidence from the HTA 09/46/01 appraisal was summarised and compared with child/adolescent evidence included in the PenTAG review.

4.2.4 Quality of included studies

We appraised both newly identified trials and those included in the previous HTA review.[1] The reasons for re-appraising trials were: first, to ensure consistency with appraisal of the new study, and second, because we have access to new information from papers published after the inclusion date for the previous review. Only primary research studies were appraised (i.e. not systematic reviews). If a trial was reported in multiple publications, only one quality assessment of the trial was conducted (all publications for that trial were assessed together).

4.2.4.1 Randomised controlled trials

In total, three RCTs were assessed; two induction studies and one maintenance study.

Overall assessment

For all three RCTs, less than half of the items constituting the quality appraisal assessment were rated as being of 'adequate' quality (Table 14). All of these trials either did not report, or lacked clarity on, at least five of the ten quality appraisal items. It is possible that items that were not clearly reported in the papers were in fact adequately conducted in the trials. Nevertheless, all three RCTs were rated as 'inadequate' for at least one item of the quality appraisal assessment.

Treatment allocation

Random allocation: The method of random allocation, including the method of sequence generation, was clearly stated and adequate in only one trial (Offner et al.2008)[70] and unclear in the other two trials.

Concealment of allocation: The method of concealment of allocation was clearly reported in only one trial (Trompeter et al. 2002)[74] and unclear in the other two trials.

Similarity of groups

Baseline characteristics: Despite stating that baseline characteristics were similar between treatments arms on a range of prognostic factors, none of the three RCTs provided sufficient supporting evidence (including statistical information) to justify these claims.

Implementation of masking

Treatment allocation masked from providers: The method was clearly stated and adequate in only one trial (Offner et al.2008).[70] In the other two trials, care providers were not blinded to treatment allocation.

Treatment allocation masked from outcome assessors: None of the three trials clearly reported whether treatment allocation was masked from outcome assessors.

Treatment allocation masked from participants: The method was clearly stated and adequate in only one trial (Offner et al.2008).[70] In the other two trials, participants were not blinded to treatment allocation.

Completeness of trials

In all three studies it was not clear whether all reported outcomes were the same as those in the trial protocol and the reporting of loss to follow-up, withdrawals and dropouts was also not clearly reported.

ITT analysis: None of the trials was rated as adequate. One induction trial investigating the effectiveness of basiliximab excluded eight participants who received a 'commercially available formulation of the drug instead of the blinded study drug Simulect' and was, therefore, rated as 'inadequate' for this item of the quality appraisal assessment (Offner et al. 2008).[70] Similarly, one study excluded participants who did not receive study medication and excluded an additional four participants because of reporting issues so was also rated as 'inadequate' for this item (Trompeter et al.2002).[74] The remaining study (Grenda et al. 2006).[72] did not clearly report the initial number of participants who were randomised, so it was unclear whether all randomised and transplanted participants were included in the analyses.

Applicability of trials to the NHS

Applicability to the current NHS in England: All three studies were considered to be applicable to the NHS because no specific limitations with regards applicability were found in the study; all three trials were conducted in Europe, patient and donor characteristics were largely representative of the NHS in England and doses of the drug under investigation were

similar to current recommended doses,(Offner et al. 2008, Trompeter et al. 2002, and Grenda et al. 2006)[70, 72, 74] although Trompeter et al. 2002 administered 10mg of basiliximab for participants <40kg and 20mg for participants ≥40kg, where as the recommended cut-off for increasing the dose from 10mg to 20mg is currently 35kg.

Table 14. Quality assessment; randomised controlled trials

Study	Was the assignment to the treatment groups really random?	Was the treatment allocation concealed?	Were the groups similar at baseline in terms of prognostic factors?	Were the care providers blinded to the treatment allocation?	Were the outcome assessors blinded to the treatment allocation?	Were the participants blinded to the treatment allocation?	Were all a priori outcomes reported?	Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?	Did the analyses include an ITT analysis?	Are there any specific limitations which might limit the applicability of this study's findings to the current NHS in England?
Offner et al. 2008[70]	Adequate	Unclear	Unclear	Adequate	Unclear	Adequate	Unclear	Unclear	Inadequate	Adequate
Grenda et al. 2006 [72]	Unclear	Unclear	Unclear	Inadequate	NR	Inadequate	Unclear	Unclear	Unclear	Adequate
Trompeter et al. 2002[74]	Unclear	Adequate	Unclear	Inadequate	NR	Inadequate	Unclear	Unclear	Inadequate	Adequate

Key: NR, not reported; ITT, intention-to-treat.

4.2.4.2 Non-randomised trials

In total, four non-randomised studies were assessed; three studies of maintenance treatments and one study of both induction and maintenance treatments.

Overall assessment

For all four non-randomised studies, less than half of the items constituting the quality appraisal assessment were adequately addressed (Table 15). However, for all studies at least five of the ten quality appraisal items were either not applicable (due to study design), not reported, or not clearly reported. It is possible that items that were not clearly reported in the papers were in fact adequately conducted in the studies.

Treatment allocation

Allocation to groups: three of the non-randomised studies adequately described what the treatment and control groups were and the general basis for allocating participants to a particular treatment. In two studies allocation to groups was dictated by changes to the treatment protocol in the study centres (i.e. they were historically controlled studies).[77, 81] One study compared two retrospective cohorts (where treatment allocation was unrelated to the study design).[79] Despite being a prospective non-randomised, controlled trial, the remaining study did not report the basis for allocation to treatment groups.[80]

Avoidance of selection bias: None of the four studies provided evidence that selection bias (to the study overall, and to treatment groups) was minimised within the context of the study design. All four studies were rated as 'unclear' with regards minimisation of selection bias. Two studies did not confirm whether all eligible participants were recruited for either group.[77, 81] The other two studies did state that all transplanted children and adolescents were included in the study but did not clearly describe how participants were allocated to treatment groups, so the extent of possible selection bias to groups is not clear.[79, 80]

Similarity of groups

Baseline characteristics: Two of the four studies did not clearly report whether treatment groups were similar at baseline on a range of prognostic factors because they omitted key statistical information.[80, 81] In the other twostudies the age of participants statistically significantly differed between treatment groups.[77, 79]

Implementation of masking

None of the four non-randomised studies reported whether treatment allocation was masked from treatment providers, outcome assessors or participants. However, for three of the studies this was not applicable, because blinding could not be reasonably expected given the study design.[77, 79, 81] The remaining study was a prospective non-randomised controlled trial, so masking of care providers, outcome assessors (by using independent assessors), and participantscould be done but was not reported.[80]

Length of follow-up

Three of the non-randomised studies had an adequate length of follow-up, with all participants followed for at least six months.[77, 80, 81] The remaining study was rated as 'partial' because not all participants were followed for at least six months but delayed graft function was included as an outcome (this outcome would usually be assessed within the first month of transplantation).[79]

Completeness of trials

All four of the non-randomised studies adequately described the completeness of the study, either by describing withdrawals or drop-outs (including reasons) or by making it clear that all enrolled participants completed the study.

Adjustment for bias in non-randomised studies

This item of the quality appraisal assessment was applicable to all four studies. However, two of the studies did not perform any adjustment for bias in their analyses.[77, 81] For the other two studies, analyses were not fully reported, so this could not be assessed.[79, 80]

Applicability of trials to the current NHS in England

None of the non-randomised studies was considered to be clearly applicable to the NHS in England. Two studies were rated as inadequate because the study population was not representative of the current NHS in England; in one of these studies all kidneys were from living-related donors[80] and in the other >90% of kidneys were from cadaveric donors.[77] The other two studies were both rated as unclear because the populations were not recruited from the EU, but it was not clear to what extent the population characteristics could generalise to the NHS in England.[79, 81]

Table 15. Quality assessment; non-randomised studies

Study	Design	Was the allocation to group(s) reported?	Is the allocation to groups or to the study a source of selection bias?	Were the groups similar at baseline in terms of prognostic factors?	Were the care providers blinded to the treatment allocation?	Were the outcome assessors blinded to the treatment allocation?	Were the participants blinded to the treatment allocation?	Was follow-up long enough for outcomes to occur?	Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?	Were analyses adjusted to remove bias in non-randomised studies?	Was the group(s) representative of NHS renal transplant patients?
Antoniadis et al. 1998[80]	Non-randomized controlled trial	NR	Unclear	Unclear	NR	NR	NR	Adequate	Adequate	NR	Inadequate
Benfield et al. 1999[81]	Historically controlled study (a)	Adequate	Unclear	Unclear	NA	NA	NA	Adequate	Adequate	Inadequate	Unclear
Garcia et al. 2002[79]	Retrospective cohort study	Adequate	Unclear	Inadequate	NA	NA	NA	Partial	Adequate	NR	Unclear
Staskewitz et al 2001[77]	Historically controlled study	Adequate	Unclear	Inadequate	NA	NA	NA	Adequate	Adequate	Inadequate	Inadequate

Key: NA; not applicable; NR, not reported. Notes: a, this was randomised trial of OKT3 vs CSA at the time of transplantation. The first 31 participants were given AZA and the subsequent 36 participants were given MMF. In addition participants were randomly assigned to receive Sandimun or Neoral CSA preparations. Therefore we consider there to be two additional studies embedded within the original RCT, one of which is applicable to this review.

4.2.5 Baseline characteristics

Randomised controlled studies

Baseline characteristics of the three included RCTs (Offner et al. 2008, Grenda et al. 2006, and Trompeter at al. 2002)[70, 72, 74] are summarised in Table 16. All three studies were conducted over multicentres in Europe. Only Offner et al. 2008 reported the countries involved (Germany, France, and Switzerland).[70] Mean age across the studies' arms ranges from 10.1 years to 11.5 years. The proportion of adolescents (with 12 or 13 years old being the cut off point for adolescence in the three studies; see Table 16 for details) is 36.6% to 54.4% across the studies' arms. Boys represented 56.0% to 67.4% of participants. Two studies had a high proportion of white participants (95%-87%),[70, 74] with one trial not reporting ethnicity.[72] The proportion of living donors across the studies' arms ranges from 15.5% to 35.8%. The proportion of first transplants is high; ranging from 85% to 96% across the studies' arms. Finally, HLA antigen mismatch ranges from 2.3 to 2.7 across the three trials. A close antigen match is no longer considered critical due to the more effective immunosuppressive therapy, but a better HLA match may lead to longer graft survival.

Table 16. Baseline characteristics; randomised controlled trials

Study id	Induction	Maintenance	N[a]	Mean age, yrs (sd)	Adolescents n/N, %	First transplant n/N, %	Male n/N, %	Donor type n/N, %		Race n/N, %	Mean HLA mismatches Mean (SD)
								Living	Deceased		
Offner et al. 2008[70]	**BAS**	CSA+MMF+CCS	100	10.7 (4.6)	43/100, 43%[b]	96/100, 96%	56/100, 56.0%	30/100, 30%	70/100, 70%	95/100, 95% White 5/100, 5% Other	2.6 (1.2)
	PBO		92	10.8 (4.9)	43/92, 46.7%[b]	88/92, 96%	62/92, 67.4%	32/92, 34.8%	60/92, 65.2%	84/92, 91.3% White 8/92, 8.7% Other	2.2 (1.0)
Grenda et al. 2006[72]	**BAS**	TAC+AZA+CCS	99	11.5 (4.1)	53/99 53.5%[c]	95/99, 96%	62/99, 62.6%	20/99 20.2%	79/99 79.8%	NR	2.5 (NR)
	NI		93	11.3 (4.0)	51/93 54.4%[c]	87/93, 93.5%	57/93, 61.3%	16/93 17.2%	77/93 82.8%	NR	2.3 (NR)
Trompeter at al. 2002[74]	Methyl-prenisolone	**TAC**+AZA+CCS	103	10.5 (4.6)	41/103 39.8%[d]	94/103, 91%	64/103, 62.1%	16/103, 15.5%	87/103, 84.5%	90/103, 87.4% White 1/103, 1% Black 1/103, 1% Oriental 11/103, 10.7% Other	2.5 (NR)
		CSA+AZA+CCS	93	10.1 (4.5)	34/93, 36.6%[d]	79/93, 85%	56/93, 60.2%	15/93, 16.1%	78/93, 83.1%	82/92, 88.2% White 0/92, 0% Black 3/92, 3.2% Oriental 8/92, 8.6% Other	2.7 (NR)

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; NA, not applicable, NI; no induction; NR, not reported; PBO, placebo; CCS, corticosteroids; TAC, tacrolimus.
Notes: a, ITT population; b, adolescents defined as >12 years and <19 years; c, adolescents defined as 12 - 18 years; d, adolescents defined as 13 - 18 years.

Non non-randomised studies

Similarly, baseline characteristics of the four included non-randomised studies (Antoniadis et al. 1998[80] [non-randomized controlled trial], Benfield et al. 1999[81] [historically controlled study], Garcia et al. 2002[79] [retrospective cohort study], and Staskewitz et al 2001[77] [historically controlled study]) are summarised in Table 17. Antoniadis et al. 1998 study was conducted in one Greek centre, Benfield et al. 1999 study was conducted in two centres in the USA and Staskewitz et al 2001 study was conducted in 12 German centres. Garcia et al. 2002 did not report where or within how many centres their study was performed, however the authors are all based in Brazil, and therefore it is likely that this study was completed in Brazil. Not surprisingly, the baseline characteristics of the non-RCTs varies not only across the studies, but also within the studies. Mean age across the studies' arms ranges from 9.0 years to 11.5 years. None of the non-RCT report the proportion of adolescents included. Boys represented 50.0% to 66.7% of participants. Two studies had a high proportion of white participants (75%-100%),[77, 79]one study reported between 19% and 25% black participants (dependent on treatment group),[81] while one study did not report ethnicity.[80] Most studies included a high proportion of living donors (75% -100%). However, one study reported only 6% living donors in one treatment group and and 9% in the other treatment group.[77] This was the only study reporting mean HLA mismatches (2.69-2.89).[77]

Table 17. Baseline characteristics; non- randomised studies

Study id	Induction	Maintenance therapy	N[a]	Mean age, yrs (sd)	Adolescents n/N, %	First transplant n/N, %	Male n/N, %	Donor type n/N, % Living	Deceased	Race n/N, %	Mean HLA mismatches (SD)
Antoniadis et al. 1998[80]	**Methyl-prednisolone**	**CSA+MMF+CCS**	7	10 [4-12][b]	NR	NR	NR	7/7, 100%	NA	NR	NR
		CSA+AZA+CCS	7		NR	NR	NR	7/7, 100%	NA	NR	NR
Benfield et al. 1999[81c]	OKT3	CSA+MMF + CCS	17	10.7 (5.3)	NR	NR	20/36, 55%	25/36, 69%	11/36, 31%	9/36, 25% Black	NR
	CSA	**CSA+MMF+ CCS**	19		NR	NR					NR
	OKT3	CSA+ AZA+CCS	17	9.4 (5.1)	NR	NR	19/31, 61%	24/31, 77%	12/31, 39%	6/31, 19% Black	NR
	CSA	**CSA+ AZA+CCS**	14		NR	NR					NR
Garcia et al. 2002[79]	**BAS**	**TAC+AZA+ CCS**	12	11.3 (9.3)	NR	NR	6/12, 50%	8/12, 66.7%	4/12, 33.3%	11/12, 91.7%	NR
		CSA+MMF+ CCS	12	9.0 (6)	NR	NR	8/12, 66.7%	7/12, 58.3%	5/12, 41.7%	9/12, 75%	NR
Staskewitz et al 2001[77]	**Prednisone/ Methyl-prednisolone**	**CSA+MMF+ CCS**	85[d]	11.5 (3.6)	NR	61/65, 94%	42/65, 65%	4/65, 6%	61/65, 94%	65/65, 100% Caucasian	2.69 (0.87)
	NR	**CSA+AZA+CCS**	54	9.9 (4.7)	NR	53/54, 98%	32/54, 59%	5/54, 9%	49/54, 91%	54/54, 100% Caucasian	2.89 (0.96)

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; DBD, donation after brain death; DCD, donation after cardiac death; MMF, mycophenolate mofetil; NA, not applicable, NI; no induction; NR, not reported; PBO, placebo; CCS, steroids; TAC, tacrolimus. Notes: Emphasis was put on treatments considered in the submission. a, ITT population; b, only median and [range] reported; c, this was randomised trial of OKT3 vs CSA at the time of transplantation. Firsts 31 participants were given AZA and subsequent 36 participants were given MMF. In addition participants were randomly assigned to receive Sandimun or Neoral CSA preparations. Numbers of participants in the OKT3 group were reported from text (17 & 19) text, however numbers reported in a table differed (16 & 20; numbers from text were reported because they were relevant to outcomes reported in this section); d, Staskiewitz et al. 2001 reported results for 65 MMF and 54 AZA participants, however the following two publications (Jungraithmayr et al. 2003 and Jungraithmayr et al. 2007) reports on 85 MMF and 54 AZA participants. d, one participant received TAC instead of AZA; e, mean and range reported.

4.3 Results of the included studies

No studies were identified that evaluated growth or health related quality-of-life in the use of induction immunosuppression therapy in renal transplantation in children and adolescents. In addition, no studies that would allow analyses of adherence to treatment and the use of treatments in conjunction with either CCS or CNI reduction or withdrawal strategies were identified.

A summary, comparing our results with those of the adult kidney transplant population (using evidence from parallel HTA 09/46/01 appraisal "Immunosuppressive therapy for kidney transplantation in adults") is made at the end of this section. Briefly, 14 induction trials, 73 maintenance trials, and two trials of both induction and maintenance were included in the parallel HTA 09/46/01.

4.3.1 Induction therapy

Two RCTs of induction therapy[70, 72] (reported in four publications and one abstract) in children and adolescents were identified in the review; the population characteristics are summarised in Table 16. **Offner et al. 2008**[70] compared basiliximab induction therapy with placebo (PBO); **BAS**+CSA+MMF+CCS versus **PBO**+CSA+MMF+CCS. **Grenda et al. 2006**[72] compared basiliximab induction therapy with no induction; **BAS**+TAC+AZA+CCS versus TAC+AZA+CCS. No RCTs were identified that evaluated **r-ATG** in children and adolescents.

No non-RCTs in the child/adolescent population evaluated induction therapies.

4.3.1.1 Mortality

Both RCTs[70, 72] provided data on mortality for BAS vs no induction or placebo (Table 18). Grenda et al. 2006[72] reported the longest follow-up data at two years post transplant. No evidence of a statistically significant difference in overall survival between BAS and comparator arms was reported at any time point.

Table 18. Mortality; randomised control trials

Study id	Treatment	3 months n/N, %	3 months OR (95%CI)	6 months n/N, %	6 months OR (95%CI)	1 year n/N, %	1 year OR (95%CI)	2 years n/N, %	2 years OR (95%CI)
Offner et al. 2008[70] a	**BAS+** CSA+MMF+CCS	1/100, 1%	2.79 (0.11; 69.31)	2/100, 2%	4.69 (0.22; 99.10)	3/100, 3%	6.64 (0.34; 130.33)	NR	NA
	PBO+ CSA+MMF+CCS	0/92, 0%		0/92, 0%		0/92, 0%		NR	
Grenda et al. 2006[72]	**BAS+** TAC+AZA+CCS	NR	NA	0/99, 0%	NA	NR	NA	0/99, 0%	0.33 (0.01; 8.20)
	NI+ TAC+AZA+CCS	NR		0/93, 0%		NR		1/93, 1%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; n, number of events; N, number of participants; NI; no induction; NR,not reported; NA, not applicable; PBO, placebo; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.

Notes: a, two additional deaths in BAS arm: one at day 21 (this participant was excluded from ITT as death occurred before TX) and one at day 397 (not included as two years data were not reported). All OR were calculated by PenTAG. OR < 1 favours BAS.

Summary

In summary, there was no evidence that BAS improved survival when compared to placebo or no induction. This is similar to the conclusions of the previous HTA.[1]

4.3.1.2 Graft loss

Both RCTs[70, 72] provided data on graft loss for BAS vs no induction or placebo (Table 19). Grenda et al. 2006[72] reported the longest follow-up data of two years. No evidence of a significant difference between the BAS and control arms was reported for any data point.

Table 19. Graft loss; randomised control trials

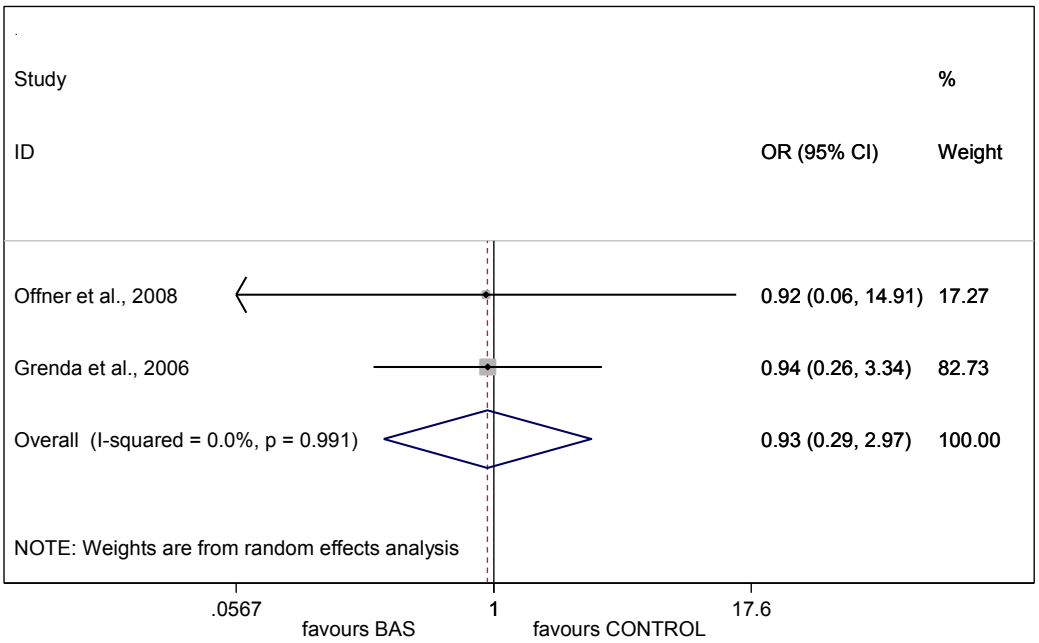
Study id	Treatment	6 months n/N, %	6 months OR (95%CI)	1 year n/N, %	1 year OR (95%CI)	2 years n/N, %	2 years OR (95%CI)
Offner et al. 2008[70] a	**BAS+** CSA+MMF+CCS	1/100, 1%	0.92 (0.06; 14.92)	1/100, 1%	0.92 (0.06; 14.92)	NR	NA
	PBO+ CSA+MMF+CCS	1/92, 1%		1/92, 1%		NR	
Grenda et al. 2006[72]	**BAS+** TAC+AZA+CCS	5/99, 5%	0.94 (0.26; 3.34)	NR	NA	5/99, 5%	0.50 (0.16; 1.54)
	NI+ TAC+AZA+CCS	5/93, 5%		NR		9/93, 10%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; n, number of events; N, number of participants; NI; no induction; NR,not reported; NA, not applicable; PBO, placebo; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.

Notes: a, concomitant therapy was CSA+MMF+CCS; b, concomitant therapy was TAC+AZA+CCS. All OR were calculated by PenTAG. OR < 1 favours BAS.

The pooled results at six months follow-up did not find any significant difference between BAS and control arms for graft loss (OR=93 favours BAS; 95%CI: 0.29; 2.97, I^2=0%, Tau^2=0).

Figure 9. Graft loss; randomised control trials



Key: BAS, basiliximab; CONTROL, no induction/placebo control arms.
Notes: Tau^2=0.

Summary

In summary, there was no evidence that BAS lowered graft loss when compared to placebo or no induction. This is similar to the conclusions of the previous HTA.[1]

4.3.1.3 Graft function

Both RCTs[70, 72] reported graft function estimated using the Schwartz equation (ml/min/1.73m^2; Table 20). There were no statistically significant differences between BAS and control arms at any data point (between six months and two years). Both RCTs reported 6-months and 2-years follow-up; no SD was reported at two years by Offner et al. 2008[70] , and no SD was reported at six months and two years by Grenda et al. 2006.[72]

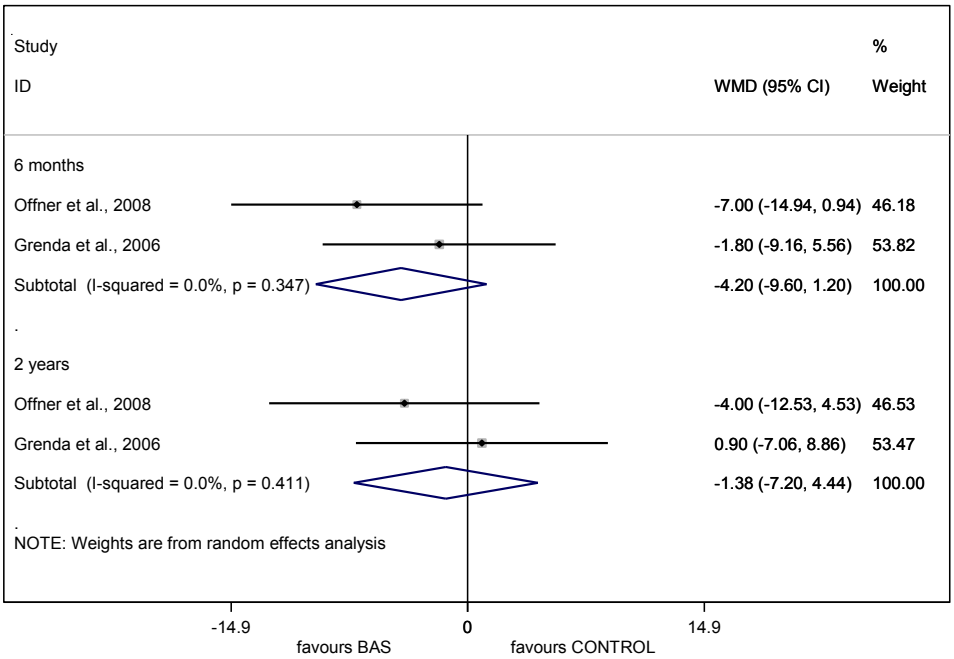
Table 20. Graft function (eGFR); randomised control trials

Study id	Treatment	6 months		1 year		2 years	
		mean (SD)	t-test (p)	mean (SD)	t-test (p)	mean (SD)	t-test (p)
Offner et al. 2008[70a]	**BAS**+ CSA+MMF+CCS	80 (27)	-1.73 (0.08)	79 (23)	-0.88 (0.38)	80 (NR)	-0.92 (0.36)
	PBO+ CSA+MMF+CCS	87 (29)		82 (24)		84 (NR)	
Grenda et al. 2006[72b]	**BAS**+ TAC+AZA+CCS	77.6 (NR)	-0.48 (0.63)	NR	NA	66.7 (NR)	0.22 (0.82)
	NI+ TAC+AZA+CCS	79.4 (NR)		NR		65.8 (NR)	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; NI; no induction; NR,not reported; NA, not applicable;PBO, placebo; CCS, steroids; SD, standard deviation; TAC, tacrolimus.
Notes: a, The number of participants evaluated at two years follow-up was 79 in BAS arm and 65 in PBO arm; b, The number of participants evaluated at two years follow-up was 84 in BAS arm and 80 in NI arm. T-test were calculated by PenTAG, for data-poits with no SD reported a SD of 26 was used. Graft function was estimated using the Schwartz equation (ml/min/1.73m2).

To allow for combining the results at six months and two years follow-up, a SD of 26 ml/min/1.73m^2 was used ("average" SD calculated from SD available at six months and two years follow-up; Figure 10). The pooled results do not suggest any difference for eGFR between BAS and control arms; WMD= -4.20 (favours controls; 95%CI -9.60 to 1.20, I^2= 0%) at six months, and WMD= -1.38 (favours controls; 95%CI -7.20 to 4.44, I^2= 0%) at two years follow-up. Grenda et al. 2006[72] also reported incidences of delayed graft function (DGF). The rate of DGF was not statistically significantly different between the two arms; 11/99, 11% and 5/93, 5% in BAS and NI arms respectively.[72]

Figure 10. Graft function (eGFR); randomised control trials



Key: BAS, basiliximab; CONTROL, no induction/placebo control arms.
Notes: For data-poits with no SD reported a SD of 26 was used. Graft function was estimated using the Schwartz equation (ml/min/1.73m^2).

Summary

In summary, there was no evidence that BAS lowered graft function when compared to placebo or no induction. The child/adolescent RCT evidence identified in the previous HTA review[1] concluded that BAS did not increase serum creatinine levels at one year follow-up when compared to no induction.

4.3.1.4 Acute rejection

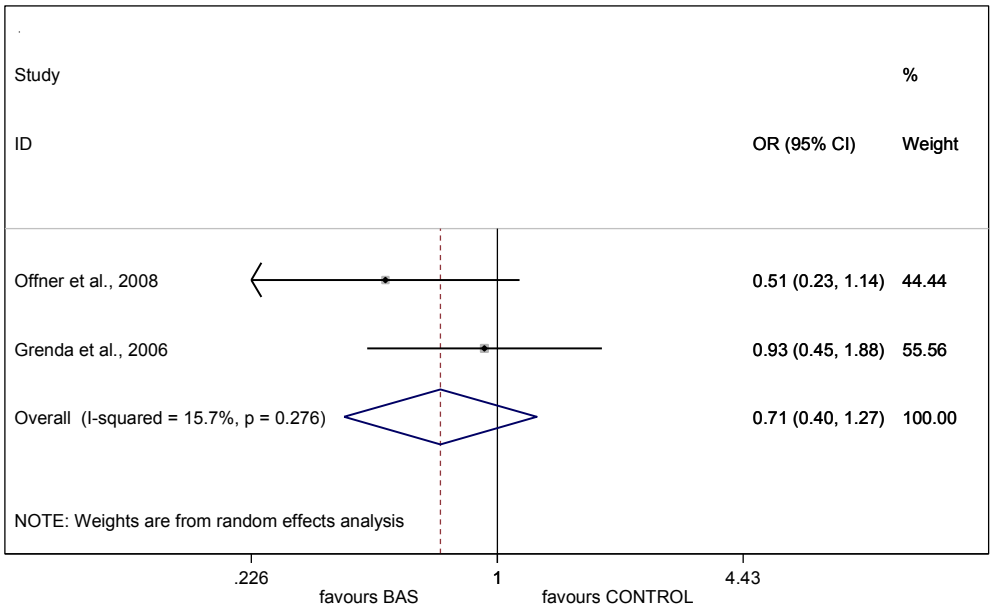
Both RCTs[70, 72] provided data on biopsy proven acute rejection (BPAR) for BAS vs no induction or placebo (Table 21). Grenda et al. 2006[72] reported the longest follow-up data of two years. No evidence of a statistically significant difference between the BAS and the comparators arms was reported for any data point. The pooled results at six months did not find any difference between BAS and control arms for BPAR; OR=0.71 (favours BAS; 95%CI 0.40-1.27, I^2= 15.7%, Tau^2=0.03; Figure 11).

Table 21. Biopsy proven acute rejection; randomised controlled trials

Study id	Treatment	3 months n/N, %	3 months OR (95%CI)	6 months n/N, %	6 months OR (95%CI)	1 year n/N, %	1 year OR (95%CI)	2 years n/N, %	2 years OR (95%CI)
Offner et al. 2008[70]	**BAS**+ CSA+MMF+CCS	6/100, 6%	0.39 (0.14; 1.07)	11/100, 11%	0.51 (0.23; 1.14)	13/100, 13%	0.51 (0.24; 1.08)	NR	NA
	PBO+ CSA+MMF+CCS	13/92, 14%		18/92, 20%		21/92, 23%		NR	
Grenda et al. 2006[72]	**BAS** + TAC+AZA+CCS	NR	NA	19/99, 19%	0.93 (0.46; 1.87)	NR	NA	23/99, 23%	0.74 (0.39; 1.40)
	NI+ TAC+AZA+CCS	NR		19/93, 20%		NR		27/93, 29%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil n, number of events; N, number of participants; CCS, steroids; NR,not reported; NA, not applicable;TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG. OR < 1 favours BAS.

Figure 11. Biopsy proven acute rejection; randomised controlled trials



Key: BAS, basiliximab; CONTROL, no induction/placebo control arms.
Notes: Tau^2=0.03

In addition, Grenda et al. 2006[72] also reported BPAR separately for younger and older age groups (< 12 years and ≥12 years). The incidence of BPAR was lower in the patients <12 years in the no induction arm (4/42; 10%) when compared to the same age group with BAS (6/46; 13%), although this difference was not statistically significant. Conversely, incidences of BPAR were higher for the patients ≥12 years with no induction (15/51; 29%) when compared to the same age group with BAS (13/53; 25%), however again this difference was not statistically significant.

Finally, the data from Offner et al. 2008 of 79 BAS and 65 placebo on study participants (reported in an abstract by Jungraithmayr et al. 2009[69]) found a cumulative AR rate of 33% vs 35% in the BAS and placebo arms respectively at two years, and a cumulative AR rate of 41% vs 45% in the BAS and placebo arms respectively at five years; results were not statistically significant at either data point.[69]

Time to BPAR (Table 22) was only reported by Grenda et al. 2006.[72] The median time to BPAR appears to be similar between the two arms (p-values were not reported in the sudy).[72] Time to first BPAR episode or treatment failure within the first six months post-transplant was the primary efficacy endpoint in Offner et al. 2008.[70] The proportion of children and adolescents (Kaplan-Meier estimates), achieving this efficacy point was 16.7% in the BAS arm and 21.7% in the placebo arm. The difference was not statistically significant; hazard ratio (HR) of 0.72 (favours BAS; 95% CI 0.42 –1.26).

Table 22. Time to biopsy proven acute rejection; randomised controlled trials

Study id	Treatment	Time to AR median [range], days
Grenda et al. 2006[72]	**BAS** + TAC+AZA+CCS	41 [2-176]
	NI+ TAC+AZA+CCS	43 [1-150]

Key: AZA, azathioprine; BAS, basiliximab; CCS, steroids; ; NI, No induction;TAC, tacrolimus.

Severity of BPAR (Table 23) was only reported by Offner et al. 2008.[70] The results indicate more Grade IIA BPAR in the PBO arm compared with the BAS arm; OR= 0.05 (favours BAS; 95% CI 0.003-0.87).

Summary

In summary, there was no evidence that BAS reduced incidences of and time to BPAR when compared to placebo or no induction. One trial[70] reported more severe BPAR (Grade IIA) in PBO compared with BAS. This is similar to the conclusions of the previous HTA.[1]

Table 23. Severity of acute rejection; randomised control trials

	Offner et al. 2008[70]		
	BAS+ CSA+MMF+CCS **n/N, %**	**PBO+** CSA+MMF+CCS **n/N, %**	**OR (95%CI)**
Grade IA	8/100, 8%	9/92, 10%	0.80 (0.30; 2.17)
Grade IB	3/100, 3%	1/92, 1%	2.81 (0.29; 27.56)
Grade IIA	0/100, 0%	8/92, 9%	**0.05** (**0.003; 0.87**)
Grade IIB	0/100, 0%	0/92, 0%	NA
Grade III	0/100, 0%	0/92, 0%	NA

Key: BAS, basiliximab; CSA, ciclosporin; CCS, steroids; MMF, mycophenolate mofetil n, number of events; N, number of participants; NA, Not applicable; PBO, placebo; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG. OR < 1 favours BAS. Evidence suggesting a statistically significant difference between treatments highlighted in bold.

4.3.1.5 Adverse events

Two RCTs[70, 72] provided data on AE for BAS vs no induction or placebo. Offner et al. 2008 reported AE that occurred in at least 10% of the safety population.[70] Grenda et al. 2006 reported AE that occurred in at least 10% in either treatment arm.[72] The AE reported in these trials are summarised in Table 24.

In one trial (Offner et al. 2008)[70] more infections were found with BAS compared with placebo (OR=2.23; favours placebo; 95%CI 1.03 - 4.68). Adverse events summarised in Table 24. In Grenda et al. 2006[72] toxic nephropathy was higher in the BAS arm compared with no induction (14.1% vs 4.3% respectively, p=0.03). Similarly, abdominal pain was higher in the BAS arm compared with no induction (11.1% vs 2.2% respectively, p=0.02).[72]

Grenda et al. 2006[72] also reported changes in glucose metabolism disorders. None of the children and adolescents had a glucose metabolism disorder (described as glucose tolerance decreased, hyperglycaemia or diabetes mellitus using the modified coding symbols for a thesaurus of adverse reaction terms [COSTART] dictionary) at baseline. However, during the study 13 patients (13.1%) in the BAS arm and 10 patients (10.8%) in the no induction arm developed a glucose metabolism disorder within the first six months. One new case of impaired glucose metabolism was noted at one year, this new case resolved at two years.

Summary

In summary, more infections were found with BAS compared with placebo (OR=2.23, favours placebo; 95%CI 1.03 - 4.68).[70] In addition, Grenda et al. 2006 found that toxic nephropathy and abdominal pain were higher in the BAS arm compared with no induction (p=0.03 and p=0.02 respectively).[72] The previous HTA only reported post-transplant diabetes mellitus in one study (Grenda et a. 2004[87]), the rest of the data was confidential and was, therefore, omitted from the report.

Table 24. Adverse events; induction regimens; randomised control trials

AE n/N, %	Follow-up	Offner et al. 2008[70] [a]			Grenda et al. 2006[72] [b]		
		BAS n/N, %	PBO n/N, %	OR (95%CI)	BAS n/N, %	NI n/N, %	OR (95%CI)
Any infections	**1 year**	104/109, 95%	84/93, 90%	**2.23 (1.03; 4.68)**	NR	NR	NA
	1-2 years	13/79, 16%	12/65, 12%	0.87 (0.37; 2.06)	NR	NR	NA
Serious infections	**1 year**	58/109, 53%	45/93, 48%	1.21 (0.72; 2.05)	NR	NR	NA
	2 years	NR	NR	NA	NR	NR	NA
Urinary tract infection	**6 months**	NR	NR	NA	19/99, 19%	26/93, 28%	0.61 (0.31; 1.20)
	1 year	38/109, 29%	21/93, 23%	1.84 (0.99, 3.40)	NR	NR	NA
Bacterial infections	**6 months**	NR	NR	NA	32/99, 32%	30/93, 32%	1.00 (0.55; 1.81)
	2 years	NR	NR	NA	47/99, 45%	45/93, 48%	0.96 (0.56; 1.65)
Viral infections	**6 months**	NR	NR	NA	15/99, 15%	15/93, 16%	0.93 (0.43; 2.02)
	2 years	NR	NR	NA	26/99, 26%	24/93, 26%	1.02 (0.54; 1.93)
CMV infections	**6 months**	NR	NR	NA	7/99, 7%	2/93, 2%	3.46 (0.70; 17.11)
	1 year	14/109, 13%	8/93, 9%	1.57 (0.63; 3.92)	NR	NR	NA
EBV infections	**1 year**	10/109, 9%	11/93, 12%	0.75 (0.30; 1.86)	NR	NR	NA
Solid tumour	**6 months**	NR	NR	NA	0/99, 0%	0/93, 0%	NA
	1 year	1/109, 1%	0/93, 0%	2.58 (0.10; 64.19)	NR	NR	NA
PTLD	**6 months**	NR	NR	NA	0/99, 0%	2/93, 2%	0.18 (0.01; 3.88)
	1 year	2/109, 2%	5/93, 5%	0.33 (0.06; 1.74)	NR	NR	NA
	2 years	NR	NR	NA	1/99, 1%	2/93, 2%	0.46 (0.04; 5.21)
Hypertension	**6 months**	NR	NR	NA	34/99, 34%	36/93, 39%	0.83 (0.47; 1.47)
Any AE	**6 months**	NR	NR	NA	91/99, 92%	84/93, 90%	1.22 (0.58; 2.57)
	1 year	108/109, 99%	92/93, 99%	1.17 (0.16, 8.59)	NR	NR	NA

Key: BAS, basiliximab; PBO, Placebo; NI, no induction; AE, adverse events; CMV, cytomegalovirus; EBV, Epstein–Barr virus; n, number of events; N, number of participants; NR, not reported; NA, Not available; PTLD, post-transplant lymphoproliferative disease; OR, odds ratio; CI, confidence intervals.

Notes: a, AE reported if incidence was ≥10% in safety population; b, AE reported if incidence was ≥10% in either treatment arm; two years follow-up data reported in Webb et al. 2009.[73] All OR were calculated by PenTAG.

4.3.2 Maintenance therapy

One RCT[74]; and four non-RCTs[77, 79, 80, 93] of maintenance therapy in children and adolescents were included in the review; RCT evidence evaluating **TAC**, and non-RCT evidence on the use of **TAC** and **MMF** was identified.

The population characteristics from the one RCT of maintenance treatment identified in the review are summarised in Table 16. **Trompeter et al. 2002**[74] compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS. No RCTs evaluated **TAC-PR**, **MMF**, **MPS**, **EVL**, **SRL**, and **BEL** in children and adolescents.

The population characteristics from the four non-RCT of maintenance treatment identified in the review[77, 79, 80, 93] are summarised in Table 17. **Garcia et al. 2002**[79] compared the use of BAS+**TAC**+**AZA**+CC and BAS+**CSA**+**MMF**+CCS in a retrospective cohort study. **Antoniadis et al. 1998**[80] compared the use of CSA+**MMF**+CCS with CSA+**AZA**+CCS in a non-randomised controlled trial. **Benfield et al. 1999**[93] reported retrospective analyses of a randomised, multi-centered trial of OKT3 versus CSA induction therapy with two types of maintenance therapies; only the comparison of CSA+**MMF**+CCS with CSA+AZA+CCS was included in this review. Finally, **Staskewitz et al. 2001**[77] compared the use of CSA+**MMF**+CCS and CSA+AZA+CCS in a historically controlled study. No non-randomised evidence was identified regarding the use of **TAC-PR**, **MPS**, **EVL**, **SRL**, and **BEL** in the child/adolescent population.

4.3.2.1 Mortality

Randomised controlled trials

Trompeter et al. 2002 compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS.[74] The trial reported similar survival rates in both arms, which were not significantly different at six months, one year, two years or four years (Table 25).

Table 25. Mortality; randomised control trials

	Trompeter et al. 2002[74]		
Follow-up	**TAC+AZA+CCS n/N, %**	**CSA+AZA+CCS n/N, %**	**OR (95%CI)**
6 months	3/103, 3%	3/93, 3%	0.9 (0.18; 4.58)
1 year	3/103, 3%	3/93, 3%	0.9 (0.18; 4.58)
2 years	3/103, 3%	4/93, 4%	0.67 (0.15; 3.07)
4 years	5/103, 5%	4/93, 4%	1.14 (0.30; 4.36)

Key: AZA, azathioprine; CSA, ciclosporin; n, number of events; N, number of participants; NI; no induction; NR,not reported; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG.

Non-randomised controlled trials

Three non-RCTs[77, 79, 80] provided data on mortality (Table 26). Two of these compared **MMF** with **AZA** (Antoniadis et al. 1998 and Staskewitz et al. 2001)[77, 80] whilst the remaining study compared **TAC**+**AZA** and **CSA**+**MMF** (Garcia et al. 2002).[79] Staskewitz et al. 2001[77] reported long-term follow-up of up to five years, however no futher deaths were recorded in either arm. No statistically significant difference in child/adolescent survival between MMF and AZA, and between TAC+AZA and CSA+MMF, was reported.

Table 26. Mortality; non-randomised studies

		3 months		6 months		1 year	
Study id	**Treatment**	**n/N, %**	**OR (95%CI)**	**n/N, %**	**OR (95%CI)**	**n/N, %**	**OR (95%CI)**
Garcia et al. 2002[79]	BAS+**TAC**+**AZA**+CCS	0/12, 0%	NA	NR	NA	NR	NA
	BAS+**CSA**+**MMF**+CCS	0/12, 0%		NR		NR	
Antoniadis et al. 1998[80]	CSA+**MMF**+CCS	NR	NA	NR	NA	0/7, 0%	NA
	CSA+**AZA**+CCS	NR		NR		0/7, 0%	
Staskewitz et al. 2001[77]	CSA+**MMF**+CCS	NR	NA	0/86, 0%	0.20 (0.008; 5.14)	0/86, 0%	0.08 (0.004; 1.67)
	CSA+**AZA**+CCS	NR		1/54, 2%		3/54, 6%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; n, number of events; N, number of participants; NI; no induction; NR,not reported;; NA, Not available; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG.

Summary

In summary, no difference in survival was found between TAC and CSA from the child/adolescent RCT. In addition, no difference was found between TAC and CSA, and between MMF and AZA, in the child/adolescent non-RCT evidence. This is similar to the conclusions of the previous HTA.[1]

4.3.2.2 Graft loss

Randomised controlled trials

Trompeter et al. 2002 compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS.[74] Graft loss appeared to be higher in the CSA arm compared with the TAC arm, especially at the longer follow-up (two-four years), but the difference was not statistically significant (Table 27).

Table 27. Graft loss; randomised control trials

	Trompeter et al. 2002[74]		
Follow-up	**TAC+AZA+CCS n/N, %**	**CsA+AZA+CCS n/N, %**	**OR (95%CI)**
6 months	6/103, 6%	13/93, 14%	0.38 (0.14; 1.05)
1 year	8/103, 8%	15/93, 16%	0.44 (0.18; 1.09)
2 years	8/103, 8%	16/93, 17%	0.41 (0.16; 1.00)
4 years	9/103, 9%	17/93, 18%	0.43 (0.18; 1.01)

Key: AZA, azathioprine; CSA, ciclosporin; n, number of events; N, number of participants; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG.

Non-randomised controlled trials

Three non-RCTs[77, 79, 80] provided data on graft loss (Table 28). Two studies compared **MMF** with **AZA** (Antoniadis et al. 1998 and Staskewitz et al. 2001)[77, 80] whilst the remaining study compared **TAC**+**AZA** and **CSA**+**MMF** (Garcia et al. 2002).[79] Staskewitz et al. 2001[77] found better graft survival in MMF compared with AZA in up to five years follow-up, while Antoniadis et al. 1998[80] did not find statistically significant difference in graft loss between MMF and AZA. No statistically significant difference in graft loss between TAC+AZA and CSA+MMF regimens was reported.[79]

Table 28. Graft loss; non-randomised studies

Study id	Treatment	3 months		1 year		2 years		3 years		4 years		5 years	
		n/N, %	OR (95%CI)	n/N, %	OR (95%CI)	n/N, %	OR (95%CI)	n/N, %	OR (95%CI)	n/N, %	OR (95%CI)	n/N, %	OR (95%CI)
Garcia et al. 2002[79]	BAS + **TAC**+**AZA** +CCS	0/12, 0%	0.30 (0.01; 8.30)	NR	NA	NR	NA	NR	NA	NR	NA	NR	NA
	BAS+ **CSA**+**MMF** +CCS	1/12, 8%		NR		NR		NR		NR		NR	
Antoniadis et al. 1998[80]	CSA+**MMF** +CCS	NR	NA	0/7, 0%	NA	NR	NA	NR	NA	NR	NA	NR	NA
	CSA+**AZA** +CCS	NR		0/7, 0%		NR		NR		NR		NR	
Staskewitz et al. 2001[77]	CSA+**MMF** +CCS	NR	NA	2/86, 2%	**0.14 (0.03; 0.68)**	4/86, 5%	**0.24 (0.07; 0.84)**	4/86, 5%	**0.15 (0.05; 0.51)**	7/86, 8%	**0.25 (0.09; 0.69)**	8/86, 9%	**0.24 (0.09; 0.63)**
	CSA+**AZA** +CCS	NR		8/54, 15%		9/54, 17%		13/54, 24%		14/54, 26%		16/54, 30%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; n, number of events; N, number of participants; NR,not reported; NA, not available; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG.

Summary

In summary, no statistically significant difference was found between TAC and CSA for graft loss. However, the RCT child/adolescent evidence identified in the previous HTA review[1] concluded that TAC lowered graft loss at two and four years follow-up. This discrepancy in result is due to the fact that we have excluded graft loss due to death from our analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related, just as mortality is to overall survival. It should be noted that after the removal of graft loss due to death from the analyses the evidence from Trompeter et al. 2002[74] suggested borderline non-significantly lower graft loss inTAC compared with CSA (OR=0.41, 95%CI: 0.16; 1.00, and OR=0.43, 95%CI: 0.18; 1.01 at two and four years follow-up respectively). In addition, the current review and the previous HTA[1] found better graft survival in MMF compared with AZA (up to five years follow-up) in one non-RCT.[77]

4.3.2.3 Graft function

Randomised controlled trials

Trompeter et al. 2002 compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS.[74] and reported graft function estimated using the Schwartz equation (ml/min/1.73m^2). Significantly higher graft function in the TAC arm compared with the AZA arm was reported (Table 29). No data on delayed graft function were reported.[74]

Table 29. Graft function (eGFR); randomised control trials

Follow-up	Trompeter et al. 2002[74]		
	TAC+AZA+CCS mean (SD), N	CSA+AZA+CCS mean (SD), N	t-test (p)
6 months	65.6 (19.9), 91	61.2 (15.8), 86	1.62 (0.11)
1 year[a]	64.9 (20.7), 84	57.8 (21.9), 77	**2.11 (0.04)**
2 years	64.9 (19.8), 71	51.7 (20.3), 66	**3.85 (<0.01)**
3 years	66.7 (26.4), 81	53.0 (23.3), 55	**3.11 (<0.01)**
4 years	71.5 (22.9), 51	53.0 (21.6), 44	**4.03 (<0.01)**

Key: AZA, azathioprine; CSA, ciclosporin; CCS, steroids; TAC, tacrolimus; SD, standard deviation; N Participant number.
Notes: a, N values reported in Trompeter et al. 2002 and Filler et al. 2005 differed; values from Filler et al. 2005 were used. T-tests were calculated by PenTAG. Evidence suggesting a statistically significant difference between treatments highlighted in bold. Graft function estimated using the Schwartz equation (ml/min/1.73m2).

Non-randomised controlled trials

Only one non-RCT provided data on graft function. Garcia et al. 2002[94] compared **TAC**+**AZA** and **CSA**+**MMF** and reported graft function at three months follow-up (Table 30). There were no significant differences between the arms for graft function (eGFR; creatinine clearance (mL/min)). Garcia et al. 2002[94] also reported incidences of DGF. The same rate of delayed graft function was reported in the two arms (1/12, 8% and 1/12, 8% respectively).[79]

Table 30. Graft function (eGFR); non-randomised studies

Study id	Treatment	3 months	
		Mean (SD)	t-test (p)
Garcia et al. 2002[94]	**BAS +TAC+AZA+CCS**	71 (23)	-1.28 (0.21)
	BAS+CSA+MMF+CCS	82 (19)	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; CCS, steroids; TAC, tacrolimus; SD, Standard Deviation
Notes: T-tests were calculated by PenTAG; graft function was estimated by measuring creatinine clearance (mL/min).

Summary

In summary, lower graft function was associated with TAC compared with CSA in the child/adolescent RCT. This is similar to the conclusions of the previous HTA.[1] In addition, no difference in graft function between TAC+AZA and CSA+MMF regimens was reported in the one non-RCT.[79] However, the the previous HTA included a non-RCT by Neu et al. 2003 which found significantly better graft function at one and two year follow-up (p<0.01).[95]

4.3.2.4 Acute rejection

Randomised controlled trials

Trompeter et al. 2002 compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS, reporting statistically significantly higher BPAR at six months follow-up, and AR (which was not biopsy proven) at six months and one year follow-up in the CSA arm compared with the TAC arm (Table 31).[74] In addition, two and four years follow-up data are available for Trompeter et al. 2002[74] in Filler et al. 2005.[76] However, these analyses do not take into account those who were lost to follow-up and those who died. In the second year of the trial, seven of 77 patients in the TAC group and nine of 71 patients in the CSA group experienced AR (p = 0.6041, Fisher's exact test).[76] In the third year, two of 70 patients in the TAC group and six of 57 patients in the CSA group experienced AR (p =0.1454, Fisher's exact test).[76] Finally, in the fourth year, two of 57 patients in the TAC group and six of 42 patients in the CSA group experienced AR (p = 0.1359, Fisher's exact test).[76] Rejection episodes frequently occurred in the same patients that experienced AR previously. Whilst overall treatment group differences were maintained after the first year, the annual differences in AR were not statistically significant for years 2, 3, and 4.[76] Time to and severity of acute rejection were not reported in Trompeter et al. 2002.[74]

Table 31. Acute rejection; randomised control trials

Study id			6 months		1 year	
		Treatment	n/N, %	OR (95%CI)	n/N, %	OR (95%CI)
Trompeter et al. 2002[74]	BPAR	**TAC**+AZA+CCS	17/94, 18%	**0.29 (0.15; 0.57)**	NR	NA
		CSA+AZA+CCS	37/86, 43%		NR	
	AR	**TAC**+AZA+CCS	38/103, 37%	**0.40 (0.23; 0.71)**	42/103, 41%	**0.43 (0.25; 0.76)**
		CSA+AZA+CCS	55/93, 59%		57/93, 62.3%	

Key: AZA, azathioprine; CSA, ciclosporin; n, number of events; N, number of participants NR,not reported; NA, not available, CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals. BPAR, biopsy proven acute rejection; AR, acute rejection

Notes: a, 94 TAC and 86 CSA participants had renal biopsies; 13 out of 18 centres reported biopsy findings, in addition biopsies were not mandatory in case of clinically suspected AR; b, one year follow-up reported in Trompeter et al. 2002: between months. six and 12, four TAC patients and two CSA patients experienced a first acute rejection. Concomitant treatments in all patients were CCS. All OR were calculated by PenTAG. Evidence suggesting a statistically significant difference between treatments highlighted in bold.

Non-randomised controlled trials

Four non-RCTs[77, 79-81] provided data on BPAR (Table 32). Three of these studies compared **MMF** with **AZA** (Antoniadis et al. 1998, Benfield et al. 1999 and Staskewitz et al. 2001)[77, 80, 81] whilst the remaining study compared **TAC**+**AZA** and **CSA**+**MMF** (Garcia et al. 2002).[79] No

statistically significant difference in BPAR was found between the MMF arm and AZA arms, and between TAC+AZA and CSA+MMF.

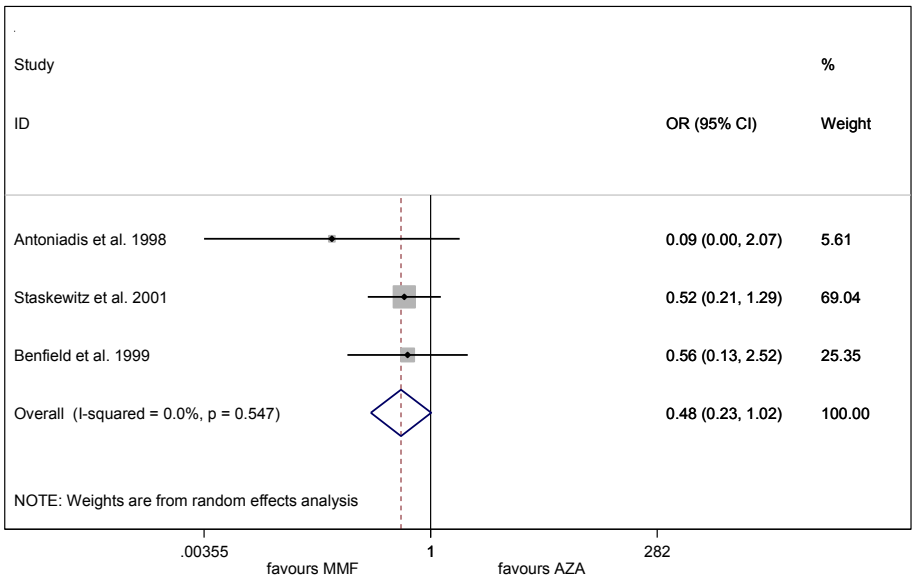
Table 32. Biopsy proven acute rejection; non-randomised studies

Study id	Treatment	3 months n/N, %	3 months OR (95%CI)	6 months n/N, %	6 months OR (95%CI)
Garcia et al. 2002[79]	BAS +**TAC**+**AZA**+CCS	1/12, 8%	0.45 (0.04; 5.78)	NR	NA
	BAS+**CSA**+**MMF**+CCS	2/12, 17%		NR	
Antoniadis et al. 1998[80]	CSA+**MMF**+CCS	NR	NA	0/7, 0%	0.08 (0.003; 1.94)
	CSA+**AZA**+CCS	NR		3/7, 43%	
Staskewitz et al. 2001[77]	CSA+**MMF**+CCS	NR	NA	10/65, 15%	0.52 (0.21; 1.29)
	CSA+**AZA**+CCS	NR		14/54, 26%	
Benfield et al. 1999[81]	CSA+**MMF**+CCS	NR	NA	4/17, 24%a	0.56 (0.13; 2.47)
	CSA+**AZA**+CCS	NR		6/17, 35%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; MMF, mycophenolate mofetil; n, number of events; N, number of participants NR,not reported; NA, not available; CCS, steroids; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: a, reported in text as 4/17, 23%. All OR were calculated by PenTAG.

The pooled results at six months follow-up suggested borderline non-significantly lower BPAR in MMF compared with AZA (OR=0.48, 95%CI: 0.23; 1.02, I^2=0%, Tau^2=0; Figure 12).

Figure 12. Biopsy proven acute rejection; non-randomised studies



Key: AZA, azathioprine; MMF, mycophenolate mofetil.
Notes: Tau^2=0.

In addition, Garcia et al. 2002[94] reported the severity of acute rejection (Table 33). There were no statistically significant differences between TAC+AZA and CSA+MMF for severity of BPAR. No study reported time to BPAR.

Table 33. Severity of acute rejection; non-randomised studies

Study id	Treatment	3 months; n/N, %					
		Banff 1	OR (95%CI)	Banff 2	OR (95%CI)	Banff 3	OR (95%CI)
Garcia et al. 2002[94]	BAS + **TAC**+**AZA**+CCS	0/12, 0%	0.17 (0.01;3.87)	0/12, 0%	NA	1/12, 8%	3.29 (0.12; 89.20)
	BAS+ **CSA**+**MMF**+CCS	2/12, 17%		0/12, 0%		0/12, 0%	

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; CCS, steroids; MMF, mycophenolate mofetil; n, number of events; N, number of participants; NA, not available; TAC, tacrolimus; OR, odds ratio; CI, confidence intervals.
Notes: All OR were calculated by PenTAG. No Banff2 AR were reported, assumed 0 and 0 events of Banff 2 in each arm.

Summary

In summary, higher rates of BPAR was found in CSA compared with TAC in the one included child/adolescent RCT with six months data.[74] The RCT child/adolescent evidence identified in the previous HTA review[1] also concluded more BPAR in the CSA arm compared with the TAC.[74] However, the limited longer follow-up data from this study did not find statistically significant differences in AR between TAC and CSA at two and four years follow-up.[74] In addition, no statistically significant difference in BPAR was found between the MMF arm and AZA arms, and between TAC+AZA and CSA+MMF, and in severity of BPAR between TAC+AZA and CSA+MMF in the non-randomised evidence. The pooled non-RCT child/adolescent evidence identified in the previous HTA review suggested less BPAR with MMF compared with AZA (RR= 0.39 favours MMF; 95%CI 0.19 to 0.79). Similarly, our analyses suggested borderline non-significantly lower BPAR in MMF compared with AZA at six months follow-up (OR=0.48, 95%CI: 0.23; 1.02, I^2=0%, Tau^2=0).

4.3.2.5 Adverse events

Randomised controlled trials

One child/adolescent RCT provided data on AE for maintenance treatments (Trompeter et al. 2002).[74] This study compared the use of **TAC**+AZA+CCS and **CSA**+AZA+CCS and reported no statistically significant differences between TAC and CSA for a range of AE

(Table 34). In addition, the incidence of NODAT (defined as insulin use for more than 30 consecutive days in previously non-diabetic patients) was not significantly different between TAC and CSA; NODAT was reported for 3/100 children and adolescents (3.0%) in the TAC group and 2/93 children and adolescents (2.2%) in the CSA group.[74] The proportion of children and adolescents withdrawing due to adverse events was 10% (10/103) in TAC and 15% (14/93) in CSA arms (OR=0.61; favours TAC; 95% CI 0.25 to 1.44).

Table 34. Adverse events, maintenance studies; randomised control trials

AE n/N, %			Trompeter et al. 2002[74]a
	TAC+AZA+CCS	CsA+AZA+CCS	OR (95%CI)
Any infections	71/103, 69%	60/93, 65%	0.88 (0.45; 1.67)
Urinary tract infection	30/103, 30%	31/93, 33%	0.82 (0.45; 1.49)
Bacterial infections	43/103, 42%	38/93, 41%	1.04 (0.60; 1.80)
Viral infections	23/103, 22%	23/93, 25%	0.88 (0.45; 1.69)
PTLD	1/103, 1%	2/93, 2%	0.45 (0.04; 5.01)
Solid tumour	1/103, 1%	0/93, 0%	2.73 (0.11; 67.99)
Hypertension	71/103, 69%	57/93, 61%	1.40 (0.83; 2.36)
Any AE	98/103, 95%	93/93, 100%	0.10 (0.01; 1.57)

Key: AE, adverse events; n, number of events; N, number of participants; PTLD, post-transplant lymphoproliferative disease ; OR, odds ratio; CI, confidence intervals; AZA, azathioprine; CSA, ciclosporin; CCS, steroids; TAC, tacrolimus
Notes: All OR were calculated by PenTAG.

Non-randomised controlled trials

Three non-RCTs[77, 79, 80] provided data on AE (Table 35). Two of these studies compared MMF with AZA (Antoniadis et al. 1998, and Staskewitz et al. 2001),[77, 80] whilst the remaining study compared TAC+AZA and CSA+MMF (Garcia et al. 2002).[79] Staskewitz et al. 2001only reported AE for the MMF group and not for the historic control AZA group.[77] No statistically significant between-group differences in AE were found (Table 35) in the non-RCTs that did compare treatment groups.

In addition, Staskewitz et al. 2001 reported AE up to five year follow-up for the MMF group (Appendix 6; Table 138).[78, 82]

Summary

The RCT results suggested no statistically significant differences between TAC and CSA for a range of AE (any infections, urinary tract infections, bacterial infections, viral infections,

PTLD, solid tumour, hypertension, any AE, and NODAT).[74] This is similar to the conclusions of the previous HTA.[1] In addition, no statistically significant differences between MMF and AZA for urinary tract infection, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhea were identified in the non-randomised evidence.[80] Similarly, no statistically significant differences between TAC+AZA and CSA+MMF in CMV infections and NODAT were identified in the non-randomised evidence.[79] In contrast, the previous HTA found significantly more CMV infection in TAC+AZA compared with CSA+MMF (4/12 vs 0/12 respectively, p=0.04 in the same non-RCT.[79] This discrepancy in results is due to different statistically analyses used; the current review calculated OR (OR=13.80, favours CSA+MMF; 95% CI 0.67; 286.10).This inconsistency highlights the small size of this study (N=24) and the uncertainties of its results.

Table 35. Adverse events, maintenance studies; non- randomised studies

AE n/N, %	Follow-up	Garcia et al. 2002[79]			Antoniadis et al. 1998[80]			Staskewitz et al 2001[77]
		TAC+ AZA	CSA+ MMF	OR (95%CI)	MMF	AZA	OR (95%CI)	MMF
Urinary tract infection	3 months	NR	NR	NA	NR	NR	NA	13/65 (20%)
	6 months	NR	NR	NA	2/7 (28%)	5/7 (71%)	0.16 (0.02; 1.55)	14/65 (22%)
CMV infections	3 months	4/12 (33.3%)	0/12 (0%)	13.80 (0.67; 286.1)	NR	NR	NA	9/65 (14%)
	6 months	NR	NR	NA	3/7 (43%)	5/7 (71%)	0.30 (0.04; 2.51)	10/65 (15%)
Respiratory infections	3 months	NR	NR	NA	NR	NR	NA	15/65 (23%)
	6 months	NR	NR	NA	1/7 (14%)	3/7 (42%)	0.22 (0.02; 2.92)	20/65 (31%)
Herpes simplex	3 months	NR	NR	NA	NR	NR	NA	6/65 (9%)
	6 months	NR	NR	NA	2/7 (28%)	1/7 (14%)	2.40 (0.17; 33.52)	8/65 (12%)
Oral thrush	3 months	NR	NR	NA	NR	NR	NA	2/65 (3%)
	6 months	NR	NR	NA	1/7 (14%)	1/7 (14%)	NA	2/65 (3%)
Diarhea	3 months	NR	NR	NA	NR	NR	NA	11/65 (17%)
	6 months	NR	NR	NA	1/7 (14%)	0/7 (0%)	3.55 (0.12; 103.51)	13/65 (20%)
Abdominal pain	3 months	NR	NR	NA	NR	NR	NA	14/65 (22%)
	6 months	NR	NR	NA	NR	NR	NA	16/65 (25%)
NODAT	3 months	1/12 (8.3%)	0/12 (0%)	3.29 (0.12; 89.20)	NR	NR	NA	NR

Key: AE, adverse events; CMV, cytomegalovirus; ; n, number of events; N, number of participants; NR, not reported; NA, not available; OR, odds ratio; CI, confidence intervals, AZA, azathioprine; CSA, ciclosporin; CCS, steroids; TAC, tacrolimus MMF, mycophenolate mofetil.

Note: Staskewitz et al. 2001did not report any AE for the historic control AZA group; only AE for MMF group were reported. All OR were calculated by PenTAG.

4.4 Comparing children and adolescents, and adult evidence

The results from the current review are contrasted with those from the parallel HTA 09/46/01 appraisal "Immunosuppressive therapy for kidney transplantation in adults".

4.4.1 Induction therapy

The current review identified two RCTs[70, 72] evaluating BAS induction therapy in children and adolescents. **Offner et al. 2008**[70] compared basiliximab induction therapy with placebo. **Grenda et al. 2006**[72] compared basiliximab induction therapy with no induction.

4.4.1.1 Mortality

Adult RCT evidence (09/46/01)

In the adult evidence identified by the parallel HTA, three RCTs comparing BAS and no induction reported mortality; Albano et al. 2013,Kyllönen et al. 2007 and Sheashaa et al. 2003.[96-98] In addition, four studies compared BAS with placebo; Kahan et al.1999, Nashan et al. 1997, Ponticelli et al. 2001, and Lawen et al. 2003.[99-102] Six studies reported results at one year follow-up.[97-102] The pooled results at one year with four studies (Kyllönen et al. 2007, Kahan et al.1999, Nashan et al. 1997, and Ponticelli et al. 2001)[97, 99-101] suggest no difference between BAS and placebo or no induction: OR=0.95 (favours BAS; 95%CI 0.49-1.87, I^2=0.7%, Tau^2=0.004); two studies (Sheashaa et al. 2003, Lawen et al. 2003)[98, 102] reported zero events in both arms.

Summary

In summary, there was no evidence that BAS improved survival when compared to placebo or no induction in the adult evidence. The child/adolescent RCT evidence is consistent with the adult RCT evidence identified in the parallel HTA.

4.4.1.2 Graft loss

Adult RCT evidence (09/46/01)

In the adult evidence identified by the parallel HTA, three studies comparing BAS and no induction reported graft loss (Albano et al. 2013,Kyllönen et al. 2007 and Sheashaa et al.

2003).[96-98] In addition, four studies compared BAS with placebo; Kahan et al.1999, Nashan et al. 1997, Ponticelli et al. 2001, and Lawen et al. 2003.[99-102] Six studies reported results at one year follow-up.[97-102] The pooled results at one year with five studies (Kyllönen et al. 2007, Kahan et al.1999, Nashan et al. 1997, Lawen et al. 2003, and Ponticelli et al. 2001)[97, 99-102] suggest no difference between BAS and placebo or no induction: OR=0.82 (favours BAS; 95%CI 0.56-1.21, I^2=0.0%, Tau^2=0.0); one study (Sheashaa et al. 2003) [98] reported zero events in both arms.

Summary

In summary, there was no evidence that BAS lowered graft loss when compared to placebo or no induction in the adult evidence. The child/adolescent RCT evidence is consistent with the adult RCT evidence identified in the parallel HTA.

4.4.1.3 Graft function

Adult RCT evidence (09/46/01)

In the adult evidence identified by the parallel HTA, graft function was reported by four studies at one year comparing BAS with placebo; Kahan et al.1999, Nashan et al. 1997, Ponticelli et al. 2001, and Sheashaa et al. 2003.[98-101]; the pooled analysis for graft function implied no beneficial effect of BAS compared to controls: WMD = 1.93 (favours BAS; 95% CI -0.97 to 4.83, I^2=23.9%). One study Sheashaa et al 2003[98] comparing BAS and no induction reported data on graft function from one year to ten years. It was summarised that up to seven years, graft function appeared to be slightly better for participants who received BAS, however, the effect reduced over time and the reverse was true at ten years. Furthermore, the difference across all time points was not statistically significant.[98]

Summary

In summary, there was no significant evidence that BAS increased graft function when compared to placebo or no induction in the adult evidence. The child/adolescent RCT evidence is consistent with the adult RCT evidence identified in the parallel HTA.

4.4.1.4 Acute rejection

Adult RCT evidence (09/46/01)

In the adult evidence identified by the parallel HTA, three studies comparing BAS and no induction reported acute rejection (Albano et al. 2013, Kyllönen et al. 2007 and Sheashaa et al. 2003)[96-98] and, four studies compared BAS with placebo (Kahan et al.1999, Nashan et al. 1997, Ponticelli et al. 2001, and Lawen et al. 2003).[99-102] The pooled results at one year with five studies[97, 99-102] suggest less BPAR in BAS compared with placebo or no induction (OR=0.53; favours BAS; 95%CI 0.40-0.70, I^2=0.0%, Tau^2=0.0). Furthermore, Sheashaa et al. 2003 reported BPAR at 10 years, where BAS continues to show a beneficial effect compared with no induction (OR=0.41, 95% CI 0.18 to 0.96).[98]

In addition, two studies comparing BAS and no induction (Albano et al. 2013, and Sheashaa et al. 2003),[96, 98] and four studies comparing BAS with placebo (Kahan et al.1999, Nashan et al. 1997, Ponticelli et al. 2001, and Lawen et al. 2003).[99-102] reported severity of BPAR. At six months, the pooled results from four studies[99-102] suggest no difference between BAS and placebo or no induction for all three Banff classifications (Table 36).

Table 36. Adult RCT evidence; Severity of acute rejection

Included studies	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Nashan et al. 1997, Lawen et al. 2003, Albano et al. 2013 and Ponticelli et al. 2001	1	3	0.89	0.59 – 1.35	10.80%	0.02
	2		0.64	0.32 – 1.28	65.30%	0.3
	3		0.56	0.28 – 1.13	0.00%	0

Key: OR, odds ratio; CI, confidence intervals.
Notes: OR < 1 favours BAS. Evidence suggesting a statistically significant difference between treatments highlighted in bold.

Summary

In summary, the adult evidence suggested less BPAR in BAS compared with placebo or no induction, however no diference in severity of BPAR was found. In contrast, the one child/adolescent RCT[70] reported more severe BPAR (Grade IIA) in placebo compared with BAS. In addition, no evidence that BAS reduced incidences of and time to BPAR when compared to placebo or no induction was found in the child/adolescent RCTs.[70, 72]

4.4.1.5 Adverse events

Adult RCT evidence (09/46/01)

Five adult RCTs comparing BAS with placebo or no induction identified by the parallel HTA reported AE at one year follow-up (Bingyi et al. 2003, Kahan et al.1999, Lawen et al. 2003, Nashan et al.1997, and Kyllönen at al. 2007).[97, 99, 100, 102, 103] No significant differences in NODAT, PTLD, malignancy, infections and CMV infections were found between basiliximab and placebo or no induction arms (Table 37).

Table 37. Adults RCTs; pooled results at one year follow-up

AE	Studies	OR	95% CI	I^2	Tau^2
NODAT	Kyllönen at al. 2007	3.79	0.43; 33.64	NA	NA
Malignancy	Kahan et al.1999 Kyllönen at al. 2007 Nashan et al.1997	0.62	0.22; 1.76	0%	0
PTLD	Nashan et al.1997	0.98	0.06; 15.77	NA	NA
Infections	Kahan et al.1999 Nashan et al.1997 Lawen et al. 2003	0.98	0.80; 1.20	0%	0
CMV	Kahan et al.1999 Kyllönen at al. 2007 Nashan et al.1997 Lawen et al. 2003	0.8	0.56; 1.13	0%	0

Key: AE, adverse events; CMV, cytomegalovirus; NA, not applicable; NODAT, new onset diabetes; PTLD, post-transplant lymphoproliferative disease; OR, odds ratio; CI, confidence intervals.

Summary

In summary, the adult RCT evidence identified in the parallel HTA did not find any significant differences in NODAT, PTLD, malignancy, infections and CMV infections. Similarly, BAS did not appear to influence the incidences of adverse events when compared to placebo or no induction.

4.4.2 Maintenance therapy

The current review identified one RCT[74] and four non-RCT[77, 79, 80, 93] evaluating maintenance therapy in children and adolescents. Trompeter et al. 2002[74] compared the use of **TAC** and **CSA**. Garcia et al. 2002[79] compared the use of **TAC**+**AZA** and **CSA**+**MMF**. Antoniadis et al. 1998, Benfield et al. 1999 and Staskewitz et al. 2001[77, 80, 93] compared the use of **MMF** and **AZA**.

4.4.2.1 Mortality

Parallel HTA adult RCT evidence (09/46/01)

Ten adult RCTs comparing TAC with CSA identified by the parallel HTA reported mortality (Schleibner et al. 1995, Margreiter et al. 2002, Charpentier et al. 2003 , Laskow et al.1996, Mayer et al. 1997, Jarzembowski et al. 2005, Campos et al. 2002, Waller et al. 2002, Hardinger et al. 2005, Weimer et al. 2006).[104-113] The pooled results at one year with eight studies [105-110, 112, 113] found no statistically significant difference between TAC and CSA (OR=1.51; favours CSA; 95% CI 0.75 to 3.06, I^2=14.8%). One study (Mayer et al. 1997)[106] reported mortality up to five years, however, the results are consistent with earlier time points and indicated no statistically significant difference between arms (OR 1.20; favours CSA; 95% CI 0.69 to 2.07).

Seven adult RCTs comparing MMF and AZA identified by the parallel HTA reported mortality (Tricontinental Study 1996, Sadek et al. 2002, Merville et al. 2004, Weimer et al. 2006, Tuncer et al. 2002, Remuzzi et al. 2007, Solinger et al. 1995).[113-119] The pooled results at one year with five studies[113, 115-118] suggest no significant difference between MMF and AZA (OR=1.19; favours AZA; 95% CI 0.47 to 3.02, I^2=0%, Tau^2=0). In addition, two studies reported mortality at three years follow-up suggesting no difference betwee MMF and AZA (OR=0.56 favours MMF; 95% CI 0.23 to 1.23, I^2=0%, Tau^2=0).[114, 117] The study reported by Tuncer et al. 2002 provided data at five years, which also indicated no preference for either MMF or AZA (OR 0.73, 95% CI 0.15 to 3.50).[117]

Summary

In summary, no difference in survival was found between TAC and CSA and between MMF and AZA in the adult evidence. The child/adolescent RCT and child/adolescent non-RCT evidence is consistent with the adult RCT evidence identified in the parallel HTA.

4.4.2.2 Graft loss

Parallel HTA adult RCT evidence (09/46/01)

Ten adult RCTs comparing TAC with CSA identified by the parallel HTA reported graft loss (Schleibner et al. 1995, Margreiter et al. 2002, Charpentier et al. 2003 , Laskow et al.1996, Mayer et al. 1997, Jarzembowski et al. 2005, Campos et al. 2002, Waller et al. 2002, Hardinger et al. 2005, Weimer et al. 2006).[104-113] The pooled results at one year with seven

studies[106-110, 112, 113] found no significant difference between TAC and CSA (OR=1.18; favours CSA; 95% CI 0.72 to 1.93, I^2=0%). As with mortality, the results for graft loss suggest no statistically significant difference between TAC and CSA. This lack of preference for either treatment remained at five years follow-up (OR 0.92, 95% CI 0.61 to 1.40).[106]

Five adult RCTs comparing MMF and AZA identified by the parallel HTA reported graft loss (Tricontinental Study 1996, Sadek et al. 2002, Merville et al. 2004, Weimer et al. 2006, Solinger et al. 1995).[113-116, 119] The pooled results at one year with four studies[113-116] suggest no significant difference between MMF and AZA (OR=0.76; favours MMF; 95% CI 0.38 to 1.50, I2=32.3%, Tau2=0.120).

Summary

In summary, no difference in graft loss was found between TAC and CSA and between MMF and AZA in the adult evidence. Similarly, no statistically significant difference was found between TAC and CSA for graft loss in the child/adolescent RCT evidence. It should be noted however, the evidence from Trompeter et al. 2002[74] suggested borderline significantly lower in graft loss with TAC compared with CSA (OR=0.41, 95%CI: 0.16; 1.00, and OR=0.43, 95%CI: 0.18; 1.01 at two and four years follow-up respectively). In addition, the current review found better graft survival in MMF compared with AZA in a five year follow-up from one child/adolescent non-RCT.[77]

4.4.2.3 Graft function

Parallel HTA adult RCT evidence (09/46/01)

Four adult RCTs comparing TAC with CSA identified by the parallel HTA reported graft function (Schleibner et al. 2005, Margreiter et al. 2002, Waller et al. 2002, van Duijnhoven et al. 2002).[104, 109, 120, 121] No meta-analysis was conducted because the results were presented in a number of ways and were not appropriate for pooling. One study[109] suggested lower graft function for TAC, as opposed to CSA at one and two years follow-up, but not at three years follow-up. Another study [120] did not find statistically significant differnce between TAC and CSA at one year follow-up. Conflicting results were reported by all four trials across all time points (one month - three years).

Summary

In summary, conflicting adult evidence was reported in the parallel HTA across all time points (one month - three years); it is not clear if there is any difference betwenen TAC and CSA in regards to graft function. In contrast, better graft function was associated with TAC compared with CSA in the one child/adolescent RCT.[74] In addition, no difference in graft function between TAC+AZA and CSA+MMF regimens was reported in the one non-RCT.[79]

4.4.2.4 Acute rejection

Parallel HTA adult RCT evidence (09/46/01)

TAC vs CSA

Nine adult RCTs comparing TAC with CSA were identified by the parallel HTA reported acute rejection at one year (Margreiter et al. 2002, Mayer et al. 1997, Jarzembowski et al. 2005, Waller et al. 2002, Hardinger et al. 2005, Weimer et al. 2006, Radermacher et al. 1998, Baboolal, et al. 2002, Campos et al. 2002).[106-110, 112, 113, 122, 123] The pooled results at one year with all nine studies found significantly higher BPAR at in the CSA arm compared with the TAC arm (OR=0.50; favours TAC; 95% CI 0.39 to 0.64, I^2=8.1%).[106-110, 112, 113, 122, 123] Mayer et al. 1997 report BPAR at four years, where the beneficial effect of TAC appeared to be maintained (OR 0.38 favours TAC, 95% CI 0.25 to 0.57).[106]

Time to first BPAR was reported by two studies[108, 123]; Baboolal et al. 2002 suggested that BPAR occurs more quickly for participants receiving TAC (35 days, SD 13) compared with CSA (59 days, SD 38),[123] while Campos et al. 2002 did not report any significant difference between the two arms.[108]

Severity of BPAR was reported by two studies (Margreiter, 2002 and Charpentier, 2003).[109, 111] The pooled results at six months found no difference between TAC and CSA for the Banff 1 classification (OR=0.77; favours TAC; 95% CI 0.29 to 2.02, I^2=77.2%), lower frequency of BPAR of Banff severity 2 and 3 occurring in the TAC arm, compared with the CSA arm (OR=0.48; favours TAC; 95% CI 0.31 to 0.72, I^2=0%) for Banff 2, and (OR=0.28;favours TAC; 95% CI 0.12 to 0.66, I^2=0%) for Banff 3.

MMF vs AZA

Six adult RCTs comparing MMF and AZA identified by the parallel HTA reported BPAR (Tricontinental Study 1996, Sadek et al. 2002, Merville et al. 2004, Weimer et al. 2006,

Remuzzi et al. 2007, Solinger et al. 1995).[113-116, 118, 119] The pooled results from three studies (Tricontinental Study 1996, Remuzzi et al. 2007, Solinger et al. 1995).[114, 118, 119] at six months follow-up suggested fewer BPAR in the MMF compared with the AZA arm (OR=0.50; favours MMF; 95% CI 0.35 to 0.72, I^2=35.1%, Tau^2=0.036). While pooled results of four RCTs (Tricontinental Study 1996, Sadek et al. 2002, Merville et al. 2004, Weimer et al. 2006).[113-116] at one year follow-up suggested no statistically significant between group differences for BPAR (OR=0.67; 95% CI 0.37 to 1.22, I^2=58.3%, Tau^2=0.198).

In addition, two RCTs identified by the parallel HTA reported severity of BPAR.[114, 119] The pooled results from these two RCTs[114, 119] at six months follow-up suggests fewer BPAR in the MMF arm compared with the AZA arm for Banff 1 classification (OR=0.35; favours MMF; 95% CI 0.35 to 0.89, I^2=0%, Tau^2=0) and for Banff 2 classification (OR=0.51; favours MMF; 95% CI 0.31 to 0.83, I^2=0%, Tau^2=0). No statistically significant difference were found for Banff 3 classification BPAR (OR=0.60; favours MMF; 95% CI 0.16 to 2.24, I^2=60.5%, Tau^2=0.555).

Insufficient data was provided for time to BPAR to allow pooled analysis since only Merville et al. 2004 reported time to BPAR as 48.5 days for MMF and 43.7 days for AZA.[116]

Summary

In summary, pooled results of nine adult RCTs identified by the parallel HTA at one year follow-up suggested fewer BPAR with TAC compared with CSA. Similarly, higher rates of BPAR were found in CSA compared with TAC in the one included child/adolescent RCT at six months follow-up.[74] The adult RCT evidence was conflicting with regards to time to BPAR, one study suggested that BPAR occured more quickly for participants receiving TAC compared with CSA, and one study did not find any statistical differences between arms. In addition, evidence of lower frequency of BPAR of Banff severity 2 and 3 occurring in the TAC arm, compared with the CSA arm was found in the adult evidence. No child/adolescent evidence on severity and time to BPAR was identified.

In addition, pooled results of three adult RCTs identified by the parallel HTA at six months follow-up suggested fewer BPAR with MMF compared with AZA (OR =0.50; favours MMF; 95% CI 0.35 to 0.72, I^2= 35.1%), however the pooled results of four adult RCTs at one year follow-up suggested no statistical significance between group differences (OR=0.67; 95% CI 0.37 to 1.22, I^2=58.3%). Similarly in the child/adolescent non-randomised evidence, no statistically significant differences in BPAR were found between the MMF and AZA arms, and

between TAC+AZA and CSA+MMF, as well as the severity of BPAR between TAC+AZA and CSA+MMF.

4.4.2.5 Adverse events

Parallel HTA adult RCT evidence (09/46/01)

Ten adult RCTs comparing TAC with CSA identified by the parallel HTA reported AE at one year follow-up; six studies compared TAC + AZA + CCS and CSA+ AZA + CCS regimens (Laskow et al. 1996, Mayer et al. 1997, Jarzembowski et al. 2005, Campos et al. 2002, Hardinger et al. 2005, Baboolal at al. 2002).[105-108, 112, 123] Two studies compared TAC + MMF + CCS and CSA+ MMF + CCS regimens (Yang et al. 1999,Weimer at al 2006),[113, 124] one study compared TAC + SRL + CS and CsA+ SRL+ CS regimens (Chen et al. 2008),[125] and one study comparing four regimens also compared low TAC + MMF + CCS and low CSA+ MMF + CCS regimens (SYMPHONY).[126] No difference in PTLD, malignancy, infections and CMV infection was found between TAC and CSA regimens at one year follow-up. The meta-analysis (including eight studies) suggested more cases of NODAT in TAC regimens compared with CSA (OR=2.22; favours CSA; 95% CI 1.16 to 3.86, I^2=0%). All meta-analyses are summarised in Table 38.

Three adult RCTs that compared MMF with AZA reported AEs; one study compared MMF + CSA + CCS and AZA + CSA+ CCS regimens (Merville et al. 2004)[116] and two three-arm studies also used MMF + CSA + CCS and AZA + CsA+ CS regimens (Sadek et al. 2002 and Weimer et al. 2006).[113, 115] No difference in infections and CMV infection were found between MMF and AZA regimens at one year follow-up. However, only two studies[113, 116] reported CMV infection, and only one study reported infections.[115]

Table 38 Adults RCTs; pooled results at one year follow-up

AE	Study	Odds ratio	95% CI	I^2	Tau^2
NODAT	Laskow et al. 1996 Mayer et al. 1997 Jarzembowski et al. 2005 Campos et al. 2002 Hardinger et al. 2005 Yang et al. 1999 SYMPHONY Chen et al. 2008	**2.22**	**1.42; 3.46**	0%	0
Malignancy	Mayer et al. 1997 Hardinger et al. 2005 Yang et al. 1999 SYMPHONY	1.36	0.54; 3.39	0%	0.57
Infections	Mayer et al. 1997 Chen et al. 2008 Yang et al. 1999 SYMPHONY	1.12	0.84; 1.49	0%	0.46
CMV	Baboolal at al. 2002 Mayer et al. 1997 Jarzembowski et al. 2005 Weimer at al. 2006 SYMPHONY Yang et al. 1999 Hardinger et al. 2005	0.8	0.59; 1.09	0%	0.6

Key: AE, adverse events; CMV, cytomegalovirus; NA, not applicable; NODAT, new onset diabetes; PTLD, post-transplant lymphoproliferative disease; OR, odds ratio; CI, confidence intervals

Summary

The result suggested no difference between TAC and CSA for mortality, graft loss and AE, while more BPAR and AR, and worse graft function was reported in CSA compared with TAC.[74]

4.5 Summary

Three RCTs are included in the clinical effectiveness systematic review presented in this report; one new RCT,[70] and two RCTs from the previous assessment.[72, 74]

Four non-randomised controlled trials (non-RCTs) are included in our review. All of these were also included in the previous assessment by Yao et al. 2006.[1] No new non-randomised studies were identified in our searches.

4.5.1 Induction therapy

Two RCTs of induction therapy (reported in four publications and one abstract) evaluating **BAS** in children and adolescents were identified in the review.[70, 72] No RCTs were identified that evaluated **r-ATG** in children and adolescents.

No non-RCTs in the child and adolescents population evaluated induction therapies.

We found no significant difference in **survival**, **graft loss**, **graft function**, and **incidences of BPAR** and **time to BPAR** between BAS and placebo/no induction. [70, 72] There was evidence of more severe BPAR (Grade IIA) in placebo compared with BAS in one study (OR= 0.05; favours BAS; 95% CI 0.003 to 0.87).[70]

Comparision with the previous HTA and the parallel HTA in adults

The results of the current review are similar to the previous HTA.[1]

In addition, the child RCT evidence is similar to the conclusions of the parallel HTA in adults. However, the adult evidence found less **BPAR** in BAS compared with placebo or no induction (OR=0.53; favours BAS; 95%CI 0.40-0.70, I^2=0.0%, Tau^2=0.0; pooled results at one year follow-up with five studies). And no difference in severity of BPAR between BAS and placebo/no induction was found in the adult evidence.

The comparison of the child/adolescent RCT evidence with the previous HTA and the parallel HTA in adults is summarised in Table 39.

Table 39. Summary of RCT evidence comparing BAS with placebo and no induction

Outcome	Follow-up	PenTAG RCTs BAS vs control	Yao et al. 2006 RCTs BAS vs control	Parallel HTA adult RCTs BAS vs control (MA at 1 year follow-up)
		OR (95% CI)	RR (95% CI)	OR (95% CI)
Mortality	3 months	2.79 (0.11, 69.31)[70]		
	6 months	4.69 (0.22, 99.10)[70] no deaths in either arm[72]	no deaths in either arm[72]	
	1 year	6.64 (0.34, 130.33)[70]		0.95 (0.49, 1.87) I^2=0.7% [97, 99-101] no deaths in either arm[98, 102]
	2 years	0.33 (0.01, 8.20)[72]		
Graft Loss	6 months	0.93 (0.29, 2.97) I^2=0% [70, 72]	0.93 (95%CI 0.28, 3.12)[72]	
	1 year	0.92 (0.06,14.92)[70]		0.82 (0.56, 1.21) I^2=0% [97, 99-102] no deaths in either arm[98]
	2 years	0.50 (0.16, 1.54)[72]		
BPAR	3 months	0.39 (0.14, 1.07)[70]		
	6 months	0.71 (0.40, 1.27) I^2=15.7% [70, 72]	0.93 (95%CI 0.53, 1.65)[72]	
	1 year	0.51 (0.24, 1.08)[70]		0.53 **(0.40, 0.70)** I^2=0% [97, 99-102]
	2 years	0.74 (0.39, 1.40)[72]		
eGFR	6 months	WMD[a] -4.20 (-9.60, 1.20) I^2=0% [70, 72]	WMD[b] 4.5 (95%CI -6.26; 5.26)[72]	
	1 year	Mean (SD)[a]: 79(23) vs 82 (24) ; p=0.38[d] [70]		WMD[c] 1.93 (-0.97, 4.83) I^2=23.9% [98-101]
	2 years	WMD[a] -1.38 (-7.20, 4.44) I^2=0% [70, 72]		

Key: BAS, basiliximab; BPAR, biopsy proven acute rejection; eGFR, estimated glomerular filtration rate; MA, meta-analysis; vs, versus.

Notes: The previous HTA by Yao et al 2006.[1] had only 6 months follow-up data for Grenda et al 2006[72] (as included in the Fujusawa/Astellas submission and an abstract by Grenda et al. 2004[87]) Evidence suggesting a statistically significant difference between treatments highlighted in bold. OR>1 favours BAS; RR>1 favours BAS; WMD >0 favours BAS; a, eGFR estimated using Schwartz equation (ml/min/1.73m^2) .b, serum creatinine (mmol/l); c; various equations (ml/min); d, result of t-test comapring means and SDs.

4.5.2 Maintenance therapy

4.5.2.1 RCT evidence

One RCT of maintenance therapy (reported in three publications) evaluating **TAC** (compared with CSA) in children and adolescents was identified.[74] No RCTs were identified that evaluated **TAC-PR**, **MMF**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

From the RCTs, we found no significant difference in **survival**, **graft loss** between TAC and CSA.[74] However, a significantly higher **graft function** (mean eGFR of 71.5 [SD 22.9] ml/min/1.73m^2 in TAC vs mean eGFR of 53.0 [SD 21.6] ml/min/1.73m^2 in CSA; t-test = 4.03, p<0.01 at four years follow-up), and less **BPAR** (OR=0.41,favours TAC, 95%CI: 0.16 to1.00 at six months follow-up) was found in TAC compared with AZA at up to four years follow-up.[74]

Comparision with the previous HTA and the parallel HTA in adults

The results of the current review for **survival, graft function,** and **BPAR** are similar to the previous HTA.[1] However, the RCT child and adolescent evidence identified in the previous HTA review[1] concluded that TAC lowered **graft loss** at two and four years follow-up. The difference in these results is because we excluded graft loss due to death from all analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related. After the removal of graft loss due to death from the analyses, the evidence from Trompeter et al. 2002[74] suggested a borderline (statistically non-significant) lower graft loss with TAC compared with CSA (OR=0.41, 95%CI: 0.16 to 1.00, and OR=0.43, 95%CI: 0.18 to 1.01 at two and four years follow-up respectively). In addition, whilst there were statistically significant treatment group differences in **BPAR** and AR at six months, the annual differences in AR were not statistically significant for years two, three, and four.[74, 76]

In addition, the child RCT evidence is similar to the conclusions of the parallel HTA in adults. The pooled result of nine studies at one yer follow-up found less **BPAR** in TAC compared with CSA; OR=0.50; (favours TAC; 95% CI 0.39 to 0.64, I^2=8.1%). Adult evidence aslo suggested lower frequency of BPAR of Banff severity 2 and 3 in the TAC compared CSA arm (the child/adolescent RCT did not report time to and severity of acute rejection).

The comparison of the child/adolescent RCT evidence with the previous HTA and the parallel HTA in adults is summarised in Table 40

Table 40.Summary of RCT evidence comparing TAC with CSA

Outcome	Follow-up	PenTAG RCTs TAC vs CSA	Yao et al. 2006 RCTs TAC vs CSA	Parallel HTA adult RCTs TAC vs CSA (MA at 1 year follow-up)
		OR (95% CI)	RR (95% CI)	OR (95% CI)
Mortality	6 months	0.9 (0.18, 4.58)[74]	0.9 (0.21, 3.84)[74]	
	1 year	0.9 (0.18, 4.58)[74]	n/N: 3/103 vs 3/93 (p=0.90)	1.51 (0.75, 3.06) I^2=14.8%[105-110, 112, 113]
	2 years	0.67 (0.15, 3.07)[74]	n/N: 3/103 vs 4/93 (ns)	
	4 years	1.14 (0.30, 4.36)[74]	n/N: 5/103 vs 4/93 (p=0.90)	
Graft Loss[d]	6 months	0.38 (0.14, 1.05)[74]	0.48 (0.22, 1.08)[74]	
	1 year	0.44 (0.18, 1.09)[74]	n/N: 10/103 vs 17/93 (p=0.082)	1.18 (0.72, 1.93) I^2=0%[106-110, 112, 113]
	2 years	0.41 (0.16, 1.00)[74]	n/N: 10/103 vs 19/93 **(p=0.03)**	
	4 years	0.43 (0.18, 1.01)[74]	n/N: 11/103 vs 20/93 **(p=0.03)**	
BPAR	6 months	0.29 **(0.15, 0.57)**[74]	0.42 **(0.26, 0.69)**[74]	
	1 year			0.50 **(0.39, 0.64)** I^2=8.1%[106-110, 112, 113, 122, 123]
eGFR[b]	6 months	Mean (SD)[a]: 65.6 (19.9) vs 61.2(15.8); p=0.11[c 74]	Mean (SD)[a]: 90.91 (34.2) vs 86.09 (26.8) [74]; p=0.09[c 74]	No MA was performed; conflicting results were reported by all four trials across all time points (one month to three years)[98-101]
	1 year	Mean (SD)[a]: 64.9 (20.7) vs 57.8 (21.9); **p=0.04**[c 74]	Mean (SD)[a]: 62.5 vs 56.4; **p<0.01**[c 74]	
	2 years	Mean (SD)[a]: 64.9 (19.8) vs 51.7 (20.3); **p<0.01**[c 74]	Mean (SD)[a]: 64.9 vs 51.7; **p<0.01**[c 74]	
	3 years	Mean (SD)[a]: 66.7 (26.4) vs 53.0 (23.3); **p<0.01**[c 74]		
	4 years	Mean (SD)[a]: 71.5 (22.9) vs 53.0 (21.6); **p<0.01**[c 74]	Mean (SD)[a]: 71.5 vs 53.0; **p<0.01**[c 74]	

Key: CSA, ciclosporin; TAC, tacrolimus; BPAR, biopsy proven acute rejection; eGFR, estimated glomerular filtration rate; MA, meta-analysis; vs, versus.

Notes: Evidence suggesting a statistically significant difference between treatments highlighted in bold. OR>1 favours TAC; RR>1 favours TAC; WMD >0 favours TAC; a, eGFR estimated using Schwartz equation (ml/min/1.73m^2); b, eGFR values reported in Trompeter et al. 2002[74] and the four year follow-up paper by Filler et al. 2005[76] differ, we used data reported in Filler et al. 2005[76] c, result of t-test comparing means and SDs; d, The discrepancy in graft loss result between PenTAG and the previous HTA is due to the fact that we have excluded graft loss due to death from our analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related, just as mortality is to overall survival. It should be noted that after the removal of graft loss due to death from the analyses the child/adolescent RCT evidence suggested borderline non-significantly lower graft loss in TAC compared with CSA.

4.5.2.2 Non-RCTs evidence

Three non-RCTs evaluating **MMF** (compared with AZA) in children and adolescents were identified.[77, 80, 93] One non-RCT compared **TAC+AZA** with **CSA+MMF**.[79] No non-RCTs were identified that evaluated **TAC-PR**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

TAC vs CSA

We found no statistically significant difference in **survival** between MMF and AZA in the non-RCTs.[77, 80] Similarly, no statistically significant difference in **BPAR** between MMF and AZA in the non-RCTs was identified.[77, 80, 93] A significantly lower **graft loss** was found in MMF compared with AZA at one to five years follow-up in one of the two non-RCTs[77] (OR=0.24 at five years follow-up; favours MMF; 95%CI: 0.09 to 0.63). However, this was not confirmed by the other non-RCT at one year follow-up.[80] **Graft function** (eGFR) was not measured in the two included non-RCTs comparing MMF and AZA.

In addition, conflicting evidence was found in the parallel HTA in adults. No difference in **graft loss** was found between MMF and AZA in the adult evidence; OR=0.76 (favours MMF; 95% CI 0.38 to 1.50, I^2=32.3%, Tau^2=0.120; pooled results of four studies a one year follow-up). The pooled results of three adult RCTs at six months follow-up suggested fewer **BPAR** with MMF compared with AZA (OR =0.50; favours MMF; 95% CI 0.35 to 0.72, I^2= 35.1%), however the pooled results of four adult RCTs at one year follow-up suggested no statistical significance between group differences (OR=0.67; 95% CI 0.37 to 1.22, I^2=58.3%). Finally no significant difference in **survival** between MMF and AZA was found in the adult evidence (OR=1.19; favours AZA; 95% CI 0.47 to 3.02, I^2=0%, Tau^2=0; pooled results of five studies at one year).

TAC+AZA vs CSA+MMF

We found no statistically significant difference in **survival**, **graft loss, BPAR, graft function,** and **delayed graft function** between TAC+AZA and CSA+MMF in the non-RCT.[79]

No adult evidence comparing TAC+AZA and CSA+MMF was identified in the parallel HTA in adults.

4.5.3 Adverse events

4.5.3.1 Induction

More infections were found in children treated with BAS compared with those treated with placebo (OR=2.23, favours PBO; 95%CI 1.03 to 4.68).[70] In addition, Grenda et al. 2006 found that toxic nephropathy and abdominal pain was higher in the BAS arm compared with no induction (p=0.03 and p=0.02 respectively).[72] The previous HTA only reported post-transplant diabetes mellitus (Grenda et a. 2004[87]), the rest of the data was confidential and was omitted from the report.[1]

In addition, the child RCT evidence is largely similar to the conclusions of the parallel HTA in adults. The adult RCT evidence identified in the parallel HTA did not find any significant differences in NODAT, PTLD, malignancy, infections and CMV infections between BAS and placebo or no induction.

4.5.3.2 Maintenance therapy

There were no statistically significant differences between TAC and CSA for a range of AE (any infections, urinary tract infections, bacterial infections, viral infections, PTLD, solid tumour, hypertension, any AE, and NODAT).[74] This is similar to the conclusions of the previous HTA.[1] In addition, there were no statistically significant differences between MMF and AZA for urinary tract infection, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhea were identified in the non-randomised evidence.[80] Similarly, no statistically significant differences between TAC+AZA and CSA+MMF in CMV infections and NODAT were identified in the non-randomised evidence.[79]

However, the parallel HTA in adults found more cases of NODAT in TAC compared with CSA (OR=2.22; favours CSA; 95% CI 1.16 to 3.86, I^2=0%; pooled results of eight studies at one year follow-up). In addition, no difference in CMV infections[113, 116] and infection[115] were found between MMF and AZA regimens in the adult evidence at one year follow-up.

4.6 Companies' reviews of clinical effectiveness

One submission (Astellas) was presented summarising evidence on the effectiveness of immunosuppressive therapies in child/adolescent renal transplantation.

Astellas submitted a systematic review summarising evidence on the clinical effectiveness and safety of immediate-release tacrolimus therapy, compared with current alternative

treatments (prolonged-release Tacrolimus (Advagraf), ciclosporin, sirolimus, belatacept, and everolimus) as primary immunosuppressive therapies in patients undergoing renal transplantation.The submission did not address the study question in full.

The literature searches were conducted in the key bibliographic databases: MEDLINE, EMBASE, the Cochrane Library and Cochrane NHS EEDS. The literature search was limited from 2002 to June 2014. The literature searches use minimal free-text search terms without the use of truncation or controlled indexing, and selective synonyms are used for the interventions/comparators. This reflects poor sensitivity and, combined with the fact that searching has been conducted on only the abstracts of potential studies; it is possible that studies may have been missed. In addition, although the submission states that evidence will be assessed from RCTs and non-RCTs, RCT study design filter was applied. It is unclear from the search strategies provided how the referenced non-RCT data would have been captured.

Only one child/adolescent RCT,[74] and two child/adolescent non-RCTs [79, 95] were included in the study submission. In addition, adult RCT evidence was summarised. An overview of adult RCTs included in Astellas submission with reasons for inclusion/exclusion in the PenTAG parallel review is provided in Appendix 7 (Table 139).

Tacrolimus versus ciclosporin

Trompeter at al. 2002,[74] is the only child/adolescent RCT comparing TAC and CSA which is included both in the Astellas submission and in the PenTAG review. Astellas reported a significantly higher graft function, BPAR and better graft survival in TAC compared with AZA.[74] However, we have excluded graft loss due to death from our analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related, just as mortality is to overall survival. After the removal of graft loss due to death from the analyses, the evidence from Trompeter et al. 2002[74] suggested borderline non-significantly lower graft loss in TAC compared with CSA (OR=0.41, 95%CI: 0.16; 1.00, and OR=0.43, 95%CI: 0.18; 1.01 at two and four years follow-up respectively).

Astellas' clinical effectiveness results from adult RCTs suggest less AR, and more NODAT for TAC compared with CSA. The findings from the adult RCTs were similar to the conclusions in the parallel HTA; more BPAR and more NODAT were found for TAC compared with CSA, however it was not clear whether TAC improved graft function when compared with CSA.

Tacrolimus versus sirolimus

No child/adolescent evidence comparing TAC and SRL was identified. Astellas' clinical effectiveness results from adult RCTs suggest better graft survival and less AR with TAC compared with SRL, however they included a trial comparing TAC and no induction based regimen with SRL + rATG induction regimen (Glotz et al. 2010[127]). The parallel PenTAG review found fewer incidences of BPAR forTAC compared with SRL. In addition, Astellas pooled results from studies comparing SRL with MMF in TAC based regimens; significantly more drug discontinuations were found in the SRL+TAC regimen compared with the MMF+TAC regimen.

Immediate-release tacrolimus versus prolonged-release tacrolimus

No child/adolescent evidence comparing immediate-release TAC and prolonged-release TAC (TAC-PR) formulations was identified. Astellas' clinical effectiveness results from adult RCTs suggest no difference between TAC and TAC-PR. The results do not conflict with conclusions in the parallel HTA review.

Tacrolimus versus belatacept

No child/adolescent evidence comparing TAC and BEL was identified. In addition, no adult RCTs comparing TAC and BEL were identified. Astellas performed an indirect treatment comparison to compare Advagraf and Prograf, with more intensive and less intensive BEL regimens. Evidence of less AR with Prograf compared with both BEL regimens was presented. In addition, better graft survival was found with Prograf compared with the more intensive BEL regimen, and better survival was found with Prograf compared with the less intensive BEL regimen. Finally, evidence of less AR with Advagraf compared with the less intensive BEL regimen was presented. However, it was not clear what TAC evidence was included and the results presented seem to be conflicted. The parallel HTA network meta-analyses results suggested that BEL+MMF may be more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF. In addition, a study directly comparing BEL and TAC regimens was identified in the parallel HTA (Ferguson et al. 2011[128]).

Tacrolimus versus everolimus

No child/adolescent evidence comparing TAC and EVL was identified. In addition, no adult RCTs comparing TAC and EVL were identified. Astellas performed an indirect treatment comparison to compare TAC with EVL. It is not clear what TAC evidence was included and why the results were not reported separately for TAC and TAC-PR (as they were presented

in the TAC vs BEL comparison). No statistically significant differences between TAC and EVL were identified in the submission. The parallel HTA network meta-analyses results did not find any difference between TAC and EVL regimens for clinical effectiveness outcomes.

5 ASSESSMENT OF COST-EFFECTIVENESS

5.1 Systematic review of existing cost-effectiveness evidence

The purpose of this section of the report is to review existing evidence on the cost-effectiveness of immunosuppressive regimens (basiliximab and rabbit anti-human thymocyte immunoglobulin as induction therapies, and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenoate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept as maintenance therapies [including a review of TA99]), in renal transplantation in children and adolescents.

5.1.1 Methods

5.1.1.1 Searches

Bibliographic literature searching was conducted on April 8th 2014. The searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a costs or economic literature search filter). The search was date limited 2002-current in line with the previous assessment and the searches were updated on January 15th 2015. The search was not limited by language and it was not limited to human only studies.

The following databases were searched: Medline and Medline In-Process (OVID), Embase (OVID), NHS EEDS (via Wiley), Web of Science (ISI – including conference proceedings), HEED (Wiley) and Econlit (Ebsco Host). The search strategies are recorded in Appendix 1.

5.1.1.2 Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (Section 4.1.3), with the following exceptions (as specified in the appraisal protocol):

- Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies).
- Full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will

only be included if the incremental ratios can be easily calculated from the published data.)

- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.
- Only economic evaluations from UK, USA, Canada, Australia, and western Europe will be included as these settings may include data generalizable to the UK.

Titles and abstracts were screened for relevance by two reviewers (RMM and LC), with disagreements resolved by discussion. Full texts were retrieved for references judged to be relevant and were screened for eligibility by the same reviewers, with disagreements resolved by discussion.

The bibliographies of review articles not judged eligible for inclusion were examined by one reviewer (LC) to identify other potentially relevant references. These references were retrieved and checked for eligibility in the same way as full texts from database searches.

5.1.1.3 Quality assessment

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers et al. 2005.[129] Where studies were based on decision models they were also quality assessed using the checklist developed BY Philips and colleagues. [130, 131]

5.1.1.4 Synthesis

Economic studies were summarised and synthesised using tabulated data and narrative synthesis.

5.1.2 Results

5.1.2.1 Identified studies

The electronic database search for cost-effectiveness evidence, including update searches conducted on 18 November 2014, identified 2090 records. After de-duplication 1,378 records remained, all of which were screened by title and abstract. Of these, 86 full texts were assessed for eligibility. Thirty-eight full texts were deemed to meet the eligibility criteria for the review

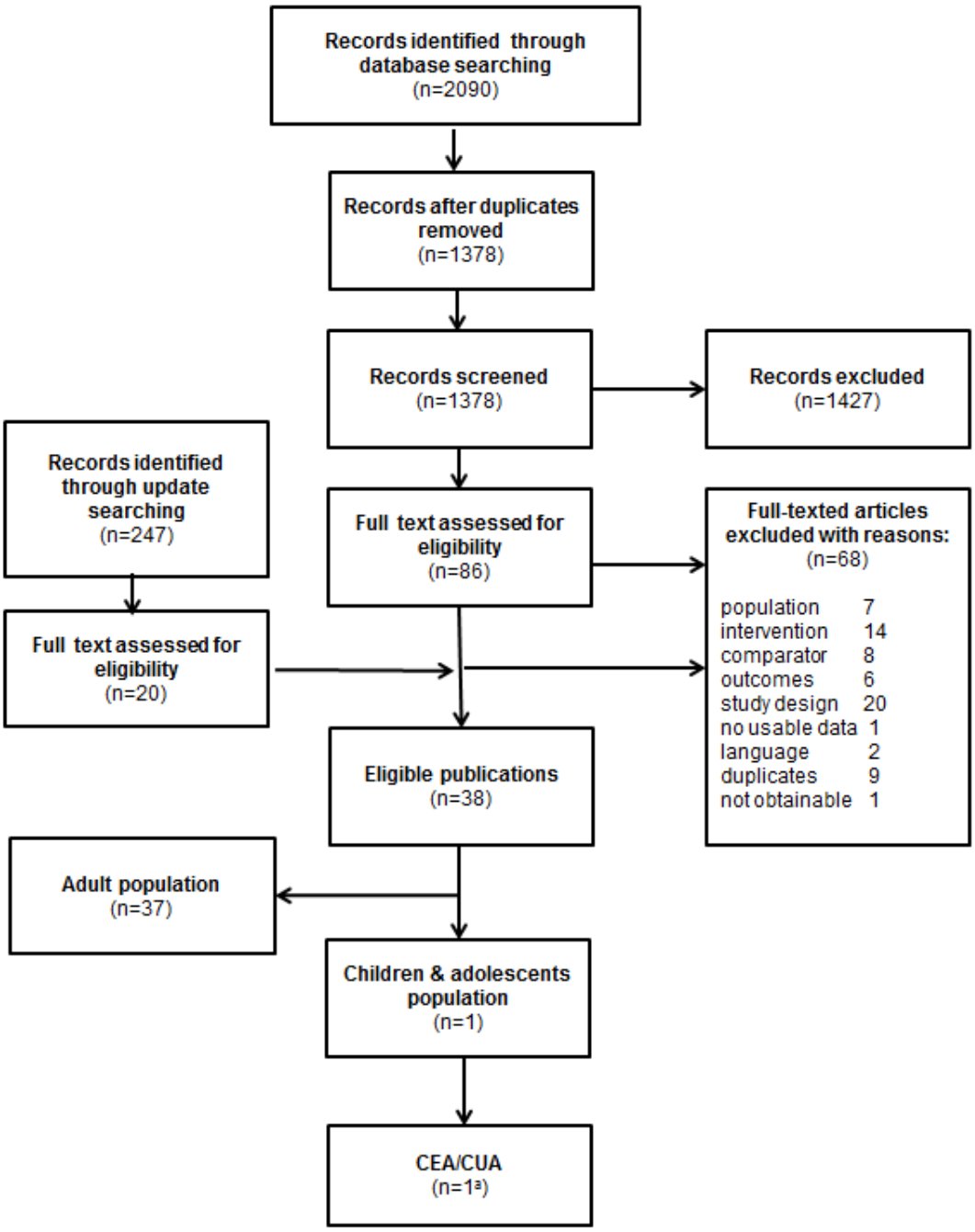
The process is illustrated in detail in Figure 13.

Only one study was identified that met the inclusion criteria (Yao et al. 2006[1]).This was the health technology assessment report of the previous NICE appraisal on the topic in children or adolescent patients. The rest of the subsection is devoted reviewing this study.

Yao et al. 2006[1] reports the methods and results of economic analyses submitted to the previous NICE appraisal on the topic by three sponsoring companies. All of these analyses used an equation estimated from regression analysis (meta-model) of child/adolescent simulation outcomes of immunosuppressive regimens derived from a model originally developed by one company (Novartis) for informing its submission to the respective NICE review on adult patients. The adult meta-model was developed by the Technology Assessment Group at Birmingham, and the individual companies adapted it to children and adolescents. After critically appraising the evidence submitted by the companies, the group at Birmingham then produced their own analysis by adapting the meta-model to children and adolescents.

Briefly the Birmingham model was a Markov model of spanning a 10-year horizon after the initial transplant. It consisted of three states, i.e. functioning graft, graft failed (dialysis), and death. In common with models in this clinical area, surrogate outcomes were used to extrapolate beyond the end of follow-up in the RCT evaluating the relative effects of immunosuppressive regimens in terms of biopsy-proven acute rejection. The model used a hazard ratio of graft failure up to seven years post-transplant for children and adolescents (18 years or younger) treated versus those not treated for an acute rejection before discharge of 1.41. The Birmingham group then used this surrogate relationship to translate 12-month differences in BPAR rates between immunosuppressive regimens from RCT studies in children and adolescents for therapies other than MMF and daclizumab, for which adult RCT data were used, into 10-year graft survival differences. The study also adjusted the resource use and costs for age-weight immunosuppressive doses in children and adolescents.

Figure 13. Cost-effectiveness review; PRISMA Flow Chart



Key: CEA, cost-effectiveness analyses; CUA, cost utility analyses.
Notes: a, Population relevant to this review a Previous HTA review (Yao et al; includes some adult evidence); b Includes studies reporting UK costs and effects without economic evaluation, and standalone cost analyses based in the UK NHS.

Table 41 presents the characteristics of the analysis by Yao et al. 2006,[1] Results were presented for two pair-wise comparisons of induction regimens and two pairwise comparisons of initial and maintenance immunosuppressive regimens. In the comparisons of induction therapy regimens basiliximab was found to result in lower total costs and higher

QALYs than no induction in patients managed with either tacrolimus or ciclosporin in a CNI-containing triple immunosuppressive therapy including azathioprine and steroids. In terms of the initial and maintenance immunosuppressive regimens, tacrolimus was found to have an incremental cost per QALY gained of £145,540 relative to ciclosporin, while the respective figure for MMF relative to Azathioprine was £194,559 when these therapies were combined with ciclosporin and steroids. It is worth noting that the latter comparison was based on efficacy data from studies on MMF use in adults. Table 42 summarises the base case results. However, altering the hazard (risk) ratio of graft loss with acute rejection from 1.41, which was based on a single observational study in children and adolescents, to a hazard ratio of 1.96, derived from a pooled analysis of adult observational studies, and arbitrarily increasing the cost of dialysis from the base case value of £21,000, which was estimated from data on adults, to £50,000, as a way of accounting for the higher staff-to-patient ratios in children and adolescents, resulted in a cost per QALY gained of £34,000 (TA99, section 4.2.7).

The technology assessment review team at Birmingham developed these analyses after considering evidence submitted by three companies using the Birmingham original model, which related to adult patients. The companies had found their respectively sponsored drugs to result in lower total costs and higher QALYs, when compared against the triple therapy of ciclosporin, azathioprine and steroids steroids (CSA + AZA + CCS). While the independent assessment by the Birmingham group confirmed the companies' finding that basiliximab induction were expected to reduce total costs and increase QALYs, its results for initial and maintenance immunosuppression were contrary to those obtained by the companies, since tacrolimus, azathioprine and steroids had an ICER above £30,000 relative to CAS, and the same was found for ciclosporin with MMF and steroids. Moreover, the technology assessment team at Birmingham found these results robust to uncertainty in the hazard rate used to extrapolate differences in acute rejection rates to long term estimates of health benefit.

These analyses represent the only available evidence about the costs and benefits of immunosuppressive regimens in recipients of kidney transplants aged 18 or younger. This evidence is however based on regimens that may no longer represent routine practice, in terms of therapies used (MMF has become part of standard immunosuppressive therapy), and dosages (lower doses of tacrolimus are being used as they are perceived to have a better efficacy and safety profile).

Table 41. Characteristics of analysis by Yao et al. 2006

Author & country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Yao et al. 2006[1] UK	Induction: BCAS vs CAS BTAS vs TAS Initial & Maintenance: TAS vs CAS CMS vs CAS	Children and adolescents with renal transplant	Cost-utility analysis	NHS & PSS	QALYs	10 years	Yes	Adapted model by Independent technology assessment group from model originally developed by Novartis for adult patients

Note: B: Basilixuimab; C: ciclosporin; A: Azathioprine; T: tacrolimus; M: mycophenolate mofetil; S: steroids

Table 42. Base case results of analyses presented by Yao et al.2006

Regiments compared	BTAS vs TAS	BCAS vs CAS	TAS vs CAS	CMS vs. CAS
Initial age (range)	3-13 years			
Time horizon	10 years			
Discounted incremental QALYs	0.038	0.074	0.090	0.049
Discounted incremental costs (£)	-451	-1,103	13,716	9,543
ICER Incremental cost per QALY gained	Dominant	Dominant	145,540	194,559
Notes	Costs discounted at 6%; QALYs discounted at 1.5%, Costs are in 2005 prices			Cost discounted at 6%, QALYS 1.5%. Efficacy data were based on meta-analysis that included studies of MMF in adults

Note: B: basiliximab; C: ciclosporin; A: azathioprine; T: tacrolimus; M: mycophenolate mofetil; S: steroids.

As for the methodology behind this evidence, the assessment was based on a meta-analysis of the evidence on acute rejection rates, although for MMF this included studies in adult patients. The study did not account for costs and health-related quality of life effects of changes in graft function, and omitted the effect of differences between regimens in terms of the graft function on longer term prognosis. Recent evidence from studies in adults suggest that quality of life (Neri et al. 2012)[132] and costs (Chamberlain et al. 2014)[60] do vary

significantly with renal function and this cast some doubt on the conclusion by the Birmingham group that small QALY differences are generally found between regimens. It is also questionable whether the surrogate relationship between acute rejection and graft survival was validly implemented, since the estimated hazard ratio used to predict graft survival was estimated from acute rejection rates occurring before discharge post-transplantation, whilst the efficacy data used to model treatment differences was based on 12-month outcomes post-transplantation. Also, lack of data prevented the analysis from accounting for side-effects differences between regimens, to which results were found to be sensitive. The quality assessment of these analyses are summarised in Table 43

Table 43. Evers checklist (Evers 2005)[129] –Review of published economic evaluations

	Yao et al. 2006
Item	
1. Is the study population clearly described?	Y
2. Are competing alternatives clearly described?	Y
3. Is a well-defined research question posed in answerable form?	Y
4. Is the economic study design appropriate to the stated objective?	Y
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	N
6. Is the actual perspective chosen appropriate?	Y
7. Are all important and relevant costs for each alternative identified?	Y
8. Are all costs measured appropriately in physical units?	?
9. Are costs valued appropriately?	?
10. Are all important and relevant outcomes for each alternative identified?	N
11. Are all outcomes measured appropriately?	?
12. Are outcomes valued appropriately?	?
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Y
14. Are all future costs and outcomes discounted appropriately?	Y
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	N
16. Do the conclusions follow from the data reported?	Y
17. Does the study discuss the generalizability of the results to other settings and patient/ client groups?	N
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Y
19. Are ethical and distributional issues discussed appropriately?	N

Y: Yes; N: No; '?': unclear

5.2 Critical appraisal of company submissions

5.2.1 Astellas submission

The submission compared

- twice daily immediate-release tacrolimus (Prograf) against
- once-daily prolonged-release tacrolimus (Advagraf),

and, using a different modelled relationship between efficacy and effectiveness to that used by the previous comparison, it separately compared

- twice daily immediate-release tacrolimus (Prograf) against
- Modigraf (tacrolimus ganules for oral solution – for three years, then switch to Prograf),
- tacrolimus specials (oral suspensions),
- everolimus,
- belatacept and
- sirolimus with low-dose ciclosporin (CNI minimisation)
- sirolimus with MMF (CNI avoidance).

Prograf was considered to be the standard treatment of choice in adult renal transplantation immunosuppression based on its UK market share, while the comparators investigated were deemed to be used infrequently. The submission cites evidence of improved outcomes for Advagraf relative to the current standard regimen, Prograf, since the former became available in 2009. In addition, as requested by the NICE scope, everolimus, belatacept and sirolimus were included in the evaluation despite their lack of market authorisation in the UK.

Astellas' analysis found that Prograf was cost-effective relative to all comparators, except sirolimus (avoidance), which the company argues is not a treatment option that is routinely considered of use for children and adolescents in general. Further, Advagraf was considered cost-effective relative to Prograf and recommended by the company to be adopted as the new standard of care. Due to limited information on children and adolescents, the model was

populated with information from adult kidney transplant recipients from a meta-analysis and network meta-analysis of evidence on short term outcomes from comparative clinical studies in adults.

The submission pointed to evidence on the relationship between adherence, acute and long-term graft rejection, and graft failure. In particular, it is stated that adherence to immunosuppressant regimens positively affects graft survival by preventing the development of de novo donor specific antibodies, which have been associated with a reduction in 10-year graft survival.[133] This is the stated justification for translating the observed improvement in adherence with once-daily tacrolimus relative to twice-daily tacrolimus (Kuypers et al. 2013) into graft and patient survival benefits in the Astellas model.[134] In addition, the company claims that once-daily prolonged-release tracolimus has a better pharmacokinetic profile than twice-daily tacrolimus (lower intra-patient variability (Wu et al. 2011), which results in a lower risk of long-term graft failure (Borra et al. 2010).[135, 136] The company also cites analyses from the Collaborative Transplant Study (CTS) for Europe presented at the 2014 World Transplant Congress, which shows that Advagraf-treated patients had higher patient and graft survival rates than Prograf-treated patients over 12 month following renal transplantation in CTS data for 2011-13. However, this observation was not robust to the adjustment for multiple confounders (HR 0.76, p=0.14, 95% CI were not stated).

The submission also cites the results of a meta-analysis pointing to increased risk of PTDM with tacrolimus (RR at 12 months 1.72, 95% CI: 1.17-2.52; RR at 36 months 2.71, 95% CI: 1.61-4.57; Kasiske et al. 2003) relative to ciclosporin, and acknowledges the evidence on the association between PTDM and reduced graft survival (RR 1.63, 95% CI: 1.46-1.84; Kasiske et al. 2003).[137] The company argues that these estimates may have been the result of patients treated with high doses of tacrolimus relative to current practice. To support this claim the submission cites the results of a Phase III study comparing Adavagraf with Prograf (Krämer et al. 2010), which used lower doses of tacrolimus and found lower incidence rates of PTDM than those in the studies included in the meta-analysis report.[138] It is noted, however, that the latter evidence is not relevant to the meta-analysis finding of a higher relative risk of PTDM with tacrolimus than ciclosporin.

5.2.1.1 Review of economic models and their results in the submission

The submission provides an overview of model structures and conclusions of previous cost-effectiveness analyses of renal transplantation immunosuppressive regimes. From searches of electronic databases (NHS EEDS, The Cochrane Library, Medline and other souces not

specified) it identified and included 12 studies in its review (although the Astellas submission states that 11 studies were included). No details were provided about the inclusion criteria for the review of economic studies but all of the reviewed studies were conducted in adults.

One of the included studies compared IR tacroliums vs. PR tacrolimus (US study, Abecassis et al. 2008); [139] four studies compared Tacrolimus vs. ciclosporin (two in Continental Europe, Craig et al. 2002, Lazzaro et al. 2002, one in the UK, Orme et al. 2003, and the remaining study was from the US and only measured costs for medication Hardinger et al. 2005)[112, 140-142]; seven studied sirolimus in CNI avoidance or minimisation strategies vs tacrolimus (one from the US, Earnshaw et al. 2008, another from the UK, McEwan et al. 2006, two more from Germany, Jurgensen et al. 2010, Jurgensen et al. 2014,[143-146],and three studies , Gamboa et al. 2001, Rely et al. 2012, and Niemczyk et al. 2006, from Colombia, Mexico and Poland, respectively.[147-149])

The submission briefly described the main results of these studies without critically assessing their validity and applicability to a UK setting, although it mentions the limited transferability of results from non-UK (10 out of the 12) studies. It concludes that the evidence supports the view that tacrolimus is cost-effective relative to ciclosporin, but that it is ambiguous in relation to the comparison against sirolimus in a CNI avoidance or minimisation strategy. The submission also includes a section where three published models are described. No assessment of their strengths and weakness was presented. These models (Earnshaw et al. 2005, Rely et al. 2014 and Gamboa et al. 2012) are all of adult patient populations and are therefore not included in the review of cost-effectiveness studies of this monograph.[143, 147, 148]

5.2.1.2 Economic Evaluation by the company

The cost-effectiveness analysis submitted by Astellas is an adaptation of a published Markov model-based assessment of the cost-effectiveness of tacrolimus, in either its extended release formulation, Advagraf, or the current standard therapy of immediate-release (Prograf, Muduma et al. 2014) in adult kidney transplant recipients (KTRs). The model describes the annual transitions between four health states starting from kidney-only transplantation: functioning graft without history of AR, functioning graft having experienced AR, graft failure (dialysis) and death (Table 44). Due to the lack of child/adolescent data, the Astellas submission is based on a review of short term safety and efficacy outcomes of immunosuppression in adults, reported by RCTs published study until June 2014. These were then extrapolated using registry data on child/adolescent graft and patient survival. The base case analyses submitted by the company discount costs and QALY outcomes at an annual rate of 3.5%.

Efficacy data

The model accounts for differences in outcomes between regimens that originate in their differing impact on biopsy confirmed acute rejection (BPAR) at 12 months post-transplant. These differences in BPAR between the regimens evaluated were estimated from RCTS of adult KTR (see Table 45). The model was based on the assumption that the effects of treatment on this surrogate outcome lasted only for the first year post-transplantation; in fact the model only allowed BPAR to occur in the first 12 months post-transplantation. This assumption, was combined with a) the estimated relative risk of graft failure for a functioning graft with previous BPAR vs. no previous BPAR and b) the one year post-transplant BPAR frequency, both from estimates reported by Opelz et al.[150] to derive the graft survival curves for grafts without prior AR and grafts with history of AR from the child 5-year graft survival profile in UK registry data ((including graft survival rates for years three and four derived by linear interpolation NHSBT 2014). The model extrapolation was complemented by using exponential survival curves to extend graft survival from five years up to 16 years post-transplantation.

With regard to patient survival, the model used the one, two and five year post-transplantation survival rates in children and adolescents from the NHSBT Report 2013-2014 (NHSBT 2014) as the estimated survival rates with a functioning graft. To populate survival probabilities in the state of graft failure, the model used annual survival rates of adult patients on dialysis followed for 10 years from the UK Renal Registry.[151] The patient survival rates were extrapolated until 18 years of age (i.e. 10 years post-transplant in the base case) by linear extrapolation of the available data, projecting survival rates from the last observed rate. There is no mention in the submission about adjusting survival for increases in background mortality as the cohort in the model ages.

Table 44. Characteristics of Astellas model

Population	Comparators Initial & maintenance	Horizon	Model structure	Surrogates to model long term	Health states/events modelled	Risk factors	Adverse events	Model drivers (sensitivity analysis)	Comments
Age 8 (minimum 2) years 26.0 kg (female) 25.6kg (male) (starting weight) England and Wales	-IR Tacrolimus (Prograf) -PR Tacrolimus (Advagraf) -Modigraf -Tacrolimus specials -Belatacept -Everolimus (CNI minimization [60% CsA reduction]) -Sirolimus (CNI minimisation [80% CsA reduction] & CNI avoidance) All given with basiliximab induction & azathioprine +corticosteroids	Ten years (maximum sixteen years; i.e. for starting age 2 years: analysis ended at age 18 in all cases)	Markov model of annual cycles with tunnel states extrapolation of one year trial outcomes	Acute rejection	Functioning graft –no previous BPAR Functioning graft –previous BPAR Failed graft (dialysis), Functioning regraft –no previous BPAR Functioning regraft – previous BPAR Death	BPAR	Malignancies CMV infections PTDM Wound healing disorders Anaemia HMGCoA Hypertension	Improved adherence with PR medication IR Tacrolimus vs. Sirolimus: Graft survival (scenario with graft survival in Symphony trial [CNI minimisation] with daclizumab induction)	Assumes that BPAR only occur in the first 12 months. Graft and patient survival were estimated from UK 5-year survival statistics in children and adolescents with renal transplant (UK NHSBT Report 2012–13) extrapolated to 10 years posttransplant by exponential and linear function of time, respectively. Survival in dialysis was estimated from 10-year UK survival statistics in adults, extrapolated by exponential function. Utility values of adverse events not accounted for. Model has flaws of implementation, especially in relation to re-transplants

Notes: BCAE: Biopsy-proven acute rejection; IR: Immediate-release formulation; ERPR: extended prolonged-release formulation; CsA: ciclosporin; CNI: Calcineurin inhibitor; HMGCoA: 3-hydroxy-3-methylglutaryl-coenzyme A.

For patients in the state of graft failure, which was assumed to be associated with the use of dialysis, the probability of receiving a re-transplant was populated with data from adults treated at a centre in Cardiff, Wales (McEwan et al. 2005[152]).

In addition to the difference in efficacy, measured in terms of AR rates (Table 53), the model allowed for differences in effectiveness between the tacrolimus arms through the differences in adherence associated with the once-daily, prolonged-release (Advagraf) vs. the twice-daily immediate-release formulations of the drug (Prograf). The model employed comparative estimates on adherence with Advagraf vs Prograf of 88.2% vs 78.8% from a published randomised study (Kuypers et al. 2013) and combined them with an estimated relative risk of graft failure in non-adherent vs adherent patients of 3.47 derived from a meta-analysis (Butler et al. 2004), to obtain a relative risk of graft failure of 0.848 which was applied to the graft survival curves (until year five and, by exponential curve extrapolation, thereafter) that were common to all other immunosuppressive treatment strategies in the model.[14, 134]

Table 45. Acute graft rejection rates used in the model

Product	Rate, %	Comment
Prograf (base comparator)	12.6	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153]
Modigraf/tacrolimus specials	12.6	Assumed the same as Prograf, due to lack of data
Advagraf	14.6	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153] and meta-analysis (Section 2)
Belatacept	30.7	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153] and meta-analysis (Sections 2, 3)
Everolimus (CNI minimization)	18.0	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153] and meta-analysis (Sections 2, 3)
Sirolimus (CNI minimization)	16.5	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153] and meta-analysis (Section 2)
Sirolimus (CNI avoidance)	28.7	Silva et al. 2007; Albano et al. 2013, Kramer et al. 2010[96, 138, 153] and meta-analysis (Section 2)

Adverse events

The model allows for seven types of adverse event following transplantation: Malignancy, Diabetes Mellitus, Anaemia, CMV infection, hypertension, HMGCoA, and wound healing

disorders. These events were assigned costs (except for the last type of event which had zero cost, and thus effectively omitted from the analysis) but no disutility. The adverse event incidence rates used in the model, reproduced in Table 46, differed across immunosuppressant treatment arms, although these had no influence on the probability of graft failure and patient death. Such differences only affected the costs differences between the treatments.

The incidence rates of adverse events were derived from a systematic review and meta-analysis published in 2006 (Webster et al. 2006),[154] the values adopted by the published economic model for adults in Germany by Jurgensen et al. (Jurgensen, et al. 2010),[145] and trial outcomes from the BENEFIT and BENEFIT-EXT trials (Vincenti 2010, Durrbach 2010).[155, 156]

The rates of adverse events were assumed to be the same with Advagraf and Prograf and for the two sirolimus regimens (CNI avoidance and CNI minimisation). According to the incidence rates figures in this model, tacrolimus has the lowest annual incidence of Malignancy (except for sirolimus from the third post-transplantation year onwards), CMV, Anaemia (except for Belatacept which had the same annual incidence rates as those of tacrolimus), dyslipidaemia and hypertension, but was associated with an excess incidence of PTDM over the other options.

Table 46. Adverse events (%)

Product	Adverse event	Year 1	Year 2	Year 3 and
Advagraf/Prograf/Modigraf /tacrolimus specials	Malignancies	0.00	0.00	0.43
	CMV infections	3.62	3.62	0.04
	PTDM	6.07	6.07	6.27
	Wound healing	4.12	4.12	0.00
	Anaemia	14.71	14.71	14.71
	HMGCoA	13.84	13.84	3.46
	Hypertension	9.17	9.17	9.17
Everolimus	Malignancies	2.43	2.43	0.64
	CMV infections	3.19	3.19	0.04
	PTDM	5.58	5.58	5.77
	Wound healing	10.72	10.72	0.00
	Anaemia	27.30	27.30	27.30
	HMGCoA	29.47	29.47	7.37
	Hypertension	31.63	31.63	31.63
Sirolimus (CNI minimisation and avoidance regimens)	Malignancies	0.20	0.20	0.05
	CMV infections	2.11	2.11	0.03
	PTDM	5.88	5.88	6.07
	Wound healing	10.72	10.72	0.00
	Anaemia	18.68	18.68	18.68
	HMGCoA	21.77	21.77	5.44
	Hypertension	15.08	15.08	15.08
Belatacept	Malignancies	2.32	2.32	0.61
	CMV infections	7.65	7.65	0.09
	PTDM	4.00	4.00	4.19
	Wound healing	4.12	4.12	0.00
	Anaemia	14.71	14.71	14.71
	HMGCoA	18.88	18.88	18.88
	Hypertension	31.12	31.12	31.12

Source: Webster et al. 2006, Jürgensen et al. 2010, Vincenti et al.2010, and Durrbach et al. 2010.[145, 154-156].

Utilities

Health-related quality of life and QALY outcomes were calculated from time spent in the graft functioning state and the graft failure state, which involved dialysis. Based on published Euro-Qol 5-dimension (EQ-5D) estimates (Lee et al. 2005), the functioning state was associated with a utility value of 0.71, regardless of any prior experience of AR, and the graft failure state was associated with a utility of 0.459, which was equal to the weighted average

of the utility of haemodialysis (0.44), experienced by 82% of dialysis patients, and peritoneal dialysis (0.53), received by the rest.[157]

Re-transplantation

The model allows for the occurrence and effects of re-transplantation, using the time to re-transplantation data reported by McEwan et al. for adult patients (McEwan et al. 2005, 2006). However, the states following the first re-transplantation (i.e. functioning graft with prior AR on the current re-transplant, functioning graft without prior AR on the current re-transplant – regardless of AR of any previous transplant-and graft failure) face the same transition probabilities, utility values and costs as the corresponding states before re-transplantation.[144, 152] This is likely biasing the analysis in favour of treatments with higher rejection rates in the model (since higher AR rate imply higher graft failure rates in this model), and may be interpreted as a conservative assumption of the relative effectiveness and incremental costs advantage of tacrolimus over the comparators.

Resource utilisation and unit costs

The amount of drug use for tacrolimus was age-dependent, and imputed according to weight by age distributions in observational data, by associating body-surface area with mean weight by age statistics from UK growth charts.[158, 159]. Dosages per kg of bodyweight for all medications were based on adult dosages as detailed in the BNF and the respective Summary Product Characteristics, with the exception of MMF, which was based on body surface area parameters, and Everolimus, which was based on data from a study in children and adolescents.[160].

The model used BNF prices for both interventions and comparators. The cost per milligram of Advagraf used was 23% lower than that of Prograf, based on the BNF list prices and information on the market share of pack sizes for Prograf. (The authors present sensitivity analyses of discounts on tacrolimus list prices [redacted]). Prices for other immunosuppressant regimens were based on BNF prices. Table 47 reproduces Table 38 in the submission, which details the prices used by the Astellas model. The submission says that tacrolimus prices were not available in the electronic market information tool, apparently to justify its deviation from the NICE methods guide (section 5.5.2), which specifies that “when there are nationally available price reductions…reduced prices(s) should be used in the reference case analysis to best reflect the price relevant to the NHS. The Commercial Medicines Unit publishes information on the prices paid for some generic drugs by NHS trusts through its Electronic Marketing

Information Tool (eMIT)" The submission does not give any further reason for their using list prices for tacrolimus and all the other drug regimens.

Table 47. Unit costs of immunosuppressive therapies in Astellas model (£)

Variable	Value	Comment
Cost per mg: Simulect®	£42.12	Injection, powder for reconstitution, basiliximab, net price 10-mg vial = £758.69, 20-mg vial = £842.38 (both with water for injections). For intravenous infusion
Cost per mg: Prograf®	£1.62	Concentrate for intravenous infusion, tacrolimus 5 mg/mL, net price 1-mL amp = £58.45. Capsules, tacrolimus (as monohydrate) 500 micrograms (yellow), net price 50-cap pack = £61.88; 1 mg (white), 50-cap pack = £80.28, 100-cap pack = £160.54; 5 mg (greyish-red), 50-cap pack = £296.58 and using market distribution of pack sizes
Cost per mg: Advagraf®	£1.24	Capsules, m/r, tacrolimus (as monohydrate) 500 micrograms (yellow/orange), net price 50-cap pack = £35.79; 1 mg (white/orange), 50-cap pack = £71.59, 100-cap pack = £143.17; 3 mg (orange), 50-cap pack = £214.76; 5 mg (red/orange), 50-cap pack = £266.92
Cost per mg: Belatacept	£1.42	Intravenous infusion, powder for reconstitution, belatacept, net price 250-mg vial = £354.52
Cost per mg: Everolimus	£5.87	No UK price available price at the time of this submission. Estimated price of everolimus based on the price of Afinitor (everolimus) white-yellow, everolimus, 5 mg, net price 30-tab pack = £2,250.00; 10 mg, 30-tab pack = £2,970.00 and assuming use of cheapest in terms of cost per mg
Cost per mg: Modigraf®	£7.22	Granules, tacrolimus (as monohydrate), 200 micrograms, net price 50-sachet pack = £71.30; 1 mg, 50-sachet pack = £356.65
Cost per mg: Specials	£3.83	Tacrolimus 2.5mg/5ml oral suspension, 100ml = £232.44; tacrolimus 5mg/5ml oral suspension, 100ml = £301.96 [161]
Cost per mg: Sirolimus (Rapamune®)	£3.45	Tablets, coated, sirolimus 500 micrograms (tan), net price 30-tab pack = £69.00; 1 mg (white), 30-tab pack = £86.49; 2 mg (yellow), 30-tab pack = £172.98
Cost per mg: Belatacept (Nulojix®)	£1.42	Intravenous infusion, powder for reconstitution, belatacept, net price 250-mg vial = £354.52
Cost per mg: Neoral®	£0.03	**Capsules**, ciclosporin 10 mg (yellow/white), net price 60-cap pack = £19.40; 25 mg (blue/grey), 30-cap pack = £19.52; 50 mg (yellow/white), 30-cap pack = £38.23; 100 mg (blue/grey), 30-cap pack = £72.57
Cost per mg: CellCept®	£0.003	Capsules, blue/brown, mycophenolate mofetil 250 mg, net price 100-cap pack = £82.26.
Cost per mg: Thymoglobuline®	£6.35	**Intravenous infusion**, powder for reconstitution, rabbit anti-human thymocyte immunoglobulin, net price 25-mg vial = £158.77.

Note: Prices of pharmaceutical products from BNF.

Treatment of acute rejection was assigned costs of IV steroids and, for the 20% of steroid resistant BPAR cases, a regimen of rATG and the cost of an inpatient hospital stay for acute kidney injury without complications (£1737 overall mean cost). This assumed zero medical management costs for the 80% of patients with steroid-sensitive AR, which ignores any follow-up costs to monitor treatment efficacy. The cost per year of dialysis was £31,806 and the cost of re-transplant was £26,639. While the latter was based on UK NHS Reference costs, the former was based on a microcosting study in seven hospital units in the UK. The study measured the average costs of dialysis per year for a 'typical patient', which is likely to be an adult. These costs were measured from the service provider's perspective and included direct costs and the costs of transport and medication usage. They excluded the costs of access of access surgery and managing dialysis complications. In addition, capital costs of the hospital building were not included. The costs of adverse events adopted are presented in Table 48, which reproduces Table 35 in the Astellas submission. The major elements of costs are summarised in Table 49.

Table 48. Costs of adverse events (per year)

Variable	Value	Comment
Malignancies	£1,388 to £4,452 depending on body surface area (m^2)	PTLD/Skin/non-Hodgkin's lymphoma (NHL). Mabthera concentrate for intravenous infusion, rituximab 10 mg/mL, **net price** 10-mL vial = £174.63, 50-mL vial = £873.15. No costs included of other treatment modailities
Cytomegalovirus (CMV) infections	£221 to £1,151 depending on weight (kg)	IV ganciclovir 14-21 days then maintenance for 8 weeks. Cymevene® intravenous infusion, powder for reconstitution, ganciclovir (as sodium salt). Net price 500-mg vial = £29.77.
Post transplant diabetes mellitus (PTDM)	£17.38	Tablets, coated, metformin hydrochloride 500 mg, **net price** 28-tab pack = 87p, 84-tab pack = £1.00; 850 mg, 56-tab pack = £1.36.
Wound healing disorders	£0.00	-
Anaemia	£16.88/kg	Binocrit® injection maintenance dose 17–33 units/kg 3 times weekly, prefilled syringe, epoetin alfa, **net price** 1000 units = £4.33; 2000 units = £8.65; 3000 units = £12.98; 4000 units = £17.31; 5000 units = £21.64; 6000 units = £25.96; 8000 units = £40.73; 10 000 units = £43.27.
LDL cholesterol	£235.03	Zocor® tablets, all f/c, simvastatin 10 mg (peach), **net price** 28-tab pack = £18.03; 20 mg (tan), 28-tab pack = £29.69; 40 mg (red), 28-tab pack = £29.69; 80 mg (red), 28-tab pack = £29.69.
Hypertension	£15.51	Capsules, ramipril 1.25 mg, **net price** 28-cap pack = 99p; 2.5 mg, 28-cap pack = £1.05; 5 mg, 28-cap pack = £1.12; 10 mg, 28-cap pack = £1.19.

Source: bnf.org 2014.

Table 49. Major cost elements in Astellas model (£)

	Astellas[a]
Tacrolimus IR therapy (per year)	1,559 (1st year) 1,366 (2nd year+)[b]
Tacrolimus PR therapy (per year)	1,322 (1st year) 1,112 (2nd year+)
Modigraf	13,654 (1st year) 13,580 (2nd year+)
Tacrolimus administration	0
MMF therapy (per year)	1,326[c]
Ciclosporin therapy	N/A[d]
Everolimus (per year)	5,086
Everolimus administration	0
Sirolimus (per year)	2,536 (1st year) 2,522 (2nd year+)
Sirolimus administration	0
Belatacept (per year)	4,018(1st year) 2,374 (2nd year+)
Belatacept administration	0
Corticosteroids	176 (1st year) 139 (2nd year+)
Acute rejection (event)	889[e]
Dialysis (per year)	31,806[f]
Re-transplantation	26,639[g]
Re-transplantation: Organ procurement	0

Notes: a, Adopted a 11-12 kg weight and body-surface area for representative patient in the model. The cost of Basilliximab induction (20 mg within two hours before transplantation and at four days post-transplant, BNF 2014 prices, £1,685) was included in all armsb Prograf; c, Based on 600 mg/m2 twice daily, valued at £82.26 price for 500mg, 50 cap pack from BNF September 2013; d, Astellas does not evaluate ciclosporin with MMF in their submission. The model only includes ciclosporin as part of the sirolimus (minimisation) comparator regimen; e, Based on BNGF prices; F, From Baboolal et al. 2008; and included direct costs and the costs of transport and medication usage. They excluded the costs of access of access surgery and managing dialysis complications. In addition, capital costs of the hospital building were not included; g, NHS Reference Costs 2013.

Results

The base case results presented by Astellas are displayed in Table 50. The expected discounted (at 3.5%) QALYs (censored after 10 years) were 5.569 for tacrolimus IR (Prograf), 5.565 for sirolimus CNI minimisation, 5.564 for everolimus, 5.553 for sirolimus CNI avoidance, and 5.551 for belatacept, in a cohort of patients of mean age 8. For tacrolimus once-daily prolonged-release formulation (Advagraf), discounted QALYs was 5.569. The Modigraf and tacrolimus specials regimens were assumed to result in the same health outcomes as Prograf.

Table 50. Results of model-based analyses submitted by Astellas

Submission	Regiments compared	Patient characteristics	Time horizon (years)	Life years (un-discounted)	Discounted costs (£)	Discounted QALYs	ICER Incremental cost per QALY
Astellas. 2003	Tacrolimus IR (Prograf)			9.472	58,471	5.569	Prograf vs. SIRI: 1,576,937
	Tacrolimus (Modigraf)			9.472	88,915	5.569	
	Tacrolimus specials	Mean age 8 yrs Weight 11.3-12.2	10	9.472	72,945	5.569	
	Sirolimus I			9.468	52,339	5.565	
	Everolimus			9.467	90,168	5.564	
	Sirolimus II			9.456	61,490	5.553	
	Belatacept			9.455	75,726	5.551	
	Tacrolimus PR (Advagraf)			9.502	53,395	5.604	Advagraf dominates
	Tacrolimus IR (Prograf)			9.472	58,471	5.569	

In the base case results, results comapring tacrolimus IR (prograf) with non-tacrolimus immunosuppressive regimens, Prograf produced more QALYs than any of the comparators and lower costs than Belatacept and Everolimus, sirolimus avoidance, Modigraf, and tacrolimus specials whereas it had higher cost against the Sirolimus minimisation regimen. The ICER against Sirolimus CNI minimisation strategy was in excess of £1 million. In the comparison of tacrolimus regimens, Advagraf dominated Prograf, given its lower costs and higher QALYs (both discounted and indiscounted).

The results were found to be sensitive to the the starting age, which was varied from the base case of eight years to two, 10 and 13 years, and the discount rate, adverse events, and half-cycle corrections. The results against Sirolimus were found to change significantly when graft survival parameters in the model were populated with data from the SYMPHONY trial instead of the NHS Blood and Transplant Service data used in the base case analyses: low dose tacrolimus was found to dominate Sirolimus as CNI avoidance regimen when both were given with daclizumab induction, two g MMF and steroids. In discussing these findings the authors note that the SYMPHONY trial has reported outcomes up to three years and is the largest prospective study in the novo kidney transplantation to date, which showed

tacrolimus to result in lower AR, better renal function and graft survival outcomes at one year than the sirolimus regimen.

On the basis of these results, the company submission concludes that tacrolimus is cost-effective and that Advagraf should become the standard of care as it produces lower costs and better health outcomes than Prograf. The latter statement is further supported, the submission claims, by the expected benefits, not accounted for in the Astellas model, arising from the improved pharmacokinetic profile of Advagraf relative to Prograf. Despite the apparent cost-effectiveness of its CNI minimisation mode, the submission states that the results of the SYMPHONY trial have discouraged the general use of Sirolimus, and that Belatacept's high cost and high acute rejection rate may do likewise, citing a report by the All Wales Medicines Strategy Group (AWMSG Secretariat Assessment Report – Advice No. 1712 Belatacept (Nulojix®) May 2012) as supportive evidence for this assertion.

5.2.1.3 Critical appraisal

The analysis presented (see Table 51 for quality checklist) by Astellas covers a number of appropriate comparators, including new regimens Belatacept and regimens with modes of action different from that of CNIs, i.e. everolimus and sirolimus, as well alternative tacrolimus formulations that are believed by the company to be used in routine practice; i.e. Modigraf and specials. However, it omits one relevant comparator: ciclosporin. There is no justification in the submission as to why this drug regimen was not considered. This suggests that the results presented may be misleading due to the exclusion of a relevant comparator. In addition, all of the regimens analysed by Astellas were evaluated in combination with MMF. This seems to contradict the assertion in the company's submission that "Most children in the UK receive triple immunosuppression therapy with a CNI (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine), and a corticosteroid following kidney transplantation (Astellas submission, page 1). Astellas also reported the results of sensitivity analyses that varied the mean starting age of patients in the cohort modelled; but since the analysis was censored/stopped at age 18, it is difficult to assign any meaningful interpretation to their findings that the results were sensitive to such variation.

There are two logical concerns with the Astellas model-based analysis. First, by accounting for the advantages in adherence of Advagraf in its comparison with Prograf, it makes the comparison of outcomes of Advagraf with those of other immunosuppressive regimens in the model invalid, since no allowance was made for any effects of adherence on graft survival for the other regimens analysed in the model. Indeed this undermines the fundamental assumption in the model that all significant differences in any drug regimen comparison may

be accounted for by the effect through the surrogate, in this case the rate of acute rejection (Taylor and Elston 2009). [162] Thus, regardless of the validity of the comparative analysis of Advagraf and Prograf, indirect comparisons of model results between Advagraf and Sirolimus, Everolimus and Belatacept are invalid.

Second, while the model was adjusted to include the effect of adherence on graft survival in the Advagraf vs Prograf comparison, the patient survival curves (for the functioning and failed graft states) were left unchanged, so that the same set of patient survival curves was applied to all immunosuppressive options analysed. This implies the empirically questionable assumption that improvements in graft survival, such as those obtained with Advagraf relative to Prograf (and indeed relative to all other model arms), do not translate in direct patient survival benefits. This inconsistent logic in turn leads to underestimating the benefits of Advagaf and overestimating its costs.

Inspection of the excel model spreadsheets revealed that the tacrolimus drug regimen options (Advagraf and Prograf) and Everolimus were the only treatment arms populated by actual data on immunosuppressive drug use from the RCT sample that served as the source for the respective efficacy data; drug consumption values for belatacept and sirolimus regimens were based on treatment guidelines (BNF or summary of product characteristics). Adult dosages (per kg bodyweight) of these treatments were used to estimate costs in the model.The only therapies for which child-specific doses were used in calculating resource utilisation in the analysis were MMF and everolimus. There are important distinctions with adults that are likely to cast doubt on these drug dosage values. In particular, as acknowledged by the authors in relation to tacrolimus PK studies, children and adolescents appear to eliminate the drug more rapidly than older adults. Further, in relation to steroids, there are concerns about the effects of the medication on growth which are likely to lead to its more limited use in children and adolescents than in adults.

There is inadequate use of the registry data used to extrapolate short term efficacy outcomes from RCT in the model. The model used the data from the NHS Blood and Transplant from 2012-2013, on patient survival rates for kidney only transplant recipients in the UK (Table 28, p. 35 in the submission by Astellas) to populate the patient survival parameters of patients with a functioning graft, ignoring the fact that such data on survival rates were likely to include deaths from both patients with a functioning and a failed graft. Instead, the probability of death in the graft functioning state should have been calculated as the remainder of the annual probability of death from the NHSBT patient survival data minus the product of probability of mortality in the graft failure state and the proportion of patients with a failed graft. In other words, the Astellas model is likely to overestimate mortality in the functioning

graft states, which in turns underestimates the benefits of gains in efficacy (i.e. reductions in AR in the model) that any regimen may have over another, e.g. tacrolimus over the comparators. Thus the results reported by Astellas in the submission may be treated as conservative estimates of the costs and benefits of its tacrolimus regimes. In relation to the evidence presented in support of Advagraf, its quality of limited by the omission of ciclosporin as comparator therapy, and the fact that the Advagraf vs Prograf comparison is based on what is in effect a different model of the outcomes of renal transplantation from that used to compare Prograf against all the other regimens. In fact, the model used for comapring Advagraf vs. Prograf contradicts the fundamental premise of the model used to compare Prograf with all regimens other than Advagraf: that acute rejection captures all important drivers of clinically meaningful outcomes.

One other issue relates to the way the model was structured. While the model allowed repeat transplantation to occur for a given individual, only for the first transplantation were the costs and health related quality of life of subsequent dialysis accounted for. Although the proportion of patients with more than one re-transplantation may be small, this assumption could have been important to the conclusions derived from the comparison with ciclosporin, had such comparator been included.

In addition, Astellas chose to use values of time to re-transplantation for patients on dialysis that were obtained from adult studies, whose mean wait for a re-transplant was three years.[152] This was in contradiction with the company's submission, which stated that "Children tend to be prioritised in deceased donor organ allocation systems: the median wait for a kidney in the UK during 2003-2006 for patients aged <18 years was 277 days".[163]

There is also an anomaly with regards to the timing of transplantation. Markov models typically imply that transitions occur at the end of the period represented by each cycle. In the present case, the cycle length was one year and the authors of the Astellas model rightly decided on using half cycle corrections to reduce the inaccuracy in expected costs and benefits calculations arising from more frequent average state transitions. The model, however, assumed that a proportion of patients undergo re-transplantation in the very first cycle, and that these made a transition from the failed graft state to a functioning graft post-re-transplantation state as if the re-transplant had occurred at the start of the period so that they spent the whole cycle length (six months due to the half-cycle correction) with a functioning graft after re-transplantation in the first cycle. This is wrong, since in a cohort of de novo kidney transplant patients, the discrete Markov process transition from a functioning first graft to a functioning re-transplant requires two sequential intervening events to occur, i.e. graft failure and re-transplantation, and a minimum of two cycles, one for each event.

In terms of the values used to populate the model, the costs of dialysis, one of the most influential parameters in the analysis, was derived from a microcosting study of the treatment pathway of a typical (i.e. adult) patient at six hospital units. This study sought to inform the introduction of Payment by Results in the NHS [164]. It did not include the costs of access surgery, managing dialysis complications, and capital building costs. Reference costs for dialysis are now available that may reflect more representative data. On this basis of this feature and the observation that children and adolescents tend to require higher staff-to – patient ratios than adults [1], it is expected that the costs of dialysis have been underestimated by the Astellas analysis.

The analysis does not account for discounts in price paid by hospitals for tacrolimus IR (Prograf), MMF, steroids and ciclosporin (in the sirolimus CNI minimisation regimen), which respectively were found to be one third, one tenth, one tenth, and one-half of the list prices (Table 47 and Table 76). The implications of these differences are further explored in the next section (6.3.3).

Table 51. Evers checklist (Evers 2005)[129] Astellas submission

	Item	Induction & Maintenance therapies
1.	Is the study population clearly described?	Y
2.	Are competing alternatives clearly described?	Y
3.	Is a well-defined research question posed in answerable form?	Y
4.	Is the economic study design appropriate to the stated objective?	Y
5.	Is the chosen time horizon appropriate to include relevant costs and consequences?	Y
6.	Is the actual perspective chosen appropriate?	Y
7.	Are all important and relevant costs for each alternative identified?	Y
8.	Are all costs measured appropriately in physical units?	Y
9.	Are costs valued appropriately?	Y
10.	Are all important and relevant outcomes for each alternative identified?	N
11.	Are all outcomes measured appropriately?	Y
12.	Are outcomes valued appropriately?	Y
13.	Is an incremental analysis of costs and outcomes of alternatives performed?	Y
14.	Are all future costs and outcomes discounted appropriately?	Y
15.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y
16.	Do the conclusions follow from the data reported?	Y
17.	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	N
18.	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	N
19.	Are ethical and distributional issues discussed appropriately?	N

6 INDEPENDENT ECONOMIC ASSESSMENT

6.1 Introduction

The objective of this independent economic assessment was to answer the following study question in line with the NICE reference case[165]:

> What is the cost-effectiveness of immunosuppressive regimens in renal transplantation in children and adolescents, of basiliximab and rabbit anti-human thymocyte immunoglobulin as an induction therapy and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept as a maintenance therapy?

We are aware of only one published economic evaluations which partially addresses the study question, which is the economic evaluation conducted to support current NICE guidance TA99, published by Yao et al.2006.[1] This evaluation did not include the interventions rabbit ATG, everolimus or belatacept. Astellas submitted an economic evaluation which also does not address the study question in full.

No economic evaluation has independently addressed the full study question in line with the NICE reference case and therefore a new economic assessment was required.

The economic assessment was conducted in parallel with an economic assessment of the same study question in the adult population (review of NICE guidance TA85) and the decision analytic model developed in Excel 2010 (Microsoft Corporation, Redmond, WA, USA) for the parallel assessment was used as the basis for answering the study question in this assessment in a cost–utility analysis with modifications to make it more relevant to the child/adolescent population.

6.2 Methods

6.2.1 Summary of changes from PenTAG model for adults

This economic assessment was conducted using an economic model originally developed by PenTAG to evaluate the cost-effectiveness of immunosuppressive agents in adult kidney transplant recipients. A summary of changes is provided here as a reference for readers familiar with the original model for adult KTRs (Table 52).

Table 52. Summary of changes from PenTAG model for adults

Type of change	Description	Detailed description and justification
Structural	Addition of two new arms: BAS+TAC+AZA and rATG+TAC+AZA	Section 6.2.2.4 (page 181)
	Change of assumed baseline regimen from BAS+TAC+MMF to BAS+TAC+AZA	Section 6.2.3 (page 185)
	Removal of DCD and living-unrelated donors for first graft	Section “Baseline” (page 202)
	Addition of extra retransplantation	Section 6.2.3.2 (page 189)
	Inclusion of six new arms (three pairs), based on child/adolescent RCTs identified in Section 4 (summarised in Table 10).	Section 6.2.3.1 (page 186)
	Inclusion of body weight and surface area as age-dependent variables affecting doses	Section 6.2.2.1 (page 178)
Natural history parameters	Baseline graft survival re-estimated for under 18s and according to age group (< 6, 6–12, > 12)	Section “Baseline” (page 202)
	Increased rate of retransplantation while under 18	Section 6.2.4.4 (page 219)
	Surrogate relationship between eGFR and graft survival re-estimated from a child/adolescent study	Section “Graft function at 12 months” (page 207)
	Baseline eGFR at 12 months re-estimated from a child/adolescent study	Section “Graft function at 12 months” (page 207)
	Probability of pre-emptive retransplantation at loss of first graft set to 20%	Section “Use of graft survival in the model” (page 200)
	Re-estimated baseline risks of acute rejection, cytomegalovirus infection and new-onset diabetes after transplantation	Section 6.2.4.3 (page 210)
	Re-estimated risk profiles for cytomegalovirus and Epstein–Barr virus	Table 89 (page 238) and Table 91 (page 240)
	Mortality rate while receiving dialysis estimated for under 18s	Section “Mortality after graft loss” (page 198)
Cost parameters (resource use)	Dosages for immediate-release tacrolimus, ciclosporin, mycophenolate mofetil, azathioprine and prednisolone updated with estimates from child/adolescent studies	Section “Maintenance therapy” (page 231)
	Cytomegalovirus prophylaxis resource use updated	Section “Infection prophylaxis” (page 237)
	Post-transplant monitoring resource use updated	Section “Monitoring” (page 238)
	Mix of haemodialysis and peritoneal dialysis estimated for under 18s	Section “Dialysis” (page 235)
Cost parameters (unit costs)	Cost of temporary access for haemodialysis estimated for under 19s[(a)]	Section “Dialysis” (page 245)
	Ongoing costs of haemodialysis and peritoneal dialysis updated for under 19s	Section “Dialysis” (page 245)

Cost of basiliximab 10 mg dose added for KTRs under 35 kg	Section "Induction" (page 243)
Costs estimated for differing severity of acute rejection (spontaneously resolving, steroid-sensitive and steroid-resistant)	Section "Acute rejection" (page 247)
Cost of post-transplant lymphoproliferative disease estimated	Section "Post-transplant lymphoproliferative disease" (page 250)
Costs of hypertension and hypomagnesaemia estimated	Sections "Hypomagnesaemia" (page 250) and "Hypertension" (page 250)
Costs of explant surgery estimated for under 19s	Section "Explant surgery" (page 254)
Costs of pre-transplant work-up and transplantation estimated for under 19s	Section "Subsequent transplant" (page 254)

a Costs are estimated for under 19s rather than under 18s as this is how NHS Reference Costs are reported

6.2.2 Modelling approach

6.2.2.1 Target population and subgroups

The target population was children and adolescents undergoing kidney-only transplantation (i.e., people receiving multi-organ transplants are not included). The upper age limit for the population "children and adolescents" is not always clear since young people aged 16–18 may receive their treatment in child/adolescent or adult centres.[166] Although some datasets only include young people aged under 16, the population for the economic assessment is children and adolescents aged under 18 years. The vast majority of transplant kidneys for this population come from DBD and living-related donors (UK Transplant Registry standard dataset, see infobox and Appendix 11 for further details).

The UK Transplant Registry standard dataset contains data on all solid organ transplants in the UK between 1995 and 2012. It allows linkage of multiple transplants for a single recipient and includes graft and patient survival (measured in days). 34,803 records refer to kidney-only transplants, of which: 29,759 recorded both graft and patient survival; 4,937 recorded graft survival only (although it may be inferred that the patient survived at least as long as the graft); 24 recorded patient survival only; and, 83 recorded neither graft nor patient survival.

The population modelled is incident kidney transplant recipients (KTRs), and did not include prevalent KTRs (i.e., people who received a kidney transplant in the past), or those suffering from acute rejection (although a number of the interventions separately have marketing authorisation for the treatment of acute rejection).

To explore the impact of age at time of transplantation on cost-effectiveness, subgroups were identified by age (Table 53). In addition to this the average cost-effectiveness of interventions was calculated by calculating weighted average total discounted costs and QALYs for each year of age. It was assumed that the same number of transplants would be conducted in 16 and 17 year olds as for 15 year olds in order to estimate the cost-effectiveness for under 18s. No other subgroups were analysed, since there was no evidence from child/adolescent RCTs identified in the systematic review of clinical effectiveness to support economic evaluation of these subgroups.

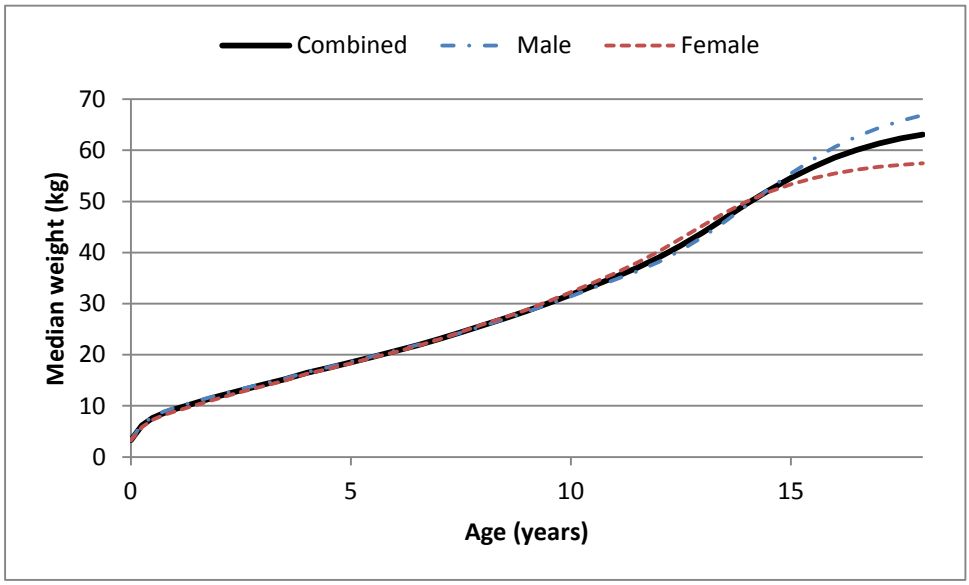
Table 53. Age distribution of child/adolescent KTRs in the UK

Age (years)	Number of transplants (2000–2013)	Proportion of transplants (2000–2013)
1	30	2.2%
2	77	5.5%
3	89	6.4%
4	83	6.0%
5	80	5.8%
6	66	4.7%
7	65	4.7%
8	80	5.8%
9	84	6.0%
10	91	6.5%
11	97	7.0%
12	120	8.6%
13	117	8.4%
14	151	10.9%
15	161	11.6%

Source: UK Renal Registry. The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

The weight and body surface area (BSA) of child/adolescent KTRs are important for dosing and are highly dependent on age. It was assumed that the weight of child/adolescent KTRs would follow the median weight of UK children and adolescents[158, 159] (Figure 14). In scenario analyses it was assumed instead that the weight of child/adolescent KTRs would follow the 9th centile weight of UK children and adolescents, to reflect the possibility that child/adolescent KTRs may have had their growth impaired by renal failure.

Figure 14. Median weight of UK children and adolescents according to age



Body surface area was then calculated from weight based on the table for BSA estimation in the BNF for Children 68[167, 168] as shown in Table 54.

Table 54. Estimated body surface area (BSA) for given weight

Weight (kg)	BSA (m²)	Weight (kg)	BSA (m²)	Weight (kg)	BSA (m²)
1	0.1	11	0.53	28–29	1.0
1.5	0.13	12	0.56	30–34	1.1
2	0.16	13	0.59	35–38	1.2
2.5	0.19	14	0.62	39–43	1.3
3	0.21	15	0.65	44–48	1.4
3.5	0.24	16	0.68	49–53	1.5
4	0.26	17	0.71	54–58	1.6
4.5	0.28	18	0.74	59–64	1.7
5	0.3	19	0.77	65–69	1.8
5.5	0.32	20	0.79	70–75	1.9
6	0.34	21	0.82	76–81	2.0
6.5	0.36	22	0.85	82–87	2.1
7	0.38	23	0.87	88–90	2.2
7.5	0.4	24	0.9		
8	0.42	25	0.92		
8.5	0.44	26	0.95		
9	0.46	27	0.97		
9.5	0.47				
10	0.49				

Source: BNFC 68

6.2.2.2 Setting and location

The NHS in England (although some data sources have been UK-wide, particularly the UK Renal Registry and the UK Transplant Registry standard dataset).

6.2.2.3 Study perspective

In line with the NICE reference case,[165] the perspective adopted on outcomes was all direct health effects for patients (and when relevant, carers), and the perspective adopted on costs was that of the NHS and personal social services (PSS).

6.2.2.4 Interventions and comparators

As the immunosuppressive agents are used in combination and in sequence we used treatment regimens as interventions and comparators rather than individual agents, although the cost-effectiveness of an individual agent versus another individual agent can then be

evaluated by considering the cost-effectiveness of regimens which are identical but for the use of the intervention agent or the comparator.

Regimens were included as interventions or comparators if they were in current use in the NHS or if they would plausibly be used in the NHS and there was sufficient clinical evidence to estimate the costs and outcomes for KTRs receiving those regimens. It was necessary to include regimens which are not in current clinical practice to allow all the interventions being appraised to have their cost-effectiveness appraised. The only regimen which is a pure "comparator regimen" (in that it contains no agents listed as interventions in the scope) is CSA+AZA.

Two regimens were included which were not included in the economic assessment for adults: BAS+TAC+AZA and rATG+TAC+AZA. The first was added as it is in common use in the NHS and the second was added to allow comparison of basiliximab and rabbit ATG in combination with immediate-release tacrolimus and azathioprine.

Table 55 presents the regimens considered in this analysis as well as an indication of whether the Assessment Group believes the regimen to be a licensed combination for children and adolescents (although no warranty or representation is given as to the correctness of the information presented in this regard, which reflects the Assessment Group's understanding of the marketing authorisation as stated in the summaries of product characteristics; this understanding has not been confirmed by a clinician or pharmacist and therefore its accuracy cannot be guaranteed, particularly as regards drug combinations).

Table 55. Immunosuppressive regimens included in independent economic assessment

Identifier	Induction therapy	Maintenance therapy[a]	Licensed
CSA+MMF	None	Ciclosporin and mycophenolate mofetil	Y
TAC+MMF	None	Immediate-release tacrolimus and mycophenolate mofetil	U
CSA+AZA	None	Ciclosporin and azathioprine	Y
TAC+AZA	None	Immediate-release tacrolimus and azathioprine	Y
CSA+EVL	None	Ciclosporin and everolimus	N
TAC+SRL	None	Immediate-release tacrolimus and sirolimus	N
TAC-PR+MMF	None	Prolonged-release tacrolimus and mycophenolate mofetil	N
BAS+CSA+MMF	Basiliximab	Ciclosporin and mycophenolate mofetil	Y
BAS+TAC+MMF	Basiliximab	Immediate-release tacrolimus and mycophenolate mofetil	U
BAS+CSA+AZA	Basiliximab	Ciclosporin and azathioprine	Y
BAS+TAC+AZA	Basiliximab	Immediate-release tacrolimus and azathioprine	U
BAS+SRL+MMF	Basiliximab	Sirolimus and mycophenolate mofetil	U
BAS+BEL+MMF	Basiliximab	Belatacept and mycophenolate mofetil	N
BAS+CSA+MPS	Basiliximab	Ciclosporin and mycophenolate sodium	N
rATG+CSA+MMF	Rabbit ATG	Ciclosporin and mycophenolate mofetil	Y
rATG+TAC+MMF	Rabbit ATG	Immediate-release tacrolimus and mycophenolate mofetil	U
rATG+CSA+AZA	Rabbit ATG	Ciclosporin and azathioprine	Y
rATG+TAC+AZA	Rabbit ATG	Immediate-release tacrolimus and azathioprine	Y

Key: Y, yes; N, no; U, uncertain
Noes: a, All maintenance regimens also included corticosteroids

Astellas in their submission also included the following regimens, which we have not modelled:

- Sirolimus and ciclosporin (with basiliximab induction) – note that we have modelled sirolimus and tacrolimus without basiliximab induction (although the SPC for sirolimus specifies it is to be used in combination with ciclosporin we found significantly more RCT evidence in the adult population where it was used in combination with tacrolimus)
- Everolimus and ciclosporin (with basiliximab induction) – note that we have modelled this without basiliximab induction because there were slightly more patients in adult RCTs receiving this regimen without induction
- Immediate-release tacrolimus ("specials" for first three years followed by Prograf for remaining life of graft) and mycophenolate mofetil (with basiliximab induction)

- Immediate-release tacrolimus (Modigraf for first three years followed by Prograf for remaining life of graft) and mycophenolate mofetil (with basiliximab induction)

The latter two regimens are for children and adolescents unable to swallow Prograf capsules (although, inconsistently, they are assumed to be able to swallow mycophenolate mofetil capsules and prednisolone tablets) and able to swallow Modigraf suspension (our expert advisory group has suggested some children cannot swallow Modigraf suspension and require fully liquid formulations, which can be purchased from specialist manufacturers rather than being prepared as specials by pharmacists or carers).

6.2.2.5 Time horizon

The time horizon was 50 years for consistency with the parallel HTA in adults and to ensure that all important differences in costs or outcomes between the technologies are included.

6.2.2.6 Discount rate

In line with the NICE reference case the discount rate for costs and health effects was 3.5% per annum.[169]

6.2.2.7 Choice of health outcomes

The primary health outcome of the independent economic assessment was quality-adjusted life years (QALYs) for each comparator regimen, in line with the NICE reference case.[169]

Secondary outcomes included:

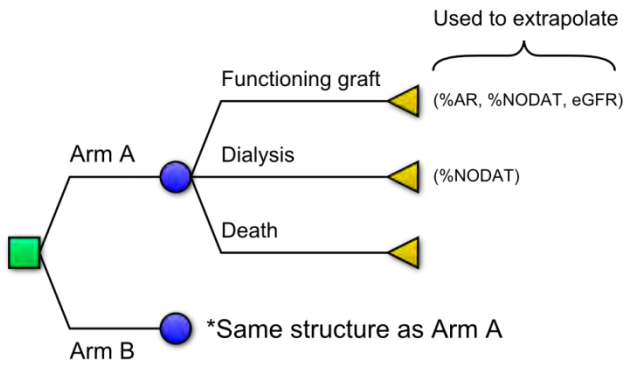
- Undiscounted life years (life expectancy)
- Undiscounted life years with a functioning graft
- Undiscounted life years on dialysis
- Likelihood of experiencing at least one episode of acute rejection
- Likelihood of developing new-onset diabetes after transplant (NODAT)
- Likelihood of receiving a 2nd, 3rd or 4th transplant

6.2.3 Model structure

Due to the paucity of RCT evidence in the child/adolescent kidney transplant population it was decided that two types of analyses would be conducted.

The first type of analysis was based on actual RCT evidence in the child/adolescent kidney transplant population meeting the inclusion criteria for our systematic review of clinical effectiveness evidence (see Section 4.1.2, page 82). For each RCT a decision tree was used to model the expected costs incurred and QALYs accrued for the duration of the trial (6.2.3.1, page186), followed by extrapolation using the Markov model (Section 6.2.3.2, page 189), as shown in Figure 15. These analyses allow for an estimation of the cost-effectiveness of the interventions basiliximab and immediate-release tacrolimus while relying on as little evidence from the adult population as possible, but do not allow for estimation of the cost-effectiveness of other interventions.

Figure 15. Simplified diagram of decision tree used for economic analyses based on child/adolescent RCTs



The second type of analysis was conducted using the Markov model only (Section 6.2.3.2, page 189) and by assuming effectiveness estimates from adults (relating to death within 12 months, graft loss within 12 months, acute rejection within 12 months, eGFR at 12 months, NODAT within 12 months, cytomegalovirus infection and dyslipidaemia) apply to children directly. This analysis allows the cost-effectiveness of all interventions and comparators to be evaluated, but relies on a strong assumption that the effectiveness estimates will not be biased when applied to a different population.

We do not present either type of analysis as a preferred base case since both have deficiencies. We attempt to draw conclusions by comparing the results of both types of analyses.

All analyses were constructed in Microsoft Excel 2010.

6.2.3.1 Decision tree

For each of the three RCTs in children and adolescents a decision tree was created which calculated the following outcomes for each arm:

- Costs (discounted and undiscounted) of immunosuppression, acute rejection and adverse events during the trial duration
- Life years up to the trial duration with functioning graft and with dialysis
- QALYs (discounted and undiscounted) during the trial duration
- For extrapolation using the Markov model:
    - Proportion of KTRs alive with functioning graft at the end of the trial duration
    - Proportion of KTRs dialysis-dependent at the end of the trial duration
    - Probability of acute rejection within 12 months
    - Probability of NODAT within 12 months
    - Graft function (mean eGFR) at 12 months

The discounted costs and QALYs from the decision tree and from the Markov model extrapolation were then combined. Cost-effectiveness results were presented both with ICERs and with incremental net health benefit figures (calculated at £20,000 and £30,000 per QALY). Cost-effectiveness results were also calculated by restricting the time horizon to the trial duration, i.e., without extrapolating using the Markov model.

For simplicity it was assumed that no KTRs losing their graft would be retransplanted within the trial duration. For Offner et al. 2008,[70] with follow-up of only one year this is likely to be a very reasonable assumption. For Grenda et al. 2006[72] and Trompeter et al. 2002,[74] with follow-up of two and five years this may result in a bias against the arm with greater graft loss.

Methods for estimating costs

Resource use as reported in the RCTs was used to estimate costs during the trial duration. Where the resource use for certain components was not reported in RCTs, either assumptions were made to extrapolate from RCT evidence in adults, or if these cost components were small and/or unlikely to vary between arms, these components were excluded from the analysis.

Immunosuppression resource use was frequently reported as dose per kg body weight or per m² body surface area, so these were estimated and were modelled to increase over the course of the trial duration in line with child/adolescent growth curves. If baseline body weight was not reported it was estimated based on age at baseline.

Methods for estimating life years

For each RCT we estimated the numbers and times of KTRs losing their grafts (any cause, including death with functioning graft) and the numbers and times of KTRs dying. It was then assumed that all KTRs not losing their graft or dying were censored at the end of the trial duration. Restricted mean survival was calculated (restricted to the trial duration), as shown in Table 56. The estimated life years with functioning graft was then the restricted mean graft survival (not censored for DWFG). Restricted mean patient survival minus restricted mean graft survival gave the estimated life years on dialysis.

Table 56. Restricted mean overall and graft surival in child/adolescent RCTs

Trial	Trompeter 2002		Grenda 2006		Offner 2008	
Arm	**TAC+AZA**	**CSA+AZA**	**TAC+AZA**	**BAS+TAC+AZA**	**BAS+CSA+MMF**	**CSA+MMF**
Overall survival						
T_{max}	4		2		1	
E[*T*]	3.921	3.852	1.996	2.000	0.984	1.000
SE[*T*]	0.0383	0.0733	0.0018		0.0057	
Graft survival						
T_{max}	4		2		1	
E[*T*]	3.769	3.609	1.840	1.884	0.975	0.994
SE[*T*]	0.0748	0.1030	0.0550	0.0503	0.0123	0.0055

For the probabilistic sensitivity analyses the restricted mean survivals were estimated by fitting a gamma random variable to the difference between follow-up and restricted mean survival using the method of moments. More specifically if T_{diff} is the difference between the follow-up duration (T_{max}) and the restricted mean survival (T):

$$T_{diff} = T_{max} - T$$

$$E[T_{diff}] = T_{max} - E[T]$$

$$SE[T_{diff}] = SE[T]$$

$$T_{diff} \sim \Gamma(\alpha, \beta)$$

$$\alpha = (E[T_{diff}]/SE[T_{diff}])^2$$

$$\beta = (SE[T_{diff}])^2/E[T_{diff}]$$

These gamma random variables were sampled separately for each arm and for graft survival and patient survival. In the event that graft survival was sampled as longer than patient survival (an impossibility) in one or both arms, graft survival was compressed in both arms by the same factor such that graft survival was equal to or less than patient survival.

If there were no events in one arm, the standard error of restricted mean survival in the total population was assumed for both arms, and a small constant was added to $E[T_{diff}]$ for both arms.

Outcomes for extrapolation

Overall survival (Kaplan–Meier) as reported by the RCTs was used to estimate the proportion of children and adolescents dead at the end of the trial duration, i.e., at the start of extrapolation using the Markov model. Kaplan–Meier graft survival (this time censored for death with functioning graft) was used to estimate the proportion of those alive who would still have a functioning graft.

Table 57. Outcomes from decision trees for extrapolation with Markov models

Trial	Trompeter 2002		Grenda 2006		Offner 2008	
Arm	**TAC+AZA**	**CSA+AZA**	**TAC+AZA**	**BAS+TAC+AZA**	**BAS+CSA+MMF**	**CSA+MMF**
KM overall survival	0.94	0.92	0.989	1.000	0.972	1.000
KM graft survival (censored for DWFG)	0.954	0.792	0.896	0.949	0.981	0.989
Acute rejection within 12 months	0.43	0.62	0.26	0.24	0.13	0.23
NODAT within 12 months	0.019	0.011	0.011	0.040	0.0	0.0
eGFR at 12 months (ml/1.73 m²)	64.9	57.8	74.9	74.0	79	82

6.2.3.2 Markov model

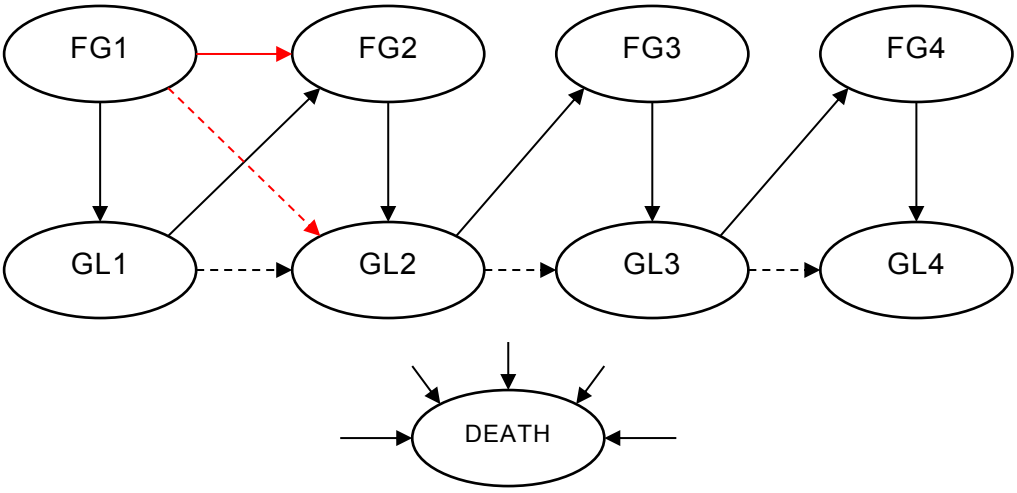
A Markov model structure was used with three main states: FUNCTIONING GRAFT, GRAFT LOSS and DEATH.

KTRs start in the FUNCTIONING GRAFT unless they suffer primary non-function, in which case they start in the GRAFT LOSS state. Transitions can occur from FUNCTIONING GRAFT to GRAFT LOSS, reflecting disease progression; transitions are not permitted in the opposite direction except through retransplantation. Up to three retransplantations are possible and therefore there are four substates for FUNCTIONING GRAFT and GRAFT LOSS reflecting the graft number (1–4). As with the initial graft it is possible that primary non-function will occur and therefore transitions can occur directly to GRAFT LOSS following second, third or fourth graft. Pre-emptive retransplantation can occur from the original FUNCTIONING GRAFT state, but not from FUNCTIONING GRAFT states 2–4. Death can occur from any state but the rate of mortality is greater in the GRAFT LOSS state (see Section 7.3.3.3, page 421) and increases with age.

Irrespective of the regimen used for immunosuppression in the first graft, a common regimen was used for subsequent grafts (BAS+TAC+MMF), since this was judged the most likely regimen for kidney transplantation in adults (and most retransplantations are expected to occur after KTRs reach adulthood).

Figure 16 gives the model diagram showing the nine states in the model. Self-links are omitted from all states in both figures for clarity (there are no tunnel states).

Figure 16. Markov model diagram



Key: FR, functioning graft; GL, graft loss.
Note that red arrows indicate pre-emptive retransplantation while dashed arrows signify primary non-function of a subsequent retransplantation

In addition to these health states, for each regimen the incidence of acute rejection, cytomegalovirus (CMV) infection, dyslipidaemia and new-onset diabetes after transplantation (NODAT) was estimated.

For each allowable transition a transition rate was modelled. The probability of each transition was then calculated using the following formula:

$$p_i = (r_i / R) \times (1 - e^{-R\Delta t})$$

Where r_i is the hazard rate of the specific transition, R is the sum of allowable transition rates (including r_i) and Δt is the time step (cycle length).

gives a summary of how the transition rates were dependent on factors such as age, acute rejection and NODAT. BAS+TAC+AZA was assumed to be the baseline regimen for the initial graft, for the following reasons:

- Only two of the four regimens in current use in the NHS (TAC+AZA and BAS+TAC+AZA) are consistent with current NICE guidance TA99
- Although the most common regimen in usage is TAC+AZA, this is also expected to result in worse outcomes than BAS+TAC+AZA, TAC+MMF and BAS+TAC+MMF (except death

within 12 months where it is expected to be superior to TAC+MMF and eGFR at 12 months where it is expected to be superior to TAC+MMF and BAS+TAC+MMF) according to network meta-analyses of adult RCT evidence, and so TAC+AZA may not be as close to average UK outcomes as BAS+TAC+AZA

Table 58. Summary of determining factors for transition rates within the Markov model

Transition	Corresponding clinical outcome	Dependent on
FUNCTIONING GRAFT to GRAFT LOSS (first graft)	Disease progression (graft loss/survival)	**First year** Time since transplantation Regimen-specific odds ratio of graft loss within 12 months **Subsequent years** Time since transplantation BPAR within 12 months NODAT within 12 months eGFR at 12 months
FUNCTIONING GRAFT to GRAFT LOSS (subsequent graft)	Disease progression (graft loss/survival)	(Constant)
FUNCTIONING GRAFT to DEATH (first graft)	Death with functioning graft	**First year** Time since transplantation Regimen-specific hazard ratio based on odds ratio of patient death within 12 months **Subsequent years** Time since transplantation Age NODAT
FUNCTIONING GRAFT to DEATH (subsequent graft)	Death with functioning graft	Age NODAT
GRAFT LOSS to subsequent FUNCTIONING GRAFT	Retransplantation	Age
GRAFT LOSS to DEATH	Mortality while receiving dialysis	Age

6.2.4 Factors included in the model

6.2.4.1 Overall survival

Overall survival was not explicitly included as an input to the model and therefore emerges from the two modelled rates of mortality (page 195 and 198).

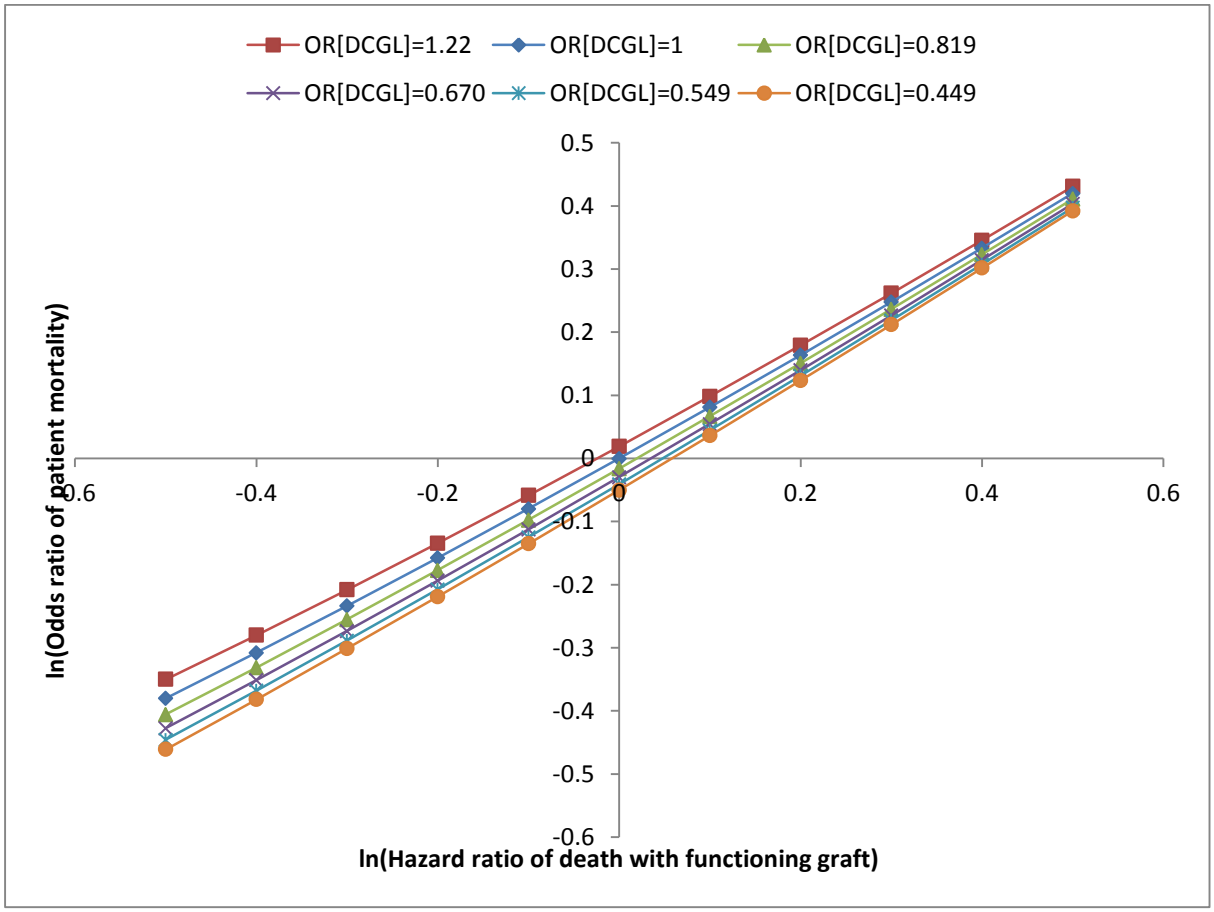
The exception to this is that the rate of death with functioning graft in the first year was adjusted using an individual hazard ratio for each regimen to achieve the desired odds ratio

of patient mortality as derived from the mixed treatment comparison and head-to-head comparisons.

While it would be possible to use numerical methods (e.g., Solver add-in for Microsoft Excel) to achieve exact patient mortality it was felt it would add significant computational burden, create significant opportunity for human error (forgetting to re-run Solver every time relevant parameters were changed), and would greatly slow down probabilistic sensitivity analyses.

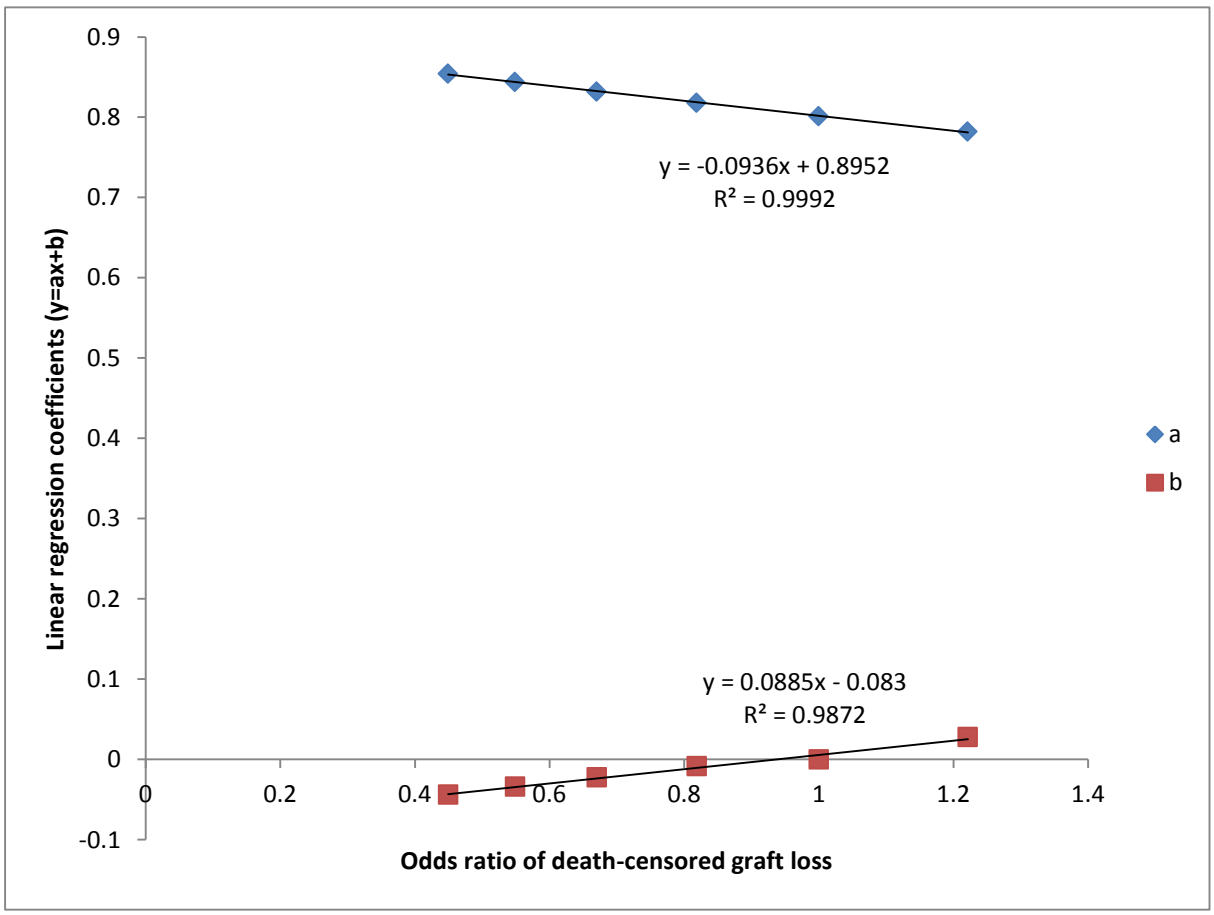
Therefore a regression approach was used instead, by running different parameter values through the model and recording the resulting odds of mortality within 12 months. The two factors driving patient survival at 12 months which could vary between regimens were identified as the odds ratio of graft loss (after returning to dialysis the mortality rate increases) and the hazard ratio of death with functioning graft. The odds ratio of patient mortality within 12 months was plotted against the hazard ratio of death with functioning graft for various different odds ratios of graft loss, and was found to be linearly dependent on a log-log plot (Figure 17).

Figure 17. Odds ratio of patient mortality is dependent on hazard ratio of death with functioning graft and odds ratio of death-censored graft loss



For each odds ratio of graft loss, linear regression of ln(Odds of patient mortality) versus ln(Hazard ratio of death with functioning graft) was performed, and the values of the linear regression coefficients were found to be linearly dependent on the odds ratio of graft loss (Figure 18).

Figure 18. Linear regression coefficients for ln(odds ratio of patient death) vs. ln(hazard ratio of death with functioning graft) plotted versus odds ratio of graft loss



The appropriate hazard ratio for death with functioning graft to achieve a desired odds ratio of patient mortality is therefore derived as follows (where $OR_{DCGL,i}$ is the odds ratio of graft loss, $HR_{DWFG,i}$ is the hazard ratio of death with functioning graft and $OR_{PD,i}$ is the odds ratio of patient death):

$$a_i = 0.8952 - 0.0936 \times OR_{DCGL,i}$$

$$b_i = 0.0885 \times OR_{DCGL,i} - 0.083$$

$$HR_{DWFG,i} = \exp\left\{\frac{\ln\left(OR_{PD,i}\right) - b_i}{a_i}\right\}$$

As can be seen in Table 59, the regression formulae perform well in most instances.

Table 59. Comparison of hazard ratios for death with functioning graft from regression and calculated using Solver

Regimen	HR for DWFG from regression	HR for DWFG from Solver
CSA+MMF	0.724	0.717
TAC+MMF	1.302	1.295
CSA+AZA	0.745	0.739
TAC+AZA	1.129	1.127
CSA+EVL	1.186	1.183
TAC+SRL	1.106	1.105
TAC-PR+MMF	1.739	1.696
BAS+CSA+MMF	0.641	0.629
BAS+TAC+MMF	1.143	1.142
BAS+CSA+AZA	0.661	0.649
BAS+SRL+MMF	1.308	1.299
BAS+BEL+MMF	0.284	0.227
BAS+CSA+MPS	0.388	0.349
rATG+CSA+MMF	0.429	0.395
rATG+TAC+MMF	0.764	0.760
rATG+CSA+AZA	0.439	0.402
rATG+TAC+AZA	0.655	0.642

Death with functioning graft

In adult KTRs death with functioning graft (DWFG) is a significant cause of graft loss. It is a less significant cause of graft loss for children and adolescents because their life expectancy is much greater.

Compared to dialysis recipients, more KTRs die from infection and malignancy, the risk of both being increased by greater immunosuppression.[170] Cardiovascular disease is also a significant cause of mortality in people who have transplants. As with members of the general population, the mortality rate increases with age, plus there are a number of

additional risks factors affecting patient survival which are adjusted for when comparing survival across different centres.[171]

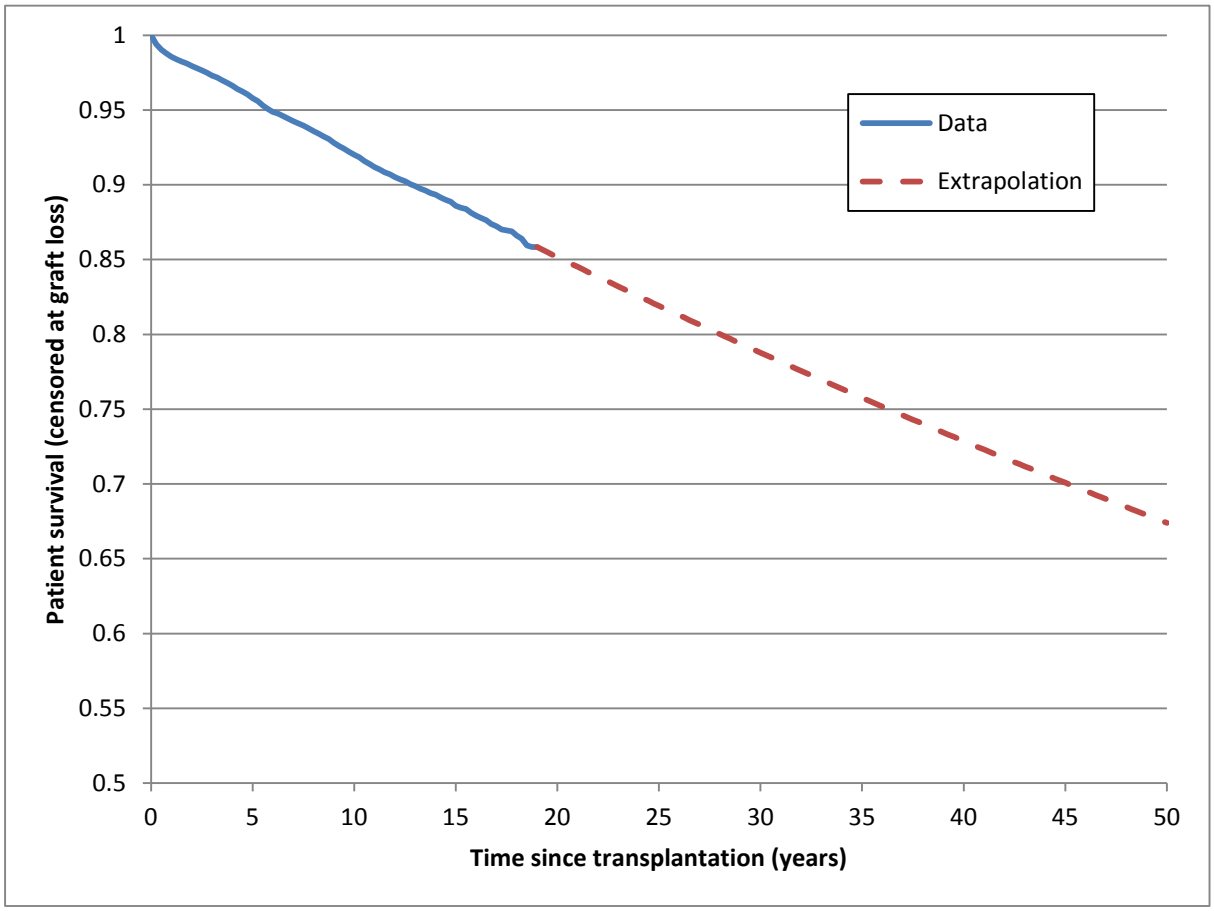
Crude estimates of DWFG will vary according to immunological risk and donor kidney type (i.e., living donor, DCD, DBD) because of differences in baseline demographics (living donor KTRs tend to be younger) and in immunosuppression (KTRs at greater immunological risk tend to receive greater immunosuppression which increases the risk of infection and malignancy).[172] The use of steroids is also linked to increased risk of death from cardiovascular disease and infection.[173]

There is also evidence to suggest that the risks of cardiovascular and infectious causes of death are elevated in KTRs with reduced graft function at one year post-transplantation.[173]

The modelling framework employed allowed flexibility in the rate of DWFG in the first graft modelled but less flexibility for subsequent grafts, for which it could not be dependent on time since transplantation.

The baseline rate of DWFG for the first graft was estimated from the UK Transplant Registry standard dataset for each donor type (DBD, DCD, living related, living unrelated) after adjusting for transplant period (adjusted to 2007–2012) and age group (adjusted to 31–50 years). The Kaplan–Meier survival function was directly used for the first nineteen years, followed by an extrapolation based on the estimated rate of DWFG from 9–19 years. The baseline survivor function is shown in Figure 19.

Figure 19. Baseline survivor function for death with functioning graft



The rate of death with functioning graft was then adjusted by sex, donor type and age based on a Cox proportional-hazards analysis of the UK Transplant Registry dataset (Table 60). For the first 12 months an individual hazard ratio was applied for each regimen to achieve a target odds ratio of patient mortality (see Section 6.2.4.1, page 192), and thereafter a hazard ratio for NODAT was applied according to Cole et al. 2008.[174]

Table 60. Hazard ratios applied to rate of death with functioning graft

Covariate	Hazard ratio
NODAT	1.41
Sex – Female	0.865
Donor type	
• DBD	1
• DCD	1.083
• Living-related	0.551
• Living-unrelated	0.703
Age	
• < 18	0.377
• 18–30	0.369
• 31–40	0.712
• 41–50	1
• 51–60	2.140
• 61–70	4.128
• 71–75	7.583
• 76–80	8.576
• 81–85	13.751
• > 85	23.552

Mortality after graft loss

Following graft loss, in the absence of an available kidney for pre-emptive re-transplantation, KTRs will be placed on dialysis. Some KTRs will be waitlisted for re-transplantation while others will be judged not fit for re-transplantation due to unsuitability for surgery or prohibitively great immunological risk. The mortality rate for dialysis recipients is known to be significantly greater than that for age-matched members of the general population.[151]

It was assumed that mortality rates following graft loss would be the same as mortality rates for dialysis recipients and dependent on age group (see Table 61). It is notable that the rate

of mortality for children and adolescents on dialysis is higher than the rates for KTRs aged 18–49.

For the probabilistic sensitivity analysis the standard error of mortality rate in each group was estimated by dividing the square root of the number of observed deaths by the estimated exposure.

Table 61. Mortality rate for dialysis recipients

Age group	Hazard rate of mortality (SE)
< 18	0.034 (0.011)
18–24	0.010 (0.003)
25–29	0.012 (0.003)
30–34	0.009 (0.002)
35–39	0.015 (0.002)
40–44	0.021 (0.002)
45–49	0.027 (0.002)
50–54	0.041 (0.003)
55–59	0.053 (0.003)
60–64	0.079 (0.004)
65–69	0.107 (0.005)
70–74	0.149 (0.006)
75–79	0.211 (0.007)
80–84	0.275 (0.011)
85+	0.408 (0.019)

Key: SE, standard error
Notes: Calculated from results in Table 8.18 of Pruthi et al. 2013[151]

6.2.4.2 Graft survival

Graft survival is a key measure of the clinical effectiveness of an immunosuppressive regimen and is critical also for cost-effectiveness since graft loss necessitates expensive dialysis treatment which has a detrimental impact on health-related quality of life or retransplantation (a costly procedure).

Use of graft survival in the model

In the model regimen-specific graft survival drives transitions from functioning graft to graft loss states for the first graft, whereas for subsequent grafts a constant rate of graft loss was assumed across all regimens (see section Subsequent grafts, page220).

The transitions for the first graft are calculated by first estimating a graft survival curve (censored for death with functioning graft) for each regimen, then multiplying this with a curve estimating patient survival (censored for graft loss) to obtain an estimate for how many KTRs should be alive and in the FUNCTIONING GRAFT state in each cycle. The rate of graft loss for cycle *i* is then calculated as:

$$r_{GL}(t_i) = [\ln(S(t_i)) - \ln(S(t_{i+1}))]/\Delta t$$

Where $S(t_i)$ is the product of survival curves for the start of cycle *i* and $\Delta t = t_{i+1} - t_i$ is the cycle length.

The details for how the survival curves are estimated were given earlier (page 195), but briefly:

- Graft survival censored for death with functioning graft is estimated by adjusting baseline graft survival from the UK Transplant Registry standard dataset in the first year according to the odds ratio of graft loss within 12 months and thereafter according to a surrogate relationship based on acute rejection within 12 months, NODAT within 12 months and eGFR at 12 months.

- Death with functioning graft is estimated by adjusting baseline patient survival estimated from the UK Transplant Registry standard dataset in the first year according to the odds ratio of patient death within 12 months and thereafter according to a surrogate relationship based on NODAT within 12 months.

To account for the possibility of pre-emptive retransplantation the rate of graft loss is partitioned between transitions from: first FUNCTIONING GRAFT to GRAFT LOSS following first graft; first FUNCTIONING GRAFT to second FUNCTIONING GRAFT (successful pre-emptive retransplantation); and, first FUNCTIONING GRAFT to GRAFT LOSS following second graft (unsuccessful pre-emptive retransplantation). It was assumed that 20% would receive pre-emptive retransplantation,[175] of which 1.6% would result in primary non-function (based on the UK Transplant Registry standard dataset).

Estimation of graft survival

It has been established in adults that acute rejection, NODAT and graft function measured at 12 months are predictive of graft survival.[174, 176-180]

For children and adolescents we identified far fewer studies estimating the relationship between the potentially predictive attributes identified for adults (acute rejection, NODAT and graft function at 12 months) and graft survival.

Muscheites et al. 2009[181] considered a number of potentially predictive factors for death-censored graft loss in 104 children and adolescents receiving kidney transplants in one of four German centres: recipient age (< 6 years, 6–12 years, > 12 years); recipient gender; donor type; number of HLA mismatches; number of rejection episodes; underlying renal disease; transplant period (1989–1995, 1996–2000); change in GFR (between 30 days and 12 months; between 6 and 12 months); GFR at 30 days, 6 months and 12 months. KTRs with graft survival less than one year were excluded, and the mean follow-up was 8.3 years. They found that in univariate Cox analyses only the absolute GFR values at 30 days, 6 months and 12 months were predictive of graft survival with a significance level of 0.05. Furthermore, when considering a multivariate Cox analysis only GFR at 12 months was predictive of long-term graft survival. This study concludes that acute rejection is not predictive (in univariate or multivariate analyses, significance level 0.05), but does not report any central estimates for the hazard ratio due to acute rejection. It is possible that the study was insufficiently powered to estimate the effect of acute rejection on graft survival with precision, and it is also possible that excluding patients with graft survival less than one year would also limit the predictive power of acute rejection. The study also does not include NODAT as a covariate.

Tejani et al. 2000[182] considered the relationship between acute rejection and “chronic rejection graft loss (CRGL)” (which accounted for 30.8% of failed grafts). Although they found that acute rejection is a significant predictor of CRGL they do not report the relationship between acute rejection and graft loss overall.

It was decided that the relationship between eGFR and graft survival would be estimated based on the results of Muscheites et al. 2009[181] as these appear to be in the relevant population and estimated using appropriate statistical methodology. It was decided that for acute rejection and NODAT the same relationship as used for the adult population would be used, since this is consistent with TA99 (where the Committee in their consideration of the evidence accepted an acute rejection surrogate relationship based on adult evidence).

It could be argued that, since no statistically significant evidence for a relationship between acute rejection and graft survival was found by Muscheites et al. 2009[181] that no such relationship should be included in the model, but it was felt that if two regimens were predicted to result in the same eGFR but one regimen was predicted to reduce the rate of acute rejection that this should be reflected in the predicted graft survival. Also since Muscheites et al. 2009[181] did not report the central estimate for the hazard ratio according to acute rejection it is possible that the central estimate may not be too different from the hazard ratio for adults.

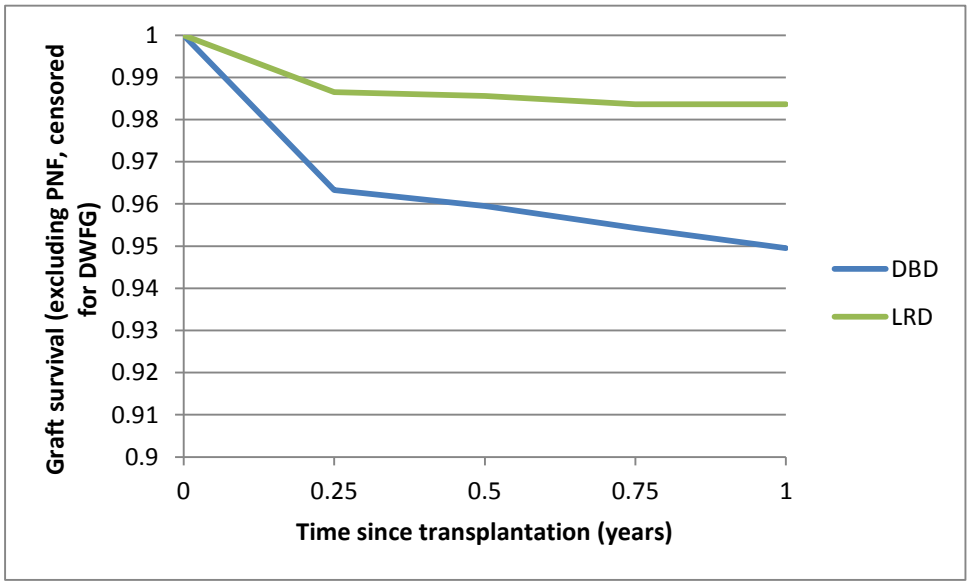
It may also be noted that the hazard ratio of graft loss (for KTRs experiencing BPAR in the first 12 months versus KTRs not experiencing BPAR) assumed in this model (1.60 on the basis of adult evidence) is less than the hazard ratio assumed to inform TA85 and TA99 (1.96), although it is greater than a hazard ratio proposed by the Assessment Group for TA99 and rejected by the NICE Appraisal Committee at that time (a value of 1.41).

Throughout this section it should be noted that graft survival (and the underlying event, graft failure) does not include death with functioning graft, i.e., only considering people who are alive and who become dependent on dialysis or require retransplantation.

Baseline

Baseline graft survival for the first year was estimated from the UK Transplant Registry standard dataset using the Kaplan–Meier method, restricting to the first graft for each recipient and adjusting to the year 2012 (using Cox proportional hazards on transplant year). Graft survival was estimated separately for DBD and living-related donors (DCD and living-unrelated donors are very rare in child/adolescent transplantation). KTRs with graft failure on the day of transplant were assumed to have primary non-function (PNF) and were excluded. Any KTRs dying with a functioning graft were censored at the time of death. Figure 20 gives the baseline graft survival.

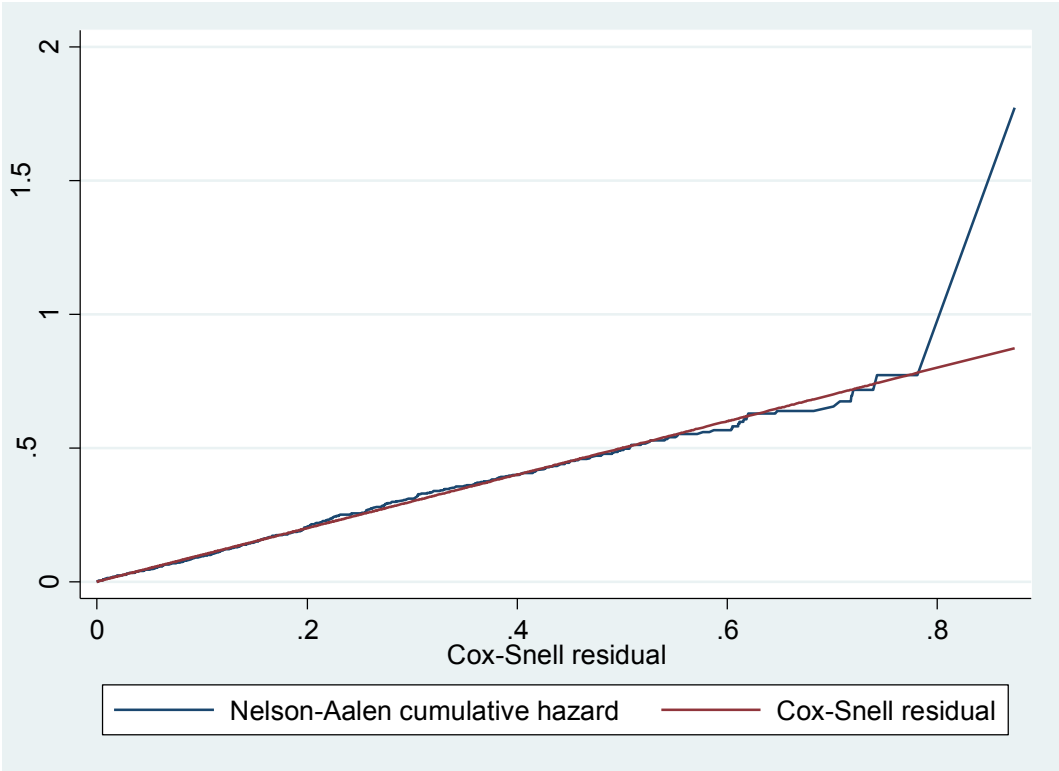
Figure 20. Graft survival in first year according to donor type



Baseline graft survival was extrapolated by fitting a Weibull curve to conditional survival from one year for first graft (i.e., fitted to KTRs whose first grafts survived at least one year), with proportional hazards covariates for donor type and transplant year. The fit of this Weibull curve was verified with a graphical test of the Cox-Snell residuals (Figure 21), which demonstrated that the fit was good since there was little deviation from the diagonal except for long follow-up (when censoring tends to cause such deviations).

Other parametric survival distributions were not explored due to the adequacy of the Weibull fit and for consistency with the parallel HTA (in which a Weibull curve was further indicated due to the need to apply hazard ratios derived from a separate Weibull fit reported by Levy et al. 2014[178]).

Figure 21. Graphical verification of the fit to graft survival



The baseline model for conditional graft survival from one year is then:

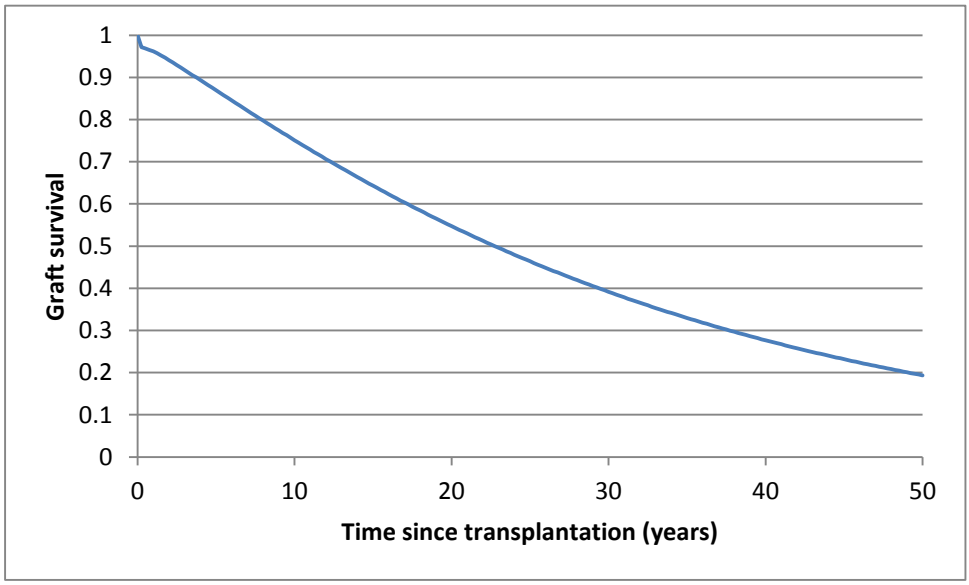
$S(t) = \exp\{-\lambda t^{\gamma}\}$

Where t is time after one year, λ is the rate parameter and γ is the shape parameter (with a value of 1.103, implying increasing hazard rate with time).

A different rate parameter is obtained for different covariate values (proportional hazards model), the baseline rate parameter was obtained by assuming the following covariate values: donor type = {(DBD, 0.638), (Living-related, 0.362)}; transplant year = 2012. These led to a baseline rate parameter value of 0.02187.

The resulting baseline graft survival in the PenTAG model is shown in Figure 22.

Figure 22. Baseline graft survival in the PenTAG model



Results presented by Hudson and Collett at the British Transplantation Society Congress (February 2014) suggest that for deceased donors the median graft survival (death-censored) for DBD grafts is 21–22 years (and higher for grafts from living donors), while estimated 30 year graft survival is 36% for DBD grafts (and expected to be higher for living donor grafts).[183] These results serve as external validation of the extrapolation in the PenTAG model.

Adjustments during the first year

Graft survival for the first year was adjusted using the proportional odds method such that for each regimen the odds ratios of graft loss (excluding death and PNF) throughout the first year matched the odds ratios of graft loss as detailed in Section 6.2.5.1 (page 222).

Adjustments after the first year

Graft survival for the first graft after the first year was modelled using the surrogate endpoints renal function at 12 months, acute rejection within 12 months and NODAT within 12 months.

The surrogate relationship was implemented using proportional hazards and summarised in Table 62 and expanded in sections below. The rate parameters for all regimens (after adjusting according to the surrogate relationship) are given in Table 63. The resulting graft survival (excluding death with functioning graft) at one, three, five and ten years for each regimen are given in Table 64.

Table 62. Surrogate relationship hazard ratios for graft survival

Relationship	Hazard ratio	Source
Acute rejection within 12 months	1.60	Cole et al. 2008[174]
Renal function (eGFR) at 12 months	eGFR > 80: 1	Muscheites et al. 2009[181]
	45 < eGFR ≤ 80: 1.59	
	eGFR ≤ 45: 55.9	
NODAT within 12 months	1.12	Cole et al. 2008[174]

Table 63. Rate parameters for graft survival after one year

Regimen	Rate parameter (λ)
CSA+MMF	0.0391
TAC+MMF	0.0300
CSA+AZA	0.0461
TAC+AZA	0.0269
CSA+EVL	0.0331
TAC+SRL	0.0424
TAC-PR+MMF	0.0303
BAS+CSA+MMF	0.0323
BAS+TAC+MMF	0.0247
BAS+CSA+AZA	0.0375
BAS+TAC+AZA	0.0219
BAS+SRL+MMF	0.0286
BAS+BEL+MMF	0.0210
BAS+CSA+MPS	0.0272
rATG+CSA+MMF	0.0346
rATG+TAC+MMF	0.0267
rATG+CSA+AZA	0.0397
rATG+TAC+AZA	0.0236

Table 64. 1-, 3-, 5- and 10-year graft survival for each regimen

Regimen	Graft survival (excluding death with functioning graft and primary non-function)			
	1 year	3 years	5 years	10 years
CSA+MMF	97.01%	89.19%	80.97%	62.34%
TAC+MMF	97.24%	91.16%	84.65%	69.27%
CSA+AZA	96.02%	86.97%	77.62%	57.06%

Regimen	Graft survival (excluding death with functioning graft and primary non-function)			
	1 year	3 years	5 years	10 years
TAC+AZA	95.47%	90.10%	84.30%	70.42%
CSA+EVL	97.51%	90.81%	83.69%	67.09%
TAC+SRL	95.37%	87.06%	78.40%	59.06%
TAC-PR+MMF	96.70%	90.60%	84.07%	68.66%
BAS+CSA+MMF	97.47%	90.94%	83.98%	67.69%
BAS+TAC+MMF	97.66%	92.61%	87.14%	73.88%
BAS+CSA+AZA	96.63%	89.15%	81.27%	63.27%
BAS+TAC+AZA	96.16%	91.74%	86.92%	75.11%
BAS+SRL+MMF	96.52%	90.76%	84.56%	69.84%
BAS+BEL+MMF	97.91%	93.59%	88.87%	77.26%
BAS+CSA+MPS	97.81%	92.25%	86.26%	71.92%
rATG+CSA+MMF	97.67%	90.66%	83.23%	66.04%
rATG+TAC+MMF	97.85%	92.39%	86.49%	72.36%
rATG+CSA+AZA	96.88%	88.96%	80.66%	61.88%
rATG+TAC+AZA	96.45%	91.69%	86.51%	73.91%

Graft function at 12 months

The average graft function (eGFR) at 12 months for each regimen was estimated by estimating the baseline average eGFR at 12 months. We were unable to find these figures in the UK Renal Registry annual reports; the best available estimate is 82 ml/min/1.73 m² (SD 27 ml/min/1.73 m²) from a German multicentre observational study.[181]

This study, by Muscheites et al.2009[181] also informs the surrogate relationship between graft function at 12 months and graft survival. Dividing eGFR into three categories (<45 ml/min/1.73 m², 45–80 ml/min/1.73 m², >80 ml/min/1.73 m²) the authors found that compared to KTRs in the highest eGFR category at 12 months, those in the lowest had significantly worse graft survival (hazard ratio 55.9, 95% CI 5.29–591), and those in the middle category had worse graft survival, but this was not shown to be statistically significant (hazard ratio 1.59, 95% CI 0.52–4.87).

The regimen-specific proportion of KTRs in each eGFR category at 12 months was estimated by first, calculating the expected mean eGFR for the regimen by adding the regimen-specific mean eGFR difference (Section 6.2.5.1, page 222) to the baseline mean eGFR; then, assuming a normal distribution with standard deviation 27 ml/min/1.73 m².

Acute rejection within 12 months

Acute rejection rates within 12 months were estimated using effectiveness estimates as described in Section 6.2.5.1 (page 222) and a baseline acute rejection rate for BAS+TAC+AZA.

The baseline acute rejection rate for BAS+TAC+AZA was estimated as 19/99 = 19.2% from Grenda et al. 2006.[72]

The effect of acute rejection on graft survival after the first year was estimated using the hazard ratio of 1.60 from Cole et al. 2008.[174] A regimen-specific raw hazard ratio was then calculated according to the weighted average of the hazard ratios for acute rejection (1.60) and no rejection (1.00) with the weights equal to the acute rejection rate for each regimen. These were then normalised to give hazard ratios versus the baseline (BAS+TAC+AZA), as shown in Table 65.

Table 65. Acute rejection rates and hazard ratio for graft survival due to acute rejection for each regimen

Regimen	Acute rejection rate	Raw hazard ratio	Hazard ratio vs. baseline
CSA+MMF	27.83%	1.167	1.046
TAC+MMF	24.57%	1.147	1.029
CSA+AZA	44.98%	1.270	1.139
TAC+AZA	32.09%	1.193	1.069
CSA+EVL	27.19%	1.163	1.043
TAC+SRL	23.89%	1.143	1.025
TAC-PR+MMF	24.11%	1.145	1.026
BAS+CSA+MMF	16.24%	1.097	0.984
BAS+TAC+MMF	14.07%	1.084	0.972
BAS+CSA+AZA	29.13%	1.175	1.053
BAS+TAC+AZA (baseline)	19.19%	1.115	1.000
BAS+SRL+MMF	15.22%	1.091	0.979
BAS+BEL+MMF	24.88%	1.149	1.031
BAS+CSA+MPS	22.37%	1.134	1.017

rATG+CSA+MMF	11.98%	1.072	0.961
rATG+TAC+MMF	10.31%	1.062	0.952
rATG+CSA+AZA	22.40%	1.134	1.017
rATG+TAC+AZA	14.30%	1.086	0.974

NODAT within 12 months

The methods for estimating the incidence of NODAT within the first 12 months since transplantation are described in the section Diabetes (page 210).

The effect of NODAT on graft survival after the first year was estimated using the hazard ratio of 1.12 from Cole et al. 2008[174] (based on the adult population) and incorporated using the same methodology as for graft function and acute rejection. Table 66 demonstrates that the impact of NODAT on graft survival is fairly small, which is to be expected given the conclusions of Cole et al. that NODAT primarily increases the rate of death with functioning graft, which is not considered here.

Table 66. Incidence of NODAT and effect on graft survival for each regimen

Regimen	Incidence of NODAT	Raw hazard ratio	Hazard ratio vs. baseline
CSA+MMF	1.83%	1.002	0.997
TAC+MMF	4.04%	1.005	1.000
CSA+AZA	1.83%	1.002	0.997
TAC+AZA	4.04%	1.005	1.000
CSA+EVL	1.74%	1.002	0.997
TAC+SRL	6.33%	1.008	1.003
TAC-PR+MMF	4.75%	1.006	1.001
BAS+CSA+MMF	1.83%	1.002	0.997
BAS+TAC+MMF	4.04%	1.005	1.000
BAS+CSA+AZA	1.83%	1.002	0.997
BAS+TAC+AZA (baseline)	4.04%	1.005	1.000
BAS+SRL+MMF	3.22%	1.004	0.999
BAS+BEL+MMF	0.79%	1.001	0.996

BAS+CSA+MPS	1.71%	1.002	0.997
rATG+CSA+MMF	1.83%	1.002	0.997
rATG+TAC+MMF	4.04%	1.005	1.000
rATG+CSA+AZA	1.83%	1.002	0.997
rATG+TAC+AZA	4.04%	1.005	1.000

6.2.4.3 Adverse events

Synthesis of adverse event data is rarely conducted across studies due to typically low incidence (resulting in low statistical power to detect differences) and heterogeneity of reporting. The challenge of synthesising such data is impossible in the case of child/adolescent kidney transplantation due to the paucity of RCT evidence. Even so, for this model and in the model for the adult population it was judged important to consider the possible impact of different regimens on adverse event rates because the profile of adverse events is considered highly clinically relevant.

Owing to the lack of RCT evidence in children and adolescents it was decided that in the analysis where effectiveness estimates are drawn from adult RCT evidence, that also the impact of regimens on adverse events should also be drawn from those adult RCTs. In the analyses based on child/adolescent RCTs, however, where possible estimates of incidence were taken from those child/adolescent RCTs, even when this meant a different set of adverse events was included.

In this section and subsections we describe how the incidence of NODAT, CMV infection, dyslipidaemia and anaemia are estimated in the analysis based on adult RCT evidence.

Cytomegalovirus infection is assumed to be a one-off event occurring in the first year, whereas NODAT, dyslipidaemia and anaemia are chronic conditions modelled for the full time horizon while patients are alive. All adverse events incur costs while NODAT additionally results in a utility decrement (see Section 6.2.6.4, page 228).

Diabetes

The incidence of diabetes in individuals receiving dialysis is higher than that in the general population, at around 6% per year, with incidence marginally higher in individuals receiving haemodialysis.[184] Kidney transplantation appears to result in a significant increase in the incidence of diabetes in the first year post-transplant (and especially in the first six months),

after which incidence falls to similar levels to those seen in people on dialysis (see Figure 2 of Woodward et al. 2003[184]). Tacrolimus has been repeatedly associated with the development of NODAT[4, 174] and the same incidence pattern is observed of significantly elevated incidence in the first year post-transplant.[184]

Pre-existing diabetes in the cohort was not modelled, only NODAT within 12 months. Based on a visual inspection of Figure 1 of Woodward et al. 2003[184] it was assumed that 75% of NODAT in the first year would occur within the first six months. Incidence of NODAT after the first year was not modelled, since the results of Woodward et al. suggest that after the first year the incidence of diabetes returns to pre-transplantation levels.

As in the model for adult KTRs we assume that after the first year there is no change in the prevalence of NODAT in the population.

Baseline 12-month incidence of NODAT for BAS+TAC+AZA was estimated to be 4.0% from Grenda et al. 2006.[72]

In the model for adult KTRs it was assumed that the effect of changing regimen from baseline (BAS+TAC+AZA) could be estimated by multiplying the effects of changing the agents TAC and AZA. In fact, no RCTs were identified comparing MMF and AZA which reported NODAT and therefore it was assumed that AZA and MMF would lead to the same incidence of NODAT.

Table 67 and Table 68 list the studies (RCTs from the systematic review of clinical effectiveness in adults) informing the impact of replacing immediate-release tacrolimus and mycophenolate mofetil respectively on 12-month NODAT incidence. The corresponding network diagrams are given in Figure 23 and Figure 24.

Table 67. Studies included to estimate the impact on NODAT incidence of replacing mycophenolate mofetil

Study	Compares	NODAT in 12 months
Ciancio 2008[185]	MMF vs. MPS	7/61 vs. 6/55
Ferguson 2011[128(a)]	MMF vs. SRL	0/33 vs. 2/26
Takahashi 2013[186]	MMF vs. EVL	3/61 vs. 7/61
Tedesco Silva 2010[187]	MMF vs. EVL	19/273 vs. 14/274
Anil Kumar 2005[188]	MMF vs. SRL	2/75 vs. 2/75
Gonwa 2003[189]	MMF vs. SRL	9/176 vs. 10/185
Sampaio 2008[190]	MMF vs. SRL	6/50 vs. 12/50

a TAC+MMF arm excluded

Figure 23. Network diagram for network meta-analysis estimating the impact on NODAT incidence of replacing mycophenolate mofetil

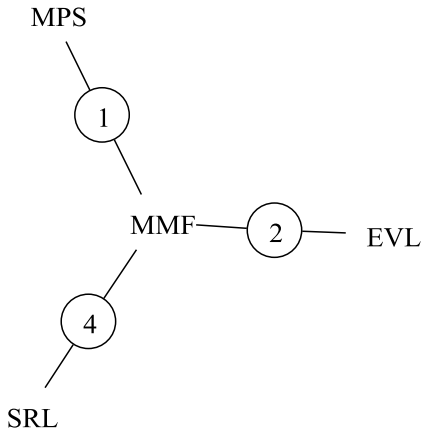


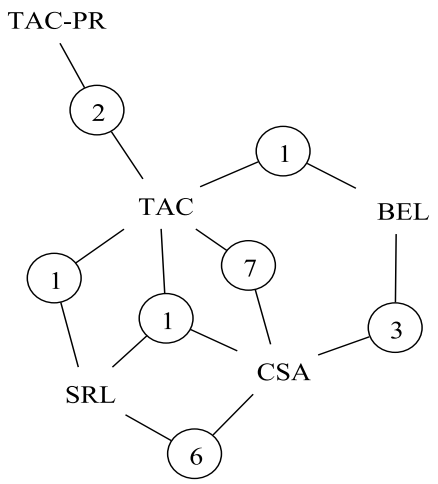
Table 68. Studies included to estimate the impact on NODAT incidence of replacing immediate-release tacrolimus

Study	Compares	NODAT in 12 months
Laskow 1996[105]	TAC vs. CSA	12/67 vs. 1/20
Mayer 1997[106]	TAC vs. CSA	17/303 vs. 3/145
Campos 2002[108]	TAC vs. CSA	10/85 vs. 3/81
Hardinger 2005[112]	TAC vs. CSA	5/134 vs. 1/66
Raofi 1999[191]	TAC vs. CSA	3/14 vs. 4/21
Yang 1999[124]	TAC vs. CSA	1/24 vs. 1/21
Kramer 2010[138]	TAC vs. TAC-PR	20/336 vs. 22/331
Tsuchiya 2013[192]	TAC vs. TAC-PR	0/52 vs. 1/50
Vincenti 2005[193(a)]	CSA vs. BEL	6/73 vs. 1/71
BENEFIT[194(a)]	CSA vs. BEL	16/221 vs. 7/226
BENEFIT-EXT[195(a)]	CSA vs. BEL	11/184 vs. 7/175
Ferguson 2011[128(b)]	TAC vs. BEL	1/30 vs. 0/33
Lebranchu 2009[196]	CSA vs. SRL	2/97 vs. 3/96
Buchler 2007[197]	CSA vs. SRL	3/74 vs. 9/71
Kreis 2000[198]	CSA vs. SRL	1/38 vs. 1/40
Guba 2010[199]	CSA vs. SRL	4/71 vs. 5/69
Martinez-Mier 2006[200]	CSA vs. SRL	1/21 vs. 1/20
Schaefer 2006[201]	TAC vs. SRL	5/39 vs. 6/41
Groth 1999[202]	CSA vs. SRL	1/42 vs. 1/41
Chen 2008[125]	TAC vs. CSA	1/21 vs. 1/20

Study	Compares	NODAT in 12 months
SYMPHONY[203]	TAC vs. CSA vs. SRL	34/403 vs. 17/408 vs. 25/380

a Less intensive belatacept arm only (more intensive belatacept arm excluded)
b BEL+SRL arm excluded

Figure 24. Network diagram for network meta-analysis estimating the impact on NODAT incidence of replacing immediate-release tacrolimus



Mixed treatment comparisons were conducted for both in both cases a fixed effects model was considered to be more appropriate due to a lower DIC (58.28 versus 60.39 and 25.52 versus 27.04). The results of the MTCs are presented in Table 69 and Table 70.

Table 69. Mixed treatment comparison estimates of impact on NODAT incidence of replacing immediate-release tacrolimus (WinBUGS; fixed effects model)

Agent	Odds ratio vs. baseline (natural logarithmic scale)					Odds ratio vs. baseline (linear scale)		
	Mean	SD	Median	95% CrI		Median	95% CrI	
TAC	(Baseline)							
TAC-PR	0.1694	0.3199	0.1687	−0.4546	0.8003	1.184	0.635	2.226
CSA	−0.8162	0.2086	−0.8136	−1.231	−0.4129	0.443	0.292	0.662
BEL	−1.671	0.381	−1.665	−2.431	−0.9394	0.189	0.088	0.391
SRL	−0.2345	0.2239	−0.2339	−0.6734	0.2016	0.791	0.510	1.223

Table 70. Mixed treatment comparison estimates of impact on NODAT incidence of replacing mycophenolate mofetil (WinBUGS; fixed effects model)

Agent	Odds ratio vs. baseline (natural logarithmic scale)	Odds ratio vs. baseline (linear scale)

	Mean	SD	Median	95% CrI		Median	95% CrI	
MMF	(Baseline)							
MPS	−0.07041	0.6122	−0.0656	−1.291	1.126	0.937	0.275	3.083
SRL	0.4739	0.3318	0.4719	−0.1688	1.131	1.603	0.845	3.099
EVL	−0.05221	0.3194	−0.05309	−0.6831	0.5742	0.948	0.505	1.776

The mean log odds ratios were combined from the MTCs to estimate an overall odds ratio for each regimen, as shown in Table 71, which when combined with the baseline incidence for BAS+TAC+MMF resulted in the estimated 12-month incidence of NODAT for each regimen as shown in Table 72.

Table 71. Calculations for the odds ratio of NODAT in 12 months

Regimen	Replace Tac	Odds ratio	Replace MMF	Odds ratio	Overall odds ratio
CSA+MMF	CSA	0.442	—	1	0.442
TAC+MMF	—	1	—	1	1
CSA+AZA	CSA	0.442	AZA	1 (assumed)	0.442
TAC+AZA	—	1	AZA	1 (assumed)	1
CSA+EVL	CSA	0.442	EVL	0.949	0.420
TAC+SRL	—	1	SRL	1.606	1.606
TAC-PR+MMF	TAC-PR	1.185	—	1	1.185
BAS+CSA+MMF	CSA	0.442	—	1	0.442
BAS+TAC+MMF	—	1	—	1	1
BAS+CSA+AZA	CSA	0.442	AZA	1 (assumed)	0.442
BAS+TAC+AZA	—	1	AZA	1 (assumed)	1
BAS+SRL+MMF	SRL	0.791	—	1	0.791
BAS+BEL+MMF	BEL	0.188	—	1	0.188
BAS+CSA+MPS	CSA	0.442	MPS	0.932	0.412
rATG+CSA+MMF	CSA	0.442	—	1	0.442
rATG+TAC+MMF	—	1	—	1	1
rATG+CSA+AZA	CSA	0.442	AZA	1 (assumed)	0.442
rATG+TAC+AZA	—	1	AZA	1 (assumed)	1

Table 72. Estimated 12-month incidence of NODAT for each regimen

Regimen	NODAT incidence
CSA+MMF	1.83%
TAC+MMF	4.04%
CSA+AZA	1.83%
TAC+AZA	4.04%
CSA+EVL	1.74%
TAC+SRL	6.33%
TAC-PR+MMF	4.75%
BAS+CSA+MMF	1.83%
BAS+TAC+MMF	4.04%
BAS+CSA+AZA	1.83%
BAS+TAC+AZA	4.04%
BAS+SRL+MMF	3.22%
BAS+BEL+MMF	0.79%
BAS+CSA+MPS	1.71%
rATG+CSA+MMF	1.83%
rATG+TAC+MMF	4.04%
rATG+CSA+AZA	1.83%
rATG+TAC+AZA	4.04%

Cytomegalovirus infection

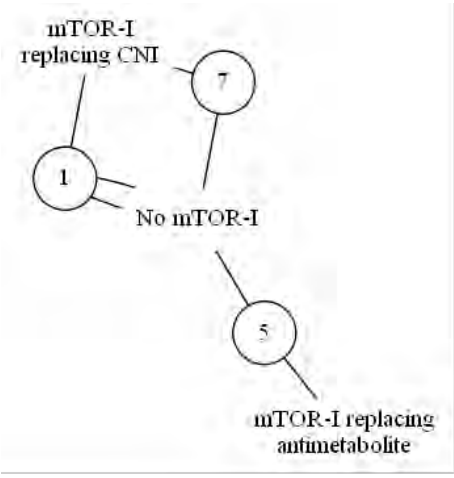
It was judged on the basis of examining the incidence of cytomegalovirus infection in RCTs included in the systematic review in the adult population, and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster et al.2005 and 2006[154, 204] that CMV infection could be affected by the use of mTOR-I (sirolimus and everolimus) and that the impact could vary depending on whether replacing a CNI or antimetabolite in the "standard triple-therapy".

Table 73 lists the studies (RCTs from the systematic review of clinical effectiveness) which could inform the estimate of the impact on CMV infection incidence of using mTOR-I. The corresponding network diagram for these studies is given in Figure 25.

Table 73. Studies included to estimate the impact on CMV infection incidence of using mTOR-I (sirolimus and everolimus)

Study	Compares	CMV infection within 12 months
Vitko 2004[205]	No mTOR-I vs. mTOR-I replacing antimetabolite	38/196 vs. 10/194
Takahashi 2013[186]	No mTOR-I vs. mTOR-I replacing antimetabolite	21/61 vs. 3/61
Tedesco Silva 2010[187]	No mTOR-I vs. mTOR-I replacing antimetabolite	16/273 vs. 2/274
Chadban 2013[206]	No mTOR-I vs. mTOR-I replacing antimetabolite	2/47 vs. 4/30
Sampaio 2008[190]	No mTOR-I vs. mTOR-I replacing antimetabolite	6/50 vs. 6/50
Mjörnstedt 2012[207]	No mTOR-I vs. mTOR-I replacing CNI	13/100 vs. 9/102
Flechner 2002[208]	No mTOR-I vs. mTOR-I replacing CNI	2/30 vs. 3/31
Lebranchu 2009[196]	No mTOR-I vs. mTOR-I replacing CNI	6/97 vs. 4/96
Büchler 2007[197]	No mTOR-I vs. mTOR-I replacing CNI	17/74 vs. 4/71
Kreis 2000[198]	No mTOR-I vs. mTOR-I replacing CNI	8/38 vs. 2/40
Guba 2010[199]	No mTOR-I vs. mTOR-I replacing CNI	20/71 vs. 5/69
Martinez-Mier 2006[200]	No mTOR-I vs. mTOR-I replacing CNI	0/21 vs. 1/20
SYMPHONY[203]	No mTOR-I vs. No mTOR-I vs. mTOR-I replacing CNI	39/403 vs. 45/408 vs. 23/380

Figure 25. Network diagram for network meta-analysis estimating the impact on CMV incidence of mTOR-I use



Fixed effects and random effects mixed treatment comparisons were conducted and the random effects model was judged to be superior on the basis of DIC (54.02 versus 59.54 for fixed effects model). The results of the random effects MTC are shown in Table 74.

Table 74. Mixed treatment comparison estimates of impact on CMV infection incidence of using mTOR-I (WinBUGS; random effects model)

mTOR-I use	Odds ratio vs. baseline (natural logarithmic scale)					Odds ratio vs. baseline (linear scale)		
	Mean	SD	Median	95% CrI		Median	95% CrI	
No mTOR-I	(Baseline)							
mTOR-I replacing CNI	−0.7981	0.3889	−0.806	−1.558	0.01047	0.447	0.211	1.011
mTOR-I replacing antimetabolite	−1.153	0.4916	−1.175	−2.091	−0.1184	0.309	0.124	0.888
σ (random effects parameter)	0.7915	0.4085	0.7538	0.08925	1.705			

The baseline incidence of CMV infection was estimated from Jongsma et al. 2013[209] who found that 25.8% of transplantations in 159 Dutch children and adolescents were followed by CMV infection within one year. The typical regimens were CSA+MMF and BAS+CSA+MMF.

Combining the baseline incidence with the treatment effects results in the incidence rates for each regimen as shown in Table 75.

Table 75. CMV infection incidence rates used in the model

Regimen	CMV incidence within 12 months
CSA+EVL	9.88%
TAC+SRL	9.88%
BAS+SRL+MMF	13.53%
No mTOR-I	25.79%

Dyslipidaemia

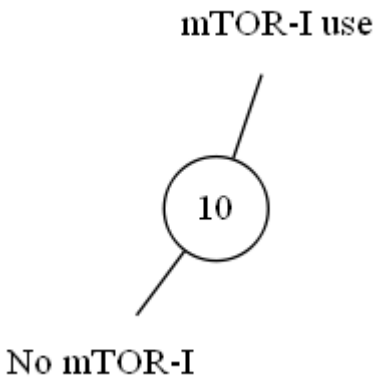
It was judged on the basis of examining the incidence of cytomegalovirus infection in RCTs in the adult population, and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster et al.2005 and 2006[154, 204] that the incidence of dyslipidaemia could be increased by the use of mTOR-I in the immunosuppressive regimen. It was considered that it was not necessary to separately estimate the risk whether used in combination with a calcineurin inhibitor or with an antimetabolite and therefore to increase statistical power the effect of mTOR-I use on dyslipidaemia incidence was estimated as the odds ratio of dyslipidaemia incidence for mTOR-I use versus no mTOR-I use.

Table 76 details the adult population RCTs which compared regimens with and without mTOR-I and which reported dyslipidaemia. The direction of effect is consistent across the studies. The corresponding network diagram of these studies is given in Figure 26.

Table 76. Studies used to estimate the impact on dyslipidaemia of mTOR-I use

Study	Compares	Dyslipidaemia within 12 months
Vitko 2004[205]	No mTOR-I vs. mTOR-I use	24/196 vs. 51/194
Takahashi 2013[186]	No mTOR-I vs. mTOR-I use	19/61 vs. 28/61
Tedesco Silva 2010[187]	No mTOR-I vs. mTOR-I use	43/273 vs. 57/274
Sampaio 2008[190]	No mTOR-I vs. mTOR-I use	8/50 vs. 11/50
Mjörnstedt 2012[207]	No mTOR-I vs. mTOR-I use	9/100 vs. 13/102
Flechner 2002[208]	No mTOR-I vs. mTOR-I use	16/30 vs. 20/31
Lebranchu 2009[196]	No mTOR-I vs. mTOR-I use	4/97 vs. 8/96
Büchler 2007[197]	No mTOR-I vs. mTOR-I use	38/74 vs. 50/71
Guba 2010[199]	No mTOR-I vs. mTOR-I use	5/71 vs. 14/69
SYMPHONY[203]	No mTOR-I vs. mTOR-I use	91/811 vs. 60/380

Figure 26. Network diagram for network meta-analysis estimating the impact on dyslipidaemia incidence of mTOR-I use



Fixed and random effects meta-analyses were conducted and it was judged on the basis of DIC (28.267 versus 29.897) that a fixed effects analysis was appropriate. The results of the fixed effects meta-analysis are shown in Table 77.

Table 77. Fixed effects meta-analysis of the impact on dyslipidaemia incidence of mTOR-I use

mTOR-I use	Odds ratio vs. baseline (natural logarithmic scale)					Odds ratio vs. baseline (linear scale)		
	Mean	SD	Median	95% CrI		Median	95% CrI	
No mTOR-I	(Baseline)							
mTOR-I use	0.5566	0.1005	0.5555	0.3604	0.7533	1.743	1.434	2.124

The baseline incidence of dyslipidaemia (without mTOR-I use) was estimated by Bonthuis et al.[210] based on European registry data for child/adolescent RRT recipients. The incidence of dyslipidaemia was 55.5% (313/564) for transplant recipients, versus 85.1% and 76.1% for HD and PD recipients respectively. This study also highlighted that sirolimus was associated with significantly increased lipid levels versus tacrolimus and ciclosporin. The incidence of dyslipidaemia with mTOR-I use was therefore estimated as 68.5%.

Anaemia

Anaemia is an adverse event which affects KTRs and people on dialysis. Since reference costs for dialysis already include anaemia costs, only anaemia in people with functioning grafts was modelled. It was assumed that there would be no difference in the prevalence of anaemia between different immunosuppressive regimens. The prevalence of anaemia requiring treatment with erythropoiesis stimulating agents was estimated as 5.2%, based on a study by Vanrenterghem et al.[211] This prevalence was assumed to be the same regardless of time since transplantation, age, or other factors.

6.2.4.4 Retransplantation

In the parallel HTA to evaluate the cost-effectiveness of immunosuppressive agents for adult kidney transplant recipients, the rate of retransplantation was estimated for under 65s as 0.1037 from the UK Transplant Registry standard dataset. To estimate the rate of retransplantation specifically for children and adolescents (who generally receive priority in DBD allocation) this rate was multiplied by 3.422 for under 18s, to reflect that median waiting time for adults is 3.422 times greater than median waiting time for children and adolescents (1,160 days versus 339 days).

Pre-emptive retransplantations were also included, as described in section Use of graft survival in the model (page 200).

Subsequent grafts

Due to limitations of Markov modelling imposed by the memory-less assumption there is reduced flexibility in the modelling of costs and outcomes for subsequent grafts. It must be assumed that the hazard rates of all transitions, costs and utilities are dependent only on time in the model and the arm under consideration.

Comprehensive information on immunosuppressive regimens used does not appear to be collected[212, 213]; the UK Renal Registry dataset does not include basiliximab induction and the UK Transplant Registry does not include any data on immunosuppressive regimens employed.

It was assumed that the same immunosuppressive regimen would be used for all subsequent grafts, regardless of the immunosuppressive regimen used for the first graft. BAS+TAC+MMF was chosen as the immunosuppressive regimen for subsequent grafts as it is believed to be the most common immunosuppressive regimen in use in the UK. People receiving subsequent grafts are more likely to receive monoclonal or polyclonal antibody induction as they are likely to be at higher immunological risk. People can become sensitised to rabbit ATG if received as induction for first graft or for treatment of steroid-resistant acute rejection so it was judged to be less likely to be used as induction compared to basiliximab.

Assuming the same immunosuppressive regimen for subsequent grafts for all regimens has the effect that the cost-effectiveness of regimens is primarily driven by outcomes for the first graft.

Table 78 summarises the parameters affecting subsequent grafts.

Table 78. Parameters affecting subsequent grafts

Parameter	Value	Source
Natural history		
Baseline rate of DWFG	0.00780	Assumed to be the same as long-running rate of DWFG for first graft
Rate of graft loss	0.03589	Exponential distribution fitted to UKTR standard dataset (first graft and PNF excluded)
Resource use		
Tacrolimus dosage	0.10 mg/kg/day	Assumed to be somewhat higher than the long-running dosage for first graft (0.08 with Aza/MMF, 0.07 with Srl) due to increased risk of rejection
MMF dosage	2 g/day	Recommended daily dose
Prednisolone dosage	16.3 mg/day	Assumed to be same as first graft
Monitoring (clinic, tacrolimus TDM, blood test, renal profile, LFT)	Once monthly	Assumption

6.2.5 Effectiveness estimates

The key effectiveness parameters driving cost-effectiveness in the model are:

- Graft loss within 12 months
- Patient death within 12 months
- Acute rejection within 12 months
- Graft function at 12 months
- NODAT at 12 months
- CMV infection within 12 months
- Dyslipidaemia at 12 months

As explained in Section 6.2.3 (page 185), it was not possible to estimate these for all interventions based on RCT evidence in the child/adolescent kidney transplant population. It was therefore decided that separate analyses would be conducted based on adult RCT

evidence (allowing comparison of all interventions) and on child/adolescent RCT evidence (only allowing a very limited number of comparisons).

The analyses based on child/adolescent RCT evidence differ somewhat from the analyses based on adult RCT evidence as they utilise a decision tree to estimate costs and QALYs in the trial duration followed by extrapolation with the Markov model. As such, graft loss and patient death are estimated at the study end and additionally the restricted mean survival of the patient and the graft are estimated (restricted to the trial duration), as described in Section 6.2.3.1 (page 186).

6.2.5.1 Based on adult RCT evidence

Graft loss, patient death, acute rejection and graft function were primarily estimated from network meta-analyses of adult RCT evidence for induction and maintenance regimens, assuming independence of treatment effects (i.e., that the effectiveness for a complete regimen can be decomposed into the effectiveness for the induction therapy and the maintenance regimen).

Some arms were included in the network meta-analyses which do not correspond to regimens in the model and the results for these arms were not included but the arms were not dropped from the network meta-analyses as they could still contribute indirect effect estimates.

The mean treatment effects from the network meta-analyses are summarised in Table 79.

Table 79. Summary of mean treatment effects from network meta-analyses of adult RCT evidence

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	−0.1168	−0.1712	+2.615	−0.6878
Rabbit ATG	−0.4605	−0.2534	+0.7524	−1.041
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
Note: The comparators here are the comparators in the network meta-analysis rather than the baseline used in the model
a Presented as log odds ratios
b Presented as mean difference

Head-to-head comparisons for prolonged-release tacrolimus versus immediate-release tacrolimus and for mycophenolate sodium versus mycophenolate mofetil were additionally used to identify any differences in effectiveness between these agents. In the network meta-analysis mycophenolate mofetil and mycophenolate sodium were assumed to be the same agent to simplify the analysis and increase the statistical power. The head-to-head comparisons did not identify any statistically significant differences in effectiveness. The effectiveness of mycophenolate mofetil was assumed to be that of mycophenolate in the network meta-analysis and the effectiveness of mycophenolate sodium was estimated by

combining the network meta-analysis and head-to-head effectiveness estimates (y_{MPA} and $y_{MPS-MMF}$ respectively) as follows (on the appropriate scale, i.e., log odds for dichotomous outcomes, linear scale for eGFR):

$y_{MMF} = y_{MPA}$

$y_{MPS} = y_{MPA} + \Delta y_{MPS-MMF}$

The effectiveness of prolonged-release tacrolimus was similarly estimated:

$y_{TAC\text{-}PR} = y_{TAC} + \Delta y_{TAC\text{-}PR-TAC}$

The effectiveness estimates were combined with the following estimated baseline values (for BAS+TAC+AZA): mortality within 12 months (odds) = 0.0052 (based on the model with baseline graft loss and death with functioning graft rates); graft loss within 12 months (odds) = 0.0400 (based on UK Transplant Registry standard dataset); eGFR at 12 months (ml/min/1.73 m²) = 82 (based on Muscheites et al. 2009[181]); acute rejection within 12 months (odds) = 0.2375 (based on Grenda et al. 2006[72]). The resulting absolute effectiveness estimates are given in Table 80.

Table 80. Summary of absolute effectiveness estimates for each regimen based on adult RCT evidence

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	0.0039	0.0245	71.7	0.386
TAC+MMF	0.0063	0.0225	76.6	0.326
CSA+AZA	0.0041	0.0329	70.1	0.818
TAC+AZA	0.0058	0.0376	79.4	0.472
CSA+EVL	0.0058	0.0203	74.9	0.373
TAC+SRL	0.0057	0.0384	69.7	0.314
TAC-PR+MMF	0.0082	0.0270	76.4	0.318
BAS+CSA+MMF	0.0035	0.0206	74.3	0.194
BAS+TAC+MMF	0.0056	0.0190	79.2	0.164
BAS+CSA+AZA	0.0037	0.0277	72.7	0.411
BAS+TAC+AZA	0.0052	0.0317	82.0	0.238
BAS+SRL+MMF	0.0064	0.0286	76.5	0.180
BAS+BEL+MMF	0.0020	0.0170	83.2	0.331
BAS+CSA+MPS	0.0024	0.0178	78.2	0.288
rATG+CSA+MMF	0.0026	0.0190	72.4	0.136
rATG+TAC+MMF	0.0040	0.0175	77.4	0.115
rATG+CSA+AZA	0.0028	0.0256	70.8	0.289
rATG+TAC+AZA	0.0037	0.0292	80.1	0.167

The effectiveness estimates for the other outcomes (NODAT, CMV infection and dyslipidaemia) are also estimated from the RCTs identified in the systematic review of clinical effectiveness, as described in sections Diabetes: (page 210), Cytomegalovirus infection (page 215) and Dyslipidaemia (page 217).

6.2.6 Health measurement and valuation

The EQ-5D (EQ-5D-3L) is the preferred instrument to measure health-related quality of life in the NICE reference case,[165] but it is designed for use in adults. An adapted version of EQ-5D, the EQ-5D-Y has been developed for children and adolescents (aged 8–17 years), but there is currently no method to value states measured in EQ-5D-Y (except naively applying the EQ-5D value set which is cautioned against).[214] Furthermore we attempted to systematically identify any health-related quality of life studies in the child/adolescent kidney transplant population and did not find any.

In the absence of any studies measuring health-related quality of life in the child/adolescent population it was assumed that the formula estimating the utility of general population health, and the utility decrements for the different methods of renal replacement therapy, and the utility decrement for diabetes, would be the same as for the adult population, as follows:

Utility was estimated for KTRs by first estimating age-dependent baseline utility for the general population, then applying a utility decrement according to whether KTRs were in the FUNCTIONING GRAFT or GRAFT LOSS state. In addition, the proportion of the population with NODAT was estimated and a utility decrement was applied to both FUNCTIONING GRAFT and GRAFT LOSS states to reflect the decreased health-related quality of life for KTRs with NODAT.

In the probabilistic sensitivity analysis utility decrements were drawn from gamma distributions to ensure they did not result in increased utility.

With the exception of the source for baseline utility (following section), sources of utility estimates were obtained from sources found through a systematic bibliographic search of the relevant literature. This search combined established terms and synonyms for identifying studies of utility and health related quality of life, with population search terms for renal transplant, dialysis, and end stage renal disease. No study design filter was used.

The search yielded 1311 titles and abstracts, which were screened by an experienced health technology assessment researcher (RA). Only 99 were studies which yielded or used EQ-5D scores (the preferred preference-based measure for informing NICE technology assessments). Studies were sought which yielded EQ-5D derived health state scores (using UK general population valuations), for health states or clinical events of relevance in our provisional model structure: functioning renal graft, failing renal graft, chronic allograft injury, acute kidney rejection, NODAT, malignancy following renal transplant, and infection following renal transplant.

6.2.6.1 Utility of general population

Baseline utility was modelled using the following equation:

$$Utility = 0.967981 - 0.001807 \times Age - 0.000010 \times Age^2 + 0.023289 \times Male$$

Where *Male* is equal to 1 for men and 0 for women. This equation was derived from the Health Survey for England (2012)[215] using the well-established methodology of Ara and Brazier.[216] The dataset includes 16 and 17 year olds but does not appear to include utility

estimates for younger individuals (all of whom had utility recorded as exactly 1), and therefore this is an extrapolation.

6.2.6.2 Utility with dialysis

A systematic review and meta-analysis by Liem et al. 2008[217] reported pooled estimates of utility for various health states of people undergoing renal replacement therapy. It reported random effects meta-analyses of six studies which had produced EQ-5D index scores (either explicitly based on the UK utility tariff or assumed to be so by the authors) for haemodialysis (range 0.44 to 0.62) and of four studies for peritoneal dialysis (range 0.53 to 0.65). The estimates used in our model are shown in Table 81 below.

Table 81. EQ-5D index utility weights for dialysis

Type of dialysis	Pooled Mean (95% CI)	n studies	No. people
Haemodialysis	0.56 (0.49 – 0.62)	6	1315
Peritoneal dialysis	0.58 (0.50 – 0.67)	4	192

Source: Table 4 (p.738) of Liem at al 2008

These estimates were then converted into utility decrements from baseline age-related general health (assuming age 60.4 years and 58% male for haemodialysis and age 57.9 and 55% male for peritoneal dialysis) in order that the utility of those on dialysis would always be lower than people in the general population of the same age and sex.

The estimated utility decrements were [mean (SE)]: haemodialysis 0.277 (0.034); peritoneal dialysis 0.264 (0.044).

6.2.6.3 Utility with functioning graft

The same systematic review and meta-analysis by Liem et al. 2008 [217] reported pooled estimates of utility for people living with a functioning renal graft. It reported a random effects meta-analysis of five studies which had produced EQ-5D index scores (either explicitly based on the UK utility tariff or assumed to be so by the authors) for people living with a functioning renal graft (range of means, some medians, 0.71 to 0.86; see Table 82).

Table 82. EQ-5D index utility weights for functioning graft

Health state	Pooled Mean (95% CI)	n studies	No. people
Functioning graft	0.81 (0.72 – 0.90)	5	673

Source: Table 4 (p.738) of Liem at al 2008.

It was assumed that the health-related quality of life for kidney transplant recipients would not exceed that of members of the general population (aged 51.4 and 60% male), so this absolute estimate was converted into a utility decrement from baseline of 0.053 (SE 0.049).

6.2.6.4 Disutility due to diabetes

Our literature search for utilities revealed one study looking specifically at disutility of new onset diabetes after transplant (NODAT) in renal transplantation patients (Dukes et al. 2013[218]). This is a recent study in the adult RRT population and reports EQ-5D utility data, with an estimated disutility of 0.06 associated with NODAT. This figure does not adjust for people with CVD complications and therefore is appropriate to how we model NODAT. We note that the study was conducted in only one hospital in USA and the valuation set for the utility values is US based (Shaw et al. 2005[219]),so the outcomes may not be generalisable to the UK population. It has been demonstrated by Johnson et al. 2005 that US valued health states are statistically higher than the UK valued health states for 31 out of 42 valued EQ-5D health states and that extreme health states are most notably different.[220] However, this does not necessarily reflect the differences between health states and we believe that having utility data from a relevant patient population is the most important factor in choosing this value.

For example, one alternative would be to use diabetes versus general population using Health Survey for England data. This would be a broader population of comparison and is unlikely to reflect the true utility impact of diabetes on someone who has received a kidney transplant.

In their submission to the parallel technology appraisal to update NICE guidance TA85 (kidney transplantation in adults), BMS incorporated disutility of 0.041 for NODAT citing Currie et al. 2005[221] as their source, which is a study looking at costs. We believe they intended to cite the other Currie et al. 2005 paper,[222] but it is still not clear how they calculated this value. In their model, the deterministic value for disutility of NODAT appears to be 0.06, which corresponds with our chosen value.

Astellas (in their submission to this technology appraisal) report the findings of Wyld et al. 2012,[223] which does report utilities, deriving a disutility of 0.10 between no diabetes and diabetes groups of people with chronic kidney disease. However this is not restricted to renal transplant population only and it is not clear which utility elicitation method is used.

6.2.7 Estimating resources and costs

Costs are incurred in the model either in the form of events (e.g., induction therapy, acute rejection, CMV infection, retransplantation) or in the form of ongoing costs (e.g., maintenance therapy, NODAT, dialysis).

The following costs are incurred exclusively in the FUNCTIONING GRAFT state (ongoing unless otherwise stated):

- Induction therapy (event)
- Maintenance therapy
- Monitoring
- Infection prophylaxis
- Acute rejection (event)
- CMV infection (event)
- Anaemia

The following costs are incurred exclusively in the GRAFT LOSS state:

- Dialysis

The following costs are incurred in both the FUNCTIONING GRAFT and GRAFT LOSS states:

- NODAT
- Dyslipidaemia

The following costs are incurred only when transitioning between states:

- From FUNCTIONING GRAFT to GRAFT LOSS: explant surgery, dialysis access surgery

- From GRAFT LOSS to FUNCTIONING GRAFT (and other retransplantation transitions): retransplantation

6.2.7.1 Currency, price date and conversion

Costs are all in 2014/15 pounds sterling (£; GBP). Costs in earlier financial years are inflated based on the Hospital & Community Health Services (HCHS) pay and prices index.[224]

Table 83. HCHS pay and prices index

Year	HCHS pay and prices index	Inflation factor
2008/09	267.0	1.106
2009/10	268.6	1.099
2010/11	276.7	1.067
2011/12	282.5	1.045
2012/13	287.3	1.028
2013/14	290.5	1.016
2014/15	295.3 (projected based on previous three years)	1

No costs were included in different currencies so conversion was not necessary.

6.2.7.2 Resource use

Induction therapy

Basiliximab can be administered by intravenous infusion or intravenous injection but it was assumed that it would be administered by intravenous infusion in accordance with Brennan et al. 2006.[225] Intravenous infusion is a more costly method administration than intravenous injection so this may overestimate the costs of basiliximab administration.

Rabbit ATG is administered only by intravenous infusion and it was assumed it would be administered as in Brennan et al. 2006,[225] which was conducted in adults. We found no RCT evidence in children or adolescents for rabbit ATG to inform dosages. We assumed no wastage of rabbit ATG, which may result in the costs being underestimated.

The dosage for basiliximab is 10 mg if the recipient's weight is below 35 kg, and 20 mg if the recipient's weight is over 35 kg.[226] This cutoff was used by Offner et al. 2008,[70] while a higher

cutoff of 40 kg was used by Grenda et al. 2006.[72] Table 84 describes resource use for induction therapy.

In the base case recipients are aged 10 with expected body weight 32 kg, and therefore they receive 10 mg doses rather than 20 mg doses.

Table 84. Resource use for induction therapy

Parameter	Value	Source
Basiliximab induction		
Basiliximab 10 mg doses	1.964	Brennan 2006[225]
Basiliximab 20 mg doses	0	(Weight under 35 kg)
Administration (IV infusion)	1.964	Brennan 2006[225]
Rabbit ATG induction		
Rabbit ATG mg/kg	6.5	Brennan 2006[225]
Administration (IV infusion)	4.525	Assumption based on Brennan 2006[225]

Nb. of doses	People
1	2
2	6
3	10
4	24
5	97
6	1
7	1

Actual breakdown not given but given that 87.9% initiated before reperfusion, 68.8% received intended five doses, one patient received six doses, also one patient received six doses. At least four doses were received by 87.2% of people.

Maintenance therapy

Dosages for under 18s were estimated from child/adolescent RCTs where possible. Where this was not possible, dosing guidelines for adults were followed where they were already weight-based. Where they were not weight-based, it was assumed that the dose for children and adolescents would be lower, and would be proportional to their weight or body surface area. Table 85 describes resource use for maintenance therapy.

Tacrolimus, sirolimus, everolimus and ciclosporin are titrated to achieve target whole blood trough concentrations, since numerous factors can affect their absorption and removal from the blood stream and therapeutic windows can be narrow.

Belatacept is administered intravenously according to a prescribed schedule. It was assumed that the "less intensive" regimen from the BENEFIT[194] and BENEFIT-EXT[195] studies would be used. We were advised that vial sharing would most likely not be feasible and therefore we assumed full wastage of excess belatacept.

Table 85. Resource use for maintenance therapy

Parameter	Value	Source
Immediate-release tacrolimus		
With azathioprine	Under 18	Trompeter 2002[74]
	Time / **Dosage (mg/m²/day)** 0–6 months: 7.57 6–12 months: 5.61 Thereafter: 4.89	
	Over 18	Margreiter 2002[109]
	Time / **Dosage (mg/kg/day)** 12–36 months: 0.09 Thereafter: 0.08	
With mycophenolate mofetil	Under 13: 0.18 mg/kg/day 13–17: 0.13 mg/kg/day Over 18: 0.08 mg/kg/day	Grenda 2010[62] (Assumed no higher than azathioprine)
With sirolimus	**Time** / **Dosage (mg/kg/day)** 0–1 month: 0.175 1–3 months: 0.110 3–6 months: 0.104 6–12 months: 0.080 12+ months: 0.070	Starting dose from Gonwa 2003[189] (0–1 month); assumed no higher than with mycophenolate mofetil (1–6 months); Gonwa 2003,[189] Anil Kumar 2008[227] (6+ months)
Prolonged-release tacrolimus		
With mycophenolate mofetil	As for immediate-release tacrolimus plus 0.015 mg/kg/day for 12 months	Wlodarczyk 2009,[228] Kramer 2010,[138] Tsuchiya 2013,[192] Oh 2014[229]
Ciclosporin		
With azathioprine	Under 18	Trompeter 2002[74]
	Time / **Dosage (mg/m²/day)** 0–6 months: 251 6–12 months: 192 Thereafter: 180	
	Over 18	Margreiter 2002[109]
	Time / **Dosage (mg/kg/day)** 12–36 months: 2.93 Thereafter: 2.84	

With mycophenolate mofetil or mycophenolate sodium

Under 18 (with induction) — Offner 2008[70]

Time	Dosage (mg/kg/day)
0–3 months	7.80
3–6 months	7.15
6–12 months	6.65
Thereafter	6.20

Under 18 (no induction)

Time	Dosage (mg/kg/day)
0–3 months	7.67
3–6 months	6.85
6–12 months	6.20
Thereafter	5.90

Over 18: 2.82 mg/kg/day — Rowshani 2006[230]

With everolimus — Vitko 2004[205]

Time	Dosage (mg/kg/day)
0–12 months	3.9
12+ months	2.1

Azathioprine

With tacrolimus

Under 18: 1.80 mg/kg/day — Trompeter 2002[74]

Over 18: 1.20 mg/kg/day — Laskow 1996[105]

With ciclosporin

Under 18: 1.80 mg/kg/day — (Assumed equal to tacrolimus)

Over 18: 1.22 mg/kg/day — Vacher-Coponat 2012[231]

Mycophenolate mofetil

With tacrolimus

Under 13: 0.54 g/m²/day — Grenda 2010[62]

13–17: 0.60 g/m²/day

Over 18: 1.47 g/day — Ekberg 2007[203]

With ciclosporin

Under 18 (with induction) — Offner 2008[70]

Time	Dosage (g/m²/day)
0–3 months	1.06
3–6 months	1.01
6–12 months	0.95
Thereafter	0.93

Under 18 (no induction)

Time	Dosage (g/m²/day)
0–3 months	1.04
3–6 months	0.93
6–12 months	0.83
Thereafter	0.82

Over 18: 1.67 g/day — Ekberg 2007[203]

With sirolimus

Time	Dosage (g/m²/day)
0–3 months	1.16
3–12 months	1.00
Thereafter	0.85

Ekberg 2007[203] (assuming adult body surface area 1.73 m²)

With belatacept

1.16 g/m²/day

Vincenti 2010[194] (assuming adult body surface area 1.73 m²)

Mycophenolate sodium

With ciclosporin

Time	Dosage (mg/kg/day)
0–3 months	22.8
3–9 months	19.2
9+ months	17.5

Mjörnstedt 2012[207] (assuming adult body weight 63 kg)

Sirolimus

With tacrolimus

Time	Dosage (mg/kg/day)
0–12 months	0.059
12–60 months	0.044
Thereafter	0.029

Anil Kumar 2008[227] (assuming adult body weight 63 kg)

With mycophenolate mofetil

Time	Dosage (mg/kg/day)
0–3 months	0.082
3–6 months	0.071
6–9 months	0.055
9–12 months	0.051
12–48 months	0.046
48+ months	0.041

Lebranchu 2009[196] (assuming adult body weight 63 kg)

Everolimus

With ciclosporin

Time	Dosage (mg/kg/day)
0–3 months	0.047
3–6 months	0.044
6–9 months	0.040
9–12 months	0.041
12–24 months	0.041
24+ months	0.032

Tedesco Silva 2010[187] and Lorber 2005[232] (assuming adult body weight 63 kg)

Belatacept

Drug acquisition

(Round up to nearest 250 mg)

Time	Doses per quarter year	
	10 mg/kg	5 mg/kg
0–3 months	5	0
3–6 months	1	2
Thereafter	0	3.26

Dosing schedule: 10 mg/kg on days 1 and 5, weeks 2, 4, 8 and 12, then 5 mg/kg every 4 weeks thereafter

Drug administration (IV infusion)

Time	Infusions per quarter
0–3 months	5
3–6 months	3
Thereafter	3.26

Prednisolone

With ciclosporin	Under 18	Trompeter 2002[74]

Time	Dosage (mg/kg/day)
0–6 months	2.4
Thereafter	0.3

Without ciclosporin	Under 18	

Time	Dosage (mg/kg/day)
0–6 months	2.1
Thereafter	0.3

All maintenance regimens	Over 18: 16.3 mg/day	Ekberg 2007[203]

Dialysis

Access surgery is required for long-term dialysis. In the case of haemodialysis the creation of an arteriovenous fistula is common, which requires time to heal and mature after surgery before use. It was therefore assumed that all people on haemodialysis would also incur the cost of one temporary tunnelled central venous catheter.

The mix of haemodialysis and peritoneal dialysis is known to vary over time, with younger people generally considered better suited to peritoneal dialysis (Table 86). The haemodialysis mix was reflected in incident and prevalent people on dialysis, but conversion costs (between dialysis modes) were not included.

Table 86. Proportion of dialysis patients receiving haemodialysis by age group

Age group	Proportion receiving haemodialysis
0–1	45.5%
2–3	46.4%
4–7	55.6%
8–11	64.5%
12–15	70.5%
16–17	62.5%
18–24	79.1%
25–34	80.4%
35–44	84.5%
45–54	84.3%

55–64	85.2%
65–74	85.8%
75–84	89.0%
85+	91.5%

Source: UK Renal Registry 16th Annual Report (Figure 2.7)[233] and UK Renal Registry 17th Annual Report (Table 4.4)[234]

Acute rejection

The number of KTRs suffering at least one acute rejection episode was derived as detailed in section Acute rejection within 12 months (page 208) and Section 6.2.5.1 (page 222).

To account for the fact that some KTRs may experience more than one acute rejection episode a study (Charpentier et al. 2003[111]) was identified which gave both the number of people experiencing at least one acute rejection episode and the total number of episodes. From this it was estimated that there would be 1.19 acute rejections expected per person suffering at least one acute rejection event.

Grenda et al. 2006[72] and Trompeter et al. 2002[74] report acute rejections in the first six months according to their response to treatments, as either "Spontaneously resolving" (i.e., not requiring changes to treatment), "Steroid-sensitive" (i.e., resolving after a short course of high-dose corticosteroids), or "Steroid-resistant" (i.e., not resolving after a short course of high-dose corticosteroids). Acute rejections between 6 and 24 months were not reported by those categories, so it was assumed that 80% were steroid-sensitive and 20% steroid-resistant. Table 87 gives the numbers of acute rejections in the RCTs in children and adolescents.

Table 87. Acute rejection and response to treatment in child/adolescent RCTs

Trial	**Trompeter 2002**		**Grenda 2006**		**Offner 2008**	
Arm	**TAC+AZA (n=103)**	**CSA+AZA (n=93)**	**TAC+AZA (n=93)**	**BAS+TAC+AZA (n=99)**	**BAS+CSA+MMF (n=100)**	**CSA+MMF (n=92)**
0–6 months					11	19
• Spontaneously resolving	2	0	2	1		
• Steroid-sensitive	45	65	14	15		
• Steroid-resistant	8	26	3	3		

Trial	Trompeter 2002		Grenda 2006		Offner 2008	
Arm	TAC+AZA (n=103)	CSA+AZA (n=93)	TAC+AZA (n=93)	BAS+TAC+AZA (n=99)	BAS+CSA+MMF (n=100)	CSA+MMF (n=92)
6–12 months	4	2	8	4	2	3
12–24 months	7	9				
24–36 months	2	6				
36–48 months	2	6				

Infection prophylaxis

Cytomegalovirus prophylaxis was included for KTRs at high risk of CMV infection (D+/R−; i.e., **D**onor is sero**positive**, **R**ecipient is sero**negative**) following the Birmingham Children's Hospital Renal Unit protocol.[235] It was assumed that all high-risk patients would receive valganciclovir at a once daily dose calculated using the formula:

Dose (mg) = 7 × Body surface area × eGFR

Doses are rounded to 450 mg or 900 mg (whichever is nearest). For example, a KTR with body surface area of 1.2 m² and eGFR 40 ml/min/1.73 m² would have a target dose of 336 mg, rounded up to 450 mg.

According to the Birmingham protocol, prophylaxis is for three months, followed by a month at half dose if quantitative PCR at three months is negative, followed by discontinuation if quantitative PCR at four months is negative. Relevant data on the proportions having negative PCR at three or four months were not available and were therefore estimated.

Humar et al. 2010[236] report a comparison of 100-day and 200-day CMV prophylaxis in adults (aged ≥ 16 years). Figure 3 suggests that at 90 days approximately 10% of patients have developed CMV viraemia, and in the month after discontinuation (100-day arm) approximately 14% of patients developed CMV viraemia. It was assumed therefore that 10% would receive three months prophylaxis plus two months pre-emptive treatment (at the same dose), 76% of patients would receive four months planned prophylaxis while the remaining 14% would receive four months planned prophylaxis plus two months pre-emptive treatment at the full target dose (see Table 88).

Table 88. Modelled cytomegalovirus prophylaxis for high-risk kidney transplant recipients

Proportion of CMV high-risk patients	Time at full dose	Time at half dose
10%	5 months	None
76%	3 months	1 month
14%	5 months	1 month

Half dosage was implemented assuming that alternate day dosing was acceptable, meaning the effective target daily dose was rounded to 225 mg, 450 mg or 900 mg (whichever is nearest).

Cytomegalovirus prophylaxis was not included for intermediate- (D±/R+) or low-risk (D−/R−) KTRs, except in the case of intermediate-risk KTRs receiving rabbit ATG, who were assumed to receive three months CMV prophylaxis (based on the Royal Devon & Exeter protocol for adults[237]).

Table 89. CMV risk for children and adolescents receiving kidney transplantation

CMV risk category	Proportion of child/adolescent KTRs
High risk (D+/R−)	54/209 = 25.8%
Intermediate risk (D±/R+)	84/209 = 40.2%
Low risk (D−/R−)	71/209 = 34.0%

Source: Jongsma et al. 2013[209]

Pneumocystis jirovecii pneumonia (PCP) and urinary tract infection (UTI) prophylaxis was assumed to be co-trimoxazole, 480 mg daily for three months.

Monitoring

KTRs receive monitoring on a frequent basis after transplantation, which is gradually tapered for KTRs with stable grafts.

The following monitoring was included:

- Full blood count
- Renal profile

- Liver function tests
- Therapeutic drug monitoring (tacrolimus, ciclosporin, sirolimus and everolimus)
- Viral quantitative PCR (CMV, BKV, EBV)

In addition KTRs attend regular outpatient clinics.

KTRs with degraded or deteriorating graft function receive more intensive monitoring to maximise graft survival.

It was assumed that children and adolescents would attend clinics and receive monitoring according to the Birmingham protocol,[235] and assumed to be tapered after a number of years to quarterly visits (Table 90).

Table 90. Frequency of attendances at clinic and monitoring

Time	Visits per month
Month 1	12
Month 2	8
Month 3	4
Months 4–6	2
Months 7–12	1
Year 2	1 (assumed)
Year 3	2/3 (assumed)
Thereafter	1/3 (assumed)

Kidney transplant recipients at high risk of CMV infection (D+/R−) were assumed to receive monthly CMV quantitative PCR for four months and CMV serology at three months, following the Birmingham protocol.[235]

According to the Birmingham protocol all CMV seronegative patients (high-risk and low-risk) should receive annual CMV serology until they are seropositive. It was assumed that on average this would require two annual tests for high-risk patients (50.9% of high-risk adult patients in Humar et al. 2010 were PCR positive at 12 months) and five annual tests for low-risk patients.[236]

It was also assumed that intermediate-risk patients would receive weekly CMV quantitative PCR for three months (based on the Bristol Royal Hospital for Children and the Royal Devon & Exeter protocols)[237, 238] unless they received induction with rabbit ATG, in which case they would receive CMV prophylaxis for three months.

BK virus quantitative PCR was assumed to be conducted for all children and adolescents at 3, 6 and 12 months (based on the Royal Devon & Exeter protocol[237]).

Epstein–Barr virus quantitative PCR was assumed to be conducted for children and adolescents at high risk of Epstein–Barr virus infection monthly for months 1–6, then at 9 months and 12 months (based on the Royal Devon & Exeter protocol[237]).

Table 91. Epstein–Barr virus risk for children and adolescents receiving kidney transplantation

Epstein–Barr virus risk category	Proportion of child/adolescent KTRs
High risk (D+/R−)	28/82 = 34.1%
Intermediate risk (D±/R+)	48/82 = 58.5%
Low risk (D−/R−)	6/82 = 7.3%

Source: Hocker et al. 2013[239]

Explant surgery

Not all grafts are explanted upon failure, with the likelihood of nephrectomy decreasing with time since transplantation. NHS Blood and Transplant provided data on the probability of nephrectomy as a function of time since transplantation for the PenTAG assessment report for NICE guidance TA165,[17] which we have reproduced in Table 92 and used to estimate resource use of explant surgery following failure of the initial graft.

For the subsequent graft it was estimated that 5.9% would be explanted upon failure by applying the proportions of grafts explanted for the first graft to the exponential graft survival curve for subsequent grafts.

Table 92. Proportion of failed grafts explanted as a function of time since transplantation

Time since transplantation	Proportion of grafts explanted
0–3 months	41%

3–12 months	23%
12–24 months	9%
24+ months	4%
Subsequent grafts	5.9%

Source: Organ Donation and Transplantation Directorate of NHS Blood and Transplant (NHSBT). Statistics prepared by NHS Blood and Transplant from the National Transplant Database maintained on behalf of transplant services in the UK and Republic of Ireland.

Subsequent retransplantation

Based on the Department for Health Reference Costs 2013/14 it was estimated that there would be 1.44 "workups for retransplantation" for each actual retransplantation (which can include a number of tests for fitness for transplant surgery, fitness for long-term immunosuppression, immunological assessment and assessment of risk factors for graft and patient survival), and that living donor costs would be incurred in 34.9% of retransplantations and deceased donor costs in 65.1%.

Diabetes medication

It was assumed that KTRs with NODAT would receive three 500 mg metformin tablets daily. While this may not be a sophisticated or accurate estimate of the cost of diabetes medication it is considered that the costs of complications incurred in and out of hospital will significantly exceed the cost of diabetes medication.

Dyslipidaemia

It was assumed that 60% of people with dyslipidaemia would receive fluvastatin as the evidence base for this with regards to safety is greatest according to clinical advice. A dosage of 40 mg per day was assumed as this is the starting dose in Riella et al. 2012.[240]

It was assumed that 30% of people would receive pravastatin as the evidence base for safety is smaller. A dosage of 20 mg per day was assumed, again as this is the starting dose in Riella et al. 2012.[240]

It was assumed that 10% of people would receive simvastatin as there have been safety warnings with respect to ciclosporin. A dosage of 10 mg per day was assumed, again as this is the starting dose in Riella et al. 2012.[240]

Medical management for dyslipidaemia was assumed to be one dietetics outpatient attendance per year and one GP appointment per year.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease (PTLD) was not included in the analyses based on adult effectiveness estimates, but was reported as an outcome in all three paediatric RCTs (Table 93).

Table 93. Post-transplant lymphoproliferative disease in RCTs in children and adolescents

Trial	Trompeter 2002		Grenda 2006		Offner 2008	
Arm	TAC+AZA (n=103)	CSA+AZA (n=93)	TAC+AZA (n=93)	BAS+TAC+AZA (n=99)	BAS+CSA+MMF (n=100)	CSA+MMF (n=92)
PTLD	3	3	2	1	3[(a)]	5[(a)]
Time to event (years)	Mean 0.41	Mean 1.09	0–0.5	0.5–1	0–1	0–1

a PTLD/malignancy

Hypomagnesaemia

Trompeter et al. 2002[74] reported hypomagnesaemia as an adverse event occurring significantly more frequently in the tacrolimus arm than in the ciclosporin arm. Hypomagnesaemia requiring medication occurred within 6 months in 42/103 tacrolimus patients and in 21/93 ciclosporin patients.

Hypomagnesaemia was assumed to last from incidence to the trial duration (four years).

Hypertension

Hypertension was the most frequent adverse event reported by Trompeter et al. 2002,[74] with 91/103 tacrolimus patients and 81/93 ciclosporin patients requiring antihypertensive medication within 6 months.

Hypertension was assumed to last from incidence to the trial duration (four years).

Anaemia

According to Vanrenterghem et al. 2003,[211] 207/3969 = 5.2% of adult KTRs required erythropoiesis stimulating agent (ESA) treatment for anaemia, with a mean weekly dose of 5,832 IU. It was therefore assumed that child and adolescent KTRs would on average receive 3,967 IU of ESA per quarter year cycle while they were not dependent on dialysis.

The NHS Reference Costs Guidance 2013-14[58] indicates that the costs of ESA treatment for anaemia (and of drug treatments for bone mineral disorders) should be included in HRG costs. It was therefore assumed that additional ESA therapy would not be included for people in the Graft loss state.

6.2.7.3 Unit costs

The following sources were used to identify unit costs for drug acquisition:

- Commercial Medicines Unit electronic market information tool (eMit)[241]
- British National Formulary Volume 68 (January 2015 online update)[226]
- British National Formulary for Children Volume 68 (January 2015 online update)[167]

The eMit national database was the preferred source as it represents the average cost actually paid by NHS hospitals, including any negotiated discounts.

For procedures the NHS Reference Costs 2013 to 2014[58] (inflated to 2014/15 prices) were the preferred source of unit costs. Where unit costs could not be found within the NHS Reference Costs a pragmatic search of England and UK-wide sources was conducted.

Induction

Drug acquisition costs for induction therapy are given in Table 94.

Table 94. Drug acquisition costs for induction therapy

Agent	Pack details	Units	Unit cost	Source
Basiliximab	Single 10 mg vial = £758.69	10 mg doses	£758.69	BNF 68
Basiliximab	Single 20 mg vial = £842.38	20 mg doses	£842.38	BNF 68
Rabbit ATG	Single 25 mg vial = £158.77	mg	£6.35	BNF 68

Maintenance immunosuppression

Although historically the prescribing of maintenance immunosuppression has in some cases been transferred to primary care physicians through shared care arrangements and dispensing in the community, at present paediatric kidney transplant recipients are not being transferred out of hospital care and hospital prescribing and KTRs previously transferred out are being repatriated (personal communication, Fiona Gamston, Renal Transplant Sister, Birmingham Children's Hospital, 10th March 2015). A similar process is underway for adult KTRs. As a result, in this analysis it is assumed that hospital prescribing and dispensing is appropriate and therefore eMit costs are preferred when available.

For prolonged-release tacrolimus there is a significant difference in unit price between 5 mg capsules (£1.07 per mg) and smaller capsules (£1.43 per mg). In the absence of data on relative quantities purchased it was assumed that virtually all KTRs receiving prolonged-release tacrolimus would receive one 5 mg capsule daily, with some KTRs also taking one or more lower dose capsules to achieve their target daily dose. The appropriate unit cost would therefore lie between £1.07 and £1.43 per mg. It was further considered that there may be scope for negotiated discounts on the more expensive capsules. Therefore it was assumed that the lower unit price (£1.07 per mg) would be used in the base case analyses.

Table 95. Drug acquisition costs for maintenance therapy

Agent	Pack details	Units	Unit cost	Source
Immediate-release tacrolimus	50 × 1 mg = £28.81 100 × 1 mg = £55.05 50 × 0.5 mg = £24.90 50 × 5 mg = £88.57	mg	£0.5201 (based on eMit market share)	CMU eMit
Prolonged-release tacrolimus	50 × 0.5 mg = £35.79 50 × 1 mg = £71.59 100 × 1 mg = £143.17 50 × 3 mg = £214.76 50 × 5 mg = £266.92	mg	£1.0677 (based on 50 × 5 mg pack)	BNF 68
Ciclosporin	30 × 100 mg = £46.15 60 × 10 mg = £16.61 30 × 25 mg = £14.55 30 × 50 mg = £25.26	mg	£0.0165 (based on eMit market share)	CMU eMit
Mycophenolate mofetil	50 × 500 mg = £9.17 100 × 250 mg = £10.94	g	£0.3774 (based on eMit market share)	CMU eMit
Mycophenolate sodium	120 × 180 mg = £96.72 120 × 360 mg = £193.43	mg	£0.004478 (based on 120 × 180 mg pack)	BNF 68
Azathioprine	28 × 25 mg = £1.63 100 × 25 mg = £9.43 56 × 50 mg = £2.53 100 × 50 mg = £5.03	mg	£0.001075 (based on eMit market share)	CMU eMit
Sirolimus	30 × 0.5 mg = £69.00 30 × 1 mg = £86.49 30 × 2 mg = £172.98	mg	£2.8830 (based on 30 × 2 mg pack)	BNF 68
Everolimus	60 × 0.25 mg = £148.50	mg	£9.9000	Novartis submission
Belatacept	Single 250 mg vial = £354.52	Vial	£354.52	BNF 68
Prednisolone	28 × 1 mg = £0.15 30 × 2.5 mg = £1.65 100 × 2.5 mg = £5.33 30 × 5 mg = £1.61 100 × 5 mg = £5.41 28 × 5 mg = £0.39	mg	£0.003286 (based on eMit market share)	CMU eMit

Dialysis

Costs of haemodialysis and peritoneal dialysis are broken down in NHS Reference Costs by mode (haemodialysis; peritoneal dialysis), age (19 and over; 18 and under), location for

haemodialysis (hospital; satellite; home), access method for haemodialysis (haemodialysis catheter; arteriovenous fistula or graft), complications for haemodialysis (blood-borne virus; no blood-borne virus), specific modality for peritoneal dialysis (continuous ambulatory; automated; assisted automated) and overall location (at base; away from base). There are 40 HRG4 codes (and corresponding currencies in the NHS Reference Costs) for dialysis in total (including four for acute kidney injury).

The costs of haemodialysis and peritoneal dialysis were estimating by dividing the HRG4s currencies by mode and age, making assumptions about the number of currency units per week, and then calculating a weighted average cost based on activity.

Haemodialysis was assumed to be performed three times weekly unless at home, in which case it was assumed to be performed 3.23 times per week on average (based on inspection of reported average number of sessions per week after removing clearly erroneous outliers). Peritoneal dialysis is explicitly costed per day according to the Reference Costs Guidance and therefore was assumed to be performed seven times weekly.

The currencies for acute kidney injury were included but these make up a vanishingly small proportion of activity and do not have a significant impact on overall cost estimates.

It was estimated for adults (in 2013/14 prices) that haemodialysis would cost £459.59 per week and peritoneal dialysis £452.57 per week. These correspond to £6,093 and £6,000 per quarter year cycle in 2014/15 prices for haemodialysis and peritoneal dialysis respectively.

It was estimated for children and adolescents (in 2013/14 prices) that haemodialysis would cost £1,529.53 per week and peritoneal dialysis £793.09 per week. These correspond to £20,278 and £10,515 per quarter year cycle in 2014/15 prices for haemodialysis and peritoneal dialysis respectively.

Dialysis access surgery

Dialysis access costs were estimated per procedure from NHS Reference Costs 2013-14 and inflated to 2014/15 prices (Table 96).

Table 96. Unit costs for dialysis access surgery in 2014/15 prices

Procedure	Unit cost (under 19)	Unit cost (19 and over)
Temporary access for haemodialysis	£1,747	£823
Long-term access for haemodialysis	£1,946	£1,946

Long-term access for peritoneal dialysis	£1,101	£1,101

Acute rejection

The only estimates of the cost of treating acute rejection in children and adolescents are:

- Yao et al. 2006[1]: £4,644 (price year not stated), which appears to be based on an amalgamation of the company submitted costs for TA85 (i.e., for the adult population)
- Astellas (estimate for TA99)[1]: "around £1,000" (price year not reported)
- Astellas (estimate for current appraisal): £889 [£38.40 for steroid-sensitive acute rejection (80% of cases), £4,292 for steroid-resistant acute rejection (20% of cases)] (presumed 2012/13 prices)

It was decided that none of these estimates were appropriate, as they were not recent, in the wrong patient population, or omitted important cost components (such as the cost of administration and hospitalisation for steroid-sensitive acute rejection in the more recent estimate by Astellas).In the absence of any appropriate costs for children and adolescents it was decided that the cost estimated by Bristol Myers Squibb in their submission to the parallel technology appraisal to update NICE guidance TA85 (kidney transplantation in adults), since it was judged the most appropriate cost for the PenTAG assessment in that technology appraisal. The cost of acute rejection was estimated as £3,217 in 2009 GBP, which was inflated to £3,557 in 2014/15 prices.

It is possible that the cost of treating acute rejection could be greater in children and adolescents than in adults, because often hospitalisation costs are greater in children and adolescents. On the other hand, it may be that reduced drug costs (due to reduced dosage requirements) counter this. Further, it may be that some expensive treatments are also deemed to be inappropriate for children and adolescents. Nevertheless, £3,557 is deemed to be an appropriate central estimate for the cost of treating acute rejection in children and adolescents.

By response to treatment

Grenda et al. 2006[72] and Trompeter et al. 2002[74] report acute rejections in the first six months according to their response to treatments, as either "Spontaneously resolving" (i.e., not requiring changes to treatment), "Steroid-sensitive" (i.e., resolving after a short course of

high-dose corticosteroids), or “Steroid-resistant” (i.e., not resolving after a short course of high-dose corticosteroids).

We assumed the cost of spontaneously resolving acute rejection would be £145 (the cost of a clinic visit), and that the cost of steroid-sensitive acute rejection could be approximated by NHS Reference Cost LA07P (Acute kidney injury without treatment CC 0-3), since the cost of high-dose corticosteroids is not significant; in 2014/15 prices this is £1,274.

We assumed that steroid-resistant acute rejection would be treated by a course of seven days rabbit ATG infusion at 1.5 mg/kg, plus the cost of steroid-sensitive acute rejection. The total medical management cost for steroid-resistant acute rejection was estimated to be £3,456, and the drug acquisition cost to be £44.46 per kg body weight. This may be an underestimate of the true cost of acute rejection.

New-onset diabetes after transplantation

To our knowledge the only estimated costs for NODAT are:

- Astellas/Fujisawa, in their submission for NICE guidance TA99, proposed a one-off cost of £533 for diabetes mellitus followed by treatment switching (although notably this switching was mostly from CSA+AZA to TAC+AZA or from TAC+AZA to TAC+MMF)[1]
- Yao et al. 2006[1] do not specifically cost for NODAT, but do include a one-off cost for side-effects (including NODAT) of £200 followed by treatment switching
- Astellas, in their submission for this appraisal, propose a yearly cost of £17.38 for NODAT, comprising metformin tablets only

We considered that the costs estimated for NICE guidance TA99 are not appropriate as sources are not given and the costs are not recent. We also considered that the costs estimated by Astellas for this appraisal are not appropriate as they do not include any possible complications resulting from NODAT.

We assumed that the costs estimated for NODAT in the adult population could be a reasonable approximation to costs in children and adolescents. Although these costs would be likely to include certain costs unlikely to be incurred in young patients (particularly cardiovascular complications), there would also be likely to be increased costs of medical management for children and adolescents with NODAT, and greater costs in the event of any complications requiring hospitalisation. The cost of diabetes in adults in the general

population was estimated as £2,028 per year (£1,352 inpatient costs, £676 non-inpatient costs).[242] This was inflated to £2,084 per year in 2014/15 prices.

Dyslipidaemia

Statin acquisition costs for the treatment of dyslipidaemia are given in Table 97 and medical management costs are given in Table 98.

Table 97. Medication (statin) unit costs for dyslipidaemia

Statin	Pack details	Units	Unit cost	Source
Fluvastatin	28 × 20 mg = £1.59 28 × 40 mg = £1.79	mg	£0.002216 (weighted by eMit market share)	CMU eMit
Pravastatin	28 × 10 mg = £4.32 28 × 20 mg = £1.85 28 × 40 mg = £0.79	mg	£0.002561 (weighted by eMit market share)	CMU eMit
Simvastatin	28 × 10 mg = £0.15 28 × 20 mg = £0.24 28 × 40 mg = £0.34	mg	£0.000339 (weighted by eMit market share)	CMU eMit

Table 98. Medical management unit costs for dyslipidaemia

Attendance	Source	Unit cost	
		2013/14 prices	2014/15 prices
Dietetics outpatient	NHS Reference Costs 2013-14: 654 [Dietetics]	£61.69	£62.70
General practice	PSSRU Unit Costs 2014[224]: General practitioner (excluding direct care staff costs, without qualification costs, per 17.2 minute clinic)	£50.00	£50.82

Infection prophylaxis

Drug acquisition costs for infection prophylaxis are given in Table 99. Costs for CMV prophylaxis (valganciclovir) are clearly much higher than costs for PCP and UTI prophylaxis.

Table 99. Drug acquisition costs for infection prophylaxis

Agent	Pack details	Units	Unit cost	Source
Co-trimoxazole (Septrin®)	100 × 480 mg = £15.52	Per 480 mg tablet	£0.1552	BNF 68
Valganciclovir (Valcyte®)	60 × 450 mg = £1,081.46	Per 450 mg tablet	£18.02	BNF 68

Cytomegalovirus infection treatment

In the parallel HTA to inform the update to NICE guidance TA85, Bristol-Myers Squibb submitted a microcosting study[243] in which the cost of CMV infection was estimated to be £2,271 in 2009 prices. This was inflated to £3,009 in 2014/15 prices.

Astellas, in their submission for this appraisal, propose a cost of £221 to £1,151 depending on body weight. This cost includes drug acquisition (ganciclovir) but does not include any other costs, including drug administration and other medical management (e.g., hospitalisation costs).

It was decided that the costs derived from adults would be more appropriate, as if anything the costs of treating CMV infection could be greater in children and adolescents than in adults.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease was assumed to incur £1,206 in drug administration (four IV infusions) and £3,040/m² body surface area in drug acquisition (four times 375 mg/m² rituximab, Mabthera, £1.7463/mg).

Hypomagnesaemia

The cost of hypomagnesaemia requiring treatment was estimated to be £290.18 per year (one sachet of Magnaspartate daily, £0.80 per sachet).[167]

Hypertension

The annual cost of hypertension requiring medication was estimated to be £120.10 (Table 100), based on resource use in John et al. 2014.[244]

Table 100. Costs of hypertension

Item	Resource use	Unit cost	Item cost (per year)
Dietetics clinic	1 per year	£62.70	£62.70
Amlodipine	5 mg per day	£0.0071 per mg	£13.04
Bendroflumethiazide	1 tablet per day	£0.0344 per 2.5 mg tablet	£12.56
Captopril	25 mg per day	£0.0035 per mg	£31.81
		Total	£120.10

Anaemia

Costs of erythropoiesis stimulating agent (ESA) therapy were estimated assuming that the ESA with lowest acquisition cost would be used (following NICE guidance TA323 which relates to cancer-treatment induced anaemia). Based on the BNF list prices Binocrit® is the cheapest ESA, although it is possible that local pharmacy negotiations may result in reduced costs to the NHS in practice.

Table 101. Drug acquisition costs for anaemia

Agent	Pack details	Units	Unit cost	Source
Epoetin alfa (Binocrit®)	1,000 IU = £4.33	Per 1,000 IU	£4.33 (based on 1,000 prefilled syringe)	BNF 68
	2,000 IU = £8.65			
	3,000 IU = £12.98			
	4,000 IU = £17.31			
	5,000 IU = £21.64			
	6,000 IU = £25.96			
	8,000 IU = £40.73			
	10,000 IU = £43.27			

Drug administration

All maintenance agents except belatacept are administered orally (unless people are unable to take medication orally) and this was assumed to not incur any cost.

Basiliximab is administered by intravenous infusion or injection and rabbit ATG is administered by intravenous infusion. Basiliximab is administered on the day of transplantation and four days after transplantation. It is very likely that KTRs will still be inpatients for the latter administration. Rabbit ATG is administered by intravenous infusion for 3–9 days. It is likely that KTRs will be inpatients for all of these infusions (a typical adult patient is estimated to require 10 days inpatient stay[245] and children and adolescents are unlikely to require significantly shorter duration).

Belatacept is administered by intravenous infusion in an outpatient setting after the KTR is discharged from hospital. It is possible that there would be some efficiency savings by combining administration attendances with regular attendances for monitoring and clinics in early months but thereafter administrations are likely to be more frequent than other visits.

The NHS Reference Costs do not estimate a cost of intravenous infusion for inpatients as it is assumed to be a part of standard care and costs assigned to procedures taking precedence (e.g., kidney transplant). Nevertheless it was considered important to estimate the cost of administration separately for induction therapies to enable fair comparison against no induction and potential future comparisons against other induction with alternative modes of administration.

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.

Kidney-transplant recipient follow-up

The unit cost of follow-up clinics was estimated from outpatient attendance costs in the nephrology service, using a weighted average of the different types of attendance (with weights based on national activity). When inflated to 2014/15 prices the unit cost of a follow-up clinic was estimated to be £145.27 (Table 102). First face-to-face attendances were included as well as follow-up clinics on the basis that some people receive follow-up at a different centre to where they received their transplant and the relative weight of these clinics in calculating the average is small.

Table 102. Unit costs of follow-up clinics

Type of attendance	Number of attendances	National average unit cost (2013/14 prices)

Consultant-led	Non-admitted face to face	First	85206	£185.95
		Follow-up	652678	£146.59
	Non-admitted non-face to face	First	1124	£143.13
		Follow-up	3033	£109.24
Non-consultant-led	Non-admitted face to face	First	7770	£140.42
		Follow-up	109174	£94.15
	Non-admitted non-face to face	First	246	£60.38
		Follow-up	5810	£42.06
			Weighted average	£142.93
			(In 2014/15 prices)	£145.27

Monitoring

The unit cost of viral quantitative PCR was assumed to be the same for cytomegalovirus, Epstein–Barr virus and BK virus. The most appropriate recent cost estimate that could be found was from University College London Hospitals provider-to-provider service 2013/14 tariff. This is a recent cost from an NHS provider. The tariffs are likely to be slightly higher than the costs of in-house laboratory tests but this was assumed to be a small effect and it was also considered that some centres might not have in-house quantitative PCR facilities. The tariff for CMV quantitative PCR was £46 in 2013/14 prices and this was inflated to £46.75 in 2014/15 prices for use in the model. The cost of CMV serology was estimated from the same source, which when inflated to 2014/15 prices is £18.29.

The unit costs of therapeutic drug monitoring were estimated from the Department of Biochemistry and Immunology, University Hospital of Wales, therapeutic drug monitoring test repertoire. Ciclosporin, tacrolimus and sirolimus therapeutic drug monitoring all incurred charges of £26.28, which was inflated to £26.71 in 2014/15 prices for use in the model. The cost of therapeutic drug monitoring was assumed to be the same as that for sirolimus.

Other tests (full blood count, renal profile and liver function tests) were estimated based on the costing template produced by NHS Kidney Care to assist in the costing of renal transplantation,[245] as shown in Table 103.

Table 103. Unit costs for other monitoring tests

Test	Unit cost (2008/09 prices)	Unit cost (2014/15 prices)
Full blood count	£4.57	£5.05
Renal profile	£4.11	£4.54
Liver function test	£4.20	£4.64

Explant surgery

The cost of explant surgery was estimated using NHS Reference Costs 2013 to 2014. The appropriate HRG4 currencies were identified using the 2013/14 Reference Cost Grouper Code to Group workbook,[246] by mapping from OPCS-4 code M026 (Excision of rejected transplanted kidney) to groups LB61, LB62 and LB63.

The average cost (weighted by activity) for adults (from HRGs LB61 and LB62) was £4,886 in 2013/14 prices (£4,966 in 2014/15 prices). The average cost (weighted by activity) for children and adolescents (from HRG LB63) was £4,751 in 2013/14 prices (£4,829 in 2014/15 prices).

Subsequent transplant

Living donor costs fall under three HRG4 currencies:

- LA10Z: Live donor kidney screening
- LA11Z: Kidney pre-transplantation work-up of live donor
- LB46Z: Live donation of kidney

The total living donor costs per live kidney donation were calculated by dividing the total cost for each currency by the activity for actual live donation, resulting in a combined cost of £8,770.60 per live kidney donation in 2013/14 prices (Table 104).

Table 104. Reference costs informing the unit cost of live kidney donation

HRG4 currency	Activity	Unit cost	Total cost
LA10Z: Live Kidney Donor Screening	801	£659.61	£528,351
LA11Z: Kidney Pre-Transplantation Work-up of Live Donor	1524	£477.95	£728,398

LB46Z: Live Donation of Kidney	805	£7,209.43	£5,803,587
		Total cost	£7,060,337
		(Per live donation of kidney)	£8,770.60

Deceased donor costs comprise the cost of retrieval, which may be divided into staffing, consumables and transport. NHS Blood and Transplant performed a service evaluation of the National Organ Retrieval Service (NORS) and reported various costs.[247] Staffing costs were reported separately for abdominal retrieval teams and these were used to estimate the staffing cost of retrieval at £6,093.49 in 2012/13 prices (Table 105). The average cost of consumables per retrieval was reported as £1,770.30, although it should be noted that this included cardiothoracic retrievals also. The total cost of transport was reported as £4,098,473.94 and this was divided by the total number of retrievals (abdominal and cardiothoracic) for a unit cost of £2,005.12 per retrieval. The total cost of retrieval was therefore estimated to be £9,869 in 2012/13 prices, which was inflated to £10,142 in 2014/15 prices for the model.

Table 105. Abdominal retrieval team staffing costs

Abdominal retrieval team	Number of retrievals	Average staffing cost per retrieval
University Hospitals Birmingham NHS FT	215	£4,440.56
Cambridge University Hospitals NHS FT	245	£4,082.34
University Hospital of Wales	72	£5,979.36
Kings College Hospital NHS FT	246	£2,865.03
Leeds Teaching Hospitals NHS Trust / Central Manchester and Manchester Children's Foundation Hospitals NHS Trust	251	£8,645.29
Newcastle-upon-Tyne NHS FT	179	£5,158.09
Oxford Radcliffe Hospitals NHS Trust	126	£6,912.76
Royal Free Hampstead NHS Trust	122	£10,800.90
Royal Infirmary of Edinburgh (SORT)	117	£10,366.39
Average		£6,093.49

Table 106. Reference costs informing the unit cost of transplant surgery

HRG4 currency	Activity	Unit cost	Total cost
LA01A: Kidney Transplant, 19 years and over, from Cadaver Non Heart-Beating Donor	553	£13,603.01	£7,522,463
LA02A: Kidney Transplant, 19 years and over, from Cadaver Heart-Beating Donor	991	£15,520.53	£15,380,850
LA03A: Kidney Transplant, 19 years and over, from Live Donor	826	£17,526.91	£14,477,231
Average (adults)		£15,772.38	
LA01B: Kidney Transplant, 18 years and under, from Cadaver Non Heart-Beating Donor	11	£27,496.72	£302,464
LA02B: Kidney Transplant, 18 years and under, from Cadaver Heart-Beating Donor	47	£18,502.00	£869,594
LA03B: Kidney Transplant, 18 years and under, from Live Donor	55	£20,964.49	£1,153,047
Average (children and adolescents)		£20,576.15	

Table 107. Unit costs for subsequent transplants

Procedure	HRG4 currency	Unit cost	
		2013/14 prices	2014/15 prices
Recipient work-up	LA12A: Kidney Pre-Transplantation Work-up of Recipient, 19 years and over	Adults: £835.06	Adults: £848.72
	LA12B: Kidney Pre-Transplantation Work-up of Recipient, 18 years and under	Children and adolescents: £496.61	Children and adolescents: £504.73
Living donor costs	See Table 104	£8,770.60	£8,914.05
Deceased donor costs	See above	£9,868.92	£10,142.05
Transplant surgery	See Table 106	Adults: £15,772.38	Adults: £16,030.35
		Children and adolescents: £20,576.15	Children and adolescents: £20,912.68

6.2.8 Summary of model parameters

See Appendix 8 for base case values and PSA distributions for the parameters in the model.

6.2.9 Model verification

The decision model was tested by an independent academic decision modeller (Andy Salmon). Extreme value testing and other black box testing techniques were applied to ensure the model performed as expected.

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)

Replaced by erratum

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	£159,900	£196,783
Discounted QALYs	13.3895	12.9169
Combined (50 years)		
Discounted costs	£177,632	£222,333
Discounted QALYs	16.7185	16.1698
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	2.7837	—
INHB at £30k/QALY	2.0387	—

Replaced by erratum

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

Replaced by erratum

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)	£8,313	£5,939
Monitoring (initial graft)	£5,167	£3,110
Dialysis	£106,436	£137,309
Retransplantation	£14,767	£18,798
Maintenance immunosuppression (subsequent grafts)	£8,721	£11,268
Monitoring (subsequent grafts)	£13,178	£17,047
Other costs	£3,318	£3,313
Total	**£159,900**	**£196,783**

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

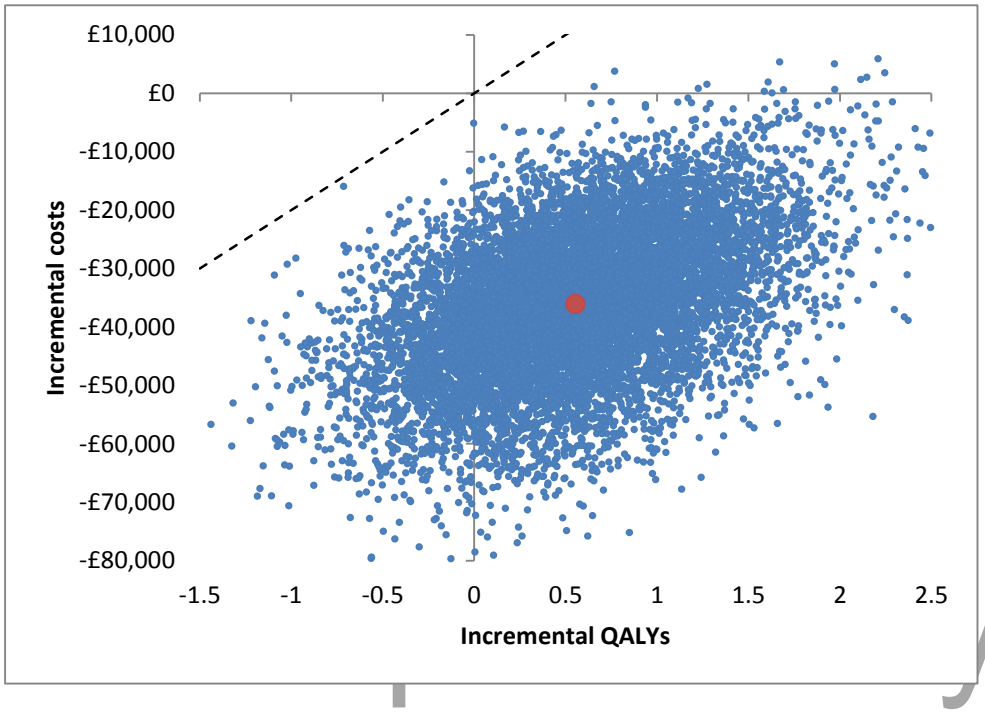
Table 111. Cost-effectiveness results based on Trompeter et al. 2002 (probabilistic analysis)

Regimen	TAC+AZA	CSA+AZA
Trial duration (4 years)		
Discounted costs	£17,867	£25,854
Discounted QALYs	3.3295	3.2533
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	0.4755	—
INHB at £30k/QALY	0.3424	—
Extrapolation (46 years)		
Discounted costs	£157,355	£193,445
Discounted QALYs	13.3802	12.9028
Combined (50 years)		
Discounted costs	£175,221	£219,299
Discounted QALYs	16.7096	16.1561
ICER (cost/QALY)	Dominant	—
INHB at £20k/QALY	2.7574	—
INHB at £30k/QALY	2.0228	—

Replaced by erratum

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 99.9% of simulations (Figure 28).

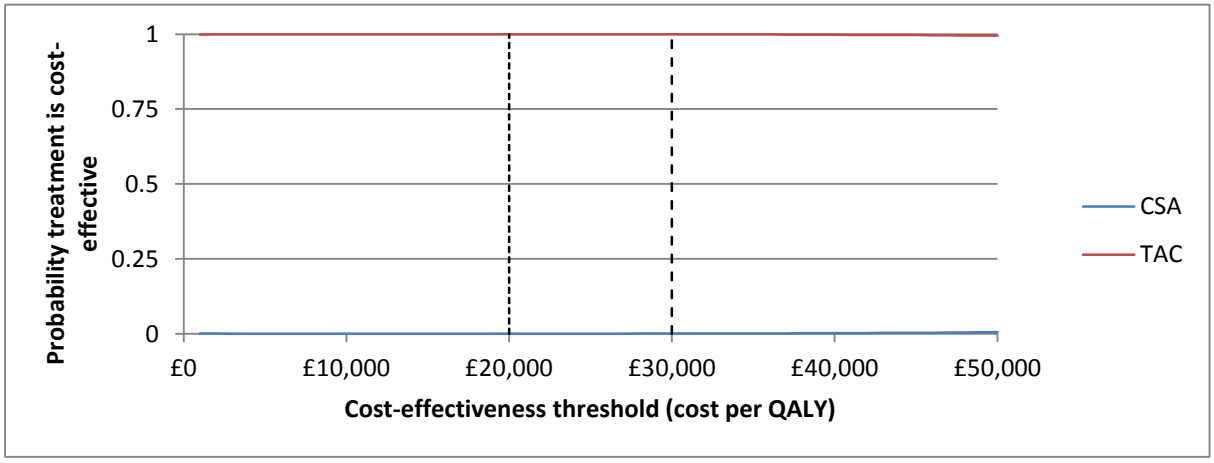
Figure 27. Probabilistic sensitivity analysis scatter cloud for Trompeter et al. 2002 (TAC versus CSA)



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

erratum

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 (2.7852 and 2.0397 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.

Replaced by erratum

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 (2.6837 and 1.9715 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	£127,804	£122,209
Discounted QALYs	15.7609	15.9309
Combined (50 years)		
Discounted costs	£141,561	£135,840
Discounted QALYs	17.4928	16.6745
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.4677
INHB at £30k/QALY	—	0.3724

Replaced by erratum

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

Replaced by erratum

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)	£13,391	£14,082
Monitoring (initial graft)	£9,207	£9,671
Dialysis	£76,015	£70,030
Retransplantation	£10,612	£9,841
Maintenance immunosuppression (subsequent grafts)	£6,147	£5,665
Monitoring (subsequent grafts)	£9,319	£8,575
NODAT	£426	£1,618
Other costs	£2,687	£2,727
Total	**£127,804**	**£122,209**

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).

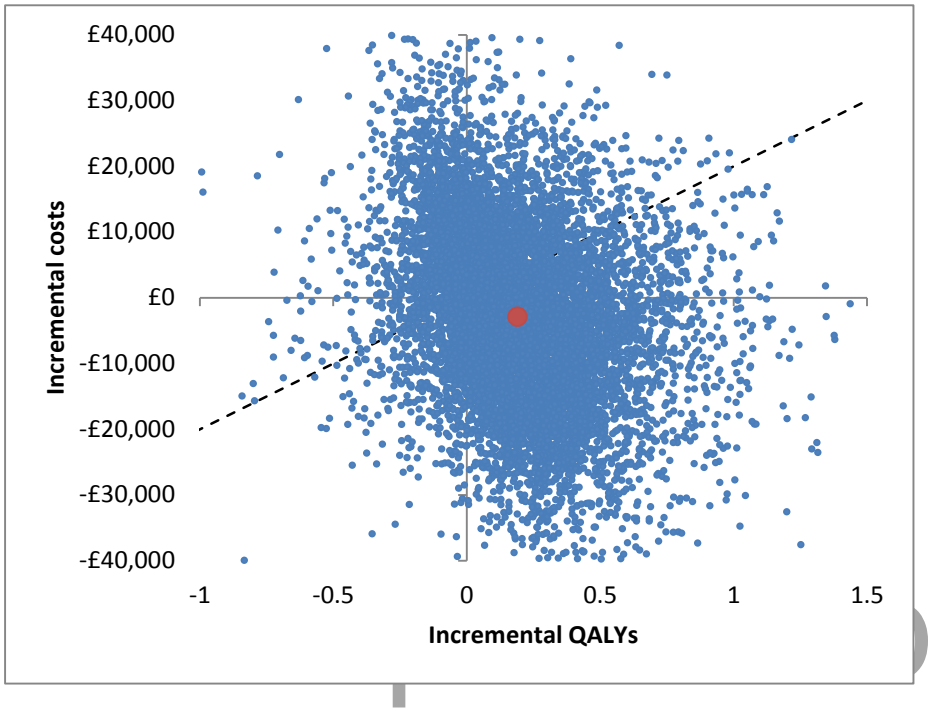
Table 115. Cost-effectiveness results based on Grenda et al. 2006 (probabilistic analysis)

Regimen	TAC+AZA	BAS+TAC+AZA
Trial duration (2 years)		
Discounted costs	£13,744	£13,648
Discounted QALYs	1.7317	1.7434
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.0164
INHB at £30k/QALY	—	0.0148
Extrapolation (48 years)		
Discounted costs	£130,227	£124,659
Discounted QALYs	15.6338	15.8127
Combined (50 years)		
Discounted costs	£143,971	£138,307
Discounted QALYs	17.3656	17.5561
ICER (cost/QALY)	—	Dominant
INHB at £20k/QALY	—	0.4737
INHB at £30k/QALY	—	0.3793

Replaced by erratum

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 67.3% of simulations and at £30,000 per QALY in 69.3% of simulations (Figure 30).

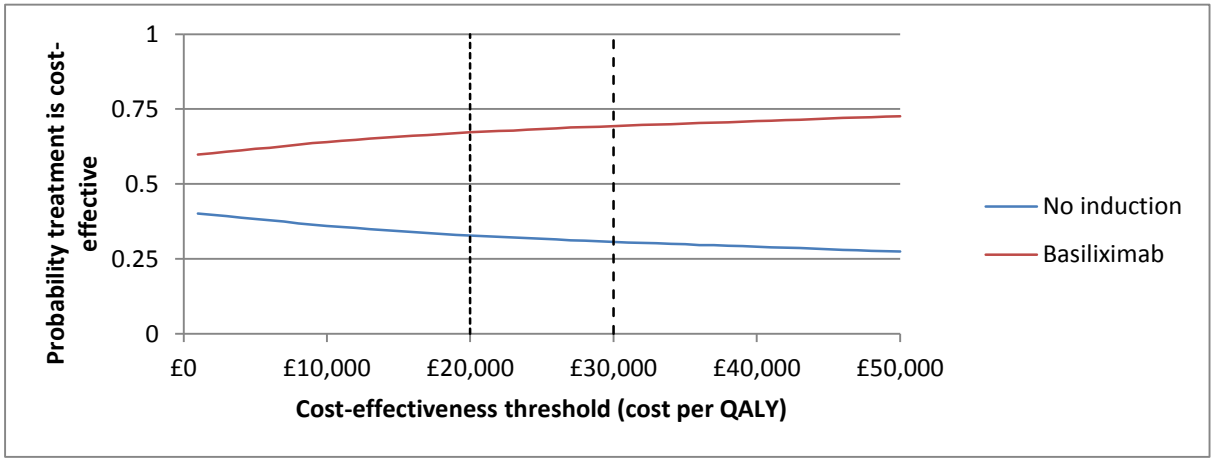
Figure 29. Probabilistic sensitivity analysis scatter cloud for Grenda et al. 2006 (basiliximab versus no induction)



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

erratum

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 (0.4737 and 0.3763 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 (0.4457 and 0.3567 respectively).

6.3.1.3 Offner et al. 2008

Replaced by erratum

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	£130,364	£123,919
Discounted QALYs	16.9461	17.4765
Combined (50 years)		
Discounted costs	£135,772	£127,216
Discounted QALYs	17.8300	18.3757
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.9734	—
INHB at £30k/QALY	−0.8308	—

Replaced by erratum

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**

Replaced by erratum

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)	£15,783	£16,552
Monitoring (initial graft)	£9,849	£10,651
Dialysis	£74,143	£68,311
Retransplantation	£11,756	£10,816
Maintenance immunosuppression (subsequent grafts)	£6,029	£5,546
Monitoring (subsequent grafts)	£9,976	£9,132
Other costs	£2,827	£2,911
Total	**£130,364**	**£123,919**

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).

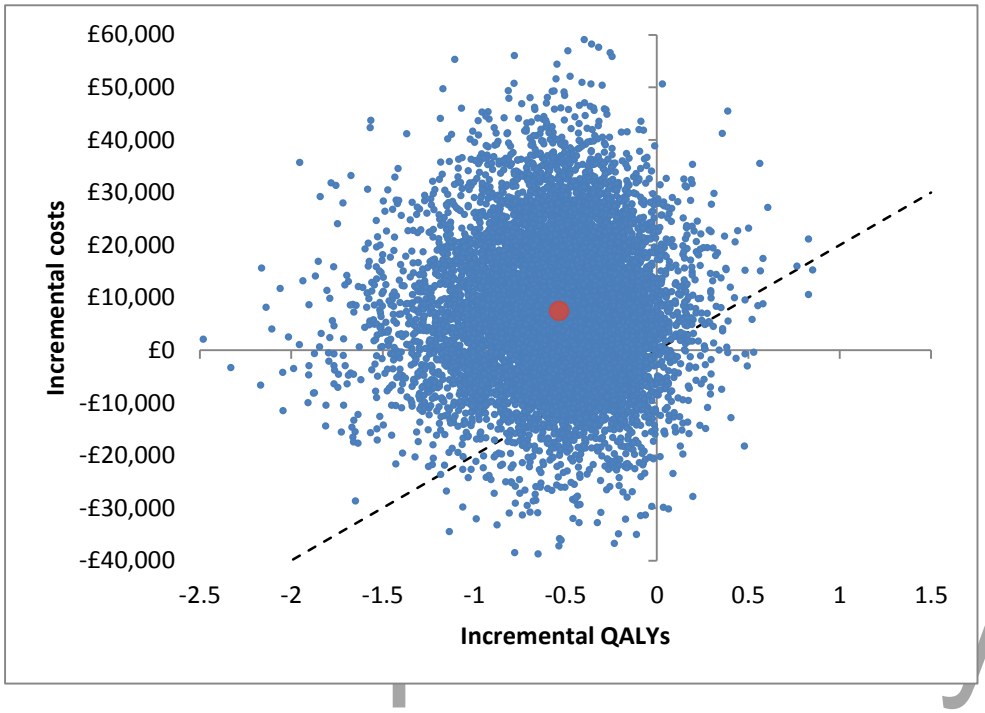
Table 119. Cost-effectiveness results based on Offner et al. 2008 (probabilistic analysis)

Regimen	BAS+CSA+MMF	CSA+MMF
Trial duration (2 years)		
Discounted costs	£5,414	£3,301
Discounted QALYs	0.8796	0.8950
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.1210	—
INHB at £30k/QALY	−0.0858	—
Extrapolation (48 years)		
Discounted costs	£130,755	£125,115
Discounted QALYs	16.8371	17.3565
Combined (50 years)		
Discounted costs	£136,169	£128,416
Discounted QALYs	17.7167	18.2515
ICER (cost/QALY)	Dominated	—
INHB at £20k/QALY	−0.9225	—
INHB at £30k/QALY	−0.7932	—

Replaced by erratum

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 9.4% and 6.7% of simulations at £20,000 and £30,000 per QALY respectively (Figure 32).

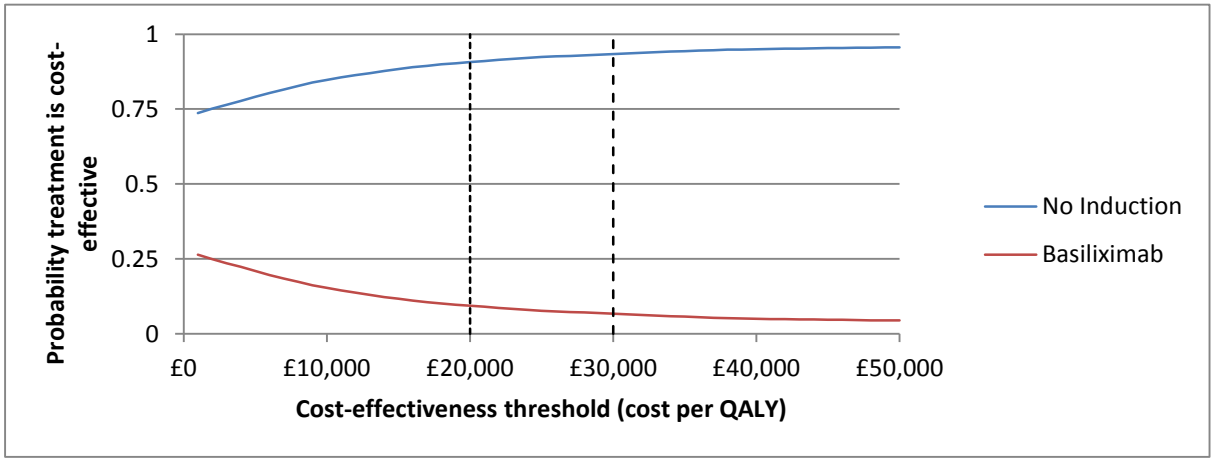
Figure 31. Probabilistic sensitivity analysis scatter cloud for Offner et al. 2008 (basiliximab versus no induction)



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

erratum

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 (−0.9757 and −0.8323 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 (−1.1429 and −0.9487 respectively).

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

Replaced by erratum

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 less costly and more effective than no induction.

The differences in QALYs from no induction to rabbit ATG and from rabbit ATG 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 greater for both agents than for 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.

Replaced by erratum

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*	
No induction	£212,626	—	17.9786	—	Dominated	−0.7885	−0.5764
Rabbit ATG	£204,260	−£8,366	18.1119	+0.1333	Dominated	−0.2369	−0.1642
Basiliximab	£199,900	−£4,360	18.1308	+0.0189	—	—	—
With CSA+MMF						*vs. Basiliximab*	
No induction	£202,424	—	18.1018	—	Dominated	−0.6823	−0.5032
Rabbit ATG	£196,997	−£5,427	18.2169	+0.1151	Dominated	−0.2959	−0.2073
Basiliximab	£191,679	−£5,318	18.2468	+0.0300	—	—	—
With TAC+AZA						*vs. Basiliximab*	
No induction	£177,360	—	18.2674	—	Dominated	−0.7752	−0.5696
Rabbit ATG	£170,112	−£7,248	18.4078	+0.1404	Dominated	−0.2724	−0.1876
Basiliximab	£165,024	−£5,087	18.4259	+0.0181	—	—	—
With TAC+MMF						*vs. Basiliximab*	
No induction	£182,163	—	18.2085	—	Dominated	−0.7135	−0.5260
Rabbit ATG	£176,691	−£5,471	18.3383	+0.1298	Dominated	−0.3101	−0.2138
Basiliximab	£170,915	−£5,776	18.3596	+0.0213	—	—	—

Replaced by erratum

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								
No induction	14.802	—	43.130	—	33.672	—	9.458	—
Rabbit ATG	16.627	+1.824	43.363	+0.232	34.302	+0.630	9.060	−0.398
Basiliximab	17.229	+0.602	43.378	+0.015	34.490	+0.187	8.888	−0.172
With CSA+MMF								
No induction	16.787	—	43.329	—	34.321	—	9.008	—
Rabbit ATG	18.371	+1.584	43.532	+0.203	34.894	+0.573	8.638	−0.370
Basiliximab	19.171	+0.800	43.566	+0.034	35.159	+0.265	8.407	−0.232
With TAC+AZA								
No induction	20.906	—	43.593	—	35.771	—	7.822	—
Rabbit ATG	22.799	+1.893	43.849	+0.257	36.510	+0.739	7.340	−0.482
Basiliximab	23.597	+0.797	43.858	+0.008	36.785	+0.275	7.073	−0.267
With TAC+MMF								
No induction	19.944	—	43.494	—	35.349	—	8.145	—
Rabbit ATG	21.559	+1.615	43.736	+0.242	35.991	+0.642	7.745	−0.400
Basiliximab	22.449	+0.890	43.746	+0.011	36.286	+0.295	7.460	−0.285

Replaced by erratum

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 £600,000 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).

Replaced by erratum

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	£202,424	—	18.1018	—	Dominated	−1.1197	−0.7820
TAC-PR	£198,433	−£3,992	18.1503	+0.0485	Dominated	−0.8717	−0.6005
TAC	£182,163	−£16,270	18.2085	+0.0581	—	—	—
With AZA						*vs. TAC*	
CSA	£212,626	—	17.9786	—	Dominated	−2.0522	−1.4644
TAC	£177,360	−£35,267	18.2674	+0.2888	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£199,145	—	18.2423	—	Dominated	−1.5287	−1.0582
CSA	£191,679	−£7,466	18.2468	+0.0045	Dominated	−1.1509	−0.8048
TAC	£170,915	−£20,763	18.3596	+0.1127	—	—	—
BEL	£324,708	+£153,792	18.5901	+0.2306	£667,031	−7.4591	−4.8958
With BAS+AZA						*vs. TAC*	
CSA	£199,900	—	18.1308	—	Dominated	−2.0389	−1.4576
TAC	£165,024	−£34,876	18.4259	+0.2951	—	—	—
With rATG+MMF						*vs. TAC*	
CSA	£196,997	—	18.2169	—	Dominated	−1.1367	−0.7983
TAC	£176,691	−£20,306	18.3383	+0.1214	—	—	—
With rATG+AZA						*vs. TAC*	
CSA	£204,260	—	18.1119	—	Dominated	−2.0034	−1.4342
TAC	£170,112	−£34,149	18.4078	+0.2959	—	—	—

Replaced by erratum

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	£212,626	—	17.9786	—	Dominated	−0.6333	−0.4633
MMF	£202,424	−£10,202	18.1018	+0.1232	—	—	—
EVL	£261,084	+£58,660	18.1905	+0.0887	£661,046	−2.8443	−1.8666
With TAC						*vs. AZA*	
SRL	£224,510	—	17.9281	—	Dominated	−2.6969	−1.9110
MMF	£182,163	−£42,348	18.2085	+0.2804	Dominated	−0.2991	−0.2191
AZA	£177,360	−£4,803	18.2674	+0.0590	—	—	—
With BAS+CSA						*vs. MMF*	
AZA	£199,900	—	18.1308	—	Dominated	−0.5271	−0.3901
MMF	£191,679	−£8,221	18.2468	+0.1161	—	—	—
MPS	£199,158	+£7,479	18.3907	+0.1438	£51,993	−0.2301	−0.1054
With BAS+TAC						*vs. AZA*	
MMF	£170,915	—	18.3596	—	Dominated	−0.3609	−0.2627
AZA	£165,024	−£5,891	18.4259	+0.0663	—	—	—
With rATG+CSA						*vs. MMF*	
AZA	£204,260	—	18.1119	—	Dominated	−0.4681	−0.3471
MMF	£196,997	−£7,263	18.2169	+0.1050	—	—	—
With rATG+TAC						*vs. AZA*	
MMF	£176,691	—	18.3383	—	Dominated	−0.3985	−0.2888
AZA	£170,112	−£6,580	18.4078	+0.0695	—	—	—

Replaced by erratum

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	16.787	—	43.329	—	34.321	—	9.008	—
TAC-PR	19.681	+2.893	43.383	+0.053	35.211	+0.890	8.172	−0.837
TAC	19.944	+0.263	43.494	+0.111	35.349	+0.138	8.145	−0.027
With AZA								
CSA	14.802	—	43.130	—	33.672	—	9.458	—
TAC	20.906	+6.104	43.593	+0.463	35.771	+2.099	7.822	−1.636
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	18.371	—	43.532	—	34.894	—	8.638	—
TAC	21.559	+3.187	43.736	+0.204	35.991	+1.097	7.745	−0.894
With rATG+AZA								
CSA	16.627	—	43.363	—	34.302	—	9.060	—
TAC	22.799	+6.173	43.849	+0.487	36.510	+2.207	7.340	−1.721

Replaced by erratum

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	14.802	—	43.130	—	33.672	—	9.458	—
MMF	16.787	+1.985	43.329	+0.199	34.321	+0.649	9.008	−0.450
EVL	18.828	+2.041	43.442	+0.112	34.972	+0.651	8.470	−0.539
With TAC								
SRL	15.569	—	43.087	—	33.860	—	9.227	—
MMF	19.944	+4.374	43.494	+0.407	35.349	+1.490	8.145	−1.083
AZA	20.906	+0.963	43.593	+0.099	35.771	+0.422	7.822	−0.323
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	16.627	—	43.363	—	34.302	—	9.060	—
MMF	18.371	+1.745	43.532	+0.169	34.894	+0.591	8.638	−0.422
With rATG+TAC								
MMF	21.559	—	43.736	—	35.991	—	7.745	—
AZA	22.799	+1.241	43.849	+0.114	36.510	+0.519	7.340	−0.405

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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 £600,000 per QALY.

As demonstrated in Table 123 (page 280), 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.

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Prolonged-release tacrolimus

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

erratum

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 £600,000 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.

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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

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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 £900,000 per QALY.

Table 124. 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	£165,024	18.4259	—	—	—
BAS+BEL+MMF	£324,708	18.5901	£972,177	−7.8199	−5.1585

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 £900,000 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.

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Figure 33. Comparison of deterministic and probabilistic total discounted costs

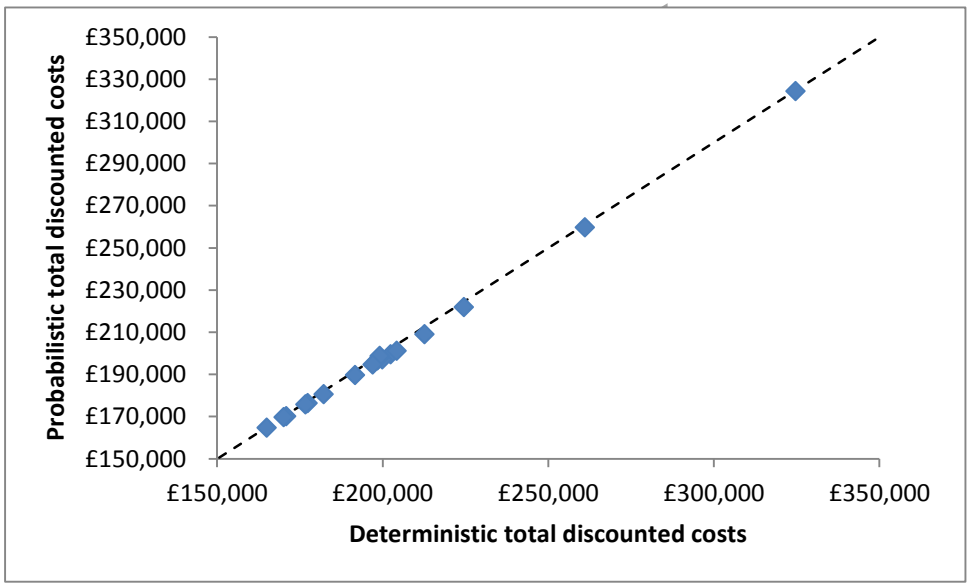
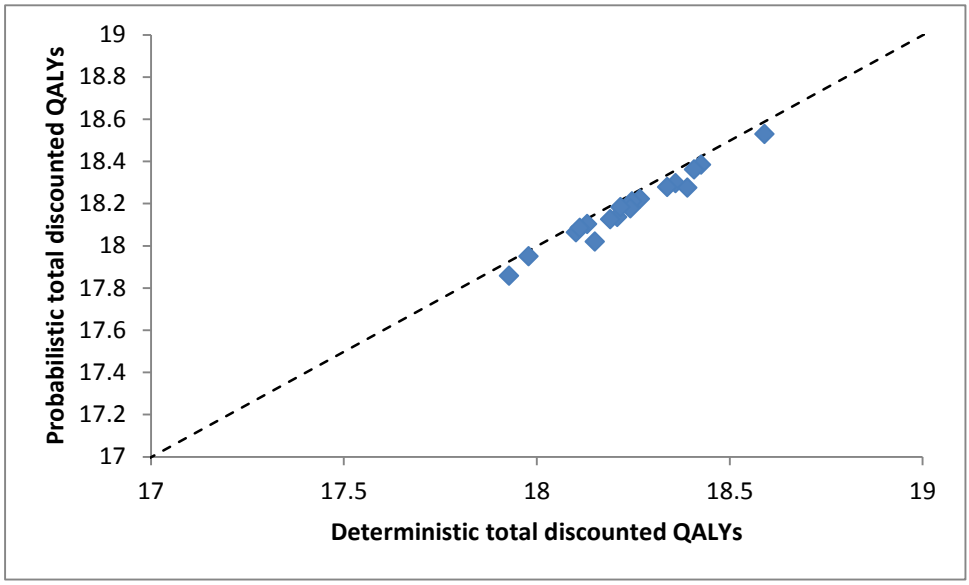


Figure 34. Comparison of deterministic and probabilistic total discounted QALYs



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Induction agents

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

There is, however, some 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 67.6% to 72.8%. It is predicted that it is possible (though 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*			
No induction	£209,016	—	17.9481	—	Dominated	-0.7482	-0.5500	0.1%	0.0%
Rabbit ATG	£201,211	-£7,805	18.0837	+0.1355	Dominated	-0.2224	-0.1543	31.6%	32.4%
Basiliximab	£197,127	-£4,084	18.1019	+0.0182	—	—	—	68.4%	67.6%
With CSA+MMF						*vs. Basiliximab*			
No induction	£199,539	—	18.0614	—	Dominated	-0.6440	-0.4783	0.2%	0.2%
Rabbit ATG	£194,609	-£4,930	18.1809	+0.1195	Dominated	-0.2780	-0.1945	27.1%	28.0%
Basiliximab	£189,597	-£5,012	18.2083	+0.0274	—	—	—	72.7%	71.8%
With TAC+AZA						*vs. Basiliximab*			
No induction	£176,305	—	18.2215	—	Dominated	-0.7394	-0.5467	0.1%	0.1%
Rabbit ATG	£169,739	-£6,566	18.3598	+0.1383	Dominated	-0.2728	-0.1895	29.1%	30.1%
Basiliximab	£164,746	-£4,993	18.3829	+0.0231	—	—	—	70.8%	69.8%
With TAC+MMF						*vs. Basiliximab*			
No induction	£180,529	—	18.1350	—	Dominated	-0.6769	-0.5044	0.2%	0.1%
Rabbit ATG	£175,703	-£4,827	18.2763	+0.1413	Dominated	-0.2943	-0.2022	27.0%	28.5%
Basiliximab	£170,179	-£5,524	18.2944	+0.0181	—	—	—	72.8%	71.4%

Replaced by erratum

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 £661,450 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 £138,196 per QALY in the probabilistic analysis compared to £51,993 per QALY in the deterministic analysis.

Replaced by erratum

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	£199,539	—	18.0614	—	Dominated	-1.0241	-0.7073	0.6%	1.0%
TAC-PR	£196,629	-£2,910	18.0181	-0.0433	Dominated	-0.9219	-0.6536	0.2%	0.3%
TAC	£180,529	-£16,100	18.1350	+0.1169	—	—	—	99.3%	98.8%
With AZA						*vs. TAC*			
CSA	£209,016	—	17.9481	—	Dominated	-1.9089	-1.3637	0.0%	0.0%
TAC	£176,305	-£32,711	18.2215	+0.2734	—	—	—	100.0%	100.0%
With BAS+MMF						*vs. TAC*			
SRL	£197,933	—	18.1753	—	Dominated	-1.5068	-1.0443	0.1%	0.1%
CSA	£189,597	-£8,336	18.2083	+0.0330	Dominated	-1.0570	-0.7334	0.4%	0.6%
TAC	£170,179	-£19,418	18.2944	+0.0861	—	—	—	99.6%	99.3%
BEL	£324,327	+£154,148	18.5275	+0.2330	£661,450	-7.4744	-4.9052	0.0%	0.0%
With BAS+AZA						*vs. TAC*			
CSA	£197,127	—	18.1019	—	Dominated	-1.9001	-1.3604	0.0%	0.0%
TAC	£164,746	-£32,381	18.3829	+0.2811	—	—	—	100.0%	100.0%
With rATG+MMF						*vs. TAC*			
CSA	£194,609	—	18.1809	—	Dominated	-1.0407	-0.7256	0.4%	0.5%
TAC	£175,703	-£18,906	18.2763	+0.0954	—	—	—	99.6%	99.5%
With rATG+AZA						*vs. TAC*			
CSA	£201,211	—	18.0837	—	Dominated	-1.8497	-1.3252	0.0%	0.0%
TAC	£169,739	-£31,472	18.3598	+0.2762	—	—	—	100.0%	100.0%

Replaced by erratum

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/QA
With CSA						*vs. MMF*			
AZA	£209,016	—	17.9481	—	Dominated	-0.5872	-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.

Replaced by erratum

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

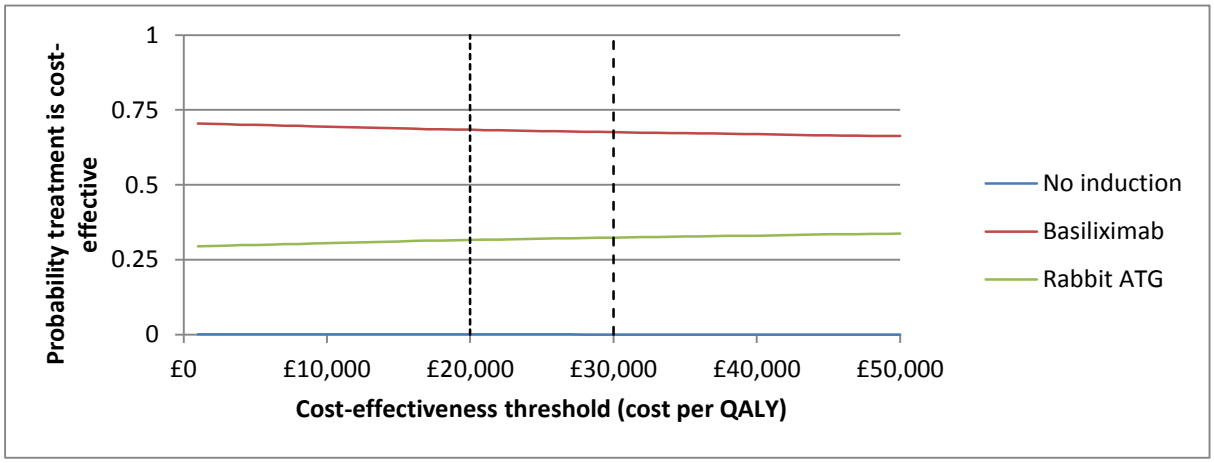


Figure 36. Cost-effectiveness acceptability curves for induction agents in combination with ciclosporin and mycophenolate mofetil

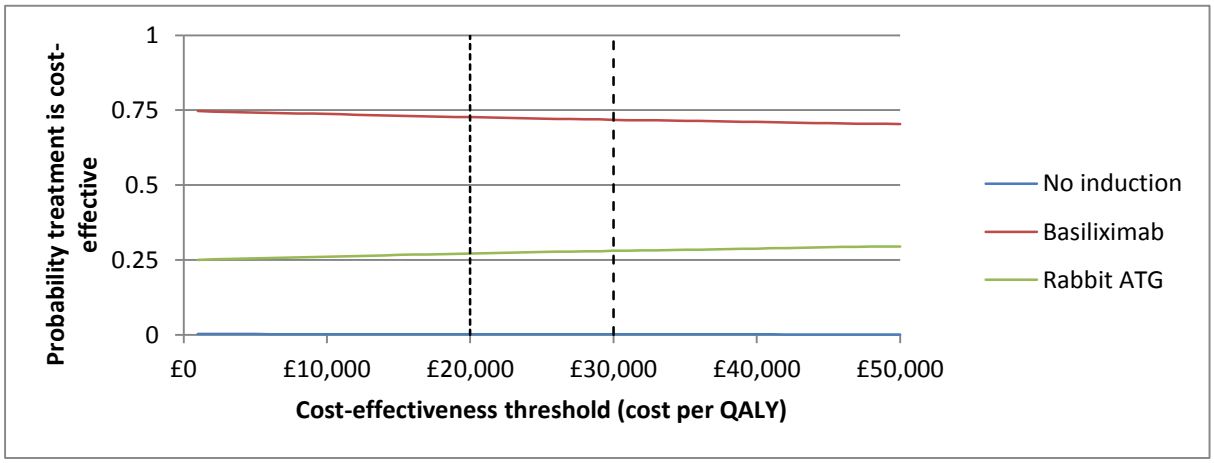


Figure 37. Cost-effectiveness acceptability curves for induction agents in combination with immediate-release tacrolimus and azathioprine

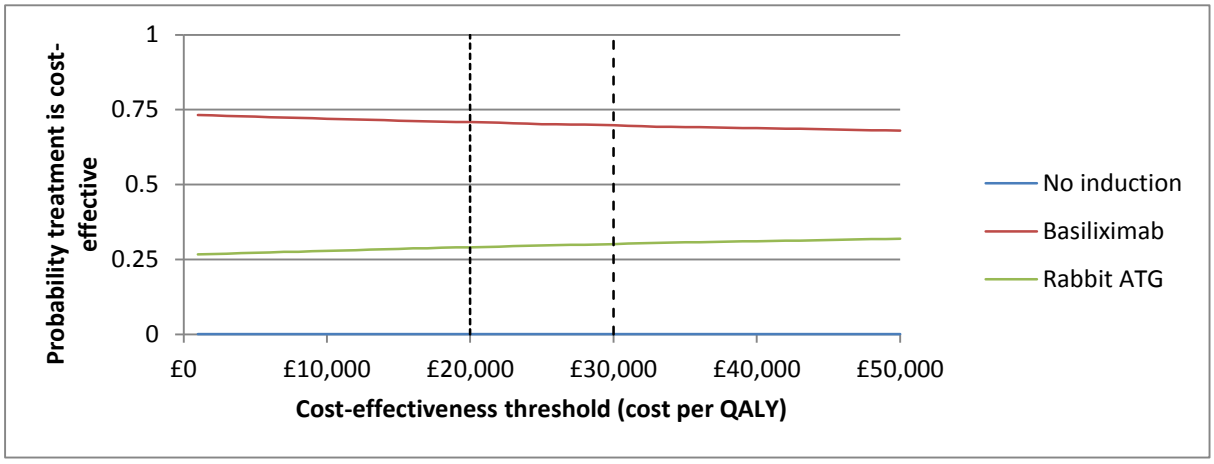
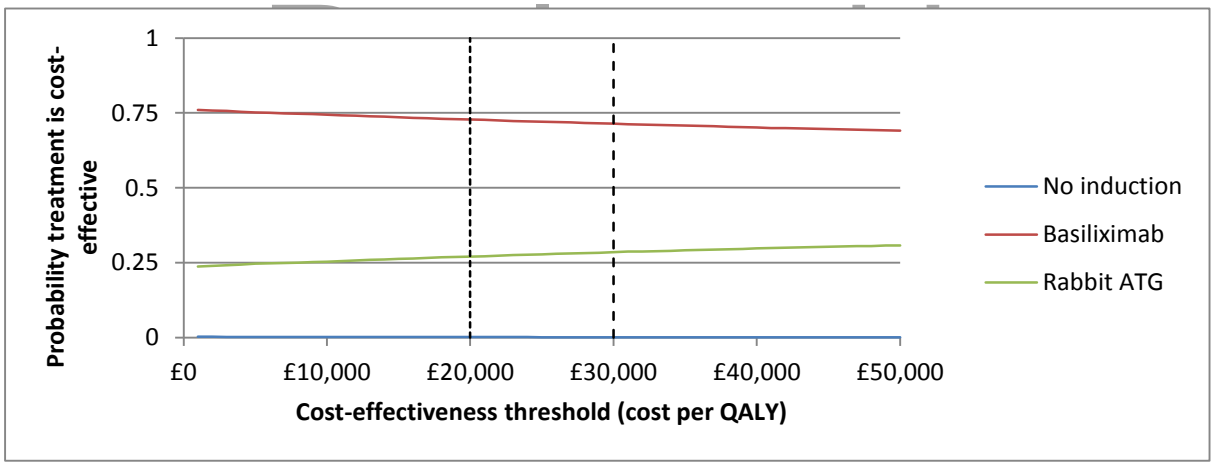


Figure 38. Cost-effectiveness acceptability curves for induction agents in combination with immediate-release tacrolimus and mycophenolate mofetil



Maintenance agents

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

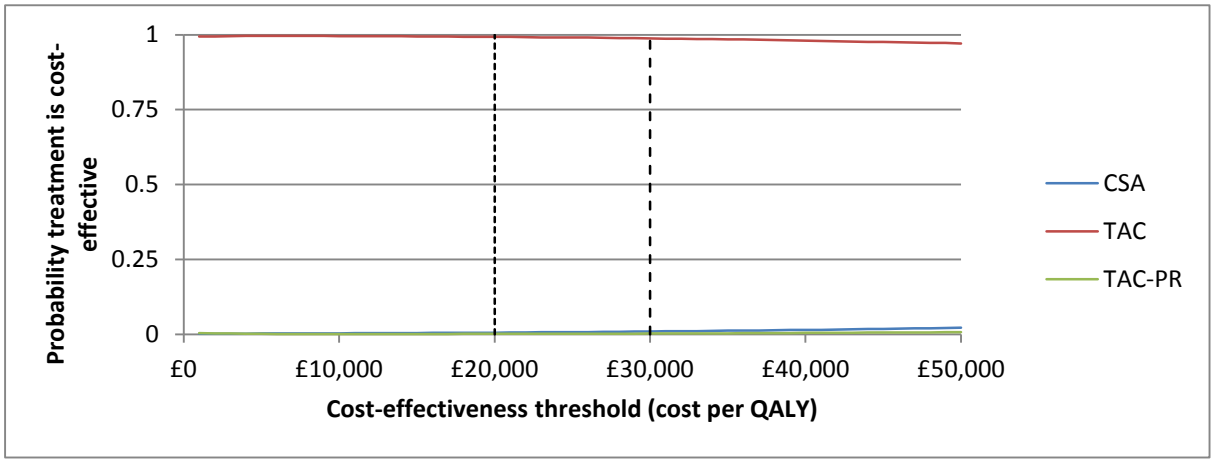


Figure 40. Cost-effectiveness acceptability curves for maintenance agents in combination with azathioprine

Replaced by

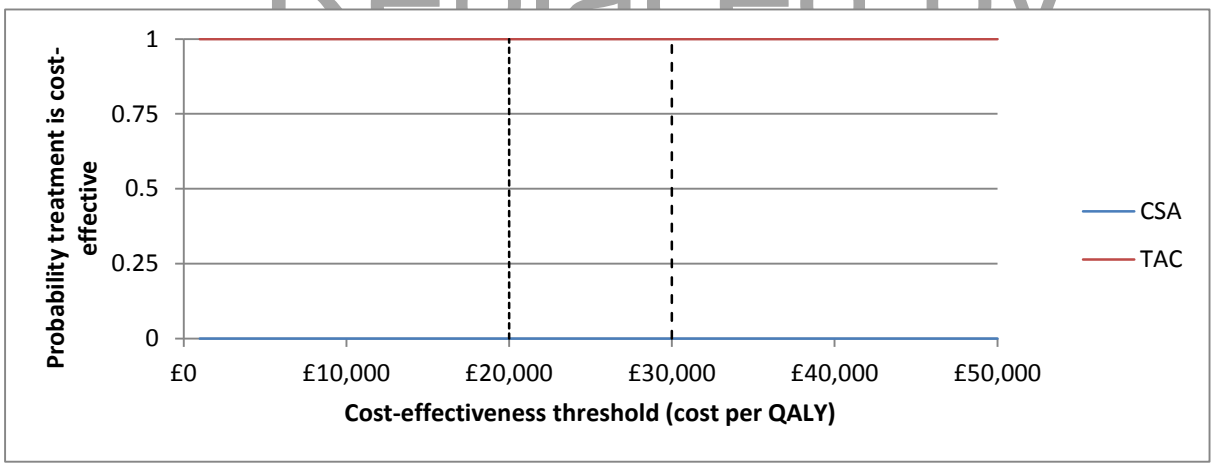


Figure 41. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and mycophenolate mofetil

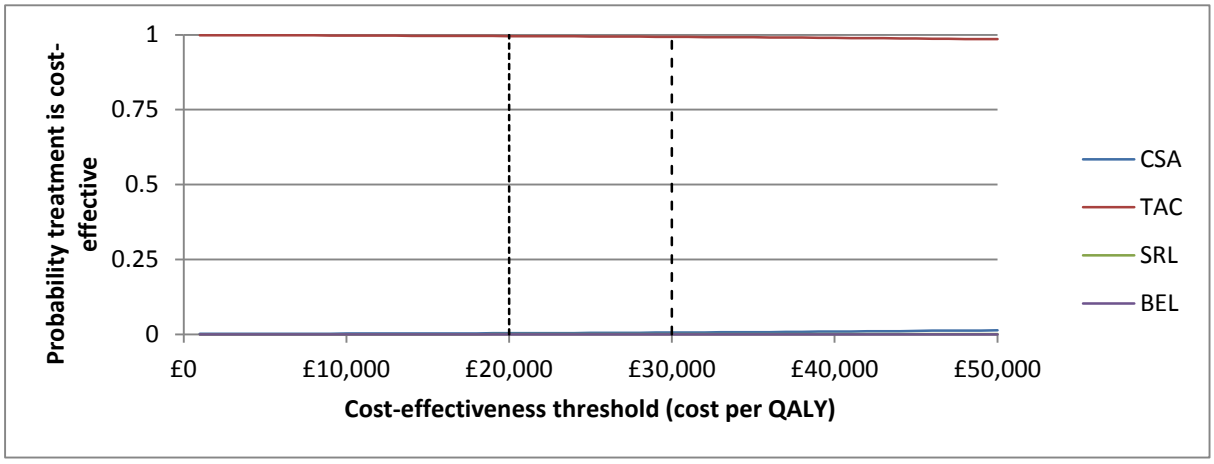


Figure 42. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and azathioprine

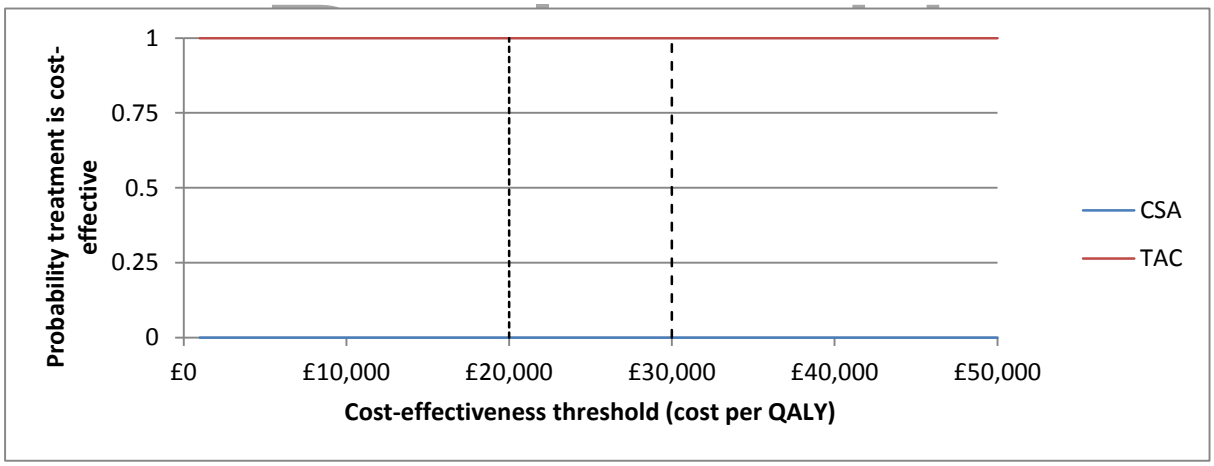


Figure 43. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and mycophenolate mofetil

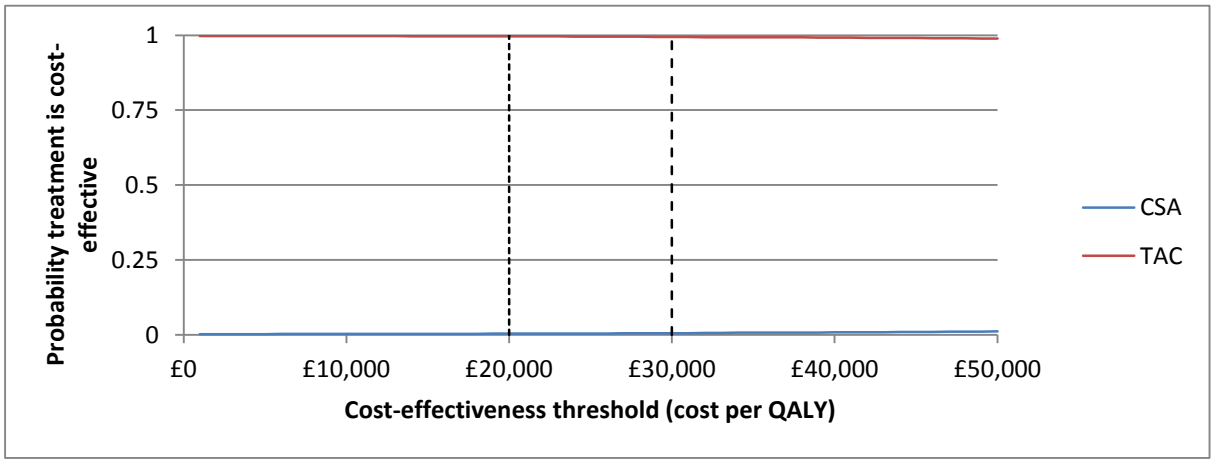


Figure 44. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and azathioprine

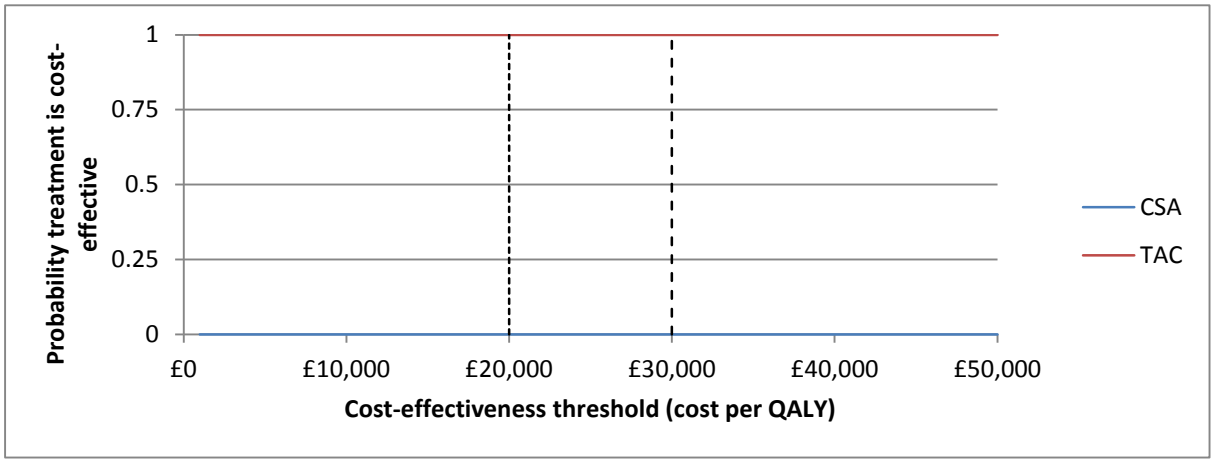


Figure 45. Cost-effectiveness acceptability curves for maintenance agents in combination with ciclosporin

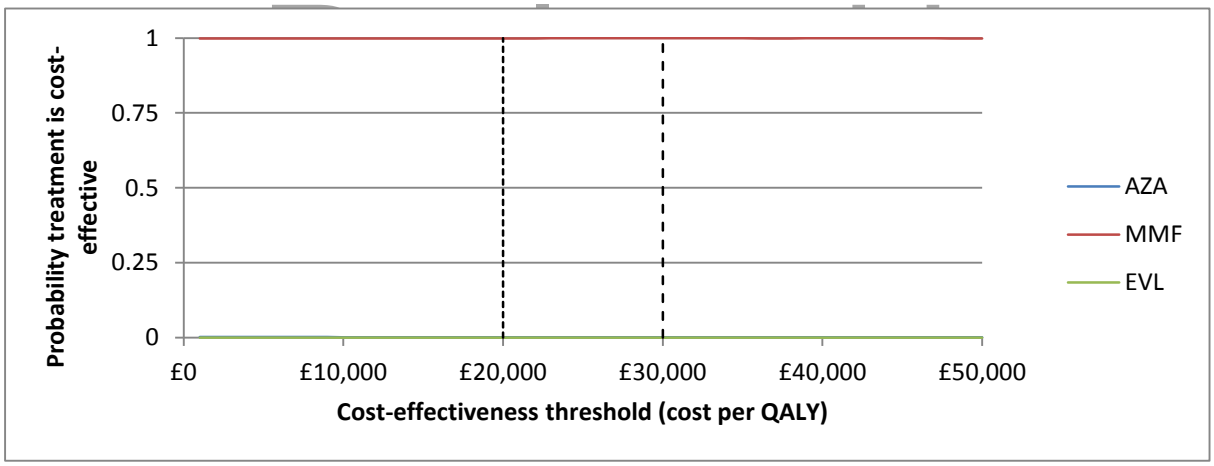


Figure 46. Cost-effectiveness acceptability curves for maintenance agents in combination with immediate-release tacrolimus

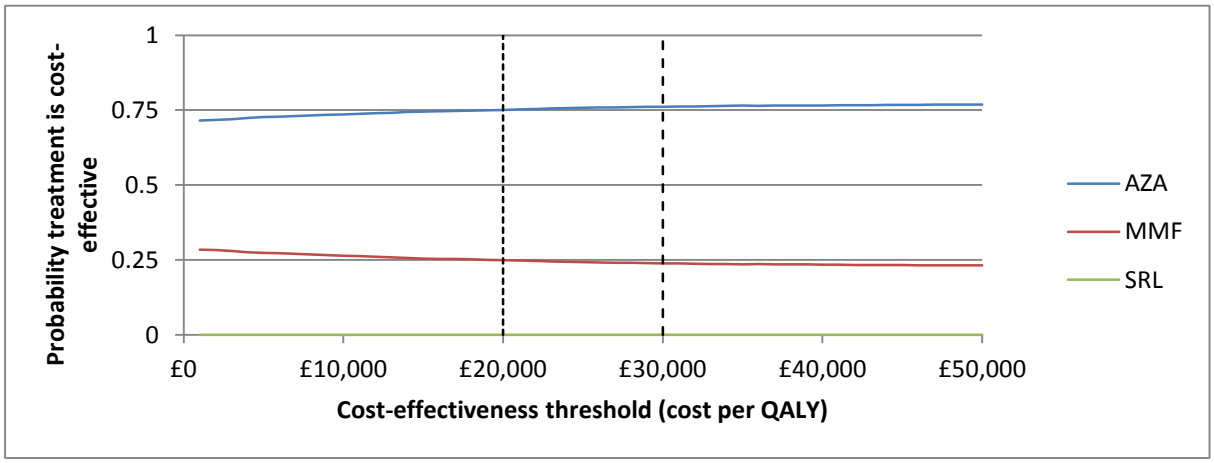


Figure 47. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and ciclosporin

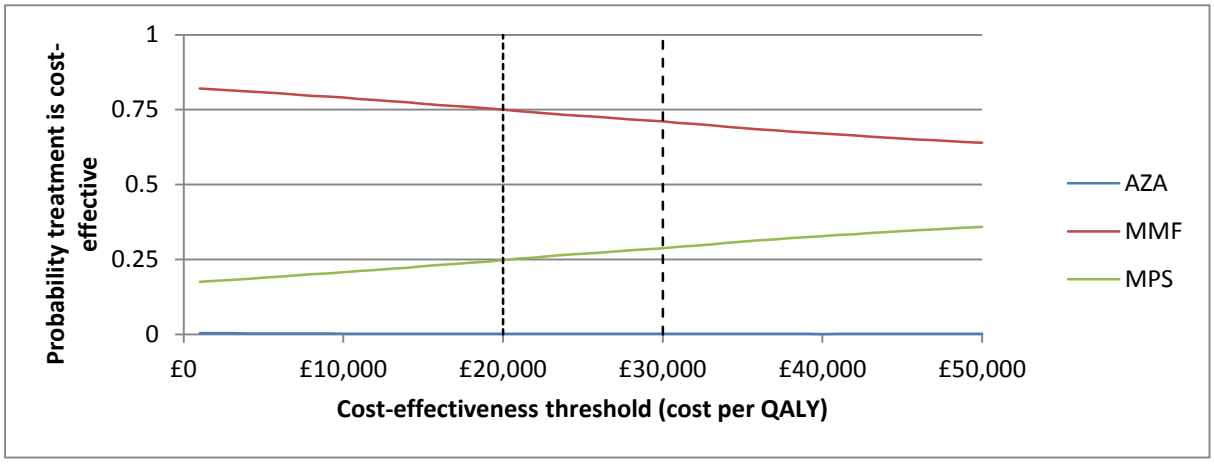


Figure 48. Cost-effectiveness acceptability curves for maintenance agents in combination with basiliximab and immediate-release tacrolimus

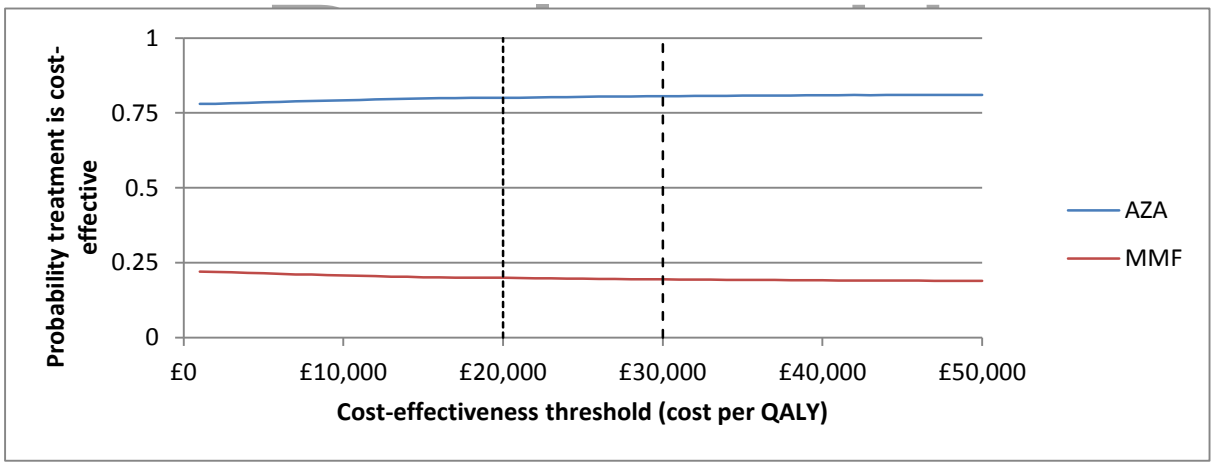


Figure 49. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and ciclosporin

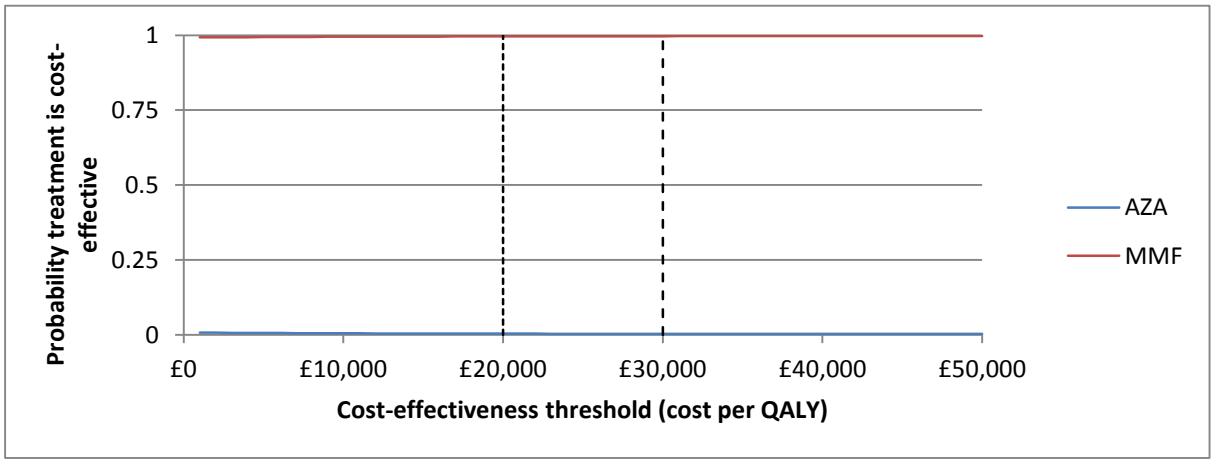
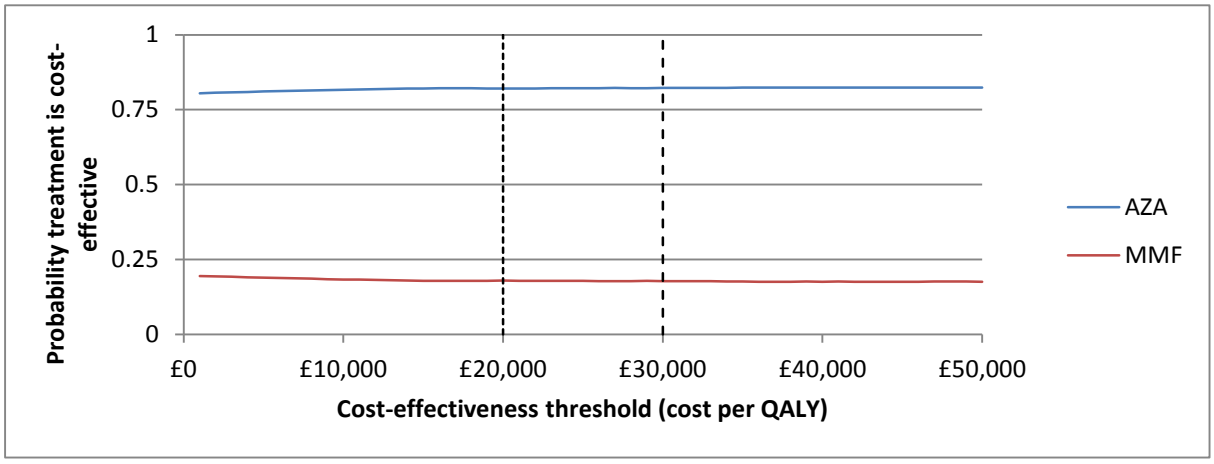


Figure 50. Cost-effectiveness acceptability curves for maintenance agents in combination with rabbit ATG and immediate-release tacrolimus



6.3.2.3 Scenario analyses

Below average weight for KTRs

Replaced by erratum

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 £27,123 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, but total discounted costs were marginally increased for BAS+BEL+MMF, because the cost of maintenance with belatacept is significantly higher than with other agents.

No incremental net health benefits changed sign at £20,000 or £30,000 per QALY, although the ICER for mycophenolate sodium drops to £33,300 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.

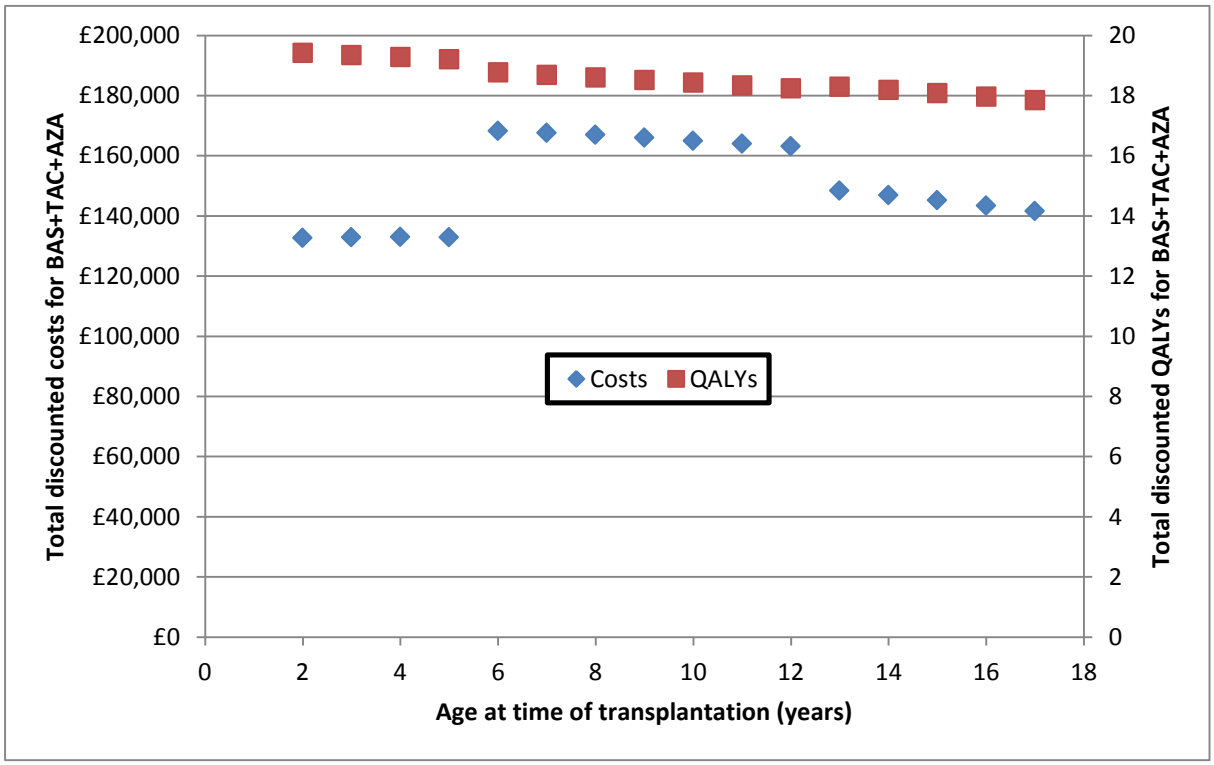
For most regimens discontinuities in total discounted costs were observed at age 6 and age 13, which are explained by the hazard ratios for graft survival according to age, taken from Muscheites et al. 2009,[181] in which graft survival was predicted to be worse for children aged 6–12 at the time of 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.

Replaced by erratum

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).

erratum

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

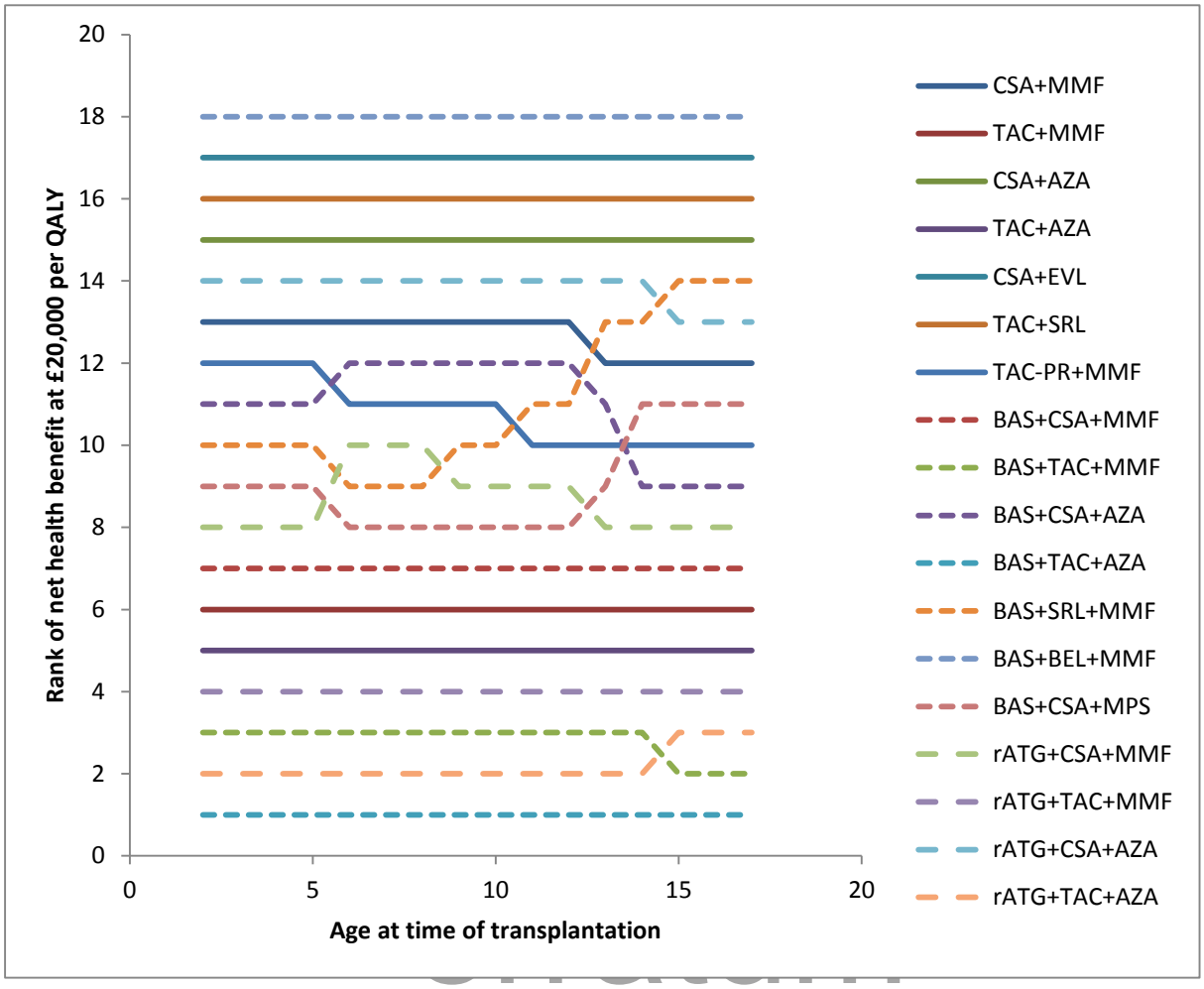
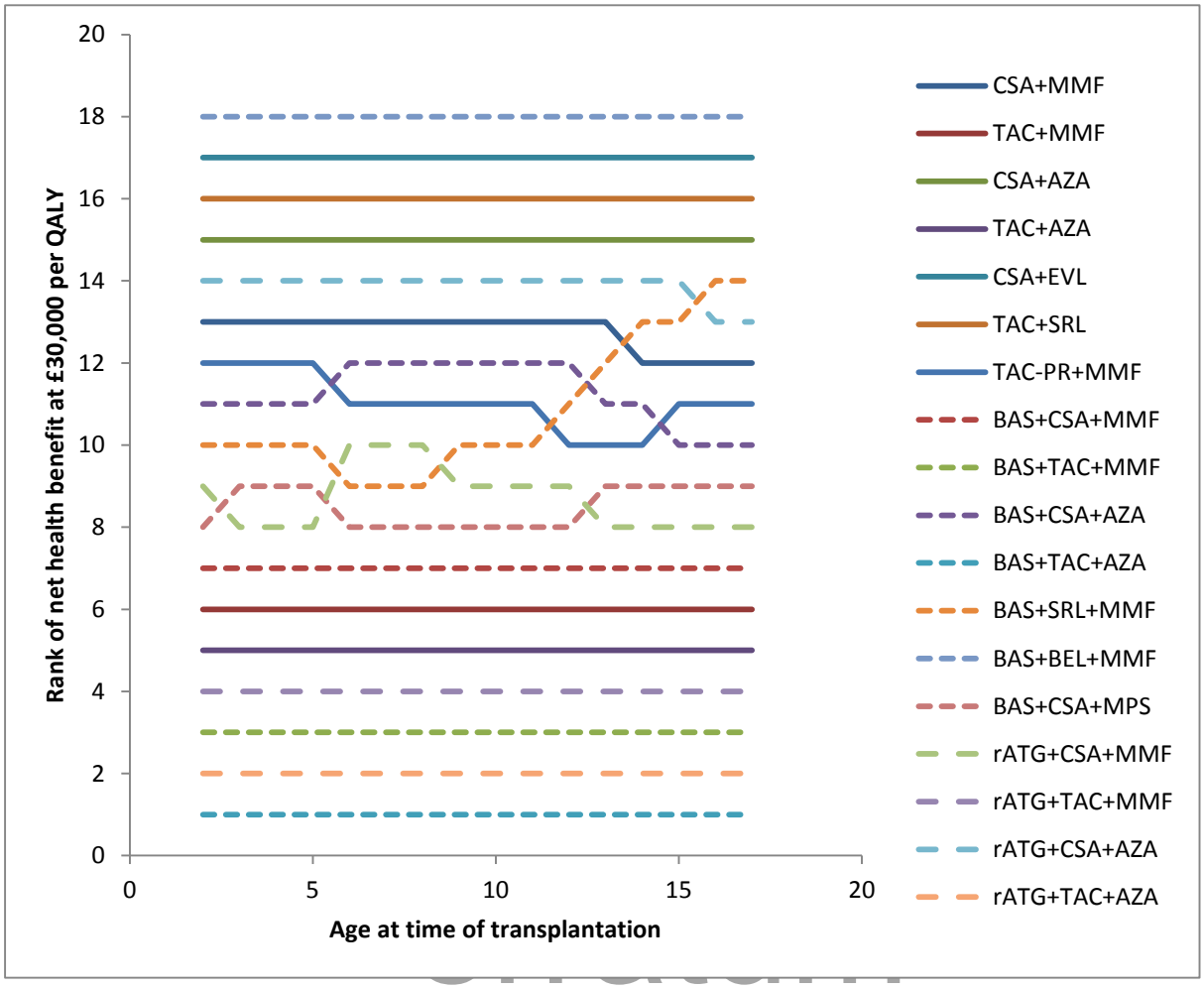


Figure 53. Rank of net health benefit at £30,000 per QALY for all regimens as the age at time of transplantation is varied



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	8.94	12.01
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

Replaced by erratum

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 (although rabbit ATG was predicted to be cost-effective versus no induction).

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.

Replaced by erratum

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.

Replaced by erratum

6.3.4 Comparison of the PenTAG, Astellas and previous assessment group's model-based analyses

In this section we compare the model-based analysis of maintenance regimens by the independent assessment group (PenTAG) with relevant analyses in the company submission (from Astellas) and with the previous analyses which informed NICE's current guidance on these technologies (Yao et al 2006[1]).

Table 128, below, shows which specific immunosuppression agents have been compared, and Table 129 shows which combination regimens have been compared by the three models for assessing immunosuppression in child/adolescent kidney transplant populations. The Astellas submission did not provide cost-effectiveness analysis of induction therapies, and only one comparison in the previous technology assessment for NICE compared induction therapies (basiliximab vs no induction).

Fully explaining the differences between the different model's cost-effectiveness outputs is more challenging than usual, because:

- The main assumptions in the Astellas model are different in very many respects, including:
    - 10 year time horizon, vs 50 years in PenTAG analyses
    - Basing effectiveness differences only on BPAR at 12-months post-transplant
    - Omission of ciclosporin as a relevant comparator for maintenance therapies
    - Large difference between the assumed utility of living with a functioning graft (0.71) compared with being on dialysis (HD 0.44, PD 0.53).
    - Drug unit costs were all based on BNF list prices in the Astellas analyses, whereas in the PenTAG analyses we used prices from the eMIT database where possible, to reflect nationally available discounted prices (i.e., for immediate-release tacrolimus, ciclosporin, azathioprine, mycophenolate mofetil, prednisolone).
    - Drug consumption values for sirolimus regimens were based on treatment guidelines rather than trial evidence of actual dosage intensity.

- The Yao et al 2006[1] model's assumptions and parameters are not fully described in any one report (and we were also unable to obtain the model files to assess it). The model used in the Yao et al analysis is:
    - A child/adolescent-adapted version of an adult post-transplant immunosuppression model, which was based on:
    - A 'meta-model' developed for the previous technology assessment for NICE of immunosuppression following kidney transplantation (Woodroffe et al 2004), which was, in turn, based on:
    - The Novartis model submitted to the previous technology appraisal process for these drugs.

It was therefore not possible to know with certainty what the input parameters and other main assumptions were in the Yao et al model. In addition, the incremental cost-effectiveness analyses produced by the Yao et al model used different discount rates for costs (6% per year) and QALYs (1.5% per year), according to the NICE methods guidance at that time. Like the current Astellas model, it also had a limited time horizon of 10 years. Without access to the original model, and no reporting of the model outputs for each comparator or as undiscounted costs or QALYs, it is impossible to adjust for these differences. The results which are most different between the Yao et al and PenTAG modelling, are those that relied upon adult RCT data – and for which the PenTAG has substantially updated the effectiveness estiamates from more recent trials. In contrast, the cost-effectiveness result for basiliximab vs no induction - which does use available child/adolescent RCT evidence in both models - arrives at the same conclusion as Yao et al did in 2006; that is, that basiliximab is both more effective and cheaper than no induction.

For reference, three larger tables in Appendix 9 compare the main cost parameters, effectiveness parameters and main cost and effectiveness results for the three models, where they are known (Table 140, Table 141, and Table 142). These show, for example, that the PenTAG model assumptions tended to include fuller costing of the administration of the maintenance therapies. Also, although applied differently in the models, the utility difference between living with a functioning graft and living on dialysis was greater in the Astellas model (difference of between ~0.25 to ~0.3) than in the PenTAG and Yao et al models (~0.2 difference).

Table 128. Immunosuppressive agents evaluated for cost-effectiveness in PenTAG analysis, Astellas analysis and NICE guidance TA99

Agent	TA99	PenTAG	Astellas
Basiliximab	Y	Y	N
Rabbit ATG	N	Y	N
(No induction)	Y	Y	N
Immediate-release tacrolimus	Y	Y	Y
Prolonged-release tacrolimus	N	Y	Y
Mycophenolate mofetil	Y	Y	N
Mycophenolate sodium	Y	Y	N
Sirolimus	Y	Y	Y
Everolimus	N	Y	Y
Belatacept	N	Y	Y
(Ciclosporin)	Y	Y	N
(Azathioprine)	Y	Y	N

Table 129. Regimens compared by the PenTAG and Astellas and models

PenTAG	Astellas
IR-Tacrolimus vs PR-Tacrolimus	IR-Tacrolimus vs PR-Tacrolimus
Tacrolimus (+ AZA) vs Ciclosporin (+ AZA) (based on one child/adolescent RCT) Also, based on Adult RCT evidence following Basiliximab induction: Tacrolimus (+ MMF) vs Ciclosporin (+ MMF) vs Sirolimus (+ MMF) vs Belatacept (+MMF)	Tacrolimus (granules for oral solution) vs Tacrolimus 'specials' (liquid preparations) vs Belatacept vs Everolimus vs Sirolimus + low-dose ciclosporin (=CNI minimization) Sirolimus + MMF (=CNI avoidance)

Table 130. Regimens and main results of the PenTAG and Yao et al models compared

	Table 56 (p.45) in Yao et al 2006		PenTAG**	
Compared regimens	**Estimate***	**ICER (£ per QALY)***	**Estimate***	**ICER (£ per QALY)***
CAS vs TAS (= CSA+AZA vs TAC+AZA)				
Incremental costs (£)	13,716	145,540	-35,267	TAS Dominant
Incremental QALYs	0.09		+0.2888	
CAS vs CMS (= CSA+AZA vs CSA+MMF)				
Incremental costs (£)	9,543	194,559	-10,202	CMS Dominant
Incremental QALYs	0.049		+0.1232	
CAS vs BCAS (= CSA+AZA vs BAS+CSA+AZA)				
Incremental costs (£)	-1,103	BCAS Dominant	-12,726	BCAS Dominant
Incremental QALYs	0.074		+0.1522	
CAS vs DCAS NB. *Daclizumab no longer licensed for use in children*				
Incremental costs (£)	-417	DCAS Dominant	N/A	
Incremental QALYs	0.05		N/A	
TAS vs BTAS (= TAC+AZA vs BAS+TAC+AZA)				
Incremental costs (£)	-451	BTAS Dominant	-12,335	BTAS Dominant
Incremental QALYs	0.038		+0.1584	

*Note that these incremental estimated are presented as in Yao et al, with 2nd regimen cost or QALY minus the 1st.
**These PenTAG analyses all based on effectiveness data from RCTs in adults

6.3.4.1 PenTAG's and Astellas's model-based analyses compared

Table 131 (below) shows the company's and the assessment group's analysis of the cost-effectiveness of the two types of tacrolimus. While the Astellas analysis estimates that prolonged-release tacrolimus dominates immediate-release tacrolimus (estimating it to be over £5,000 cheaper over 10 years, and generate 0.035 extra discounted QALYs, the PenTAG analysis produces the opposite result – based on effectiveness evidence from adult RCTs; prolonged release tacrolimus is dominated by both immediate-release tacrolimus and ciclosporin. In the PenTAG analysis, prolonged-release tacrolimus is over £18,000 more costly than immediate-release and generates 0.06 fewer discounted QALYs (both over a time horizon of 50 years).

This opposite result in incremental QALYs mostly arises because of the different trial data used within the two models and the fact that long-term outcomes in the Astellas model are driven entirely by rates of acute rejection. For informing the effectiveness parameters of the drugs on BPAR, mortality, graft loss and renal function, the PenTAG analysis uses meta-analysis of two direct head-to-head trials of the two comparators (Kramer et al 2010 and Tsuchiya et al 2013). All of the pooled odds ratios are not statistically significant, and all except the comparison for BPAR favour the IR-tacrolimus. In contrast, the Astellas review reports using three trials (Kramer et al 2010, Silva et al 2007, Albano et al 2013[72 87 237]) and one meta-analysis which they conclude show the two types of tacrolimus to be of 'similar efficacy and safety'. In their model, however, these data sources are then used to justify IR tacrolimus having a 2% point higher rate of acute rejection than PR-tacrolimus, which then drives differences in long-term graft survival (and costs). In their modelling they also factor in greater adherence to treatment with PR-tacrolimus, which departs from the ITT analysis of the trials

Table 131. PenTAG's and Astellas' analysis of prolonged-release tacrolimus compared

Agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG					
CSA	£202,424	—	18.1018	—	Dominated
TAC-PR	£198,433	-£3,992	18.1503	+0.0485	Dominated
TAC-IR	£182,163	-£16,270	18.2085	+0.0581	—
Astellas					
TAC-PR	£53,395	—	5.604		—
TAC-IR	£58,471	+£5,076	5.569	-0.035	Dominated

Table 132 (below) shows the company's and the assessment group's analysis of the cost-effectiveness of tacrolimus, belatacept, sirolimus and ciclosporin. In particular, it shows the impact of the very different time horizons of the two models on the accumulated costs and QALYs. The other main differences are that in the Astellas model belatacept is the least effective treatment (but the most effective in the PenTAG model) and only about £20,000 more expensive than tacrolimus (compared with £153,000 more expensive in the PenTAG model). The omission of ciclosporin from the Astellas modelling does not invalidate comparisons between the two analyses, because in the PenTAG model the ciclosporin regime is dominated (less effective and and more costly) than tacrolimus – and so effectively ruled out of further consideration.

Despite these substantial differences in assumptions and included comparators, in both model-based analyses tacrolimus (immediate release) is found to be the most cost-effective regimen.

Table 132. PenTAG's and Astellas' analysis of tacrolimus, belatacept, and sirolimus

Agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG *(all with BAS+MMF)*					
SRL	£199,145	—	18.2423	—	Dominated
CSA	£191,679	-£7,466	18.2468	+0.0045	Dominated
TAC	£170,915	-£20,763	18.3596	+0.0485	—
BEL	£324,708	+£153,792	18.5901	+0.0581	£667,031
Astellas					vs TAC
SRL I (CNI minimisation)	£52,339	-£6,132	5.565	-0.004	£1,576,937
SRL II (CNI avoidance)	£61,490	+£3,019	5.553	-0.016	Dominated by TAC
TAC	£58,471	—	5.569	—	—
TAC 'specials'	£72,945	+£14,474	5.564	-0.001	Higher cost similar QALYs
BEL	£75,726	+£17,255	5.551	-0.014	Dominated by TAC

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Aim

This remit for this report was to review and update the evidence used to inform the current NICE guidance (TA99) on the clinical and cost-effectiveness of immunosuppressive therapies in renal transplantation in children and adolescents. The systematic review and economic evaluation developed to support current NICE guidance TA99 was published by Yao et al. in 2006.[1] We have incorporated relevant evidence presented in this previous report and reported new evidence from 2002 to the present. This includes a new decision analytic model of kidney transplantation outcomes to investigate which regimen is the most cost-effective option.

In this section we will not re-state the previous evidence, but assume that the discussion will be read in the context of the previous evidence summaries and the decisions which flowed from them. The conclusions will focus on implications of the new effectiveness and cost-effectiveness evidence for service provision.

7.1.2 Clinical effectiveness systematic review

Three RCTs are included in the clinical effectiveness systematic review presented in this report; one new RCT,[70] and two RCTs from the previous assessment.[72, 74]

Four non-randomised controlled trials (non-RCTs) are included in our review. All of these were also included in the previous assessment by Yao et al. 2006.[1] No new non-randomised studies were identified in our searches.

7.1.2.1 Induction therapy

Two RCTs of induction therapy (reported in four publications and one abstract) evaluating **BAS** in children and adolescents were identified in the review.[70, 72] No RCTs were identified that evaluated **r-ATG** in children and adolescents.

No non-RCTs in the child and adolescents population evaluated induction therapies.

We found no significant difference in **survival**, **graft loss**, **graft function**, and **incidences of BPAR** and **time to BPAR** between BAS and placebo/no induction. [70, 72] There was evidence

of more severe BPAR (Grade IIA) in placebo compared with BAS in one study (OR=0.05; favours BAS; 95% CI 0.003 to 0.87).[70]

The results of the current review are similar to the previous HTA.[1]

7.1.2.2 Maintenance therapy

RCT evidence

One RCT of maintenance therapy (reported in three publications) evaluating **TAC** (compared with CSA) in children and adolescents was identified.[74] No RCTs were identified that evaluated **TAC-PR**, **MMF**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

From the RCT, we found no significant difference in **survival** or **graft loss** between TAC and CSA.[74] However, a significantly higher **graft function** (mean eGFR of 71.5 [SD 22.9] ml/min/1.73m^2 in TAC vs mean eGFR of 53.0 [SD21.6] ml/min/1.73m^2 in CSA; t-test=4.03, p<0.01 at four years follow-up), and less **BPAR** (OR=0.41,favours TAC, 95%CI: 0.16 to1.00 at six months follow-up) was found in TAC compared with AZA at up to four years follow-up.[74]

The results of the current review for **survival, graft function,** and **BPAR** are similar to the previous HTA.[1] However, the RCT child and adolescent evidence identified in the previous HTA review[1] concluded that TAC lowered **graft loss** at two and four years follow-up. The difference in these results is because we excluded graft loss due to death from all analyses. This was, firstly, to avoid double counting with another key outcome (mortality) and, secondly, because death censored graft survival is a well-established clinical outcome, to which death with functioning graft is intrinsically related. After the removal of graft loss due to death from the analyses, the evidence from Trompeter et al. 2002[74] suggested a borderline (statistically non-significant) lower graft loss with TAC compared with CSA (OR=0.41, favours TAC; 95%CI: 0.16 to 1.00, and OR=0.43, favours TAC; 95%CI: 0.18 to 1.01 at two and four years follow-up respectively). In addition, whilst there were statistically significant treatment group differences in **BPAR** and AR at six months, the annual differences in AR were not statistically significant for years two, three, and four.[74, 76]

Non-RCTs evidence

Three non-RCTs evaluating **MMF** (compared with AZA) in children and adolescents were identified.[77, 80, 93] One non-RCT compared **TAC+AZA** with **CSA+MMF**.[79] No non-RCTs were identified that evaluated **TAC-PR**, **MPA**, **SRL**, **EVL** or **BEL** in children and adolescents.

We found no statistically significant difference in **survival** between MMF and AZA in the non-RCTs.[77, 80] Similarly, no statistically significant difference in **BPAR** between MMF and AZA in the non-RCTs was identified.[77, 80, 93] A significantly lower **graft loss** was found in MMF compared with AZA at one to five years follow-up in one of the two non-RCTs[77] (OR=0.24 at five years follow-up; favours MMF; 95%CI: 0.09 to 0.63). However, this was not confirmed by the other non-RCT at one year follow-up.[80] In addition, we found no statistically significant difference in **survival**, **graft loss, BPAR, graft function,** and **delayed graft function** between TAC+AZA and CSA+MMF in the non-RCTs.[79]

7.1.2.3 Adverse events

Induction

More infections were found in children treated with BAS compared with those treated with placebo (OR=2.23, favours PBO; 95%CI 1.03 to 4.68).[70] In addition, Grenda et al. 2006 found that toxic nephropathy and abdominal pain were higher in the BAS arm compared with no induction (p=0.03 and p=0.02 respectively).[72] The previous HTA only reported post-transplant diabetes mellitus (Grenda et a. 2004[87]), the rest of the data they found was confidential and was excluded from the report.[1]

Maintenance therapy

There were no statistically significant differences between TAC and CSA for a range of AE (any infections, urinary tract infections, bacterial infections, viral infections, PTLD, solid tumour, hypertension, any AE, and NODAT).[74] This is similar to the conclusions of the previous HTA.[1] In addition, there were no statistically significant differences between MMF and AZA for urinary tract infection, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhea were identified in the non-randomised evidence.[80] Similarly, no statistically significant differences between TAC+AZA and CSA+MMF in CMV infections and NODAT were identified in the non-randomised evidence.[79]

7.1.2.4 Previous technology assessment

The previous assessment (TA99) in 2006 found scarce RCT evidence on the clinical effectiveness of immunosuppressive agents in renal transplantation in children and adolescents. Only three child and adolescent RCTs were identified (Grenda et al. 2004,Trompeter et al. 2002, [74, 87] and the Wyeth submission 2005). Child and adolescent RCT evidence was identified for **TAC** (Trompeter et al. 2002[74]), **BAS** (Grenda et a. 2004[87])

and **SRL** (Wyeth submission 2005). Only non-RCT evidence was identified for **MMF** (Antoniadis et al. 1998, Steffen et al. 2003, and Staskewitz et al 2001[77, 80, 81]). Finally, no child and adolescent evidence was identified for **MPS** and **DAC** (since the previous assessment, the marketing authorisation of DAC has been withdrawn at request of the manufacturer). In addition, three non-RCTs were identified for **BAS** (Duzova et al. 2003, Pape et al. 2002, and Swiatecka-Urban et al. 2001[88-90]), one non-RCT for **TAC** (Neu et al. 2003[91]), and one non-RCT compared TAC+AZA with MMF+CSA (Garcia et al. 2002[79]).

The addition of induction therapy (BAS) was not found to be beneficial. The only child and adolescent induction therapy RCT found that the addition of BAS failed to significantly improve BPAR, graft function, graft loss, mortality and AE. Similarly, a meta-analysis of adult RCTs, found no significant difference in graft loss, mortality or AE. In general, compared with a triple regimen of CSA+AZA+CCS, the newer immunosuppressive agents were found to lead to lower rates of BPAR. One included child and adolescent RCT found that TAC led to lower BPAR at six months follow-up (RR=0.42 favours TAC; 95%CI 0.26 to 0.69) and higher eGFR at one year follow up (p=0.003; 6 months follow-up data were not statistically significantly different), compared with CSA. This lower rate of BPAR with TAC was also shown in the meta-analysis of six adult RCTs at one year follow-up (RR=0.61 favours TAC; 95%CI 0.53 to 0.71). The total level of withdrawal in children and adolescents was reduced in those receiving TAC compared with CSA (RR=0.61 favours TAC; 95%CI 0.39 to 0.96). Pooled results of two adult RCTs found that compared with AZA, SRL reduced BPAR (RR=0.60 favours SRL; 95%CI 0.45 to 0.80), improved eGFR (MD=28.7 favours SRL; 95%CI 18.8 to 38.5), and increased the level of hyperlipidaemia (RR=1.57 favours AZA; 95%CI 1.19 to 2.07).

In summary, important gaps in the evidence concerning the impact of the newer immunosuppressants on AE, long-term outcomes (including graft loss and survival), growth, and overall health-related quality were identified by the previous technology assessment.

7.1.3 Published economic evaluations

Only one previous cost-effectiveness study of immunosuppressive regimens in children and adolescents was identified.[1] It was conducted by the technology assessment group at the University of Birmingham as part of the previous NICE technology appraisal process. The study evaluated the cost-effectiveness of adding basiliximab induction to CNI maintenance therapy with tacrolimus or ciclosporin combined with azathioprine and steroids. The study also compared ciclosporin with tacrolimus when given in combination with azathioprine and

steroids, and separately, MMF versus azathioprine as part of the triple therapy containing ciclosporin and steroids.

The analysis was conducted using a Markov model of a cohort with starting age ranging between 3-13 years and a 10-year horizon. The study found that basiliximab induction resulted in higher costs and more QALYs than the alternative of no induction in both the tacrolimus and ciclosporin containing regimens. Tacrolimus was found to have a base case ICER (incremental cost per QALY) of £145,000 relative to ciclosporin, whilst MMF had an ICER of £195,000 relative to azathioprine when given as part of ciclosporin-containing triple therapy. Although some of the methodological details were not provided in the study report (Yao et al. 2006[1]) the sensitivity analysis showed that these results were subject to a high degree of uncertainty. In particular, when the costs of dialysis were increased to reflect high possible levels of staff requirements of dialysis treatment in children and adolescents and the estimated treatment effects on acute rejection based on data from adults were used, the ICER for the comparison of tacrolimus vs. ciclosporin triple therapy reduced to £35,000. This uncertainty, and the fact that the underlying model used in this analysis only accounted for BPAR as the surrogate measure of effectiveness (ignoring the role of renal function) suggest that new evidence on the cost-effectiveness of immunosuppressive regimens in children and adolescents is warranted.

7.1.4 Independent economic assessment

The PenTAG economic assessment included two types of analyses.

The first type of analysis used only effectiveness estimates from RCTs in children and adolescents, and therefore can only evaluate the cost-effectiveness of basiliximab (versus no induction) and immediate-release tacrolimus (versus ciclosporin).

The second type of analysis extrapolated effectiveness estimates from RCTs in adults, and allows for the cost-effectiveness of all interventions to be evaluated. Although effectiveness estimates in these analyses were restricted to adults, a significant amount of evidence from children and adolescents was used, including baseline characteristics, costs, baseline graft and overall survival, and the relationship between graft function and graft survival. The analysis produced different results to those in the parallel HTA for adults to inform an update of NICE guidance TA85.

Neither type of analysis is presented as a preferred base case, since both have their deficiencies.

7.1.4.1 Induction agents

Using effectiveness estimates from RCTs in children and adolescents

Analyses based on evidence from RCTs in children and adolescents led to contradictory conclusions regarding the cost-effectiveness of basiliximab versus no induction.

In the analysis based on Grenda et al. 2006,[72] basiliximab was predicted to be more effective and less costly than no induction (in combination with immediate-release tacrolimus and azathioprine) using either a two-year time horizon (corresponding to the trial follow-up) or 50-year time horizon. Basiliximab was therefore dominant over no induction using a two-year or 50-year time horizon. The probability of basiliximab being cost-effective at £20,000 to £30,000 per QALY was 67.3–69.3% (50-year time horizon).

In the analysis based on Offner et al. 2008,[70] basiliximab was predicted to be more costly and less effective than no induction (in combination with ciclosporin and mycophenolate mofetil) using either a one-year time horizon (corresponding to the trial follow-up) or 50-year time horizon. Basiliximab was therefore dominated by no induction at either time horizon. The probability of basiliximab being cost-effective at £20,000 to £30,000 per QALY was 6.7–9.4% (50-year time horizon).

The results of both analyses were robust to scenario analyses in which the surrogate relationship between acute rejection and graft survival was removed, and the 9th centile for body weight for age was used (instead of median weight).

No economic analyses of rabbit ATG could be conducted based on RCTs in children and adolescents, since no such RCTs were identified.

Using effectiveness estimates from RCTs in adults

Analyses based on evidence from RCTs in the adult population suggested that basiliximab induction is likely to be cost-effective at £20,000 to £30,000 per QALY versus no induction and rabbit ATG induction.

Depending on the maintenance regimen used, the probability of basiliximab being cost-effective at £20,000 to £30,000 per QALY was 67.6–72.8%, while the probability of rabbit ATG being cost-effective at £20,000 to £30,000 per QALY was 27.0–32.4%. The probability of no induction being cost-effective at £20,000 to £30,000 per QALY was 0.0–0.2%.

Results were robust to removal of the surrogate relationship between acute rejection and graft survival and/or assuming 9th centile weight according to age rather than median weight.

7.1.4.2 Maintenance agents

Using effectiveness estimates from RCTs in children and adolescents

An analysis based on an RCT in children and adolescents suggested that immediate-release tacrolimus is likely to be cost-effective at £20,000 to £30,000 per QALY. In the analysis based on Trompeter et al. 2002,[74] immediate-release tacrolimus in combination with azathioprine was predicted to be more effective and less costly than ciclosporin, whether using a four-year time horizon (corresponding to the trial follow-up) or a 50-year time horizon. The probability of basiliximab being cost-effective at £20,000 to £30,000 per QALY was over 99.9% (50-year time horizon).

Results were robust to removal of the surrogate relationship between acute rejection and graft survival, and to assuming 9th centile weight according to age rather than median weight.

No economic analyses of prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus or belatacept could be conducted based on RCTs in children and adolescents since no such RCTs were identified.

Using effectiveness estimates from RCTs in adults

Analyses using effectiveness estimates from RCTs in adults suggested that:

- **Immediate-release tacrolimus is likely to be cost-effective** at £20,000 to £30,000 per QALY (99.3–100.0% of PSA simulations)
- **Prolonged-release tacrolimus is unlikely to be cost-effective** at £20,000 to £30,000 per QALY (expected to be dominated by immediate-release tacrolimus and cost-effective in only 0.2–0.3% of PSA simulations)
- **Mycophenolate mofetil is likely to be cost-effective** at £20,000 to £30,000 per QALY when used with or without induction and **in combination with ciclosporin** (cost-effective in 71.1–99.9% of PSA simulations)
- **Mycophenolate mofetil is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used with or without induction and **in combination with immediate-release**

tacrolimus (expected to be dominated by azathioprine and cost-effective in only 17.8–24.9% of PSA simulations)

- **Mycophenolate sodium is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used in combination with basiliximab induction and ciclosporin (ICER over £50,000 per QALY and cost-effective in 24.8–28.8% of PSA simulations)
- **Sirolimus is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used in combination with basiliximab induction and mycophenolate mofetil (expected to be dominated by ciclosporin and immediate-release tacrolimus and cost-effective in only 0.1% of PSA simulations)
- **Sirolimus is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used in combination with immediate-release tacrolimus (expected to be dominated by mycophenolate mofetil and azathioprine and cost-effective in 0.0% of PSA simulations)
- **Everolimus is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used in combination with ciclosporin (ICER over £600,000 per QALY and cost-effective in 0.0% of PSA simulations)
- **Belatacept is unlikely to be cost-effective** at £20,000 to £30,000 per QALY when used in combination with basiliximab induction and mycophenolate mofetil (ICER over £600,000 per QALY and cost-effective in 0.0% of PSA simulations)

If 9th centile weight according to age is assumed (instead of median weight), in the deterministic analysis mycophenolate sodium becomes cost-effective at £30,000 per QALY but not at £20,000 per QALY (ICER £27,000 per QALY), although the assumed weight–dose relationship may not be accurate (the relationship was assumed to be directly proportional, e.g. patients weighing 50% of median adult weight would require 50% of the average adult dose) and this assumes kidney transplant patients do not move from the 9th centile of weight.

Results are robust to removal of the surrogate relationship between acute rejection and graft survival, although the deterministic ICER for mycophenolate sodium is lowered to £33,000 per QALY.

7.1.5 Company submissions

The only cost-effectiveness analysis submitted by pharmacuetical companies was that of Astellas, the sponsor of two immediate-release tacrolimus formulations (Prograf and Modigraf) and prolonged-release tacrolimus (Advagraf). It compared tacrolimus immediate

release (Prograf) with tacrolimus oral solutions (specials), sirolimus with MMF (CNI avoidance regimen), sirolimus with ciclosporin (CNI minimisation regimen), everolimus, and belatacept. Although Tacrolimus IR was found to have an ICER relative to sirolimus CNI minimisation of £1,600,000 the company concluded that sirolimus is unlikely to be used routinely for recipients of kidney transplants in general. Since tacrolimus dominated all other regimens it was deemed to be cost-effective. In a separate analysis, immediate-release tacrolimus (Prograf) was compared with prolonged-release tacrolimus (Advagraf), by modelling the effects of the different adherence profiles between the two regimens on biopsy proven acute rejection and, independently, on graft survival. Advagraf was found to result in lower costs and more QALYs than Prograf and was therefore recommended as the cost-effective treatment option.

Although these analyses were set out to meet the specification of the NICE reference case, they are subject to limitations that question the validity of the results and conclusions derived from them. The most important problem is that the model uses efficacy data from RCTs conducted in adult patients. The triple regimen of ciclosporin + MMF + steroids was an important omission from the list of comparators and for which no reason was given in the submission. The unit cost values adopted for the analysis reflect drug list prices as opposed to prices actually paid by hospitals at a discount, as evidenced from eMIT data. Also the drug dosages used for regimens other than MMF and everolimus in the cost analysis were derived from those specified by national prescribing guidelines for adults (BNF). In addition, by truncating the analysis at age 18, the sensitivity analysis conducted by Astellas based on starting age become meaningless. The model ignored important recent evidence about renal graft function as an important outcome for both costs and health related quality of life. Further, the Markov model structure used by Astellas was based on annual cycles and assumed that within the first year after transplantation some patients would experience graft failure and re-transplantation. Although some patients may experience this in reality, the way the model implemented this effectively assumed that all such patients would experience failure and re-transplantation on day one. This suggests that the cycle length chosen by Astellas inadequately reflected the patient experience that they sought to model. These limitations cast more uncertainty on the results than seems justified by the available data and knowledge of the disease, and suggest more evidence addressing some of those limitations would benefit NICE recommendations in this area.

7.1.6 Comparison of the PenTAG, Astellas and previous assessment group's model-based analyses

We attempted to compare and explain the main differences in cost, effectiveness and cost-effectiveness estimates between the three models. In the case of the Astellas analyses this was hampered by the substantial number of important differences in modelling assumptions (such as the much shorter time horizon – 10 years, and reliance on data from different trials and different outcome measures from those trials to drive effectiveness differences).

For comparing IR-tacrolimus with PR-tacrolimus, the PenTAG and Astellas analyses arrive at opposite conclusions (the Astellas analysis in favour of PR tacrolimus). This is primarily due reliance on BPAR at 12 months post-transplant as the main surrogate outcome driving QALY differences, different unit cost sources, and using outcome data from different trials to those on which the PenTAG analysis is based. The other analysis by Astellas, comparing a larger range of maintenance therapies (but omitting ciclosporin), showed that sirolimus would be the most cost-effective treatment (although their report does not highlight this) whereas the PenTAG analysis shows IR-tacrolimus to be the most cost-effective. However, there is considerable uncertainty and the Astellas analysis is based on very small differences in estimated QALYs.

It was virtually impossible to compare our model-based analyses with those by Yao et al (2006) which informed NICE's current guidance on these drugs for children and adolescents (TA99). This is because the Yao et al model is not fully described in a single report, the model itself is not available, and even the results were only reported at the level of incremental costs and QALYs (i.e. no separately reported total costs and QALYs by model comparator). Their cost-effectiveness results also reflect differential discounting of future QALYs (1.5% per year) and costs (6%), and a limited 10 year time horizon. Despite these major differences, the findings in favour of the use of basiliximab as an induction therapy were similar between the Yao et al and current PenTAG analyses. In contrast, based on more adult RCT evidence and a 50 year time horizon, the PenTAG analysis found that tacrolimus (with azathioprine) was more effective and less costly than ciclosporin, and that MMF (with ciclosporin) was more effective and less costly than azathioprine.

7.2 Strengths and limitations

7.2.1 Systematic review of studies of clinical effectiveness

7.2.1.1 Strengths

- The systematic review is conducted by an independent research team using the latest evidence.
- The literature searches were not restricted to child/adolescent populations so to preserve the sensitivity of the searches and enable identifing RCTs where mixed populations may have been recruited, but outcomes were reported according to age.

7.2.1.2 Limitations

- The number of included RCTs is low; child/adolescent-specific evidence was identified only for basiliximab and immediate-release tacrolimus. No RCT evidence from children or adolescents was identified for rabbit ATG, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept.
- Databases were searched to identify systematic reviews of non-RCTs, however individual non-RCTs were not searched for directly. It is likely that some non-RCT comparative evidence was missed. In addition, results from non-randomised studies may differ from RCT evidence. It can be argued that large, prospective and comprehensive case series may achieve high external validity, but we did not search for such studies.
- There is a possibility of spuriously positive tests for statistical significance arising from conducting multiple tests; we did not formally make adjustments for multiple testing. In addition, due to a small number of included studies publication bias were not assessed.
- For all included studies, less than half of the items constituting the quality appraisal assessment were adequately addressed in the research articles.
- No studies reporting on quality of life, adherence, and growth were identified.
- No RCTs were found to support the subgroup analyses specified in the review protocol.

In addition, this report highlights some methodological issues. Some of the newer immunosuppressive drugs, such as everolimus and sirolimus, would normally be given to children and adolescents after an initial maintenance therapy that consists of more

conventional drugs. This makes it challenging to compare the clinical effectiveness of such regimens as only children and adolescents who are well maintained on their initial maintenance therapy would be given such drugs.

7.2.2 Economic model by PenTAG

7.2.2.1 Strengths

- This is an analysis conducted by an independent academic group, adhering to the NICE reference case where possible.
- All interventions and relevant allowable comparators are included and evaluated for cost-effectiveness.
- The natural history of disease is based on UK data, either published by the UK Renal Registry or from new analyses of the UK Transplant Registry standard dataset.
- Important differences in the costs of dialysis between under 19s and adults have been included.
- Analyses have been conducted based on all available RCTs in children and adolescents eligible for inclusion.
- Additional analyses have been conducted based on a systematic review and network meta-analysis of RCTs in the adult population to allow comparison of all interventions even when no relevant RCTs in children and adolescents were identified.
- The surrogate relationship between graft function (eGFR) at 12 months and graft survival has been estimated from a study of children and adolescents.
- Pre-emptive retransplantations are included for a minority of kidney transplant recipients following failure of the initial graft (avoiding dialysis which is costly and reduces health-related quality of life).
- Unit costs are those relevant to the NHS (e.g., CMU eMit costs were used when available).
- Dosages for under 18s is based, where possible, on RCTs in children and adolescents, while dosages for over 18s are estimated from RCTs in adults.

- Probabilistic sensitivity analyses are presented to reflect the possible impact of parameter uncertainty.

7.2.2.2 Limitations

- Graft function has not been modelled over time, but is only estimated at 12 months in order to estimate graft survival thereafter.
- The cost-effectiveness of reducing or eliminating corticosteroids has not been evaluated.
- The cost of NHS funded transport for haemodialysis patients has not been included.
- Treatment discontinuation and treatment switching are not modelled except in the events of graft failure (treatment discontinuation) and retransplantation (treatment switched to BAS+TAC+MMF regardless of previous treatment).
- Independence of acute rejection, NODAT and eGFR at 12 months was assumed when predicting graft survival.
- The surrogate relationships from acute rejection and NODAT to graft survival are based on the adult population.
- Continuing immunosuppression following graft loss was not modelled, although it may occur in clinical settings.
- A proportional hazards assumption was made for the graft survival surrogate relationship.
- No attempt was made to explicitly model adherence to immunosuppressive agents due to the absence of evidence on this outcome in identified RCTs; it is thought that non-adherence is a significant cause of late acute rejection and graft loss, but any gains in clinical effectiveness owing to improved adherence attributable to any individual agent or regimen are considered speculative.
- It was assumed that there would be no treatment interactions between induction and maintenance therapies affecting clinical effectiveness outcomes; it is, however, known, that there is a pharmacokinectic interaction between basiliximab and MMF which results in prolonged basiliximab half-life (and similar interactions may exist between other induction and maintenance therapies).

- Due to inconsistent reporting of adverse events in randomised controlled trials included in our systematic review a limited range of adverse events were modelled: NODAT, CMV infection, dyslipidaemia and anaemia (of these anaemia was assumed not to vary between regimens); induction agents were assumed not to affect the incidence of adverse events; malignancy, PTLD, proteinuria, hypertension, Epstein–Barr virus infection, BK virus infection, other infections and other adverse events were not modelled.

- No drug wastage (e.g., part used packs/vials) was assumed for any intervention except belatacept; the other agent for which wastage may be likely to occur is rabbit ATG.

- The generalisability of cost-effectiveness results hinges on the generalisability of the clinical effectiveness evidence. Most of the interventions being considered (except basiliximab and immediate-release tacrolimus) have not been evaluated in RCTs of children and adolescents, but only in adults.

7.2.2.3 Areas of uncertainty

This technology assessment was conducted by an independent academic group, builds on existing secondary research, economic evaluations and adheres to the NICE reference case where possible. However, there are some important sources of uncertainty that impact on the conclusions:

- Most of the interventions being considered (except basiliximab and immediate-release tacrolimus) have not been evaluated in published RCTs in children and adolescents.

- Follow-up in RCTs is limited and therefore it has not been possible to externally validate predicted survival differences between regimens.

- RCTs have not provided evidence to support pre-specified subgroup analyses.

- There was no evidence to support analyses of the cost-effectiveness of interventions for children and adolescents unable to swallow tablets, for whom the following may or may not be appropriate:

    - Immediate-release tacrolimus oral suspension (Modigraf®, Astellas)

    - Immediate-release tacrolimus liquid (from specials manufacturers)

    - Ciclosporin solution (Neoral®, Novartis)

    - Sirolimus solution (Rapamune®, Pfizer)
    - Azathioprine oral suspension (from specials manufacturers)
    - Mycophenolate mofetil oral suspension (CellCept®, Roche)
- The costs for diabetes are highly uncertain, especially as the costs relate to the general adult diabetic population.
- It is not known whether NHS hospitals might secure discounts from list prices where these were assumed in the model (i.e., for basiliximab, rabbit ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept).
- Other combinations of immunosuppressive agents than those considered could be used in clinical practice (the PenTAG model can be extended to include additional combinations).

8 CONCLUSION

Cost-effectiveness estimates for immunosuppressive agents in children and adolescents based on effectiveness estimates in children and adolescents are only available for basiliximab and immediate-release tacrolimus. For immediate-release tacrolimus the economic analysis based on one RCT suggests that immediate-release tacrolimus is cost-effective (versus ciclosporin, in combination with azathioprine) at £20,000 to £30,000 per QALY. For basiliximab, the analysis based on one RCT found basiliximab to be dominant, while the analysis based on the other RCT found basiliximab to be dominated.

Consideration of the cost-effectiveness of immunosuppressive agents in children and adolescents by extrapolating effectiveness estimates from the adult population (where there is considerable RCT evidence) suggest that at a cost-effectiveness threshold of £20,000 to £30,000 per QALY, basiliximab and immediate-release tacrolimus are cost-effective in all considered combinations, while mycophenolate mofetil is cost-effective only if used in combination with ciclosporin. Basiliximab induction, immediate-release tacrolimus and azathioprine was predicted to be cost-effective at £20,000 to £30,000 per QALY when all regimens were compared.

8.1 Implications for service provision

Basiliximab is used regularly as induction therapy for child/adolescent kidney transplant patients in the NHS, but is not routinely used in all centres. Basiliximab is recommended as an option for induction therapy by current NICE guidance (TA99). Conflicting results from the new economic analyses conducted mean it is not possible to conclude whether induction with basiliximab is more or less costly than no induction, but the magnitude of the cost difference is unlikely to be great since induction therapy is only administered at the time of transplantation and is not an ongoing cost.

Rabbit ATG is not currently used routinely in the NHS and was not considered by current NICE guidance TA99. Economic analyses based on extrapolation from adult effectiveness estimates suggest that induction with rabbit ATG is more costly than induction with basiliximab, but less costly than no induction.

For maintence therapy, immediate-release tacrolimus is the current standard of care in the NHS and was recommended as an option for maintenance therapy by current NICE guidance TA99. If prolonged-release tacrolimus, sirolimus or belatacept were to be used in place of immediate-release tacrolimus this would be likely to increase costs. It is also

predicted that if ciclosporin were to be used in place of immediate-release tacrolimus this would lead to increased costs.

Azathioprine and mycophenolate mofetil are both widely and routinely used in the NHS, although current NICE guidance (TA99) only recommended mycophenolate mofetil as an option for maintenance therapy in a restricted population. Economic analyses based on extrapolation from adult effectiveness estimates suggest that mycophenolate mofetil is likely to be more costly than azathioprine in combination with immediate-release tacrolimus. These analyses also suggest that replacing azathioprine or mycophenolate sodium with sirolimus, everolimus or mycophenolate mofetil would lead to increased costs.

Belatacept, which is administered intravenously, would be expected to add an extra burden to service providers, although given the limited number of children and adolescents receiving kidney transplantation the additional burden of drug administration may be able to be accommodated without significant changes to staffing levels.

8.2 Suggested research priorities

It is recommended that high-quality primary research be conducted into the effectiveness of immunosuppressive agents for kidney transplantation in children and adolescents. This could be experimental or observational research.

In particular, it may be possible to conduct a prospective study using the UK Renal Registry dataset. Such a study would ideally include longitudinal recording of immunosuppression (combination and doses, reflecting changes as soon as they are made), as well as recording acute rejection episodes and regular graft function measurements. A study would also need to ensure that all covariates for effectiveness outcomes (especially potential confounders) were recorded. Such a study could also include health-related quality of life measurements, preferably using a generic instrument validated in the child and adolescent population such as EQ-5D-Y or CHU9D, and measurements of growth.

In addition, given the perceived importance of adherence to immunosuppression, it may also be desirable to establish an objective and practical measure of adherence so that any differences in adherence between regimens can be identified, as well as any effect this has on outcomes.

Finally, although limitations of non-RCT evidence were noted above, a systematic review of non-RCTs (not limited to search for systematic reviews of non-RCTs) to map all available child and adolescents' evidence in this topic may be recommended.

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10 APPENDICES

Appendix 1 Literature searching strategies

Clinical effectiveness searches

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Wednesday 7th January 2015

Hits: 95

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	81673
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34747
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41731
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36959
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46496
6	1 or 2 or 3 or 4 or 5	115157
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1080
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6436
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	17526
10	Tacrolimus/	13172
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	228
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28566
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	22525
14	Sirolimus/	14642

15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3203
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	75480
17	6 and 16	9696
18	Randomized Controlled Trial.pt.	405805
19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	863332
20	clinical trial.pt.	503357
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	356127
22	18 or 19 or 20 or 21	1343010
23	6 and 16 and 22	2481
24	limit 23 to yr="2014 -Current"	95

Notes: N/A

File: N/A

Database: EMBASE
Host: OVID

Data Parameters: 1974 to 2015 January 05

Date Searched: Wednesday 7th January 2015

Hits: 272

Search Strategy:

#	Searches	Results
1	kidney transplantation/	97857
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51138
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56254
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52314
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66083
6	1 or 2 or 3 or 4 or 5	154370
7	basiliximab/	6754
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2323
9	thymocyte antibody/	20451

10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8932
11	tacrolimus/	54178
12	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	26496
13	belatacept/	1003
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10124
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36223
17	rapamycin/	36866
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29130
19	everolimus/	14653
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7135
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	149906
22	6 and 21	25851
23	randomized controlled trial/	358007
24	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	1039570
25	("controlled trial$" or "clinical trial$").ti,ab,ot.	434667
26	23 or 24 or 25	1314663
27	22 and 26	3526
28	limit 27 to yr="2014 -Current"	272

Notes: N/A

File: N/A

Database: Cochrane CENTRAL
Host: Wiley

Data Parameters: Issue 12 of 12, December 2014

Date Searched: Wednesday 7th January 2015

Hits: 75

#	Searches	Results
1	MeSH descriptor: [Kidney Transplantation] this term only	3313
2	(Kidney* near/3 transplant*)	5959
3	(Renal near/3 transplant*)	4492
4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5192
6	#1 or #2 or #3 or #4 or #5	9188
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")	2587
10	MeSH descriptor: [Tacrolimus] this term only	1181
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")	87
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)	3477
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989")	2199

14 MeSH descriptor: [Sirolimus] this term only	1071
15 (Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")	939
16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	7471
17 #6 and #16 Publication Year from 2014 to 2015	102

Notes: This search strategy represents the whole of the Cochrane Library but only CENTRL was downloaded in this instance (CENTRAL 75, EEDS 2, Groups 2, CDSR 20, DARE 3)

File: N/A

Database: Web of Science

Host: ISI Thompson Reuters

Data Parameters: 1900-2014

Date Searched: Wednesday 7th January 2015

Hits: 183

# 16	**183**	#14 AND #13 **Refined by: PUBLICATION YEARS:** (2014) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 15	**2,702**	#14 AND #13 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 14	**1,421,223**	**TOPIC:** ((((random* or rct* or "controlled trial*" or "clinical trial*")))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 13	**13,127**	#12 AND #5 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 12	**142,824**	#11 OR #10 OR #9 OR #8 OR #7 OR #6 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 11	**5,570**	**TOPIC:** (((Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH* *Timespan=All years*
# 10	**111,240**	**TOPIC:** ((("Mycophenolic acid" or MPA or

		Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 9	**486**	**TOPIC:** (((Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 8	**23,942**	**TOPIC:** (((Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 7	**6,468**	**TOPIC:** ((((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 6	**1,475**	**TOPIC:** (((Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 5	**125,548**	#4 OR #3 OR #2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 4	**53,666**	**TOPIC:** ((((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 3	**50,443**	**TOPIC:** ((((kidney or renal) near/3 (recipient* or dono* or donation* or replac*)))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 2	**60,478**	**TOPIC:** (((Renal near/3 transplant*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*
# 1	**47,055**	**TOPIC:** (((Kidney* near/3 transplant*))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years*

Notes: auto-suggest was turned off. No records for 2015 on date of search.

File: N/A

Database: HMIC
Host: OVID

Data Parameters:

Date Searched: Wednesday 7th January 2015

Hits: 0

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	121
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	84
3	(Renal adj3 transplant$).ti,ab,kw,ot.	81
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	152
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	28
6	1 or 2 or 3 or 4 or 5	314
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	1
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	8
10	Tacrolimus/	0
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	0
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	23
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	11
14	Sirolimus/	0
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	2
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	33
17	6 and 16	3
18	Randomized Controlled Trial.pt.	0
19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	10914
20	clinical trial.pt.	0
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	5640
22	18 or 19 or 20 or 21	12174
23	6 and 16 and 22	1
24	limit 23 to yr="2014 -Current"	0

Notes: N/A

File: N/A

Systematic reviews search strategy; Clinical effectiveness searches

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Thursday 8th January 2015

Hits: 10

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	81679
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34743
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41731
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36952
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46489
6	1 or 2 or 3 or 4 or 5	115148
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1080
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6435
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	17524
10	Tacrolimus/	13170
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	228
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28558
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	22498
14	Sirolimus/	14646

15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3201
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	75448
17	6 and 16	9694
18	(systematic adj3 review$).ti,ab,kw,ot.	67562
19	17 and 18	50
20	limit 19 to yr="2014 -Current"	10

Notes: N/A

File: N/A

Database: EMBASE

Host: OVID

Data Parameters: 1974 to 2015 January 07

Date Searched: Thursday 8th January 2015

Hits: 19

Search Strategy:

#	Searches	Results
1	kidney transplantation/	97867
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51145
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56258
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52323
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66091
6	1 or 2 or 3 or 4 or 5	154387
7	basiliximab/	6757
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2323
9	thymocyte antibody/	20454
10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8933
11	tacrolimus/	54192

12	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	26500
13	belatacept/	1004
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10128
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36231
17	rapamycin/	36874
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29138
19	everolimus/	14659
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7137
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	149945
22	6 and 21	25858
23	(systematic adj3 review$).ti,ab,kw,ot.	79043
24	22 and 23	127
25	limit 24 to yr="2014 -Current"	19

Notes: N/A

File: N/A

Database: Cochrane CDSR & DARE

Host: Wiley

Data Parameters: CDSR Issue 1 of 12, January 2015, DARE & HTA Issue 4 of 4, Oct 2014

Date Searched: Thursday 8th January 2015

Hits: 23 (102 in total: CDSR 20, DARE 3, CENTRAL 75, NHS EEDS 2, Groups 2, HTA 0)

Search strategy:

#	Searches	Results

#1	MeSH descriptor: [Kidney Transplantation] this term only	3313
#2	(Kidney* near/3 transplant*)	5959
#3	(Renal near/3 transplant*)	4492
#4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
#5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5192
#6	#1 or #2 or #3 or #4 or #5	9188
#7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
#8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364
#9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")	2587
#10	MeSH descriptor: [Tacrolimus] this term only	1181
#11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")	87
#12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)	3477
#13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989")	2200
#14	MeSH descriptor: [Sirolimus] this term only	1071
#15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")	940
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	7472
#17	#6 and #16 Publication Year from 2014 to 2015	102

Notes: The search strategy represents the whole of the Cochrane Library. CDSR & DARE results downloaded but not CENTRAL or NHS EEDS as hits/results would have been picked up in the effectiveness and cost-effectiveness searches.

File: N/A

Database: HMIC
Host: OVID

Data Parameters: 1979 to November 2014

Date Searched: Thursday 8th January 2015

Hits: 0

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	121
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	84
3	(Renal adj3 transplant$).ti,ab,kw,ot.	81
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	152
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	28
6	1 or 2 or 3 or 4 or 5	314
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	1
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	8
10	Tacrolimus/	0
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	0
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	23
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	11
14	Sirolimus/	0
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	2
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	33
17	6 and 16	3
18	16 and 17	3
19	limit 18 to yr="2014 -Current"	0

Notes: N/A

File: N/A

Ongoing studies

(Basiliximab OR Basiliximabum OR Simulect OR "interleukin 2 receptor antibody") AND (kidney* OR renal)

((rabbit AND Anti-thymocyte*) OR (rabbit AND Antithymocyte*) OR (rabbit AND thymocyte*) OR (rabbit* AND polyclonal) OR (rabbit* AND ATG) OR RATG OR thymoglobulin*) AND (kidney* OR renal)

(Tacrolimus OR Fujimycin OR Prograf OR Advagraf OR Adoport OR Capexion OR Modigraf OR Perixis OR Tacni OR Vivadex OR Protopic OR Tsukubaenolide OR "FK 506" OR "FK-506" OR "FK506" OR "fr-900506") AND (kidney* OR renal)

(Belatacept OR Nulojix OR "lea29y" OR "lea 29y" OR "bms 224818") AND (kidney* OR renal)

("Mycophenolic acid" OR MPA OR Mycophenolate OR Arzip OR CellCep* OR Myfenax OR Myfortic OR Mofetil) AND (kidney* OR renal)

(Sirolimus OR Rapamune OR Rapamycin OR "ay 22-989") AND (kidney* OR renal)

(Everolimus OR Zortress OR Certican OR Afinitor OR Evertor OR "SDZ RAD") AND (kidney* OR renal)

Cost effectiveness searches

Database: MEDLINE

Host: OVID

Data Parameters: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Date Searched: Thursday 15th January 2015

Hits: 34

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	79778
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34082
3	(Renal adj3 transplant$).ti,ab,kw,ot.	40996
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	35985
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	45333
6	1 or 2 or 3 or 4 or 5	112264
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1054
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6278
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	16989
10	Tacrolimus/	12817
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	217
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	27735
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	20509
14	Sirolimus/	13403
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3038
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	71697
17	6 and 16	9482
18	Economics/	26539
19	exp Economics, Pharmaceutical/	2535
20	exp Economics, Medical/	13480
21	exp Economics, Hospital/	19774
22	(pharmacoeconomic* or socioeconomics or economic$).ti,ab,kw.	180610
23	ec.fs.	339974
24	exp "Costs and Cost Analysis"/	183530
25	Cost of Illness/	18219
26	(cost* or cba or cea or cua or (value adj2 money) or pric$ or fiscal or funding or financial or finance or budget$ or (expenditure$ not Energy)).ti,ab,kw.	517055

27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	872822
28	17 and 27	431
29	limit 28 to yr="2014 -Current"	34

Notes: N/A

File: N/A

Database: EMBASE

Host: OVID

Data Parameters: Embase 1974 to 2015 January 14

Date Searched: Thursday 15th January 2015

Hits: 139

Search Strategy:

#	Searches	Results
1	kidney transplantation/	97901
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51174
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56282
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52361
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66121
6	1 or 2 or 3 or 4 or 5	154466
7	basiliximab/	6765
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2325
9	thymocyte antibody/	20465
10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8936
11	tacrolimus/	54246
12	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	26521
13	belatacept/	1006
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10141
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36267
17	rapamycin/	36926
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29195
19	everolimus/	14696

20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7151
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	150139
22	6 and 21	25879
23	exp Economics/	220609
24	models, economic/	105274
25	exp health economics/	636555
26	exp "Costs and Cost Analysis"/	263409
27	Cost of illness/	14621
28	resource allocation/	15767
29	pe.fs.	62540
30	(cost$ or cba or cea or cua or (value adj2 money) or pric$ or fiscal or funding or financial or finance or budget$ or (expenditure$ not Energy)).ti,ab,kw.	673305
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1300678
32	22 and 31	1475
33	limit 32 to yr="2014 -Current"	139

Notes: N/A

File: N/A

Database: Cochrane NHS EEDS

Host: Wiley

Data Parameters: Issue 4 of 4, October 2014

Date Searched: Thursday 15th January 2015

Hits: 2

Search Strategy:

ID	Search	Hits
#1	MeSH descriptor: [Kidney Transplantation] this term only	3313
#2	(Kidney* near/3 transplant*)	5959
#3	(Renal near/3 transplant*)	4493
#4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
#5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5193
#6	#1 or #2 or #3 or #4 or #5	9189
#7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
#8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364

#9 (Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506") 2587

#10 MeSH descriptor: [Tacrolimus] this term only 1181

#11 (Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818") 87

#12 ("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil) 3477

#13 (Sirolimus or Rapamune or Rapamycin or "ay 22-989") 2200

#14 MeSH descriptor: [Sirolimus] this term only 1071

#15 (Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD") 941

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 7473

#17 #6 and #16 Publication Year from 2014 to 2015 102

Notes: This search strategy represents the whole of the Cochrane Library (NHS EEDS 2, Groups 2, CENTRAL 75, CDSR 20, DARE 3).

File: N/A

Database: Web of Science

Host: ISI Thompson Reuters

Data Parameters: 1900-Current

Date Searched: Thursday 15th January 2015

Hits: 55

Search Strategy:

# 16	**55**	#14 AND #13 **Refined by: PUBLICATION YEARS:** (2014) *Timespan=All years* *Search language=Auto*
# 15	**697**	#14 AND #13 *Timespan=All years* *Search language=Auto*
# 14	**Approximately 3,354,783**	**TOPIC:** (((pharmacoeconomic* or socioeconomics or economic* or pric* or cost* or cba or cea or cua or "health utilit*" or "value for money”))) *Timespan=All years* *Search language=Auto*
# 13	**Approximately 30,726**	#12 AND #5 *Timespan=All years* *Search language=Auto*
# 12	**Approximately 261,400**	#11 OR #10 OR #9 OR #8 OR #7 OR #6 *Timespan=All years* *Search language=Auto*
# 11	**Approximately 12,458**	**TOPIC:** (((Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD"))) *Timespan=All years* *Search language=Auto*

# 10	**Approximately 175,118**	**TOPIC:** ((("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil))) *Timespan=All years* *Search language=Auto*
# 9	**554**	**TOPIC:** (((Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818"))) *Timespan=All years* *Search language=Auto*
# 8	**Approximately 65,143**	**TOPIC:** (((Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506"))) *Timespan=All years* *Search language=Auto*
# 7	**Approximately 21,632**	**TOPIC:** ((((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*))) *Timespan=All years* *Search language=Auto*
# 6	**2,283**	**TOPIC:** (((Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody"))) *Timespan=All years* *Search language=Auto*
# 5	**Approximately 332,469**	#4 OR #3 OR #2 OR #1 *Timespan=All years* *Search language=Auto*
# 4	**Approximately 158,169**	**TOPIC:** ((((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)))) *Timespan=All years* *Search language=Auto*
# 3	**Approximately 122,313**	**TOPIC:** ((((kidney or renal) near/3 (recipient* or dono* or donation* or replac*)))) *Timespan=All years* *Search language=Auto*
# 2	**Approximately 145,513**	**TOPIC:** (((Renal near/3 transplant*))) *Timespan=All years* *Search language=Auto*
# 1	**Approximately 163,622**	**TOPIC:** (((Kidney* near/3 transplant*))) *Timespan=All years* *Search language=Auto*

Notes: Auto-suggest was turned off.

File: N/A

Database: Econlit

Host: EBSCO Host

Data Parameters: 1886-Current

Date Searched: Thursday 15th January 2015

Hits: 0

Search Strategy:

(Basiliximab or Basiliximabum or Simulect or Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or

Tsukubaenolide or Belatacept or Nulojix or "Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep or Myfenax or Myfortic or Mofetil or Sirolimus or Rapamune or Rapamycin or Everolimus or Zortress or Certican or Afinitor or Evertor) AND (kidney or renal)

Notes: N/A
File: N/A

Database: HEED

Host: via the Cochrane Library
Date Searched: Monday, April 14th 2014
Hits: 35

(Basiliximab or Basiliximabum or Simulect or Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or Belatacept or Nulojix or "Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep or Myfenax or Myfortic or Mofetil or Sirolimus or Rapamune or Rapamycin or Everolimus or Zortress or Certican or Afinitor or Evertor) AND (kidney or renal)
Notes: The search recorded here was our initial search. HEED had closed by the time we updated the searches, so we were unable to update our HEED searches.
File: N/A

Searches for utility data; search strategy

The searches for utility data are recorded below. These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft or renal dialysis) AND (terms for utility questionnaires such as SF36 or CHU 9D) and were run from database inception.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID
Data Parameters: 1946 to Present
Date Searched: 03/09/2014
Volume: 714
Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	79870
2	(Kidney$ adj3 transplant$).ti,ab,kw.	33553
3	(Renal adj3 transplant$).ti,ab,kw.	40747
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	35663
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	45183

6	1 or 2 or 3 or 4 or 5	112067
7	Renal Dialysis/	73812
8	Peritoneal Dialysis/	14950
9	((kidney or renal or peritoneal) and (dialysis or dialyses)).ti,ab,kw.	48847
10	7 or 8 or 9	107010
11	6 or 10	201694
12	(euroqol or euro qol or eq5d or eq 5d or EQ-5D or EQ-5D-Y).ti,ab,kw.	4481
13	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kw.	1391
14	(sf10 or sf 10 or short form 10 or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,kw.	77
15	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,kw.	3016
16	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	24
17	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,kw.	341
18	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	17026
19	(health utilities index$ or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,kw.	1172
20	("time trade off" or "time tradeoff" or TTO).ti,ab,kw.	1234
21	standard gamble$.ti,ab,kw.	697
22	(CHU9D or CHU 9D or "Child Health Utility").ti,ab,kw.	13
23	"discrete choice".ti,ab,kw.	713
24	(AQoL or "Assessment of Quality of Life").ti,ab,kw.	1274
25	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	28980
26	11 and 25	766
27	limit 26 to english language	714

Notes: N/A

File Name: MEDLINE.txt

Database: EMBASE

Host: OVID

Data Parameters: 1974 to 2014 Week 34

Date Searched: 03/09/2014
Volume: 915
Search Strategy:

#	Searches	Results
1	kidney transplantation/	96703
2	(Kidney$ adj3 transplant$).ti,ab,kw.	50181
3	(Renal adj3 transplant$).ti,ab,kw.	55376
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	51117
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	64806
6	1 or 2 or 3 or 4 or 5	151605
7	renal replacement therapy/	36722
8	peritoneal dialysis/	23371
9	((kidney or renal or peritoneal) and (dialysis or dialyses)).ti,ab,kw.	64637
10	7 or 8 or 9	97785
11	6 or 10	224149
12	(euroqol or euro qol or eq5d or eq 5d or EQ-5D or EQ-5D-Y).ti,ab,kw.	7316
13	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kw.	1533
14	(sf10 or sf 10 or short form 10 or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,kw.	109
15	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,kw.	4428
16	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	35
17	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,kw.	333
18	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	23918
19	Short Form 36/	12496
20	(health utilities index$ or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,kw.	1547
21	("time trade off" or "time tradeoff" or TTO).ti,ab,kw.	1599
22	standard gamble$.ti,ab,kw.	812

23	(CHU9D or CHU 9D or "Child Health Utility").ti,ab,kw.	13
24	"discrete choice".ti,ab,kw.	958
25	(AQoL or "Assessment of Quality of Life").ti,ab,kw.	1812
26	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	43846
27	11 and 26	991
28	limit 27 to english language	915

Notes: N/A
File Name: EMBASE.txt

Database: Cochrane Library (CENTRAL, HTA and NHS EEDS)

Host: Wiley interface
Data Parameters: CENTRAL Issue 8 of 12, August 2014; HTA & NHS EEDS Issue 3 of 4 Jul 2014
Date Searched: 03/09/2014
Volume: 174
Search Strategy:

ID Search Hits
#1 MeSH descriptor: [Kidney Transplantation] this term only 3298
#2 (Kidney* near/2 transplant*) 5497
#3 (Renal near/2 transplant*) 3841
#4 ((kidney or renal) near/2 (recipient* or dono* or donation* or replac*)) 3399
#5 ((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)) 4785
#6 #1 or #2 or #3 or #4 or #5 8307
#7 MeSH descriptor: [Renal Dialysis] this term only 3496
#8 MeSH descriptor: [Peritoneal Dialysis] this term only 417
#9 ((kidney or renal or peritoneal) and (dialysis or dialyses)) 8888
#10 #7 or #8 or #9 8888
#11 #6 or #10 15502
#12 (euroqol or euro qol or eq5d or eq 5d or EQ-5D or EQ-5D-Y) 2221
#13 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) 11746
#14 (sf10 or sf 10 or short form 10 or shortform 10 or sf ten or sften or shortform ten or short form ten) 12533
#15 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve) 9569
#16 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen) 6668
#17 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty) 7393

#18 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six) 9081
#19 (health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)) 6541
#20 ("time trade off" or "time tradeoff" or TTO) 512
#21 standard gamble* 521
#22 (CHU9D or CHU 9D or "Child Health Utility") 3
#23 "discrete choice" 47
#24 (AQoL or "Assessment of Quality of Life") 302
#25 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 22511
#26 #11 and #25 847

Notes: N/A
File Name: Cochrane.txt

Resource: ScHARR HUD

URL: (http://update-sbs.update.co.uk/scharr11/index.php?recordsN1&m=search)
Date Searched: 03/09/2014
Volume: 9
Search Strategy:

kidney* or renal or dialysis

Notes:
File Name:

Resource: Euroqol website

URL: http://www.euroqol.org/eq-5d-references/reference-search.html
Date Searched: 03/09/2014
Volume: 24
Search Strategy:

kidney or renal or dialysis

Notes: 5/24 were unique when de-duplicated against the EMBASE search
File Name:

Resource: HERC database of mapping studies

URL: http://www.herc.ox.ac.uk/downloads/mappingdatabase
Date Searched: 03/09/2014
Volume: 0
Search Strategy:

a hand-search of the excel database was performed.

Notes: Dakin, H, 2013. Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. Health and Quality of Life Outcomes. 11:151. HERC database of mapping studies, Version 3.0 (Last updated: 26th June 2014). Available at: http://www.herc.ox.ac.uk/downloads/mappingdatabase.

Appendix 2 Data extraction forms

Available on request

Appendix 3 Excluded studies

Table 133. Excluded studies

No	Study	Reason
1	(2012) Erratum: Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: An open-label, randomised, controlled trial (The Lancet (2011) 377 (837-47)). *The Lancet*. **380,** 1994	No data
2	(2014) Erratum: The OSAKA Trial: A Randomized, Controlled Trial Comparing Tacrolimus QD and BD in Kidney (Transplantation (2013) 96 (897)). *Transplantation*. **97,** e38	No data
3	Abou-Jaoude M.M., Ghantous I. & Almawi W.Y. (2003) Tacrolimus (FK506) versus cyclosporin A microemulsion (Neoral) maintenance immunosuppression: effects on graft survival and function, infection, and metabolic profile following kidney transplantation (KT). *Molecular Immunology*. **39,** 1095-1100	Population
4	Abou-Jaoude M.M., Irani-Hakime N., Ghantous I., Najm R., Afif C. & Almawi W.Y. (2003) Cyclosporine microemulsion (Neoral) versus tacrolimus (FK506) as maintenance therapy in kidney transplant patients. *Transplantation Proceedings*. **35,** 2748-2749	Study design
5	Abou-Jaoude M.M., Najm R., Shaheen J. *et al.* (2005) Tacrolimus (FK506) versus cyclosporine microemulsion (neoral) as maintenance immunosuppression therapy in kidney transplant recipients. In *Transplantation Proceedings*, pp. 3025-3028	Study design
6	Abramowicz D., Carmen Rial M., Vitko S. *et al.* (2005) Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. In *Journal of the American Society of Nephrology : JASN*, pp. 2234-2240	Population
7	Adu D., Cockwell P., Ives N.J., Shaw J. & Wheatley K. (2003) Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ*. **326,** 789	Study design
8	Agha I.A. & Brennan D.C. (2002) BK virus and current immunosuppressive therapy. *Graft*. **5,** S65-S72	Study design
9	Ahlenstiel-Grunow T., Koch A., Grosshennig A. *et al.* (2014) A multicenter, randomized, open-labeled study to steer immunosuppressive and antiviral therapy by measurement of virus (CMV, ADV, HSV)-specific T cells in addition to determination of trough levels of immunosuppressants in pediatric kidney allograft recipients (IVIST01-trial): study protocol for a randomized controlled trial. *Trials*. **15**	Study design - update search
10	Ahsan N., Holman M.J., Jarowenko M.V., Razzaque M.S. & Yang H.C. (2002) Limited dose monoclonal IL-2R antibody induction protocol after primary kidney transplantation. *American Journal of Transplantation*. **2,** 568-573	Intervention

11	Albano L., Alamartine E., Toupance O. *et al.* (2012) Conversion from everolimus with low-exposure cyclosporine to everolimus with mycophenolate sodium maintenance therapy in kidney transplant recipients: a randomized, open-label multicenter study. In *Annals of Transplantation*, pp. 58-67	Population
12	Albano L., Banas B., Klempnauer J.L., Glyda M., Viklicky O. & Kamar N. (2013) OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. In *Transplantation*, pp. 897-903	Population
13	Alberú J., Pascoe M.D., Campistol J.M. *et al.* (2011) Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. In *Transplantation*, pp. 303-310	Population
14	Alloway R., Steinberg S., Khalil K. *et al.* (2005) Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. In *Transplantation Proceedings*, pp. 867-870	Study design
15	Almeida C.C., Silveira M.R., Araujo V.E. *et al.* (2013) Safety of immunosuppressive drugs used as maintenance therapy in kidney transplantation: A systematic review and meta-analysis. In *Pharmaceuticals*, pp. 1170-1194	Sr
16	Andrassy J., Hoffmann V.S., Rentsch M. *et al.* (2012) Is cytomegalovirus prophylaxis dispensable in patients receiving an mtor inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation*. **94,** 1208-1217	Duplicate
17	Andrassy J., Hoffmann V.S., Rentsch M. *et al.* (2012) Is cytomegalovirus prophylaxis dispensable in patients receiving an mtor inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation*. **94,** 1208-1217	Sr
18	Andrés A., Budde K., Clavien P.A. *et al.* (2009) A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. In *Transplantation*, pp. 1101-1108	Study design
19	Andres A., Delgado-Arranz M., Morales E. *et al.* (2010) Extended-release tacrolimus therapy in de novo kidney transplant recipients: Single-center experience. *Transplantation Proceedings*. **42,** 3034-3037	Study design
20	Anil Kumar M.S., Heifets M., Fyfe B. *et al.* (2005) Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. In *Transplantation*, pp. 807-814	Population
21	Anil Kumar M.S., Irfan Saeed M., Ranganna K. *et al.* (2008) Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. In *Transplant Immunology*, pp. 32-42	Population
22	Anonymous (2014) Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ*. **349,** g7543	No data-update search

23	Araki M., Flechner S.M., Ismail H.R. *et al.* (2006) Posttransplant diabetes mellitus in kidney transplant recipients receiving calcineurin or mTOR inhibitor drugs. *Transplantation*. **81,** 335-341	Study design
24	Arns W., Breuer S., Choudhury S. *et al.* (2005) Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. In *Clinical Transplantation*, pp. 199-206	Outcome
25	Arora S., Tangirala B., Osadchuk L. & Sureshkumar K.K. (2012) Belatacept: a new biological agent for maintenance immunosuppression in kidney transplantation. *Expert Opinion on Biological Therapy*. **12,** 965-979	Study design
26	Artz M.A., Boots J.M., Ligtenberg G. *et al.* (2002) Randomized conversion from cyclosporine to tacrolimus in renal transplant patients: improved lipid profile and unchanged plasma homocysteine levels. *Transplantation Proceedings*. **34,** 1793-1794	Population
27	Artz M.A., Boots J.M., Ligtenberg G. *et al.* (2003) Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *Journal of the American Society of Nephrology*. **14,** 1880-1888	Population
28	Artz M.A., Boots J.M., Ligtenberg G. *et al.* (2004) Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. *American Journal of Transplantation*. **4,** 937-945	Population
29	Åsberg A., Apeland T., Reisaeter A.V. *et al.* (2013) Long-term outcomes after cyclosporine or mycophenolate withdrawal in kidney transplantation - results from an aborted trial. In *Clinical Transplantation*, pp. E151-156	Population
30	Asberg A., Midtvedt K., Line P.D. *et al.* (2006) Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. In *Transplantation*, pp. 62-68	Comparator
31	Baas M.C., Gerdes V.E.A., Berge I.J.M. *et al.* (2013) Treatment with everolimus is associated with a procoagulant state. In *Thrombosis research*, pp. 307-311	Outcome
32	Baas M.C., Kers J., Florquin S. *et al.* (2013) Cyclosporine versus everolimus: Effects on the glomerulus. *Clinical Transplantation*. **27,** 535-540	Study design
33	Baczkowska T., Perkowska-Ptasi?ska A., Sadowska A. *et al.* (2005) Serum TGF-beta1 correlates with chronic histopathological lesions in protocol biopsies of kidney allograft recipients. In *Transplantation Proceedings*, pp. 773-775	Intervention
34	Bakker R.C., Hollander A., Mallat M.J.K., Bruijn J.A., Paul L.C. & de Fijter J.W. (2003) Conversion from cyclosporine to azathioprine at three months reduces the incidence of chronic allograft nephropathy. *Kidney International*. **64,** 1027-1034	Intervention
35	Bakr M.A., Gheith O.A., Ismael A.M., Baz M.E., Shehab El-Dein A.B. & Ghoneim M.A. (2008) Rescue immunosuppressive therapies in living-related renal allotransplant: a long-term prospective randomized evaluation. In *Experimental and Clinical Transplantation*, pp. 48-53	Population

36	Balbontin F.G., Kiberd B., Belitsky P., Singh D., Fraser A. & Lawen J.G. (2004) Six month randomized study comparing cyclosporine microemulsion with C2 monitoring and tacrolimus in de novo kidney transplantation. *Journal of Urology*. **171,** 515-515	Outcome
37	Bansal D., Yadav A.K., Kumar V., Minz M., Sakhuja V. & Jha V. (2013) Deferred Pre-Emptive Switch from Calcineurin Inhibitor to Sirolimus Leads to Improvement in GFR and Expansion of T Regulatory Cell Population: A Randomized, Controlled Trial. In *PLoS ONE*	Study design
38	Barsoum R.S., Morsey A.A., Iskander I.R. *et al.* (2007) The Cairo kidney center protocol for rapamycin-based sequential immunosuppression in kidney transplant recipients: 2-year outcomes. In *Experimental and Clinical Transplantation*, pp. 649-657	Population
39	Bataille S., Moal V., Gaudart J. *et al.* (2010) Cytomegalovirus risk factors in renal transplantation with modern immunosuppression. In *Transplant Infectious Disease*, pp. 480-488	Outcome
40	Bemelman F.J., Maar E.F., Press R.R. *et al.* (2009) Minimization of maintenance immunosuppression early after renal transplantation: an interim analysis. In *Transplantation*, pp. 421-428	Population
41	Benfield M.R., Tejani A., Harmon W.E. *et al.* (2005) A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. In *Pediatric Transplantation*, pp. 282-292	Study design
42	Bertoni E., Larti A., Rosso G., Zanazzi M., Maria L. & Salvadori M. (2011) Good outcomes with cyclosporine very low exposure with everolimus high exposure in renal transplant patients. In *Journal of Nephrology*, pp. 613-618	Population
43	Birnbaum L.M., Lipman M., Paraskevas S. *et al.* (2009) Management of chronic allograft nephropathy: A systematic review. *Clinical Journal of the American Society of Nephrology*. **4,** 860-865	Population
44	Blydt-Hansen T.D., Gibson I.W. & Birk P.E. (2010) Histological progression of chronic renal allograft injury comparing sirolimus and mycophenolate mofetil-based protocols. A single-center, prospective, randomized, controlled study. In *Pediatric Transplantation*, pp. 909-918	No data
45	Boggi U., Danesi R., Vistoli F. *et al.* (2004) A benefit-risk assessment of basiliximab in renal transplantation. *Drug Safety*. **27,** 91-106	Study design
46	Bolin P., Shihab F.S., Mulloy L. *et al.* (2008) Optimizing tacrolimus therapy in the maintenance of renal allografts: 12-month results. In *Transplantation*, pp. 88-95	Study design
47	Borda B., Lengyel C., Varkonyi T. *et al.* (2014) Side effects of the calcineurin inhibitor, such as new-onset diabetes after kidney transplantation. *Acta Physiologica Hungarica*. **101,** 388-394	Population-update search
48	Bowman L.J., Edwards A. & Brennan D.C. (2014) The role of rabbit antithymocyte globulin in renal transplantation. *Expert Opinion on Orphan Drugs*. **2,** 971-987	Study design - update search

49	Brar J.E. & Nader N.D. (2014) Immune Minimization Strategies in Renal Transplantation. *Immunological Investigations*. **43,** 807-818	Study design - update search
50	Brennan D.C., Agha I., Bohl D.L. *et al.* (2005) Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. In *American Journal of Transplantation*, pp. 582-594	Population
51	Brennan D.C., Daller J.A., Lake K.D., Cibrik D. & Castillo D. (2006) Rabbit antithymocyte globulin versus basiliximab in renal transplantation. In *New England Journal of Medicine*, pp. 1967-1977	Population
52	Brooks R.J., Higgins G.Y. & Webster A.C. (2010) Systematic review of randomized controlled trial quality in pediatric kidney transplantation. *Pediatric Nephrology*. **25,** 2383-2392	Sr
53	Budde K., Becker T., Arns W. *et al.* (2011) Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial [Erratum appears in Lancet. 2011 Jun 11;377(9782):2006 Note: Wuthrich, Rudolf P [added]] CM Comment in: Lancet. 2011 Mar 5;377(9768):788-9; PMID: 21334739, Comment in: Nat Rev Nephrol. 2011 May;7(5):243; PMID: 21525959 SO Lancet. 377(9768):837-47, 2011 Mar 5. In *Lancet*, pp. 837-847	Population
54	Budde K., Bunnapradist S., Grinyo J.M. *et al.* (2014) Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: One-year results of phase III, double-blind, randomized trial. *American Journal of Transplantation*. **14,** 2796-2806	Population- update search
55	Budde K., Curtis J., Knoll G. *et al.* (2004) Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. In *American journal of transplantation*, pp. 237-243	Population
56	Budde K., Glander P., Diekmann F. *et al.* (2004) Enteric-coated mycophenolate sodium: safe conversion from mycophenolate mofetil in maintenance renal transplant recipients. *Transplantation Proceedings*. **36,** 524S-527S	Population
57	Budde K., Knoll G., Curtis J. *et al.* (2005) Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. In *Transplantation Proceedings*, pp. 912-915	Study design
58	Budde K., Knoll G., Curtis J. *et al.* (2006) Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, myfortic (R)). *Clinical Nephrology*. **66,** 103-111	Study design
59	Budde K., Knoll G., Curtis J. *et al.* (2006) Long-term safety and efficacy after conversion of maintenance renal transplant recipients from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPA, myfortic). [German] Langfristige sicherheit und wirksamkeit nach der umstellung von nierentransplantatempfangern in der erhaltungstherapie von mycophenolat-mofetil (MMF) auf magensaft-resistentes mycophenolat-natrium (EC-MPA, myfortic). *Nieren- und Hochdruckkrankheiten*. **35,** 454-464	Language

60	Budde K., Lehner F., Sommerer C. *et al.* (2012) Conversion from cyclosporine to everolimus at 4.5 months posttransplant: 3-year results from the randomized ZEUS study. In *American Journal of Transplantation*, pp. 1528-1540	Population
61	Buechler M., Caillard S., Barbier S. *et al.* (2007) Sirolimus versus cyclosporine in kidney recipients receiving Thymoglobulin (R), mycophenolate mofetil and a 6-month course of steroids. *American Journal of Transplantation*. **7,** 2522-2531	Population
62	Bunnapradist S., Ciechanowski K., West-Thielke P. *et al.* (2013) Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. In *American Journal of Transplantation*, pp. 760-769	Population
63	Burke G.W. (2011) Randomized trial of 2 antibody induction steroid avoidance protocols accompanied by maintenance therapy with Prograf and Myfortic. In *clinicaltrials.gov/ct2/show/NCT01172418*	Comparator
64	Burke G.W., Ciancio C., Blomberg B.B. *et al.* (2002) Randomized trial of three different immunosuppressive regimens to prevent chronic renal allograft rejection. *Transplantation Proceedings*. **34,** 1610-1611	Comparator
65	Burkhalter F., Oettl T., Descoeudres B. *et al.* (2012) High incidence of rejection episodes and poor tolerance of sirolimus in a protocol with early steroid withdrawal and calcineurin inhibitor-free maintenance therapy in renal transplantation: experiences of a randomized prospective single-center study. In *Transplantation Proceedings*, pp. 2961-2965	Study design
66	Busque S., Cantarovich M., Mulgaonkar S. *et al.* (2011) The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. In *American Journal of Transplantation*, pp. 2675-2684	Outcome
67	Cabello-Diaz M., Gutierrez-Vilchez E., Gonzalez-Molina M. *et al.* (2011) Pharmacokinetics of the two tacrolimus formulations in older patients who receive a cadaveric kidney graft from an expanded criteria donor. Randomized single-centre study. *Basic and Clinical Pharmacology and Toxicology*. **109,** 32	Population
68	Campbell S.B., Walker R., Tai S.S., Jiang Q. & Russ G.R. (2012) Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. In *American Journal of Transplantation*, pp. 1146-1156	Population
69	Campistol J.M., Holt D.W., Epstein S., Gioud-Paquet M., Rutault K. & Burke J.T. (2005) Bone metabolism in renal transplant patients treated with cyclosporine or sirolimus. In *Transplant International*, pp. 1028-1035	Study design
70	Campos H.H. & Abbud Filho M. (2002) One-year follow-up of a Brazilian randomized multicenter study comparing tacrolimus versus cyclosporine in kidney transplantation. In *Transplantation proceedings*, pp. 1656-1658	Population
71	Cantarovich D., Rostaing L., Kamar N. *et al.* (2014) Early corticosteroid avoidance in kidney transplant recipients receiving ATG-F induction: 5-year actual results of a prospective and randomized study. *American Journal of Transplantation*. **14,** 2556-2564	Population-update search

72	Cantarovich M., Durrbach A., Hiesse C., Ladouceur M., Benoit G. & Charpentier B. (2008) 20-Year Follow-Up Results of a Randomized Controlled Trial Comparing Antilymphocyte Globulin Induction to No Induction in Renal Transplant Patients. *Transplantation*. **86,** 1732-1737	Study design
73	Cao X. & Colombel J.F. (2013) A systematic review of de novo IBD in solid organ transplant recipient. *Journal of Gastroenterology and Hepatology*. **28,** 590	Intervention
74	Carroll R.P., Hester J., Wood K.J. & Harden P.N. (2013) Conversion to sirolimus in kidney transplant recipients with squamous cell cancer and changes in immune phenotype. In *Nephrology, dialysis, transplantation*, pp. 462-465	Population
75	Cataneo-Davila A., Zuniga-Varga J., Correa-Rotter R. & Alberu J. (2009) Renal Function Outcomes in Kidney Transplant Recipients After Conversion to Everolimus-Based Immunosuppression Regimen with CNI Reduction or Elimination. In *Transplantation Proceedings*, pp. 4138-4146	Population
76	Chadban S.J., Eris J.M., Kanellis J. *et al.* (2014) A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. *Transplant International*. **27,** 302-311	Population
77	Chan L., Greenstein S., Hardy M.A. *et al.* (2008) Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. In *Transplantation*, pp. 821-826	Comparator
78	Charpentier B. (2002) A three arm study comparing immediate tacrolimus therapy with ATG induction therapy followed by either tacrolimus or cyclosporine in adult renal transplant recipients. *Transplantation Proceedings*. **34,** 1625-1626	Population
79	Charpentier B., Groth C.G., Bäckman L. *et al.* (2003) Bicêtre hospital experience with sirolimus-based therapy in human renal transplantation: the Sirolimus European Renal Transplant Study. In *Transplantation proceedings*, pp. 58s-61s	Population
80	Charpentier B., Medina Pestana J.O., M C.R. *et al.* (2013) Long-term exposure to belatacept in recipients of extended criteria donor kidneys. In *American Journal of Transplantation*, pp. 2884-2891	Population
81	Charpentier B., Rostaing L., Berthoux F. *et al.* (2003) A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. *Transplantation*. **75,** 844-851	Population
82	Chen K.H., Tsai M.K., Lai I.R., Lin Wu F.L., Hu R.H. & Lee P.H. (2008) Favorable results of concomitant tacrolimus and sirolimus therapy in Taiwanese renal transplant recipients at 12 months. In *Journal of the Formosan Medical Association / Taiwan yi zhi*, pp. 533-539	Population
83	Cheung C.Y., Chan H.W., Liu Y.L., Chau K.F. & Li C.S. (2009) Long-term graft function with tacrolimus and cyclosporine in renal transplantation: paired kidney analysis. In *Nephrology (Carlton, Vic.)*, pp. 758-763	Study design

84	Cheung C.Y., Wong K.M., Chan H.W. *et al.* (2006) Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. In *Transplant International*, pp. 657-666	Study design
85	Chhabra D., Alvarado A., Dalal P. *et al.* (2013) Impact of calcineurin-inhibitor conversion to mTOR inhibitor on renal allograft function in a prednisone-free regimen. In *American Journal of Transplantation*, pp. 2902-2911	Population
86	Chhabra D., Skaro A.I., Leventhal J.R. *et al.* (2012) Long-term kidney allograft function and survival in prednisone-free regimens: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. In *Clinical Journal of the American Society of Nephrology*, pp. 504-512	Population
87	Chisholm M.A. & Middleton M.D. (2006) Modified-release tacrolimus. *Annals of Pharmacotherapy*. **40,** 270-275	Study design
88	Cianci G., Burke G.W., Gaynor J.J. *et al.* (2004) Randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate mofetil versus cyclosporine (Neoral)/sirolimus in renal transplantation. II. Survival, function, and protocol compliance at 1 year. *Transplantation*. **77,** 252-258	Study design
89	Ciancio (2004) A randomized long-term trial of tacrolimus and sirolimus versus tacrolimus and mycophenolate mofetil versus cyclosporine (Neoral) and sirolimus in renal transplantation. 1. Drug interactions and rejection at one year (vol 77, pg 244, 2004). *Transplantation*. **77,** 1131-1131	Duplicate
90	Ciancio (2004) Erratum: A randomized long-term trial of tacrolimus and sirolimus versus tacrolimus and mycophenolate mofetil versus cyclosporine (Neoral) and sirolimus in renal transplantation. I. Drug interactions and rejection at one year (Transplantation (January 27, 2004) 77,2 (244-251)). *Transplantation*. **77,** 1131	Study design
91	Ciancio G., Burke G.W., Gaynor J.J. *et al.* (2004) A randomized long-term trial of tacrolimus and sirolimus versus tacrolimus and mycophenolate mofetil versus cyclosporine (neoral) and sirolimus in renal transplantation. I. Drug interactions and rejection at one year. *Transplantation*. **77,** 244-251	Population
92	Ciancio G., Burke G.W., Gaynor J.J. *et al.* (2006) A randomized long-term trial of tacrolimus/sirolimus versus tacrolimums/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. In *Transplantation*, pp. 845-852	Population
93	Ciancio G., Burke G.W., Gaynor J.J. *et al.* (2008) Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplant recipients given tacrolimus and daclizumab/thymoglobulin: one year follow-up. In *Transplantation*, pp. 67-74	Population
94	Ciancio G., Gaynor J.J., Guerra G. *et al.* (2014) Randomized Trial of Three Induction Antibodies in Kidney Transplantation: Long-Term Results. *Transplantation*. **97,** 1128-1138	Population-update search

95	Ciancio G., Gaynor J.J., Zarak A. *et al.* (2011) Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplantation with tacrolimus and steroid avoidance: four-year analysis. In *Transplantation*, pp. 1198-1205	Population
96	Ciancio G., Miller J. & Gonwa T.A. (2005) Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation*. **80,** S191-200	Study design
97	Cibrik D., Silva H.T., Vathsala A. *et al.* (2013) Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. In *Transplantation*, pp. 933-942	Study design
98	Citterio F., Scata M.C., Romagnoli J., Pozzetto U., Nanni G. & Castagneto M. (2002) Conversion to tacrolimus immunosuppression in renal transplant recipients: 12-month follow-up. *Transplantation Proceedings*. **34,** 1685-1686	Population
99	Claes K., Meier-Kriesche H.U., Schold J.D., Vanrenterghem Y., Halloran P.F. & Ekberg H. (2012) Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. In *Nephrology, dialysis, transplantation*, pp. 850-857	Population
100	Clayton P.A., McDonald S.P., Chapman J.R. & Chadban S.J. (2012) Mycophenolate versus azathioprine for kidney transplantation: a 15-year follow-up of a randomized trial. In *Transplantation*, pp. 152-158	Population
101	Cransberg K., Cornelissen M., Lilien M., Hoeck K., Davin J.C. & Nauta J. (2007) Maintenance immunosuppression with mycophenolate mofetil and corticosteroids in pediatric kidney transplantation: temporary benefit but not without risk. In *Transplantation*, pp. 1041-1047	Population
102	Cruzado J.M., Bestard O., Riera L. *et al.* (2007) Immunosuppression for dual kidney transplantation with marginal organs: The old is better yet. *American Journal of Transplantation*. **7,** 639-644	Study design
103	Dantal J., Berthoux F., Moal M.C. *et al.* (2012) Efficacy and safety of de novo or early everolimus with low cyclosporine in deceased-donor kidney transplant recipients at specified risk of delayed graft function: 12-month results of a randomized, multicenter trial (vol 23, pg 1084, 2010). *Transplant International*. **25,** 138-138	Population
104	Dantal J., Berthoux F., Moal M.C. *et al.* (2012) Erratum: Efficacy and safety of de novo or early everolimus with low cyclosporine in deceased-donor kidney transplant recipients at specified risk of delayed graft function: 12-month results of a randomized, multicenter trial (Transplant International (2010) 23 (1084-1093) DOI: 10.1111/j.1432-2277.2010. 01094.x). *Transplant International*. **25,** 138	Duplicate
105	Dean P.G., Grande J.P., Sethi S. *et al.* (2008) Kidney transplant histology after one year of continuous therapy with sirolimus compared with tacrolimus. In *Transplantation*, pp. 1212-1215	Study design

106	Dean P.G., Lund W.J., Larson T.S. *et al.* (2004) Wound-healing complication after kidney transplantation: A prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation*. **77,** 1555-1561	Outcome
107	Demirbas A., Hugo C., Grinyó J. *et al.* (2009) Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study. In *Transplant International*, pp. 1172-1181	Population
108	Dharnidharka V.R., Fiorina P. & Harmon W.E. (2014) Kidney Transplantation in Children. *New England Journal of Medicine*. **371,** 549-558	Study design - update search
109	Diekmann F., Gutierrez-Dalmau A., Lopez S. *et al.* (2007) Influence of sirolimus on proteinuria in de novo kidney transplantation with expanded criteria donors: comparison of two CNI-free protocols. *Nephrology Dialysis Transplantation*. **22,** 2316-2321	Population
110	Dobbels F., Ruppar T., De Geest S., Decorte A., Van Damme-Lombaerts R. & Fine R.N. (2010) Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: A systematic review. *Pediatric Transplantation*. **14,** 603-613	Study design
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448	Vitko S., Margreiter R., Weimar W. *et al.* (2004) Everolimus (certican) 12-month safety and efficacy versus mycophenolate mofetil in de Novo renal transplant recipients. *Transplantation*. **78,** 1532-1540	Population
449	Vítko S., Margreiter R., Weimar W. *et al.* (2005) Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. In *American Journal of Transplantation*, pp. 2521-2530	Population
450	Wagner M., Balk E.M., Webster A.C. *et al.* (2009) Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. *Cochrane Database of Systematic Reviews*. **(2)**	No data
451	Waid T. (2005) Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. In *Clinical Transplantation*, pp. 573-580	Intervention
452	Walker R.G., Cottrell S., Sharp K. *et al.* (2007) Conversion of cyclosporine to tacrolimus in stable renal allograft recipients: quantification of effects on the severity of gingival enlargement and hirsutism and patient-reported outcomes. In *Nephrology (Carlton, Vic.)*, pp. 607-614	Outcome
453	Waller J.R., Murphy G.J., Metcalfe M.S., Sandford R.M., Pattenden C.J. & Nicholson M.L. (2002) Primary immunosuppression with tacrolimus is associated with a reduction in renal allograft fibrosis compared with neoral therapy. *Transplantation Proceedings*. **34,** 1587-1588	Population
454	Wang K., Zhang H., Li Y. *et al.* (2004) Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplantation Proceedings*. **36,** 2071-2072	Population
455	Wang K., Zhang H., Li Y. *et al.* (2004) Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. *Transplantation Proceedings*. **36,** 2068-2070	Population
456	Wang R., Xu Y., Wu J., Wang Y., He Q. & Chen J. (2013) Reduced-dose Cyclosporine with Mycophenolate Mofetil and Prednisone Significantly Improves the Long-term Glomerular Filtration Rate and Graft Survival. *Internal Medicine*. **52,** 947-953	Study design
457	Warejko J.K. & Hmiel S.P. (2014) Single-center experience in pediatric renal transplantation using thymoglobulin induction and steroid minimization. *Pediatric Transplantation*. **18,** 816-821	Study design - update search
458	Watorek E., Szymczak M., Boratynska M., Patrzalek D. & Klinger M. (2011) Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. In *Transplantation Proceedings*, pp. 2967-2969	Comparator

459	Watson C.J., Firth J., Williams P.F. *et al.* (2005) A randomized controlled trial of late conversion from CNI-based to sirolimus-based immunosuppression following renal transplantation. In *American Journal of Transplantation*, pp. 2496-2503	Population
460	Webb N.J., Prokurat S., Vondrak K. *et al.* (2009) Multicentre prospective randomised trial of tacrolimus, azathioprine and prednisolone with or without basiliximab: two-year follow-up data. In *Pediatric nephrology (Berlin, Germany)*, pp. 177-182	In
461	Webster A., Woodroffe R.C., Taylor R.S., Chapman J.R. & Craig J.C. (2005) Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. *Cochrane database of systematic reviews (Online)*, CD003961	Sr
462	Webster A.C., Lee V.W., Chapman J.R. & Craig J.C. (2006) Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. *Cochrane database of systematic reviews (Online)*, CD004290	Sr
463	Webster A.C., Lee V.W.S., Chapman J.R. & Craig J.C. (2006) Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: A systematic review and meta-analysis of randomized trials. *Transplantation*. **81,** 1234-1248.e1238	Sr
464	Webster A.C., Playford E.G., Higgins G., Chapman J.R. & Craig J. (2004) Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane Database of Systematic Reviews*, CD003897	Sr
465	Webster A.C., Playford E.G., Higgins G., Chapman J.R. & Craig J.C. (2004) Interleukin 2 receptor antagonists for renal transplantation recipients: A meta-analysis of randomized trials. *Transplantation*. **77,** 166-176	Sr
466	Webster A.C., Ruster L.P., McGee R. *et al.* (2010) Interleukin 2 receptor antagonists for kidney transplant recipients. *Cochrane database of systematic reviews (Online)*, CD003897	Sr
467	Webster A.C., Woodroffe R.C., Taylor R.S., Chapman J.R. & Craig J.C. (2005) Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: Meta-analysis and meta-regression of randomised trial data. *British Medical Journal*. **331,** 810-814	Sr
468	Weimer R., Susal C., Yildiz S. *et al.* (2005) sCD30 and neopterin as risk factors of chronic renal transplant rejection: impact of cyclosporine A, tacrolimus, and mycophenolate mofetil. In *Transplantation Proceedings*, pp. 1776-1778	Population
469	Weimer R., Susal C., Yildiz S. *et al.* (2006) Post-transplant sCD30 and neopterin as predictors of chronic allograft nephropathy: Impact of different immunosuppressive regimens. *American Journal of Transplantation*. **6,** 1865-1874	Population
470	Welberry Smith M.P., Cher G.A., Newstead C.G. *et al.* (2013) Alemtuzumab induction in renal transplantation permits safe steroid avoidance with tacrolimus monotherapy: A randomized controlled trial. In *Transplantation*, pp. 1082-1088	Population

471	Williams P. (2003) An open label randomised study of sirolimus in patients with impaired renal function following renal transplantation. In National Research Register, UK [http://www.nrr.nhs.uk/]	Unobtainable
472	Wiseman A.C., McCague K., Kim Y., Geissler F. & Cooper M. (2013) The effect of everolimus versus mycophenolate upon proteinuria following kidney transplant and relationship to graft outcomes. In *American Journal of Transplantation*, pp. 442-449	Outcome
473	Wissing K.M. & Pipeleers L. (2014) Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: Prevention and treatment. *Transplantation Reviews*. **28,** 37-46	Study design - update search
474	Wissing K.M., Fomegne G., Broeders N. *et al.* (2008) HLA mismatches remain risk factors for acute kidney allograft rejection in patients receiving quadruple immunosuppression with anti-interleukin-2 receptor antibodies. *Transplantation*. **85,** 411-416	Study design
475	Wlodarczyk Z., Ostrowski M., Mourad M. *et al.* (2012) Tacrolimus pharmacokinetics of once- versus twice-daily formulations in de novo kidney transplantation: a substudy of a randomized phase III trial. In *Therapeutic Drug Monitoring*, pp. 143-147	Population
476	Wlodarczyk Z., Squifflet J.P., Ostrowski M. *et al.* (2009) Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial. In *American Journal of Transplantation*, pp. 2505-2513	Population
477	Wlodarczyk Z., Walaszewski J., Perner F. *et al.* (2002) Freedom from rejection and stable kidney function are excellent criteria for steroid withdrawal in tacrolimus-treated kidney transplant recipients. *Annals of Transplantation*. **7,** 28-31	Population
478	Wlodarczyk Z., Walaszewski J., Perner F. *et al.* (2005) Steroid withdrawal at 3 months after kidney transplantation: a comparison of two tacrolimus-based regimens. In *Transplant International*, pp. 157-162	Population
479	Wohlfahrtova M. & Viklicky O. (2014) Recent trials in immunosuppression and their consequences for current therapy. *Current Opinion in Organ Transplantation*. **19,** 387-394	Study design - update search
480	Woodroffe R., Yao G.L., Meads C. *et al.* (2005) Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: A systematic review and modelling study. *Health Technology Assessment*. **9,** i-179	Duplicate
481	Wu B., Wu F.B., Yu L., Li T.P. & Tang Y. (2010) Effectiveness and safety of calcineurin inhibitor withdrawal from target-of-rapamycin-inhibitor-based immunosuppression in kidney transplantation: a meta analysis (Provisional abstract). In *Chinese Journal of Evidence-Based Medicine*, pp. 33-39	Study design
482	Wu F.L., Tsai M.K., Chen R.R. *et al.* (2005) Effects of calcineurin inhibitors on sirolimus pharmacokinetics during staggered administration in renal transplant recipients. In *Pharmacotherapy*, pp. 646-653	Population

483	Xue W., Zhang Q., Xu Y., Wang W., Zhang X. & Hu X. (2014) Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis. *Chinese Medical Journal*. **127,** 2376-2381	Population-update search
484	Yan H.L., Zong H.T., Cui Y.S., Li N. & Zhang Y. (2014) Calcineurin Inhibitor Avoidance and Withdrawal for Kidney Transplantation: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Transplantation Proceedings*. **46,** 1302-1313	SR-update search
485	Yao G., Albon E., Adi Y. *et al.* (2006) A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children (Structured abstract). In *Health Technology Assessment Database*, p. 1. Health Technology Assessment	Duplicate
486	Yao G., Albon E., Adi Y. *et al.* (2006) A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. *Health Technology Assessment*. **10,** iii-65	Sr
487	Yaqoob M., Pattison J., Riad H., Cornu-Artis C., Wang Z. & Shihab F. (2011) Cytomegalovirus and BK virus infections are less frequent with everolimus versus mycophenolate immunosuppression: 24-month update from the 2309 study in de novo renal transplant recipients. *Transplant International*. **24,** 40-41	Unobtainable
488	Zachariah M., Nader N.D., Brar J. *et al.* (2014) Alemtuzumab and Minimization Immunotherapy in Kidney Transplantation: Long-Term Results of Comparison With Rabbit Anti-Thymocyte Globulin and Standard Triple Maintenance Therapy. *Transplantation Proceedings*. **46,** 94-100	Study design
489	Zadrazil J., Horak P., Strebl P. *et al.* (2012) In vivo oxidized low-density lipoprotein (ox-LDL) aopp and tas after kidney transplantation: a prospective, randomized one year study comparing cyclosporine A and tacrolimus based regiments. In *Biomedical papers of the Medical Faculty of the University Palacký, Olomouc, Czechoslovakia*, pp. 14-20	Population
490	Zhang Y.G., Teng D.H., Wang L. *et al.* (2006) Effectiveness and safety of rapamycin-based immunosuppression regimen with or without CsA in renal transplantation: a systematic review (Provisional abstract). In *Chinese Journal of Evidence-Based Medicine*, pp. 94-106	Study design
491	Zhong J.-y., Qu L.-x., Zhang M., Jiao Z. & Lu F.-m. (2005) Application of basiliximab in prevention of acute allograft rejection in kidney transplantation recipients. *Zhongguo Xinyao yu Linchuang Zazhi*. **24,** 468-471	Language
492	Zhu Q.G., Zhao Y.K., Liu W., Luo H., Qiu Y. & Gao Z.Z. (2008) Two-year observation of a randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplantation. In *Chinese medical sciences journal = Chung-kuo i hsüeh k'o hsüeh tsa chih / Chinese Academy of Medical Sciences*, pp. 244-248	Study design

Key:No, number; PenTAG, PenTAG systematic review.

Table 134. Mixed population RCTs

Study	Treatment comparisons and (n)	Eligibility Criteria	Age mean (SD), Median [range] years
Ciancio (2004) A randomized long-term trial of tacrolimus and sirolimus versus tacrolimus and mycophenolate mofetil versus cyclosporine (Neoral) and sirolimus in renal transplantation. I. Drug interactions and rejection at one year. *Transplantation*. **77,** 244-251	TAC + SRL (50) vs TAC + MMF (50) vs CsA + SRL (50)	13 years and over	50 (13) vs 47 (16) vs 44 (16)
Flechner S.M., Gurkan A., Hartmann A. *et al.* (2013) A randomized, open-label study of sirolimus versus cyclosporine in primary de novo renal allograft recipients. In *Transplantation*, pp. 1233-1241	SRL (314) vs CsA (161)	13 years and over	42.9 (SE 0.8) vs 42.7 (SE 1.1)
Gaber A.O., Kahan B.D., Buren C., Schulman S.L., Scarola J. & Neylan J.F. (2008) Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. In *Transplantation*, pp. 1187-1195	Tac (224) vs CsA (224)	13 years and over	46.4 [15-73] vs 44.4 [15-80]
Kahan B.D. for The Rapamune US Study Group. (2000) Efficacy of sirolimus compared with azathoprine for reduction of acute renal allograft rejection: a randomised multicentre study. *The Lancet.* **356,** 194-202[a]	SRL 2mg (284) vs SRL 5mg (274) vs AZA (161)	13 years and over[b]	44.9 (13.6) vs 46.8 (13.0) vs 45.6 (13.0)

MacDonald A.S. for The Rapamune US Study Group. (2001) A worldwide, phase III ranomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rehection in recipients of primary mismatched renal allografts. *Transplantation.* **71,** 271-280[a]	SRL 2mg (227) vs SRL 5mg (219) vs Placebo (130)	Included participants aged 15-71 years[c]	45.6 (12.3), [15-71] vs 45.1 (12.2), [17-68] vs 46 (13.1), [16-72]
Lee Y.J., Kim B., Lee J.E. *et al.* (2010) Randomized trial of cyclosporine and tacrolimus therapy with steroid withdrawal in living-donor renal transplantation: 5-year follow-up. In *Transplant International*, pp. 147-154	CsA (55) vs TAC (62)	Older than 15 years	38.5 (9.5) vs 38.8 (9.2)
Machado P.G., Felipe C.R., Hanzawa N.M. *et al.* (2004) An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone combination. *Clinical Transplantation*. **18,** 28-38	SRL (35) vs AZA (35)	13 years of age or older	35.8 (10.5) vs 32.7 (10.4)
Wu F.L., Tsai M.K., Chen R.R. et al. (2005) Effects of calcineurin inhibitors on sirolimus pharmacokinetics during staggered administration in renal transplant recipients. In Pharmacotherapy, pp. 646-653	TAC (11) vs CsA (10)	13 to 65 years[d]	40.4 (10.4) vs 36.9 (8.1)

Silva H.T., Yang H.C., Abouljoud M. *et al.* (2007) One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. In *American Journal of Transplantation*, pp. 595-608 Silva H.T., Yang H.C., Meier-Kriesche H.U. et al. (2014) Long-term follow-up of a phase III clinical trial comparing tacrolimus extended-release/MMF, tacrolimus/MMF, and cyclosporine/MMF in de novo kidney transplant recipients. Transplantation. 97, 636-641	TAC QD (214) vs TAC BD (212) vs CsA (212)	12 years or older	47.8 (13), 48 [17-77] vs 48.6 (12.9), 50.5 [19-74] vs 47.6 (13), 48.5 [17-77]

Notes: a, Identified from Kahan et al. 2003[248]; b, Yao et al. 2006 [1]states:" participants between 12-18 years were assigned as 6 vs 3 vs 3"; c, Yao et al. 2006 [1]states:" participants under 18 years were assigned as 1 vs 1 vs 1; d, This is unclear as the aper aslo states:" study recruited 22 adults"; All the above studies were excluded from the current review based on population characteristics.

Appendix 4 Systematic reviews

Table 135. Included Systematic reviews

No	Trial ID	Aim	Idenitfied RCTs	Identified non-RCTs
1	Almeida et al. 2013[249]	To evaluate the safety of the most commonly used immunosuppressive regimens.	0	0
2	Andrassy et al. 2012[250]	To summarise clinical trials after solid organ transplantation and describe potential mechanisms involved in the anti-CMV effect of mTOR-inhibitors.	0	0
3	Brooks et al. 2010[251]	To evaluate the quality of reporting of transplantation trials in children published in contemporary biomedical literature.	2	0
4	Ho et al. 2013[252]	To evaluate the benefits and harms of sustained-release daily dosing formulation compared with standard twice daily tacrolimus in kidney transplant recipients.	0	0
5	Kasiske et al. 2008[253]	To conduct a systematic review of randomized controlled trials (RCTs) to critically examine the incidence and type of dyslipidemia associated with mTOR inhibitors.	0	0
6	Knight et al. 2009[254]	To identify whether or not MMF improves outcomes compared with AZA in renal transplant recipients, particularly in incidence of acute rejection, patient and graft survival, and toxicity.	0	0
7	Liu et al. 2010[255]	To compare the efficacy and safety of basiliximab versus antithymocyte globulin for induction therapy.	0	0
8	Masson et al. 2014[256]	To synthesise data from RCTs that compared belatacept with other primary maintenance immunosuppression regimens.	0	0
9	Moore et al. 2009[257]	To assess transplant outcomes after CNI sparing with mycophenolate as sole adjunctive immunosuppression.	0	0
10	Mulay et al. 2006[258]	To systematically review all clinical studies that evaluated calcineurin inhibitor conversion to sirolimus in patients with chronic nephropathy.	0	0

11	Peddi et al. 2013[259]	To evaluate the efficacy and safety of immunosuppressive regimens containing a mammalian target of rapamycin (mTOR) inhibitor with tacrolimus (TAC) minimization therapy in solid organ transplant recipients.	0	0
12	Pengel et al. 2011[260]	To evaluate the occurrence of wound complications and lymphoceles in solid organ transplant recipients receiving mTOR inhibitors from the time of transplantation compared with patients not receiving mTOR inhibitors.	0	0
13	Su et al. 2011[261]	To evaluate clinical consequences of and mycophenolate mofetil dose reduction in renal transplant recipients on tacrolimus based regimens.	0	0
14	Webster et al. 2004[262]	To systematically identify and summarize the effects of IL-2Ra as induction agents, as an addition to standard therapy, or as an alternative to other antibody therapies in common use (antithymocyte globulins, antilymphocyte globulins, monomurab-CD3).	0	0
15	Webster et al. 2004[263]	To systematically identify and summarise the effects of using an IL2Ra, as an addition to standard therapy, or as an alternative to other antibody therapy.	0	0
16	Webster et al. 2005[204]	To systematically review randomised controlled trials in which tacrolimus had been compared with ciclosporin as initial immunosuppressive therapy in the treatment of kidney transplant recipients.	0	0
17	Webster et al. 2005[264]	To compare the effects of tacrolimus with cyclosporin as primary therapy for kidney transplant recipients.	0	0
18	Webster et al. 2006 [154]	To identify systematically and summarize the current available evidence of the short- and long-term benefits and harms of sirolimus and everolimus when used in primary immunosuppressive regimens for kidney transplant recipients.	0	0
19	Webster et al. 2006[265]	To investigate the benefits and harms of immunosuppressive regimens containing TOR-I when compared to other regimens as initial therapy for kidney transplant recipients.	0	0
20	Webster et al. 2010 (update of Webster et al. 2004)[266]	To systematically identify and summarise the effects of using an IL2Ra, as an addition to standard therapy, or as an alternative to another immunosuppressive induction strategy	0	0
21	Woodroffe et al. 2005[267] [267]	To examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus.	1	0

22	Yan et al. 2014[268]	To evaluate the efficacy and safety of CNI avoidance, CNI withdrawal, and CNI regimens on postoperative patient and graft survival, acute rejection, renal function, and adverse events.	0	0
23	Yao et al. 2006[1]	To establish the clinical effectiveness (harms and benefits) and cost-effectiveness of four of the newer immunosuppressive drugs for renal transplantation, namely basiliximab, daclizumab, tacrolimus and mycophenolate mofetil and sodium), and of sirolimus in children.	2	4

Key: ID, identification; No, number; non-RCT, non-randomised study; RCT, randomised control trial.

Appendix 5 Ongoing trials

Table 136. Ongoing trials

No	Study ID	Sponsor/ Collaborators	Trial name	N	Status	Included in PenTAG (reason)
1	NCT01791491	Bristol-Myers Squibb	Phase II Pharmacokinetics, Efficacy, and Safety of Belatacept in Pediatric Renal Transplant Recipients	54	Recruiting	NA
2	NCT01544491, A2314; , Gupta et al. 2013, Langer et al. 2013, Tonshoff et al. 2012 and Tonshoff et al. 2013[83-86]	Novartis Pharmaceuticals	Efficacy, Tolerability and Safety of Early Introduction of Everolimus, Reduced Calcineurin Inhibitors and Early Steroid Elimination Compared to Standard CNI, Mycophenolate Mofetil and Steroid Regimen in Paediatric Renal Transplant Recipients	106	Recruiting	NA
3	NCT01550445 Oh et al. 2012[269]	Ajou University School of Medicine	Steroid Withdrawal Immunosuppression After Renal Transplantation	30	Unknown	Not included (design)
4	NCT00023244, study 315 (mentioned in Yao et al. 2006[1] as ongoing; Benfield et al. 2010)[270]	National Institute of Allergy and Infectious Diseases (NIAID), Cooperative Clinical Trials in Pediatric Transplantation; Pfizer (formerly Wyeth)	Steroid Withdrawal in Pediatric Kidney Transplant Recipients	274	Terminated	Not included (steroid withdrawal)
5	NCT00137345 Flechner et al. 2013[271]	Pfizer (formerly Wyeth)	Study Comparing Sirolimus With Cyclosporine in a Calcineurin Inhibitor (CNI)-Free Regimen in Kidney Transplant Recipients	500	Terminated	Not included (population)
6	NCT00005113 (included in Yao et al. 2006[1]; 0468E1-217-	Children's Hospital Boston; Pfizer (formerly	A Study to Compare Treatment With Sirolimus Versus Standard Treatment in Patients Who Have	213	Terminated	Not included (no data available &

	US	Wyeth)	Received a Kidney Transplant			population)
7	NCT00228020 Offner et al. 2008[70]	Novartis	Study of Safety and Efficacy of a Basiliximab, Mycophenolate Mofetil, Cyclosporine Microemulsion and Prednisone Combination Treatment Regimen in Pediatric Renal Allograft Recipients	212	Completed	Included
8	NCT00141037 Sarwal et al. 2012[272]	National Institute of Allergy and Infectious Diseases (NIAID) Astellas Pharma Inc Hoffmann-La Roche	Steroid-Free Versus Steroid-Based Immunosuppression in Pediatric Renal (Kidney) Transplantation	130	Completed	Not included
9	NCT00296348	Astellas Pharma Inc	Comparing Efficacy and Safety of Steroid Withdrawal With Tacrolimus and MMF With Induction in Children After Kidney Transplantation (TWIST)	198	Completed	Not included
10	NCT00166244 van Gelder et al. 2008[273]	Erasmus Medical Hoffmann-La Roche Center	Fixed Dose MMF vs Concentration Controlled MMF After Renal Transplantation	901	Completed	Not included (population)
11	ISRCTN89278733 Cransberg et al. 2007[274]	Erasmus Medical Center	Safety and efficacy of mycophenolate mofetil in pediatric renal transplantation	44	Completed	Not included (design)

Key: ID, identification number; NA, not applicable; No, number; PenTAG, PenTAG systematic review.

Appendix 6 Clinical effectiveness; additional information

Table 137. TA 99; included adult randomised control trials

No	Study ID	Multiple ID	Treatments	Included in PenTAG (reason)
1	Vincenti et al. 1998[275]	Vincenti et al. 1998;[276] Hengster et al 1999;[277] Bumgarden et al. 2001[278]	DAC vs PBO	No (treatment)
2	Bingyi et al. 2003[103]	NA	BAS vs PBO	Yes
3	Ponticelli et al. 2001[101]	Ponticelli et al. 2001[279]	BAS vs PBO	Yes
4	Sheashaa et al. 2003[98]		BAS vs NI	Yes
5	Folkmane at al. 2001[280]	Folkmane at al. 2002[281] (a)	BAS vs NI and MMF vs AZA	No (design)
6	Shapiro et al. 1991[282]		TAC vs CSA	No (design)
7	Mayer et al. 1997[106]	Mayer et al. 1999;[283] Mayer et al. 2002;[284] Mayer et al. 2002;[285] European Tacrolimus Multicentre Renal Study	TAC vs CSA	Yes
8	Radermacher et al. 1998[122]	NA	TAC vs CSA	No (design)
9	Van Duijnhoven et al. 2002	NA	TAC vs CSA	Yes
10	Jurewicz et al. 1999[286]	Baboolal et al. 2002;[123] Jurewicz et al. 2003;[287] Welsch Transplant Research group	TAC vs CSA	Yes
11	Sperschneider et al. 2001[288]	Kramer et al. 2003;[289] Dietl et al. 2002;[290] Margreiter et al. 2002.[109]	TAC vs CSA	Yes
12	Töz et al. 2004[291]	NA	TAC vs CSA	Yes
13	Campost et al. 2003[108]	Brazilian tacrolimus Study	TAC vs CSA	Yes
14	Murphy et al. 2003[292]	NA	TAC vs CSA	Yes

15	Mathew et al. 1998[293]	Tricontinental Mycophenolate Mofetil Renal Transplantation Study 1996	MMF vs AZA	Yes
16	Miladipour et al. 2002[294]	NA	MMF vs AZA	No (design)
17	Sadek et al. 2002[115]	NA	MMF vs AZA	Yes
18	Tuncer et al. 2002[117]	NA	MMF vs AZA	Yes
19	Sollinger et al. 1995[119]	MMF Acute Renal transplantation Study Group 1996	MMF vs AZA	Yes
20	Baltar et al. 2002[295]	NA	MMF vs AZA	No (language)
21	Salvadori et al. 2004[296]	NA	MPS vs MMF	Yes
22	Kahan 2000[297]	Rapamune US study	SRL vs AZA	No (design)
23	Machado et al. 2004[298]	NA	SRL vs AZA	No (design)
24	Groth et al. 1999[202]	Sirolimus European Renal transplantation Study group	SRL vs CSA	Yes
25	Johnson et al. 2001[299]	Rapamune Maintenance Regimen (RMR) study	Addition of SRL and CSA removal	No (design)

Key: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin; DAC, daclizumab; ID, identification; No, number ; MMF, mycophenolate mofetil; CCS, steroids; OKT3, Orthoclone OKT3; PBO, placebo; SRL, sirolimus; TAC, tacrolimus.

Table 138. Adverse events, long-term follow-up; Staskewitz et al 2001[77]

AE	Follow-up	CSA+MMF+CCS		
		n	N	%
Respiratory infections	1 year	24	69	35
	1-2 years	6	57	11
	2-3 years	4	44	9
Urinary tract infections	1 year	14	69	20
	1-2 years	6	57	11
	2-3 years	4	44	9
CMV infections	1 year	11	69	16
	1-2 years	2	57	4
	2-3 years	0	44	0
	3-5 years	2	44	5
EBV infections	1 year	2	69	3
	1-2 years	8	57	14
	2-3 years	2	44	5
	3-5 years	3	78	4
Solid tumour	1 year	0	69	0
	1-2 years	0	57	0
	2-3 years	1	44	2
	3-5 years	0	78	0
PTLD	1 year	1	69	1
	1-2 years	0	57	0
	2-3 years	0	44	0
	3-5 years	0	78	0
Herpes simplex	1 year	11	69	16
	1-2 years	4	57	7
	2-3 years	0	44	0
	3-5 years	8	78	10
HPV6	1 year	1	69	1
	1-2 years	2	57	4
	2-3 years	1	44	2
	3-5 years	3	78	4
Oral thush	1 year	3	69	4
	1-2 years	2	57	4
	2-3 years	0	44	0
Diarhea	1 year	37	69	54
	1-2 years	9	57	16
	2-3 years	3	44	7
Abdiminal pain/nausea	1 year	12	69	17
	1-2 years	5	57	9
	2-3 years	3	44	7

Key: AE, adverse events; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HPV, Human papillomavirus; n, number of events; N, number of participants; NR, not reported; PTLD, post-transplant lymphoproliferative disease; OR, odds ratio; CI, confidence intervals;CSA, ciclosporin; CCS, steroids; mycophenolate mofetil.

Note: Staskewitz et al. 2001did not report any AE for the historic control AZA group; only AE for MMF group were reported. All OR were calculated by PenTAG.

Appendix 7 Astellas submission

Table 139. Astellas submission included studies

Study	Arm 1	Arm 2	Arm 3	Arm 4	Parallel Adult HTA (reason)
Ekberg H, et al. 2007[203]	CSA+MMF+CCS	DAC+LOW CSA+MMF+ CCS	DAC+LOW TAC+MMF+ CCS	DAC+LOW SRL+MMF+ CCS	Included
Abou-Jaoude et al. 2003[300]	DAC/rATG/NON +TAC+AZA+CCS	DAC/rATG/NON +CSA+AZA+CCS	NA	NA	Excluded (study design)
Abou-Jaoude et al. 2005[301]	DAC/ZENA/NONE +TAC +AZA/MMF+CCS	DAC/ZENA/NONE +CSA+AZA/MMF+CCS	NA	NA	Excluded (study design)
Busque et al. 2001[302]	TAC+MMF+CCS	TAC+AZA+CCS	CSA+MMF+CCS	NA	Excluded (study design)
Campos et al. 2002[108]	TAC+AZA+CCS	CSA+AZA+CCS	NA	NA	Included
Hardinger et al. 2005[112]	rATG+ TAC+AZA+CCS	rATG+ CSA+AZA+CCS	NA	NA	Included
Johnson et al. 2000[303]	TAC+AZA+CCS	CSA+MMF+CCS	TAC+MMF+CCS	NA	Excluded (population)
Margreiter et al. 2002[109]	TAC+AZA+CCS	CSA+AZA+CCS	NA	NA	Included
Martin Garcia et al. 2003[304]	CSA+CCS	BAS+CSA+CCS	BAS+ TAC+CCS	NA	Excluded (study design)
Morris-Stiff et al. 2000[305]	TAC+AZA+CCS	CSA+AZA+CCS	NA	NA	Excluded (population)

Murphy et al 2003[292]	TAC+AZA+CCS	CSA+AZA+CCS	NA	NA	Included
Raofi et al. 1999[191]	OKT3+ TAC+CCS	OKT3+ CSA+CCS	NA	NA	Included
Silva et al. 2007[153]	BAS+ TAC PR+MMF+CCS	BAS+ TAC+MMF+ CS	BAS+ CSA+MMF+CCS	NA	Excluded (population)
Toz et al. 2004[291]	TAC+AZA+CCS	CSA+AZA+CCS	NA	NA	Included
Vincenti et al. 2007[306]	BAS+ TAC+MMF/MPS+CCS	BAS+ CSA+MMF/MPS + CCS	NA	NA	Excluded (intervention)
Wang et al. 2000[307]	TAC+MMF+CCS	CSA+MMF+CCS	NA	NA	Abstract
White et al. 2000[308]	TAC+CCS	CSA+CCS	NA	NA	Abstract
Williams et al. 1999[309]	TAC+CCS	CSA+CCS	NA	NA	Abstract
Yang et al. 1999[124]	TAC+MMF+CCS	CSA+MMF+CCS	NA	NA	Included
Flechner et al. 2011[310]	DAC+ TAC+SRL+CCS	DAC+ MMF+SRL+CCS	NA	NA	Included
Glotz et al. 2010[127]	TAC+MMF+CCS	rATG+ SRL+MMF+CCS	NA	NA	Excluded (intervention)
Larson et al. 2006[311]	rATG+ TAC+MMF+CCS	rATG+ SRL+MMF+CCS	NA	NA	Included
Vincenti et al. 2010[194]	BAS+BEL LOW+MMF+CCS	BAS+BEL HIGH+MMF+ CCS	BAS+ CSA+MMF+CCS	NA	Included
Durrbach et al. 2010[195]	BAS+BEL LOW+MMF+CCS	BAS+BEL HIGH+MMF+CCS	BAS+	NA	Included

			CSA+MMF+CCS		
Bertoni et al. 2011[312]	BAS+ EVL+CSA+CCS	BAS+ MPS+CSA+CCS	NA	NA	Included
Tedesco Silva et al. 2010[313]	BAS+EVL LOW+CSA+CCS	BAS+EVL HIGH+CSA+ CCS	BAS+ MPA+CSA+CCS	NA	Included
Albano et al. 2013[96]	TAC+MMF+CCS	TAC(0.2 MG)+MMF+CCS	TAC PR (0.3 MG)+MMF+CCS	BAS+TAC PR+MMF+CCS	Included
Kramer et al. 2010[138]	TAC+MMF+CCS	TAC+MMF+CCS	NA	NA	Included
Ciancio et al. 2004[314]	SRL+TAC+CCS	MMF+TAC+CCS	SRL+CSA+CCS	NA	Excluded (population)
Gonwa et al. 2003[189]	SRL+TAC+CCS	MMF+TAC+CCS	NA	NA	Included
Mendez et al. 2005[315]	SRL+TAC+CCS	MMF+TAC+CCS	NA	NA	Included

Key: AZA, azathioprine; BAS, basiliximab; BPAR, biopsy proven acute rejection; CSA, ciclosporin; MMF, mycophenolate mofetil; NI; no induction; No, number; CCS, steroids; TAC, tacrolimus; TAC PR, prolong-release tacrolimus.

Appendix 8 Summary of model parameters

Parameter	Value	PSA distribution
Study characteristics (based on adult effectiveness estimates)		
Patient age (years)	10	Not varied
Patient weight (kg)	31.8	Not varied
Proportion male	0.598	Not varied
Donor type (first graft)		
■ DBD	0.645	Not varied
■ Living-related	0.355	Not varied
Donor type (subsequent grafts)		
■ DBD	0.833	Not varied
■ Living-related	0.167	Not varied
Study characteristics (Trompeter et al. 2002)		
Patient age (years)	10.3	Normal(10.31, 0.325)
Patient weight (kg)	32.6	Normal(32.58, 1.159)
Proportion male	0.612	Beta(120, 76)
Study characteristics (Grenda et al. 2006)		
Patient age (years)	11.4	Normal(11.40, 0.292)
Proportion male	0.620	Beta(119, 73)
Study characteristics (Offner et al. 2008)		
Patient age (years)	10.7	Normal(10.75, 0.342)
Proportion male	0.615	Beta(118, 74)
Surrogate relationships		
Graft survival (censored for DWFG)		
■ Acute rejection	1.60	Log-Normal(0.47, 0.037)

Parameter	Value	PSA distribution
■ NODAT	1.12	Log-Normal(0.113, 0.061)
■ eGFR (ml/min/1.73 m²)		
□ ≥ 80	1	Not varied
□ 45–80	1.59	Log-Normal(0.463, 0.571)
□ < 45	55.9	Log-Normal(4.024, 1.203)
Death with functioning graft		
■ NODAT	1.41	Log-Normal(0.113, 0.061)
■ Sex = female	0.865	Log-Normal(−0.145, 0.036)
■ Donor type		
□ DBD	1	Not varied
□ Living-related	0.551	Log-Normal(−0.595, 0.071)
■ Age		
□ 0-17	0.377	Log-Normal(−0.975, 0.186)
□ 18-30	0.369	Log-Normal(−0.996, 0.117)
□ 31-40	0.712	Log-Normal(−0.339, 0.091)
□ 41-50	1	Not varied
□ 51-60	2.140	Log-Normal(0.761, 0.059)
□ 61-70	4.128	Log-Normal(1.418, 0.053)
Effectiveness estimates from adult RCTs		
Mortality within 12 months [ln(Odds ratio)]		
■ Induction agents (vs. no induction)		Multivariate normal
□ Basiliximab	−0.117	
□ Rabbit ATG	−0.461	
■ Maintenance regimens (vs. CSA+AZA)		Multivariate normal
□ TAC+AZA	0.323	
□ CSA+MMF	−0.057	

Parameter	Value	PSA distribution
◻ TAC+MMF	0.422	
◻ BEL+MMF	−0.763	
◻ CSA+EVL	0.333	
◻ TAC+SRL	0.325	
◻ SRL+MMF	0.542	
■ Head-to-head		
◻ MPS vs. MMF	−0.435	Normal(−0.435, 1.231)
◻ TAC-PR vs. TAC	0.245	Normal(0.245, 0.481)
Graft loss within 12 months [ln(Odds ratio)]		
■ Induction agents (vs. no induction)		Multivariate normal
◻ Basiliximab	−0.171	
◻ Rabbit ATG	−0.253	
■ Maintenance regimens (vs. CSA+AZA)		Multivariate normal
◻ TAC+AZA	0.135	
◻ CSA+MMF	−0.297	
◻ TAC+MMF	−0.379	
◻ BEL+MMF	−0.492	
◻ CSA+EVL	−0.484	
◻ TAC+SRL	0.159	
◻ SRL+MMF	0.032	
■ Head-to-head		
◻ MPS vs. MMF	−0.148	Normal(−0.148, 0.524)
◻ TAC-PR vs. TAC	0.183	Normal(0.183, 0.290)
Biopsy-proven acute rejection within 12 months [ln(Odds ratio)]		
■ Baseline (BAS+TAC+AZA)	0.192	Beta(19, 80)
■ Induction agents (vs. no induction)		Multivariate normal

Parameter	Value	PSA distribution
◻ Basiliximab	−0.688	
◻ Rabbit ATG	−1.041	
■ Maintenance regimens (vs. CSA+AZA)		Multivariate normal
◻ TAC+AZA	−0.548	
◻ CSA+MMF	−0.752	
◻ TAC+MMF	−0.921	
◻ BEL+MMF	−0.216	
◻ CSA+EVL	−0.784	
◻ TAC+SRL	−0.957	
◻ SRL+MMF	−0.828	
■ Head-to-head		
◻ MPS vs. MMF	0.396	Normal(0.396, 0.678)
◻ TAC-PR vs. TAC	−0.025	Normal(−0.025, 0.383)
Graft function at 12 months [Mean difference (ml/min/1.73 m²)]		
■ Baseline (BAS+TAC+AZA)	82 (SD 27)	Not varied
■ Induction agents (vs. no induction)		Multivariate normal
◻ Basiliximab	2.615	
◻ Rabbit ATG	0.752	
■ Maintenance regimens (vs. CSA+AZA)		Multivariate normal
◻ TAC+AZA	9.304	
◻ CSA+MMF	1.609	
◻ TAC+MMF	6.531	
◻ BEL+MMF	10.550	
◻ CSA+EVL	4.863	
◻ TAC+SRL	−0.352	
◻ SRL+MMF	3.846	

Parameter	Value	PSA distribution
■ Head-to-head		
□ MPS vs. MMF	3.9	Normal(3.9, 2.9)
□ TAC-PR vs. TAC	−0.211	Normal(−0.211, 1.302)
Effectiveness estimates (Trompeter et al. 2002)		
Mortality within 4 years		
■ TAC+AZA	0.06	Beta(6, 97)
■ CSA+AZA	0.08	Beta(7, 86)
Graft loss (excluding DWFG) within 4 years		
■ TAC+AZA	0.046	Beta(5, 98)
■ CSA+AZA	0.208	Beta(19, 74)
Acute rejection within 12 months		
■ TAC+AZA	0.43	Beta(44, 58)
■ CSA+AZA	0.62	Beta(58, 35)
eGFR at 12 months (ml/min/1.73 m²)		
■ TAC+AZA	64.9	Normal(64.9, 2.17)
■ CSA+AZA	57.8	Normal(57.8, 2.27)
Effectiveness estimates (Grenda et al. 2006)		
Mortality within 48 months		
■ TAC+AZA	0.011	Beta(1.5, 92.5)
■ BAS+TAC+AZA	0.000	Beta(0.5, 99.5)
Graft loss (excluding DWFG) within 48 months		
■ TAC+AZA	0.104	Beta(10.2, 83.8)
■ BAS+TAC+AZA	0.051	Beta(5.5, 94.5)
Acute rejection within 12 months		
■ TAC+AZA	0.26	Beta(24, 69)

Parameter	Value	PSA distribution
■ BAS+TAC+AZA	0.24	Beta(23.5, 75.5)
eGFR at 12 months (ml/min/1.73 m²)		
■ TAC+AZA	74.9	Normal(74.9, 2.04)
■ BAS+TAC+AZA	74.0	Normal(74.0, 1.98)
Effectiveness estimates (Offner et al. 2008)		
Mortality within 48 months		
BAS+CSA+MMF	0.028	Beta(3.3, 97.7)
CSA+MMF	0.000	Beta(0.5, 92.5)
Graft loss (excluding DWFG) within 48 months		
BAS+CSA+MMF	0.019	Beta(1.9, 98.1)
CSA+MMF	0.011	Beta(1.0, 91.0)
Acute rejection within 12 months		
BAS+CSA+MMF	0.13	Beta(13, 87)
CSA+MMF	0.23	Beta(21, 71)
eGFR at 12 months (ml/min/1.73 m²)		
BAS+CSA+MMF	79	Normal(79, 2.3)
CSA+MMF	82	Normal(82, 2.5)
NODAT within 12 months		
Based on adult evidence		
■ Baseline	0.040	Beta(4, 95)
■ Maintenance agents (vs. TAC) [ln(Odds ratio)]		Multivariate normal
□ TAC-PR	0.169	
□ CSA	−0.816	
□ BEL	−1.671	
□ SRL	−0.234	
■ Maintenance agents (vs. MMF) [ln(Odds ratio)]		Multivariate normal

Parameter	Value	PSA distribution
◻ MPS	−0.070	
◻ SRL	0.474	
◻ EVL	−0.052	
Trompeter et al. 2002		
■ TAC+AZA	0.019	Beta(2,101)
■ CSA+AZA	0.011	Beta(1, 92)
Grenda et al. 2006		
■ TAC+AZA	0.011	Beta(1, 92)
■ BAS+TAC+AZA	0.040	Beta(4, 95)
Offner et al. 2008		
■ BAS+CSA+MMF	0.0	Beta(0.5, 100.5)
■ CSA+MMF	0.0	Beta(0.5, 92.5)
Adverse events		
CMV		
Based on adult evidence		
■ Baseline	0.258	Beta(41, 118)
■ Maintenance agents (vs. no mTOR-I) [ln(Odds ratio)]		Multivariate normal
◻ mTOR-I replacing calcineurin inhibitor	−0.798	
◻ mTOR-I replacing antimetabolite	−1.153	
Grenda et al. 2006		
■ TAC+AZA	0.022	Beta(2, 91)
■ BAS+TAC+AZA	0.071	Beta(7, 92)
Offner et al. 2008		
■ BAS+CSA+MMF	0.128	Beta(14, 95)
■ CSA+MMF	0.086	Beta(8, 85)
Dyslipidaemia		

Parameter	Value	PSA distribution
Based on adult evidence		
■ Baseline	0.555	Beta(313, 251)
■ Maintenance agents (vs. no mTOR-I) [ln(Odds ratio)]		
□ mTOR-I	0.557	Normal(0.557, 0.100)
PTLD		
Trompeter et al. 2002		
■ TAC+AZA	0.029	Beta(3, 100)
■ CSA+AZA	0.032	Beta(3, 90)
Grenda et al. 2006		
■ TAC+AZA	0.022	Beta(2, 91)
■ BAS+TAC+AZA	0.010	Beta(1, 98)
Offner et al. 2008		
■ BAS+CSA+MMF	0.028	Beta(3, 106)
■ CSA+MMF	0.054	Beta(5, 88)
Toxic nephropathy		
Grenda et al. 2006		
■ TAC+AZA	0.043	Beta(4, 89)
■ BAS+TAC+AZA	0.141	Beta(14, 85)
Abdominal pain		
Grenda et al. 2006		
■ TAC+AZA	0.022	Beta(2, 91)
■ BAS+TAC+AZA	0.111	Beta(11, 88)
Delayed graft function		
Grenda et al. 2006		
■ TAC+AZA	0.054	Beta(5, 88)
■ BAS+TAC+AZA	0.111	Beta(11, 88)
Hypertension		

Parameter	Value	PSA distribution
Trompeter et al. 2002		
■ TAC+AZA	0.883	Beta(91, 12)
■ CSA+AZA	0.871	Beta(81, 12)
Hypomagnesaemia		
Trompeter et al. 2002		
■ TAC+AZA	0.408	Beta(42, 61)
■ CSA+AZA	0.226	Beta(21, 72)
Anaemia		
Based on adult evidence	0.052	Beta(207, 3762)
Retransplantation		
Probability of pre-emptive retransplantation on loss of 1st graft	0.2	Beta(3, 12)
Rate of retransplantation (by age)		
■ < 18 (hazard ratio)	3.422	Normal(3.422, 0.397)
■ 18–64	0.104	Normal(0.104, 0.0023)
■ (Rate declines after 65 years)		
Baseline rate of death with functioning graft (subsequent grafts)	0.0078	Log-Normal(−4.853, 0.472)
Baseline rate of graft loss (subsequent grafts)	0.0359	Log-Normal(−3.327, 0.084)
Mortality		
Rate of death on dialysis following graft loss (by age)		
■ 0–17	0.034	Normal(0.034, 0.010)
■ 18–24	0.010	Normal(0.010, 0.003)
■ 25–29	0.012	Normal(0.012, 0.003)
■ 30–34	0.009	Normal(0.009, 0.002)
■ 35–39	0.015	Normal(0.015, 0.002)
■ 40–44	0.021	Normal(0.021, 0.002)

Parameter	Value	PSA distribution
■ 45–49	0.027	Normal(0.027, 0.002)
■ 50–54	0.041	Normal(0.041, 0.003)
■ 55–59	0.053	Normal(0.053, 0.003)
■ 60–64	0.079	Normal(0.079, 0.004)
■ 65–69	0.107	Normal(0.107, 0.005)
Other natural history parameters		
Probability of primary non-function		
■ DBD	0.014	Beta(21, 1456)
■ Living-related	0.019	Beta(15, 755)
Proportion of NODAT in first 6 months	0.75	Beta(75, 25)
Risk stratification for CMV infection		Dirichlet(54, 84, 71)
■ High risk (D+/R−)	0.258	
■ Intermediate risk (D±/R+)	0.402	
■ Low risk (D−/R−)	0.340	
Risk stratification for EBV infection		Dirichlet(28, 48, 6)
■ High risk (D+/R−)	0.341	
■ Intermediate risk (D±/R+)	0.585	
■ Low risk (D−/R−)	0.073	
Utilities		
Baseline utility		Multivariate normal
■ Constant	0.9679812	
■ Coefficient for Age	−0.001807	
■ Coefficient for Age²	−0.00000971	
■ Coefficient for Sex (male)	0.0232887	
Disutilities		
■ Functioning graft	0.053	Gamma(1.179, 0.045)
■ Haemodialysis	0.277	Gamma(66.90, 0.004)

Parameter	Value	PSA distribution
■ Peritoneal dialysis	0.264	Gamma(35.73, 0.007)
Resource use		
Induction therapy		
Basiliximab (10 mg if weight under 35 kg; 20 mg if weight over 35 kg)	1.964	1+Beta(95, 4)
Rabbit ATG drug acquisition (mg/kg)	6.5	Normal(6.5, 0.126)
Rabbit ATG IV administration	4.525	Normal(4.525, 0.079)
Maintenance therapy		
See Table 85 (page 232)		Unless SE reported or could be calculated, a Log-Normal distribution was fitted using the method of moments and assuming coefficient of variation of 10% with following exceptions: ■ Cv = 50% for TAC-PR vs TAC resource use ■ Cv = 2% for BEL resource use
Trompeter et al. 2002		
■ TAC (with AZA) [mg/m²/day]		X1 ~ Normal(8.80, 0.240) X2 ~ Normal(6.33, 0.292) X3 ~ Normal(4.89, 0.329)
□ 0–6 months	7.565	(X1+X2)/2
□ 6–12 months	5.610	(X2+X3)/2
□ Thereafter	4.890	X3
■ CSA (with AZA) [mg/m²/day]		X1 ~ Normal(299.4, 10.4) X2 ~ Normal(203.3, 5.1) X3 ~ Normal(180.0, 6.6)
□ 0–6 months	251.35	(X1+X2)/2
□ 6–12 months	191.65	(X2+X3)/2
□ Thereafter	180.00	X3
■ AZA [mg/kg/day]	1.80	Normal(1.80, 0.04)
■ Prednisolone [mg/kg/day]		X1 ~ Normal(3.9, 0.19) X2 ~ Normal(4.5, 0.37)

Parameter	Value	PSA distribution
		X3 ~ Normal(0.3, 0.02)
◻ 0–6 months (with TAC)	2.1	(X1+X3)/2
◻ 0–6 months (with CSA)	2.4	(X2+X3)/2
◻ Thereafter (with TAC or CSA)	0.3	X3
Grenda et al. 2010		
■ TAC (with MMF) [mg/kg/day]		
◻ Throughout (prepubertal)	0.180	Normal(0.180, 0.014)
◻ Throughout (pubertal)	0.130	Normal(0.130, 0.010)
■ MMF (with TAC) [g/m²/day]		
◻ Throughout (prepubertal)	0.54	Normal(0.54, 0.002)
◻ Throughout (pubertal)	0.60	Normal(0.60, 0.003)
Offner et al. 2008		
■ CSA (with BAS+MMF) [mg/kg/day]		
◻ 0–3 months	7.80	Normal(7.80, 0.34)
◻ 3–6 months	7.15	Normal(7.15, 0.33)
◻ 6–12 months	6.65	Normal(6.65, 0.29)
◻ Thereafter	6.20	Normal(6.20, 0.27)
■ CSA (with MMF) [mg/kg/day]		
◻ 0–3 months	7.67	Normal(7.67, 0.34)
◻ 3–6 months	6.85	Normal(6.85, 0.30)
◻ 6–12 months	6.20	Normal(6.20, 0.28)
◻ Thereafter	5.90	Normal(5.90, 0.26)
■ MMF (with BAS+CSA) [g/m²/day]		X1 ~ Normal(1.06, 0.03) X2 ~ Normal(1.06, 0.03) X3 ~ Normal(0.96, 0.04) X4 ~ Normal(0.93, 0.04)
◻ 0–3 months	1.06	(X1+2×X2)/3

Parameter	Value	PSA distribution
◻ 3–6 months	1.01	(X2+X3)/2
◻ 6–12 months	0.95	(X3+X4)/2
◻ Thereafter	0.93	X4
■ MMF (with CSA) [g/m²/day]		X1 ~ Normal(1.11, 0.03) X2 ~ Normal(1.00, 0.04) X3 ~ Normal(0.85, 0.04) X4 ~ Normal(0.82, 0.04)
◻ 0–3 months	1.04	(X1+2×X2)/3
◻ 3–6 months	0.93	(X2+X3)/2
◻ 6–12 months	0.83	(X3+X4)/2
◻ Thereafter	0.82	X4
Graft loss		
Proportion of failed grafts explanted by time since transplantation		
■ 0–3 months	0.41	Beta(1.95, 2.81)
■ 3–12 months	0.23	Beta(2.85, 9.54)
■ 12–24 months	0.09	Beta(3.55, 35.9)
■ 24+ months	0.04	Beta(3.80, 91.2)
Proportion of failed grafts explanted (subsequent grafts)	0.056	Linear combination of above
Subsequent transplantation		
Workup for retransplantation	1.44	Normal(3423, 58.5) / 2370
Living donor costs	0.349	Beta(826, 1544)
Deceased donor costs	0.651	1 minus above
Maintenance immunosuppression		
■ TAC (mg/kg/day)	0.1	Log-Normal(−2.31, 0.1)
■ MMF (g/day)	2	Log-Normal(0.688, 0.1)
■ Prednisolone (mg/day)	16.3	Log-Normal(2.79, 0.1)
Infection prophylaxis		

Parameter	Value	PSA distribution
Co-trimoxazole (PCP and UTI prophylaxis): Septrin (480 mg tablets in first three months)	90	Log-Normal(4.49, 0.1)
Valganciclovir (CMV prophylaxis) [proportion of affected patients multiplied by time]		
Full dose 0–3 months	1	Not varied
Half dose 3–6 months	0.3	Beta(3, 7)
Full dose 3–6 months	0.16	Beta(1.6, 8.4)
Valganciclovir dosage according to target dose	[Daily only/Alternate days allowed]	
■ 0–337.5	450/225	
■ 337.5–675	450/450	
■ 675+	900/900	
GFR for target dose calculation	80	Normal(80, 2)
Acute rejection		
Expected number of AREs per patient experiencing 1+ ARE	1.193	Normal(136, 11.7) / 114
CMV infection treatment		
Expected number of CMV infections per patient experiencing 1+ CMV infection	1	Not varied
Diabetes		
Antidiabetic medication: metformin 500 mg tablets per 3 months	273.9	Log-Normal(5.61, 0.1)
Complications (inpatient)	0.25	Not varied
Complications (non-inpatient)	0.25	Not varied
Dyslipidaemia		
Statins (mg per cycle per affected patient)		
■ Fluvastatin	2191	Log-Normal(7.66, 0.25)
■ Pravastatin	548	Log-Normal(6.28, 0.25)
■ Simvastatin	91	Log-Normal(4.48, 0.25)
Medical management (attendances per		

Parameter	Value	PSA distribution
cycle per affected patient)		
■ Dietetics outpatients	0.25	Log-Normal(−1.42, 0.25)
■ GP	0.25	Log-Normal(−1.42, 0.25)
Anaemia		
Proportion requiring ESA treatment	0.052	Beta(207, 3762)
Mean weekly dose	5.832	Normal(5.832, 0.067)
Monitoring		
Clinics (first 3 months)	26.1	Log-Normal(3.26, 0.05)
Blood tests (first 3 months)	26.1	Log-Normal(3.26, 0.05)
Clinics + Bloods (per cycle)		
■ 3–6 months	6.5	Log-Normal(1.87, 0.1)
■ 6–12 months	3	Log-Normal(1.09, 0.1)
■ 12–24 months	3	Log-Normal(1.09, 0.1)
■ 24–36 months	2	Log-Normal(0.69, 0.1)
■ 36+ months	1	Log-Normal(1.87, 0.1)
■ Subsequent grafts	3	Log-Normal(1.07, 0.25)
Viral PCR		
■ 0-3 months (CMV) [if no rATG]	6.02	Log-Normal(1.76, 0.25)
■ 0-3 months (CMV) [with rATG]	1.98	Log-Normal(0.65, 0.25)
■ 3-6 months (CMV)	0.26	Log-Normal(−1.38, 0.25)
■ 0-6 months (BKV)	1	Log-Normal(−0.03, 0.25)
■ 6-12 months (BKV)	0.5	Log-Normal(−0.72, 0.25)
■ 0-6 months (EBV)	1.02	Log-Normal(−0.01, 0.25)
■ 6-12 months (EBV)	0.34	Log-Normal(−1.10, 0.25)
Viral serology (per cycle)		
■ 0-3 months (CMV)	0.26	Log-Normal(−1.38, 0.25)
■ At 12 and 24 months (CMV)	0.60	Log-Normal(−0.54, 0.25)

Parameter	Value	PSA distribution
■ At 36, 48 and 60 months (CMV)	0.34	Log-Normal(−1.11, 0.25)
Dialysis		
Proportion of dialysis patients receiving haemodialysis (by age)		
■ 0-1	0.455	Beta(10, 12)
■ 2-3	0.464	Beta(13, 15)
■ 4-7	0.556	Beta(15, 12)
■ 8-11	0.645	Beta(20, 11)
■ 12-15	0.705	Beta(31, 13)
■ 16-17	0.625	Beta(15, 9)
■ 18-24	0.791	Beta(276, 73)
■ 25-34	0.804	Beta(913, 223)
■ 35-44	0.845	Beta(1853, 340)
■ 45-54	0.843	Beta(3358, 624)
■ 55-64	0.852	Beta(4408, 768)
■ 65-74	0.858	Beta(5824, 967)
■ 75-84	0.890	Beta(5533, 681)
■ 85+	0.915	Beta(1246, 116)
Access surgery		
■ Temporary access (for HD)	1	Not varied
■ Long-term access (for HD)	1	Not varied
■ Long-term access (for PD)	1	Not varied
Unit costs		
Dialysis		
Access surgery		
■ Long-term access for HD	£1,946	Normal(1946, 98)
■ Temporary access for HD		

Parameter	Value	PSA distribution
◻ Under 19	£1,747	Normal(1747, 113)
◻ 19 and over	£823	Normal(823, 40)
■ Long-term access for PD	£1,101	Normal(1101, 120)
Ongoing costs (per cycle)		
■ Haemodialysis		
◻ Under 19	£20,278	Normal(20278, 3134)
◻ 19 and over	£6,093	Normal(6093, 164)
■ Peritoneal dialysis		
◻ Under 19	£10,515	Normal(10515, 881)
◻ 19 and over	£6,000	Normal(6000, 183)
Induction agents		
Basiliximab and rabbit ATG	See Table 94 (page 243)	Not varied
Maintenance agents		
Prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept	See Table 94 (page 243)	Not varied
Immediate-release tacrolimus, ciclosporin, mycophenolate mofetil, azathioprine and prednisolone	See Table 95 (page 245)	Mixture models
Acute rejection treatment		
Acute rejection (per episode)	£3,557	Log-Normal(8.15, 0.25)
Spontaneously resolving	£145	Log-Normal(4.97, 0.1)
Steroid-sensitive	£1,274	Log-Normal(7.14, 0.1)
Steroid-resistant (medical management)	£3,456	Log-Normal(8.12, 0.25)
Steroid-resistant (drug acquisition per kg)	£44.46	Log-Normal(0.64, 0.25)
Infection prophylaxis		
Septrin (per 480 mg tablet)	£0.16	Not varied
Valcyte (per 450 mg tablet)	£18.02	Not varied
Infection treatment		

Parameter	Value	PSA distribution
CMV infection	£3,009	Log-Normal(7.98, 0.25)
Anaemia		
Binocrit (per 1,000 IU)	£4.33	Not varied
Diabetes		
Metformin (per 500 mg tablet)	£0.0054	Normal(0.0054, 0.00001)
Complications (annual cost)		
■ Inpatient	1389	Normal(1389, 99)
■ Non-inpatient	695	Normal(695, 19)
Dyslipidaemia		
Statins (per mg)		
■ Fluvastatin	£0.0022	Mixture model
■ Pravastatin	£0.0026	Mixture model
■ Simvastatin	£0.0003	Mixture model
Medical management		
■ Dietetics	£62.70	Normal(62.70, 2.76)
■ GP	£50.82	Normal(50.82, 5.38)
PTLD		
MabThera (per mg)	£1.75	Not varied
Hypertension		
Amlodipine (per mg)	£0.0071	Not varied
Bendroflumethiazide (per 2.5 mg tablet)	£0.0344	Not varied
Captopril (per mg)	£0.0035	Not varied
Hypomagnesaemia		
Magnaspartate (per sachet)	£0.80	Not varied
Drug administration		
IV infusion (first)	£228.95	Normal(228.95, 15.54)
IV infusion (subsequent)	£325.59	Normal(325.59, 45.74)

Parameter	Value	PSA distribution
Monitoring		
Clinic	£145	Log-Normal(4.97, 0.1)
Viral PCR (CMV, EBV, BKV)	£46.75	Log-Normal(3.81, 0.25)
CMV serology	£18.29	Log-Normal(2.88, 0.25)
Therapeutic drug monitoring (CSA, TAC, SRL, EVL)	£26.71	Log-Normal(3.25, 0.25)
Full blood count	£5.05	Log-Normal(1.62, 0.1)
Renal profile	£4.54	Log-Normal(1.51, 0.1)
Liver profile	£4.64	Log-Normal(1.53, 0.1)
Explant		
Under 19	£4,829	Normal(4829, 483)
19 and over	£4,966	Normal(4966, 497)
Subsequent retransplantation		
Recipient work-up		
■ Under 19	£505	Normal(505, 50)
■ 19 and over	£849	Normal(849, 84)
Living donor costs	£8,914	Normal(8914, 891)
Deceased donor costs	£10,142	Normal(10142, 1014)
Transplant surgery		
■ Under 19	£20,913	Normal(20913, 2091)
■ 19 and over	£16,030	Normal(16030, 1603)

Appendix 9 Comparison of the PenTAG, Astellas and previous assessment group's model-based analyses

Table 140. Major cost elements in the different analyses (£)

Cost parameter	Yao et al 2006	PenTAG	Astellas[1]
Tacrolimus therapy (per year)	(£1.70/mg) 3,909	With MMF 1,114 (1st year) 1,234–1,527 (2nd year to age 17) 959 (age 18+) With AZA 1,376 (1st year) 1,115–1,579 (2nd year to age 17) 959 (age 18+) With SRL TODO?	1,559 (1st year) 1,366 (2nd year)
Tacrolimus administration	0	1,031 (1st year) 321 (2nd year) 214 (3rd year) 107 (4th year+)	0
MMF therapy (per year)	2,737	With TAC 82–141 (1st year to age 17) 203 (age 18+) With CSA 138 (1st year) 135–191 (2nd year to age 17) 230 (age 18+)	1,326

Cost parameter	Yao et al 2006	PenTAG	Astellas[1]
Ciclosporin therapy (per year)	1,368	With MMF 1,317 (1st year) 1,281–2,194 (2nd year to age 17) 1,071 (age 18+) With AZA 1,466 (1st year) 1,299–1,841 (2nd year to age 17) 1,078 (age 18+)	N/A
Ciclosporin administration	0	1,031 (1st year) 321 (2nd year) 214 (3rd year) 107 (4th year+)	N/A[5]
Belatacept (per year)	N/A	7,276 (1st year) 4,624 (thereafter for weight ≤ 50 kg) 9,249 (thereafter for weight > 50 kg)	4,018 (1st year) 2,374 (2nd year+)
Belatacept administration	N/A	4,632 (1st year) 4,247 (thereafter)	0
Corticosteroids	0	46 (1st year) 13–20 (thereafter)	176 (1st year) 139 (2nd year+)
Acute rejection (event)	4,644	3,557 (4,244 per patient experiencing AR)	2,536 (1st year) 2,522 (2nd year+)
Dialysis (per year)	21,060	Under 19 81,112 (HD) 42,058 (PD) 19 and over 24,372 (HD) 24,000 (PD)	0

Cost parameter	Yao et al 2006	PenTAG	Astellas[1]
Re-transplantation	N/A	Under 19 20,913 (Procedure only) 19 and over 16,030 (Procedure only)	5,086
Re-transplantation: Organ procurement	N/A	9,714	0

[1] Adopted a 31.5 kg weight for representative patient in the model.. [2] Adopted a 31.5 kg weight for representative patient in the model. [3] Induction cost were not accounted for in model but their omission might have had negligible effects since it would only affect ICER through the small differences in the proportion of re-transplants between arms.. [4] Based on 1 g daily starting within 72 h of transplantation, valued at £82.26 price for 500mg, 30 cap pack from BNF March 2014. [5] Astellas does not evaluate ciclosporin as a comparator in their submission. However, the model speadsheets include information where the annual costs of cyclosporine are calculated based on market shares to be £3,731 for the first and £3,514 for subsequent years.[6] From Beaudet et al. 2011

Table 141. Key effectiveness assumptions and outcomes in economic models compared

Effectiveness parameter	Yao et al 2006	PenTAG	Astellas
Time to graft failure (median)	NR	(To nearest 0.25 years, excluding DWFG) CSA+MMF: 14.00 y TAC+MMF: 17.50 y CSA+AZA: 12.00 y TAC+AZA: 18.75 y CSA+EVL: 16.25 y TAC+SRL: 12.75 y TAC-PR+MMF: 17.25 y BAS+CSA+MMF: 16.50 y BAS+TAC+MMF: 21.00 y BAS+CSA+AZA: 14.50 y BAS+TAC+AZA: 22.75 y BAS+SRL+MMF: 18.00 y BAS+BEL+MMF: 24.25 y BAS+CSA+MPS: 19.25 y rATG+CSA+MMF: 15.75 y rATG+TAC+MMF: 19.50 y rATG+CSA+AZA: 13.75 y rATG+TAC+AZA: 21.50 y	Time to 15% failure (median not achieved withing model horizon) Without BCAR at 12 months: 7 years With BCAR at 12 months: 6 years*
Time to transplantation from graft failure (mean unless otherwise stated)	NR	Mean time to transplantation or death following failure of initial graft 4.86 years (range 4.39–5.17)	3.5 years (median)
Annual change in GFR	N/A	N/A	N/A
Utility of functioning graft –first transplant	0.84 (NR, assumed is same as Woodroffe et al)	0.909 (age 10) 0.888 (age 20) 0.866 (age 30) 0.841 (age 40) 0.815 (age 50) 0.786 (age 60)	0.712

Effectiveness parameter	Yao et al 2006	PenTAG	Astellas
Utility of functioning graft -2nd+ transplants	0.84 (NR, assumed is same as Woodroffe et al)	As 1st	0.712
Utility of dialysis state	0.65 (NR, assumed is same as Woodroffe et al)	0.691 (age 10) 0.668 (age 20) 0.645 (age 30) 0.619 (age 40) 0.592 (age 50) 0.564 (age 60)	0.483

*Model was driven by surrogate marker of acute rejection.

Table 142. Results of the Astellas and PenTAG model-based analyses compared

Model	Regimens compared	Functioning first graft (years)	Funct-ioning graft (years)	Years with Graft loss/dialysis	Life years	QALYs*	Costs (£)*	ICER Incremental cost per QALY
Astellas	Tacrolimus TD (+MMF+St)	NR	NR	NR	9.472	5.569	58,471	Tacrolimus TD vs. Sirolimus I: 1,576,937 (other options are dominated by tacrolimus TD)
	Sirolimus I (+MMF+St)				9.468	5.565	52,339	
	Everolimus (+MMF+St)				9.467	5.564	90,168	
	Sirolimus II (+MMF+St)				9.456	5.553	61,490	
	Belatacept (+MMF+St)				9.455	5.551	75,726	
	Tacrolimus TC# (+MMF+St)	NR	NR	NR	9.472	5.569	58,471	Tacrolimus OD dominates
	Tacrolimus OD# (+MMF+St)				9.502	5.604	53,395	
Assessment Group (PenTAG)	Tacrolimus TD (+ MMF)	19.94	35.35	8.14	43.49	18.21	182,163	**CSA vs. TAC:** TAC dominates
	Tacrolimus TD (+**BAS+**MMF)	22.45	36.29	7.46	43.75	18.36	170,915	
	Sirolimus I (+**BAS+**MMF)	20.38	35.53	8.00	43.53	18.24	199,144	
	Belatacept (+**BAS+** MMF)	24.62	37.24	6.89	44.12	18.59	324,708	**AZA vs. MMF:** AZA dominates (with TAC) MMF dominates (with CSA)
	Ciclosporin (+AZA)	14.80	33.67	9.46	43.13	17.98	212,626	
	Ciclosporin (+MMF)	16.79	34.32	9.01	43.33	18.10	202,424	
	Tacrolimus TD (+AZA)	20.91	35.77	7.82	43.59	18.27	177,360	
	Tacrolimus OD (+MMF)	19.68	35.21	8.17	43.38	18.15	198,433	**SRL vs. TAC:** TAC dominates
								BEL vs. TAC: £667,031

* Discounted at 3.5% per year. # tacrolimus OD = once daily (prolonged release); TD = twice daily (immediate release)

Appendix 10 Additional results from PenTAG model

Table 143. Disaggregated discounted costs (based on adult effectiveness estimates)

Regimen	Induction (first graft)	Maintenance immunosuppression (first graft)	Acute rejection (first graft)	Graft loss (first graft)	Infection prophylaxis (first graft)	CMV infection (first graft)	Monitoring (first graft)
CSA+MMF	£0	£17,779	£1,162	£165	£552	£763	£17,066
TAC+MMF	£0	£16,341	£1,026	£147	£553	£763	£18,138
CSA+AZA	£0	£14,193	£1,878	£189	£550	£763	£16,275
TAC+AZA	£0	£15,428	£1,340	£170	£548	£763	£18,307
CSA+EVL	£0	£87,220	£1,135	£148	£553	£293	£20,263
TAC+SRL	£0	£27,999	£998	£195	£548	£293	£18,778
TAC-PR+MMF	£0	£31,004	£1,007	£156	£551	£763	£17,994
BAS+CSA+MMF	£2,027	£19,978	£678	£147	£554	£763	£17,921
BAS+TAC+MMF	£2,027	£17,670	£587	£130	£554	£763	£18,984
BAS+CSA+AZA	£2,027	£15,619	£1,216	£169	£552	£763	£17,192
BAS+TAC+AZA	£2,027	£16,658	£801	£148	£550	£763	£19,215
BAS+SRL+MMF	£2,027	£34,030	£636	£156	£551	£400	£18,219
BAS+BEL+MMF	£2,027	£186,069	£1,039	£118	£555	£763	£16,964
BAS+CSA+MPS	£2,027	£39,728	£934	£133	£555	£763	£18,675
rATG+CSA+MMF	£2,687	£19,490	£500	£148	£1,199	£763	£17,490
rATG+TAC+MMF	£2,687	£17,235	£431	£131	£1,200	£763	£18,544
rATG+CSA+AZA	£2,687	£15,303	£935	£168	£1,195	£763	£16,824
rATG+TAC+AZA	£2,687	£16,339	£597	£147	£1,193	£763	£18,821

Table 143. Disaggregated discounted costs (based on adult effectiveness estimates) (cont.)

Regimen	Retransplantation	Immunosuppression (subsequent grafts)	Monitoring (subsequent grafts)	Graft loss (subsequent grafts)	Dialysis	NODAT	Anaemia	Dyslipidaemia
CSA+MMF	£17,160	£10,012	£15,252	£69	£118,705	£816	£1,239	£1,683
TAC+MMF	£14,972	£8,655	£13,185	£60	£103,554	£1,808	£1,272	£1,686
CSA+AZA	£18,649	£10,936	£16,672	£76	£128,740	£813	£1,215	£1,677
TAC+AZA	£14,558	£8,388	£12,802	£58	£100,212	£1,811	£1,284	£1,689
CSA+EVL	£15,691	£9,104	£13,864	£63	£108,632	£776	£1,260	£2,080
TAC+SRL	£18,092	£10,572	£16,126	£73	£124,733	£2,815	£1,222	£2,068
TAC-PR+MMF	£15,140	£8,754	£13,343	£61	£104,588	£2,121	£1,267	£1,682
BAS+CSA+MMF	£15,533	£9,004	£13,713	£62	£107,521	£819	£1,267	£1,690
BAS+TAC+MMF	£13,381	£7,686	£11,706	£53	£92,562	£1,816	£1,302	£1,694
BAS+CSA+AZA	£16,899	£9,845	£15,003	£68	£116,801	£817	£1,244	£1,684
BAS+TAC+AZA	£12,859	£7,362	£11,234	£51	£88,524	£1,819	£1,315	£1,696
BAS+SRL+MMF	£14,771	£8,527	£12,999	£59	£101,965	£1,443	£1,277	£2,083
BAS+BEL+MMF	£12,154	£6,948	£10,583	£48	£84,049	£356	£1,330	£1,705
BAS+CSA+MPS	£14,133	£8,146	£12,403	£56	£97,846	£768	£1,293	£1,697
rATG+CSA+MMF	£16,066	£9,335	£14,214	£65	£111,272	£819	£1,258	£1,689
rATG+TAC+MMF	£13,955	£8,035	£12,235	£56	£96,614	£1,817	£1,293	£1,694
rATG+CSA+AZA	£17,316	£10,107	£15,399	£70	£119,752	£817	£1,238	£1,684
rATG+TAC+AZA	£13,347	£7,657	£11,678	£53	£92,004	£1,820	£1,308	£1,697

Table 144. Health outcomes for different regimens (based on adult effectiveness estimates)

Regimen	Life expectancy	Undiscounted LYs with functioning graft	Undiscounted life years on dialysis	Acute rejection within 12 months	NODAT within 12 months	Proportion receiving 2nd transplant	Proportion receiving 3rd transplant	Proportion receiving 4th transplant
CSA+MMF	43.33	34.32	9.01	0.278	0.018	0.785	0.330	0.083
TAC+MMF	43.49	35.35	8.14	0.246	0.040	0.722	0.288	0.070
CSA+AZA	43.13	33.67	9.46	0.450	0.018	0.817	0.356	0.091
TAC+AZA	43.59	35.77	7.82	0.321	0.040	0.698	0.278	0.068
CSA+EVL	43.44	34.97	8.47	0.272	0.017	0.746	0.303	0.074
TAC+SRL	43.09	33.86	9.23	0.239	0.063	0.801	0.345	0.088
TAC-PR+MMF	43.38	35.21	8.17	0.241	0.048	0.724	0.291	0.071
BAS+CSA+MMF	43.57	35.16	8.41	0.162	0.018	0.741	0.300	0.073
BAS+TAC+MMF	43.75	36.29	7.46	0.141	0.040	0.669	0.258	0.062
BAS+CSA+AZA	43.38	34.49	8.89	0.291	0.018	0.777	0.324	0.081
BAS+TAC+AZA	43.86	36.78	7.07	0.192	0.040	0.638	0.245	0.059
BAS+SRL+MMF	43.53	35.53	8.00	0.152	0.032	0.711	0.283	0.069
BAS+BEL+MMF	44.12	37.24	6.89	0.249	0.008	0.623	0.234	0.055
BAS+CSA+MPS	43.81	35.98	7.83	0.224	0.017	0.698	0.273	0.066
rATG+CSA+MMF	43.53	34.89	8.64	0.120	0.018	0.758	0.310	0.076
rATG+TAC+MMF	43.74	35.99	7.74	0.103	0.040	0.691	0.269	0.065
rATG+CSA+AZA	43.36	34.30	9.06	0.224	0.018	0.789	0.333	0.083
rATG+TAC+AZA	43.85	36.51	7.34	0.143	0.040	0.660	0.255	0.062

Table 145. Total discounted costs and QALYs for scenario analyses

Regimen	Total discounted costs			Total discounted QALYs		
	Base case	Scenario 1	Scenario 2	Base case	Scenario 1	Scenario 2
CSA+MMF	£202,424	£199,519	£198,194	18.1018	18.1327	18.1018
TAC+MMF	£182,163	£180,350	£178,410	18.2085	18.2279	18.2085
CSA+AZA	£212,626	£204,271	£209,107	17.9786	18.0647	17.9786
TAC+AZA	£177,360	£173,214	£173,968	18.2674	18.3119	18.2674
CSA+EVL	£261,084	£259,907	£244,721	18.1905	18.2196	18.1905
TAC+SRL	£224,510	£223,132	£218,176	17.9281	17.9445	17.9281
TAC-PR+MMF	£198,433	£196,927	£192,051	18.1503	18.1680	18.1503
BAS+CSA+MMF	£191,679	£192,699	£187,246	18.2468	18.2358	18.2468
BAS+TAC+MMF	£170,915	£172,644	£167,106	18.3596	18.3407	18.3596
BAS+CSA+AZA	£199,900	£196,526	£196,305	18.1308	18.1663	18.1308
BAS+TAC+AZA	£165,024	£165,024	£161,578	18.4259	18.4259	18.4259
BAS+SRL+MMF	£199,145	£200,311	£192,260	18.2423	18.2277	18.2423
BAS+BEL+MMF	£324,708	£324,773	£315,241	18.5901	18.6097	18.5901
BAS+CSA+MPS	£199,158	£198,244	£191,147	18.3907	18.4023	18.3907
rATG+CSA+MMF	£196,997	£199,537	£192,344	18.2169	18.1895	18.2169
rATG+TAC+MMF	£176,691	£179,788	£172,650	18.3383	18.3048	18.3383
rATG+CSA+AZA	£204,260	£203,145	£200,436	18.1119	18.1235	18.1119
rATG+TAC+AZA	£170,112	£171,746	£166,432	18.4078	18.3902	18.4078

Scenario 1: Surrogate relationship between acute rejection and graft survival is removed
Scenario 2: Body weight follows 9th centile for age (instead of median)

Appendix 11 UK Transplant Registry standard national organ transplant dataset

The UK Transplant Registry maintains a standard dataset which is available on request without the need for prior approval (http://www.odt.nhs.uk/uk-transplant-registry/data/). The dataset contains details of all solid organ transplants (kidney, liver, pancreas, intestine, heart, lung and multi-organ) between 1995 and 2012. The dataset contains limited information about the donor, recipient and match between them.

Key variables in the dataset which have been used in analyses supporting the economic modelling:

- RECIP_ID – allows subsequent retransplantations to be identified and graft number to be estimated
- DTYPE (DBD; DCD; living related; living unrelated; domino; living – relationship unspecified; living unrelated – pooled; living unrelated – altruistic) – classification of donor type (it was assumed that relationships from domino onwards are living unrelated)
- RAGE_GRP (< 18; 18–30; 31–50; 51–60; 61–70; > 70) – recipient age group
- RSEX (male; female) – recipient sex
- TY_YR (1995; 1996; …; 2012) – transplant year
- TX_TYPE (kidney only; …) – used to restrict to kidney only transplants
- KID_GSURV – kidney (graft) survival (days since transplantation)
- KID_GCENS – 0 if graft survival was censored; 1 if graft failed
- KID_PSURV – patient survival following kidney transplant (days since transplantation)
- KID_PCENS – 0 if patient survival was censored; 1 if patient died