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

A SYSTEMATIC REVIEW AND ECONOMIC MODEL

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About PenTAG

The Peninsula Technology Assessment Group is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments (HTA) for the UK HTA Programme, systematic reviews and economic analyses for other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Institute of Health Research is made up of discrete but methodologically related research groups, among which HTA is a strong and recurring theme.

Recent PenTAG HTA projects inlude:

- Ofatumumab in combination with chlorambucil or bendamustine for previously untreated chronic lymphocytic leukaemia
- Obinutuzumab for previously untreated chronic lymphocytic leukaemia
- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model
- Bosutinib for previously treated chronic myeloid leukaemia a single technology appraisal
- Erythropoiesis stimulating agents (epoetin and darbepoetin) for cancer-treatment induced anaemia
- Diagnostic strategies for identifying Lynch syndrome in early-onset colorectal cancer patients
- Sysmex RD-100i OSNA system and Metasin for intraoperative detection of sentinel lymph node metastases in breast cancer

For a full list of previous projects please see
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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Cadaveric transplant	A transplant kidney removed from someone who has died.
Calcineurin inhibitor	Ciclosporin or tacrolimus
Cold ischaemia time	Period during which a donated kidney is transported in ice from donor to recipient. Duration is related to extent of kidney damage.
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).
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 transplant	A kidney transplant from a living person who is biologically unrelated to 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.
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

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	donors after brain death
DCD	donors after circulatory death
DGF	delayed graft function
EBV	Epstein–Barr virus
ECD	extended 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
MPA	mycophenolic acid
MMF	mycophenolate mofetil
MPGN	membranoproliferative glomerulonephritis
MPS	mycophenolate sodium
NAPRTCS	North American Paediatric Renal Transplant Cooperative Study
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NODAT	new-onset diabetes after transplant
NRR	National Research Register
OHE HEED	Office of Health Economics Health Economic Evaluation Database
PCR	polymerase chain reaction
PNF	primary non-function
PTLD	post-transplant lymphoproliferative disease
QALY	quality-adjusted life-year
rATG	rabbit anti-human thymocyte immunoglobulin
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
ScHARR	School of Health and Related Research
SD	standard deviation
TAC	tacrolimus
TAC PR	tacrolimus prolonged release
TCMR	T-cell-mediated rejection
TMA	thrombotic microangiopathy
UNOS	United Network of Organ Sharing

1. Executive Summary

1.1. Background

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. An estimated 4% of people in the UK with CKD progress to ESRD over a 5.5 year follow-up period.

RRT as a treatment for ESRD can take a number of forms: (kidney transplantation, haemodialysis and peritoneal dialysis. The preferred option for people with ESRD is kidney transplantation. This is due to improved duration and quality of life with transplantation compared with dialysis.

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) or donation after circulatory death (DCD).

Following kidney transplantation, major clinical concerns are acute kidney rejection and graft loss. Acute kidney rejection occurs when the immune response of the host 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. However, whilst kidney transplantation relieves the person with ESRD from lengthy dialysis, the strict regimen of immunosuppressant medication required may produce unpleasant side effects, including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain. Nevertheless, a large number of studies have documented, the clear quality of life improvements of having a functioning kidney transplant compared with being on dialysis.

Various factors may influence patient survival following kidney transplantation, (including factors related to the donor and to the patient. In people who survive transplantation, acute rejection may occur when the immune response of the host attempts to destroy the graft as the graft is deemed foreign tissue. Acute rejection, which may be experienced by a third of recipients, is treated using changes to 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.

Between April 2013 and March 2014, 2,464 adult kidney transplant operations were performed in England, 97 in Northern Ireland, 112 in Wales and 242 in Scotland. The number of adult transplants from donors after circulatory death (DCD) has been steadily increasing over the time period to 779 in the last financial year. The number of adult transplants from donors after brain death (DBD) has increased in the last two years to 1,101 in 2013/2014 after remaining fairly constant for the previous four financial years. The number of adult living kidney transplants performed has also increased over the time period and 1,049 were performed in the last financial year. Patient survival following a kidney transplant over five years for deceased and living donors is 89% (95% CI 88 to 90) and 95% (95% CI 95 to 96), respectively.

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

The first of these steps is organ procurement which includes the identification of potential donors, assessment of donor suitability, determination of donor brain death (where applicable) and medical management of the donor.

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 immunosuppressive drugs can be divided into induction and maintenance drugs. Induction drugs are powerful antirejection drugs that are taken at the time of transplantation, and close 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.

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/or other complications.

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 in renal transplantation. The two interventions considered for induction therapy are **basiliximab** (Simulect® [Novartis Pharmaceuticals]) which is a monoclonal antibody acting as an

interleukin-2 receptor antagonist and **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. They are as follows: **immediate realease tacrolimus** (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]) and **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 mycophenolate mofetil (MPS) (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

Adults undergoing kidney transplantation only and receiving immunosuppressive therapy were included in this review. Multi-organ transplantation, the use of these drugs for the treatment of episodes of acute rejection and individuals who have previously received a renal transplant and immunosuppression (i.e., individuals not undergoing the process of a new renal transplant) are outside the scope of this appraisal.

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 – where graft loss is defined as return to chronic dialysis, retransplant, graft removal or death,
    - Graft function – (estimated) glomerular filtration rate (eGFR), which is an estimate of actual glomerula filtration rate, using a formula involving age, weight, gender, and serum creatinine.
    - Time to and incidence of biopsy proven acute rejection
    - Severity of acute rejection according to Banff classification (Grade I, II, III).
- Adverse events (AEs):
    - cardiovascular complications,
    - malignancies,
    - diabetes,
    - infections
    - nephrotoxicity.
- Health-related quality of life (HRQoL), including data on validated quality of life measures, e.g. EQ-5D, SF-36, KTQ-25.

Study design

Only randomised controlled trials (RCTs) were included or systematic reviews of RCTs.

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 adult renal transplantation. This was 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 (TA85). In addition, we conducted a systematic review of relevant economic evaluations and a summary and critique of the three economic analyses submitted by companies (Astellas, Novartis and Bristol Myers Squib). The current NICE guidance was primarily based on research evidence presented to NICE in the assessment report by Woodroffe et al. 2005.

1.3. Methods

1.3.1. Clinical effectiveness systematic review

Identification of studies

Bibliographic literature searching was conducted on April 14th 2014 and updated 18th November 2014. The effectiveness 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 study design limit to RCTs or controlled trials). The search was date limited 2002-current in line with the previous assessment. The search was not limited by language or human only studies to ensure records were not missed in error. Instead, these exclusion criteria were implemented during the screening process.

The following databases were searched for RCTs: Medline (OVID), Embase (OVID), CENTRAL (Wiley) and Web of Science (ISI – including conference proceedings). The following trials registries were hand-searched: Clinical Trails.Gov (https://clinicaltrials.gov/) and Controlled Trials (http://www.controlled-trials.com/).

A separate search was undertaken to identify systematic reviews. 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 (OVID), Embase (OVID), CDSR, DARE and HTA (The Cochrane Library via Wiley) and HMIC (OVID). The search was not limited by language and it was not limited to human only studies.

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 for inclusion independently by two researchers, with TJ-H as first reviewer and LC, MHa, MB or HC as second reviewer. Disagreements were resolved by discussion, with involvement of a third reviewer (MHa or HC). Full texts of identified studies were obtained and screened in the same way.

Data extraction

Included full papers were split between five reviewers (TJH, MHa, HC, LC and MB) for the purposes of data extraction using a standardised data extraction form, and checked independently by another reviewer. Discrepancies were resolved by discussion with the involvement of an additional review team member (MHa or HC) if necessary.

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

Where data permitted the results of individual studies were pooled using the methods described below for:

- Estimation of overall treatment effect
- Assessment of heterogeneity
- Subgroup analysis
- Assessment of publication bias

Due to the heterogeneity of population and study characteristics, a random-effects model was assumed for all meta-analyses. For binary data, odds ratio (OR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling. For continuous data (such as eGFR), mean differences were calculated if the outcome was measured on the same scale in all trials. A narrative synthesis accompanies all included study data.

Network meta-analyses were also undertaken within a Bayesian framework in WinBUGS (version 1.4.3). Fixed and random effects network meta-analyses were analysed and

compared using the Deviance Information Criteria (DIC). Models with the lowest DIC were assumed to have a better fit to the data. To assess inconsistency in the network, the inconsistency degrees of freedom (ICDF) were calculated and inconsistency networks (where only direct evidence for a comparison between treatments is used) were modelled. Results from the inconsistency models were compared to those from the consistency models to help identify inconsistencies within the network. The model with the lowest DIC was assumed to be a better fit to the data.

Outcomes analysed at one year were graft loss, mortality, biopsy proven acute rejection and graft function. Induction interventions were basiliximab, rabbit ATG and placebo. Maintenance therapies were as follows:

- SRL + AZA
- EVL
- BEL + SRL
- EVL + MPS
- BEL + MMF
- SRL + CSA
- CSA + AZA
- TAC + AZA
- MMF + CSA
- EVL + CSA
- SRL + TAC
- SRL + MMF
- TAC + MMF

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 November 18th 2014. 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 (as specified in the appraisal protocol):

- 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 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 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 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.

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers et al. (2005). Where studies are based on decision models they will be 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). The utility decrements were based on a published systematic review and meta-analysis of preference-based quality of life studies in patients undergoing renal replacement therapy (RRT), with EQ-5D (EQ-5D-3L) used for measurement and most likely valued using the UK valuation tariff based on a representative sample of the general population. 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:

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- 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.

Sixteen regimens were modelled in total:

Regimens following no induction immunosuppression:

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

Regimens following basiliximab induction:

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

- BAS+BEL+MMF
- BAS+CSA+MPS

Regimens following rabbit ATG induction:

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

1.3.4.2. Model structure

Kidney transplant recipients (KTRs) were assumed to be in one of three health states at any time: FUNCTIONING GRAFT, GRAFT LOSS or DEATH. In the FUNCTIONING GRAFT state, KTRs were not dependent on dialysis whereas in the GRAFT LOSS state, KTRs 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) was estimated, with corresponding costs (during the first year for acute rejection and CMV infection; ongoing for dyslipidaemia and NODAT). NODAT was also associated with a utility decrement based on EQ-5D measurements from kidney transplant patients in a US clinic, valued according to a US valuation tariff. The incidence of acute rejection and NODAT were also used as surrogate determinants of graft survival and death with functioning graft (NODAT only).

Up to two retransplantations were modelled, which could take place from the graft loss state or from the functioning graft state (for the initial graft only) corresponding to pre-emptive retransplantation. KTRs would transition to the next FUNCTIONING GRAFT state if the retransplantation was successful or to the next GRAFT LOSS state if it was unsuccessful (i.e., in the event of primary non-function). The rate of retransplantations was assumed to reduce with age past 65 years, reaching zero by age 80 years.

Transitions out of the FUNCTIONING GRAFT state correspond to the clinical outcome of graft loss/survival 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 functioning graft were calculated from data from the UK Transplant Registry standard dataset. The rate of mortality following graft loss 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 and from the first year onwards a Weibull curve was fitted which was demonstrated to fit the data well.

Death-censored graft survival at one year was estimated for each regimen based on the odds ratios of graft loss within 12 months. This was incorporated into the model by applying a proportional-odds assumption to death-censored graft survival in the first year.

A surrogate relationship between acute rejection, NODAT and graft function (eGFR) at 12 months and graft survival was modelled, based on applying a hazard ratio to the Weibull curve after the first year. The hazard ratio for acute rejection was 1.6, for NODAT was 1.12 and for eGFR was 1–5.80 depending on the eGFR interval.

Patient survival at one year was estimated for each regimen based on the odds ratio of mortality within 12 months. This was incorporated into the model by applying a regimen-specific hazard ratio of death with functioning graft within the first year.

A surrogate relationship between NODAT and death with functioning graft after the first year was also modelled, with a hazard ratio of 1.41.

1.3.4.3. Source of effectiveness estimates

The odds ratios for the incidence of biopsy-proven acute rejection (BPAR), graft loss and patient mortality, and the absolute difference in eGFR, were primarily estimated from the network meta-analyses of clinical effectiveness evidence. The results for induction agents and maintenance regimens were chained assuming independence. The results for TAC-PR+MMF and BAS+CSA+MPS were based on results for TAC+MMF and BAS+CSA+MMF with additional adjustment based on head-to-head comparisons.

The incidences of NODAT, CMV and dyslipidaemia were also estimated using network meta-analyses of RCTs from the systematic review of clinical effectiveness, although some simplifying assumptions were made to overcome the more limited amount of evidence for these outcomes.

1.3.4.4. Costs

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

The costs of acute rejection and CMV infection were taken from a microcosting study commissioned by Bristol Myers Squibb.

The significant costs of NODAT were estimated from a recent publication based on the UK Prospective Diabetes Study (UKPDS), which was conducted in the general population with type 2 diabetes.

The costs of KTR follow-up and monitoring were estimated based on a database study commissioned by Bristol Myers Squibb.

Infection prophylaxis costs were estimated based on the kidney transplant protocol of a UK hospital. Additional CMV prophylaxis costs for regimens containing rabbit ATG induction.

1.3.4.5. Uncertainty analyses

A probabilistic sensitivity analysis (PSA) was conducted to estimate the joint effect of parameter estimation uncertainty on cost-effectiveness. Structural sensitivity analyses relating to graft survival were conducted. A scenario analysis in which list prices were adopted for all drug acquisition costs was performed and a two-way threshold analysis was conducted relating to the costs of belatacept.

1.4. Clinical effectiveness results

1.4.1. Number and quality of studies

We screened the titles and abstracts of 5079 unique references identified by the searches, with 750 papers retrieved for detailed consideration. Eighty nine RCTs were found that matched our inclusion criteria, 21 of which were originally identified by Woodroffe et al. 2005. Of these RCTs, 14 investigated induction therapies, 73 investigated maintenance therapies and 2 investigated both.

Overall, the RCTs were of variable quality, but all appear to be flawed. However, due to reporting omissions, for most of the trials it was difficult to make a general assessment regarding quality, for example eight of the 14 induction trials, 41 of the 73 maintenance trials, and one of the two trials of both induction and maintenance either did not report, or lacked clarity on, at least five of the ten items constituting the quality appraisal assessment.

1.4.2. Summary of benefits and risks

In total, 68 new RCTs were included in the clinical effectiveness review presented in this report, with an additional 21 RCTs meeting our inclusion criteria from the previous assessment.

For the head-to-head comparisons of **induction therapies**, from 0.5 years to 10 years post-transplant, we found no evidence to suggest that BAS or rATG are more effective than placebo, no induction or each other in reducing the odds of mortality (overall survival). Similarly, for graft loss, we found no evidence of a statistically significant difference for BAS or rATG vs placebo, no induction or each other.

We found evidence to suggest that rATG and BAS are more effective than placebo or no induction at reducing BPAR (rATG at 1 yr, OR 0.34, 95%CI 0.22 to 0.52, I^2 8.9%; BAS at 1 yr, OR 0.53, 95% CI 0.40 to 0.70, I^2 0.0%). A statistically significant difference was found for the severity of BPAR, comparing BAS vs rATG, where BAS was associated with lower odds of Banff 3, the most severe classification of acute rejection (1 year, OR 0.04, 95%CI 0.00 to 0.65).

We found no evidence that any **maintenance therapies** were preferable to others in terms of mortality.

For **graft loss** outcomes reported by maintenance studies, we found evidence that at five years that BEL+MMF may be superior to CSA+MMF (OR 0.40, 95%CI 0.19 to 0.87, I^2 0.0%). At 0.5 years, there are reduced odds of graft loss for CSA+MMF as compared to CSA+AZA (OR 0.58, 95%CI 0.04 to 0.59, I^2 72.2%).

Several treatments showed a beneficial effect with regard to reducing **BPAR**, although this varied across time points. For all the following comparisons, the arm containing TAC displayed lower odds of BPAR:

- TAC+AZA vs CSA+AZA (0.5 years OR 0.50 95%CI 0.32 to 0.79, I2 50.1%; 1 year OR 0.50, 95%CI 0.39 to 0.64, I2 8.1%; 4 years OR 0.38, 95%CI 0.25 to 0.57);

- TAC+MMF vs CSA+AZA (0.5 year OR 0.64, 95%CI 0.41 to 0.98; 1 year OR 0.35, 95% CI 0.15 to 0.82);
- TAC+MMF vs CSA+MMF (1 year OR 0.59, 95%CI 0.37 to 0.94, I^2 19.3%);
- TAC+MMF vs SRL+MMF (1 year OR 0.32, 95%CI 0.12 to 0.87, I^2 0.0%);
- TAC+SRL vs TAC+MMF (0.5 years OR 0.65 95%CI 0.44 to 0.96).

For CSA+MMF vs CSA+AZA, at 0.5 years and one year, there is statistically significant evidence to suggest MMF is more effective (0.5 years OR 0.50, 95%CI 0.35 to 0.72, I^2 35.1%).

TAC is also associated with a higher level of **graft function** for the following regimens:

- TAC+MMF vs CSA+MMF (at 3 years, eGFR WMD 4.60 ml/min, 95%CI 1.35 to 7.85);
- TAC+MMF vs TAC PR+MMF (at 0.5 years, eGFR WMD 1.90 ml/min, 95%CI 1.70 to 2.10);
- TAC+SRL vs CSA+SRL (at 0.5 years, eGFR MD 6.35 ml/min, p<0.0001; 1 year MD 5.25, p=0.0004).

For MMF+TAC vs MPS+TAC, MPS at 1 year and 3 years is more effective (1 year, MD 1.9 ml/min, p<0.0001; 3 years eGFR MD 0.5 ml/min, p=0.0016). BEL appears more effective at one year and three years for BEL+MMF vs CSA+MMF (1 year, eGFR WMD 7.83 ml/min, 95%CI 1.57 to 4.10, I^2 73.6%; 3 years WMD 16.08 ml/min, 95%CI 5.59 to 26.56, I^2 89.5%) however, heterogeneity across studies is substantial. Where there are two comparisons involving SRL and CSA, the regimen including MMF suggests CSA to be more beneficial up to five years (5 years, eGFR WMD 9.10 ml/min, 95%CI 1.68 to 16.52), yet in contrast, the regimen including AZA suggests SRL to be more effective (1 year, eGFR MD 10.8 ml/min, p<0.0001).

Time to BPAR is generally poorly reported and therefore it is challenging to form a conclusion. Again, TAC+AZA vs CSA+AZA shows conflicting results for two studies, however, the statistically significant result in one of the two studies suggests that BPAR occurs more quickly for participants receiving TAC rather than CSA (MD 24 days, p=0.0033). This is also true for TAC+MMF vs CSA+MMF (MD 46.7 days, p<0.0001). Where SRL+TAC and MMF+TAC are compared, a reduced time to BPAR is seen for MMF (MD 48.6 days, p=0.0017). For SRL+MMF vs CSA+MMF, one of three studies demonstrates a statistically

significant difference in favour of CSA (MD 38 days, p=0.0035), however, the other two studies show no difference.

BPAR severity. For TAC+AZA vs CSA+AZA, there are lower odds of the more severe BPAR for the arm containing TAC, although there is substantial heterogeneity across studies (Banff 3 OR 0.28, 95%CI 0.12 to 0.66). Similarly, for TAC+MMF vs TAC PR+MMF, TAC has a lower proportion of people experiencing the more severe BPAR of Banff 3 (OR 0.11, 95%CI 0.01 to 0.87, I^2 0.0%).

Following **network meta-analysis** for **induction therapy**, there is no evidence to suggest BAS or ATG are more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality. ATG and BAS were both estimated to be more effective than placebo/no induction, with ATG being more effective than BAS at reducing BPAR. There is evidence to suggest that BAS is more effective than placebo/no induction at achieving better graft function.

With regard to **maintenance therapy**, the network meta-analysis showed none of the maintenance regimens performed consistently well on all four outcomes and a great deal of heterogeneity was noted:

- No evidence was found to suggest that one treatment was any more effective at reducing the odds of graft loss than any other treatment.

- There is evidence to suggest that BEL+MMF is more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF, but no other treatments are estimated to be any more effective at reducing mortality than any other treatment.

- MMF+CSA, TAC+MMF and SRL+TAC are estimated to be more effective than CSA+AZA and EVL+MPS at reducing the odds of BPAR. In addition,TAC+AZA and EVL+CSA are also estimated to be more effective than and CSA+AZAat reducing the odds of BPAR. However, apart from CSA+AZA and EVL+MPS performing poorly in some comparisons, it is difficult to say that any one treatment is more effective at reducing BPAR than another as the 95% CIs are very wide.

- Similarly, a number of treatments TAC+AZA, TAC+MMF and BEL+MMF, are estimated to be more effective than CSA+AZA and MMF+CSA at increasing graft function. In addition, SRL+AZA is estimated to be more effective than CSA+AZA at increasing graft function. However, due to the limited direct evidence informing many

of the comparisons and the 95% CIs being very wide, we can only conclude that CSA+AZA and MMF+CSA are performing poorly in some comparisons.

Overall, we found that despite the volume of evidence, there is little impact on effectiveness conclusions from the head-to-head comparisons, particularly for graft loss and mortality. However, this may be a reflection of the lack of long term data since very few studies reported all outcomes beyond one year, and also the frequently substantial level of heterogeneity across studies. Furthermore, the quality of trials was variable and, due to reporting omissions, it was difficult to make a general assessment regarding quality.

1.5. Cost-effectiveness results

1.5.1. Review of cost-effectiveness evidence

There is limited evidence on costs and benefits of induction regimens, as studies are typically economic evaluations conducted alongside single-centre randomised controlled trials of one year duration or less, involving small samples and reporting insufficient data in order to evaluate their generalisability.

- Studies of initial and maintenance immunosuppression are all sponsored by the industry or conducted by a person affiliated to them (except for the analysis by the Birmingham TAG that reviewed the evidence on behalf of NICE during the previous appraisal on the topic)

- Studies of initial and maintenance immunosuppression typically use a biomarker as a surrogate to extrapolate outcomes from randomised controlled trials of 1-3 year duration to the long term (i.e. 10 to 50 years after initial transplantation)

- Since the previous NICE appraisal, the main development in economic evaluation modelling of immunosuppressive regimens is the use of renal function as a surrogate outcome in addition to acute rejection for extrapolating trial efficacy outcomes to long term graft and patient survival

- In addition, new evidence has emerged that changes in renal function directly impact on current health related quality of life and costs and this is now recognised by the more recently published models

- In the UK, however, only one study of initial and maintenance immunosuppression has accounted for these methodological developments but it suffers from a lack of a

systematic approach to evidence synthesis on the efficacy of relevant UK treatments in routine use.

- Evidence from other countries is of questionable generalizability due to inadequate reporting or the regimens being compared
- A new study would fill a gap the evidence base required to inform NHS decision making by adopting a systematic approach to evidence synthesis on all relevant comparators, from an independent standpoint and incorporating the latest methodological developments and evidence on the topic.

1.5.2. PenTAG economic model

1.5.2.1. Base case analysis

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

- Basiliximab (BAS)
- Immediate-release tacrolimus (TAC)
- Mycophenolate mofetil (MMF)

Relevant ICERs do not exist 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+MMF was predicted to be cost-effective at £20,000 and £30,000 per QALY.

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

- No induction (three comparisons): Dominated in deterministic and probabilistic analyses
- Rabbit ATG (three comparisons): Deterministic ICERs £133,000–£369,000 per QALY; Probabilistic ICERs £200,000–£1,185,000 per QALY

- Ciclosporin (four comparisons): Deterministic ICERs £161,000–£256,000 per QALY (three comparisons) or dominated (one comparison); Probabilistic ICERs £204,000–£384,000 per QALY (three comparisons) or dominated (one comparison)
- Prolonged-release tacrolimus (one comparison): Dominated in deterministic and probabilistic analyses
- Azathioprine (four comparisons): Dominated in deterministic and probabilistic analyses
- Mycophenolate sodium (one comparison): Deterministic ICER £145,000 per QALY; Dominated in probabilistic analysis
- Sirolimus (two comparisons): Dominated in deterministic and probabilistic analyses
- Everolimus (one comparison): Deterministic ICER £1,744,000 per QALY; Probabilistic ICER £5,425,000 per QALY
- Belatacept (one comparison): Deterministic ICER £519,000 per QALY; Probabilistic ICER £546,000 per QALY

1.5.2.2. Scenario analyses

In a scenario analysis investigating the impact of structural uncertainty in the surrogate effect of acute rejection, NODAT and graft function at 12 months on graft survival it was found that if the surrogate effect was weakened (by limiting its duration), no induction and ciclosporin became cost-effective at £20,000 and £30,000 per QALY versus basiliximab induction and immediate-release tacrolimus, respectively. The duration of surrogate effect had to be limited to one year for no induction to be cost-effective versus basiliximab at £20,000 per QALY and eliminated entirely to be cost-effective at £30,000 per QALY. The duration of surrogate effect had to be limited to 3–8 years or less (depending on the comparison) for ciclosporin to be cost-effective versus immediate-relase tacrolimus at £20,000 or £30,000 per QALY.

A second structural uncertainty analysis considered the possibility that calcineurin inhibitor-free regimens could result in prolonged graft survival by avoiding the nephrotoxic effects of calcineurin inhibitors. The graft survival for the sirolimus-containing regimen BAS+SRL+MMF had to be markedly different to the base case for sirolimus to become cost-effective at £20,000 or £30,000 per QALY and the belatacept-containing regimen BAS+BEL+MMF was not cost-effective at £20,000 or £30,000 per QALY at any point in the analysis.

When list prices were adopted instead of average NHS acquisition costs for drug acquisition costs, ciclosporin and azathioprine became cost-effective at £20,000 to £30,000 per QALY in some combinations (when ciclosporin was used in combination with mycophenolate mofetil and when azathioprine was used in combination with tacrolimus) with immediate-release tacrolimus and mycophenolate mofetil remaining cost-effective at £20,000 to £30,000 per QALY in other comparisons.

Belatacept was not found to be cost-effective at £20,000 to £30,000 per QALY even at zero price, or at list price with zero administration cost.

1.5.3. PenTAG and the companies' model-based analyses compared

We compared the main deterministic analyses from three of the company submissions with those produced by the independent Assessment Group (PenTAG). These assessed the cost-effectiveness of: prolonged-release tacrolimus versus immediate-release tacrolimus (Astellas), everolimus (Novartis), enteric-coated mycophenolate sodium (Novartis) and belatacept (BMS). While some of the PenTAG analyses contained a larger set of comparator treatments, they were generally comparable after dominated comparators were excluded from the PenTAG analyses.

Overall, the PenTAG analyses of cost-effectiveness were considerably less favourable than the company analyses of their own products. This could mostly be attributed to: the company analyses basing their effectiveness assumptions on the results of specific RCTs (rather than meta-analysis), combined with using different surrogate endpoints and/or US cohort data to extrapolate long-term outcomes such as graft survival.

The economic modelling by PenTAG tended to include fuller costing of the administration of the maintenance therapies, and more realistic relatively lower annual costs of dialysis (except Novartis). Also, the utility difference between living with a functioning graft and living on dialysis was generally greater in the three company's analyses (typical difference of between ~0.25 to ~0.3) than in the PenTAG model (~0.2 difference). Overall, these differences in the company's models will tend to magnify the impact on QALYs of any incremental effectiveness differences which affect long-term graft survival, and also reduce their associated incremental cost.

1.6. Discussion

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

The strengths of this systematic review are that is was conducted by an independent research team using the latest evidence.

There are a number of limitations:

- Due to level of reporting detail, we were unable to perform subgroup analysis according to donor or HLA matching.
- Study design and participant characteristics varied widely across studies, leading to substantial heterogeneity
- The 89 included RCTs were of variable quality, but all appear to be flawed. However, due to reporting omissions, for most of the trials it was difficult to make a general assessment regarding quality. The quality appraisal should, therefore, be noted with caution.
- Very few trials reported longer term follow up, with the majority reporting data at one year.

1.6.2. Strengths and limitations of the analyses and uncertainties

1.6.2.1. PenTAG economic model

Key strengths:

- Conducted by an independent academic group and comparing all interventions listed in the scope and relevant comparators within scope;
- Adherent to the NICE reference case where possible, and in particular including expected NHS acquisition costs where these could be estimated rather than list prices;
- Baseline natural history predominantly based on UK data and effectiveness estimates based on a high quality systematic review of clinical effectiveness evidence and subsequent network meta-analyses.

Key limitations:

- Inconsistent reporting of adverse events in identified RCTs meant that only a minority of adverse events were modelled: NODAT, CMV infection, dyslipidaemia and anaemia. Anaemia was assumed not to vary between regimens. Induction agents were assumed not to affect the incidence of adverse events. Significant adverse events not included were malignancy, post-transplant lymphoproliferative disorder and non-CMV infections.

- The severity of acute rejections was assumed to be the same across regimens. Different severity profiles would be expected to affect cost-effectiveness.

- Treatment discontinuation and switching were not modelled; discontinuation of corticosteroids may be a goal of long-term maintenance and patients may be switched between maintenance agents in the event of efficacy failure or adverse events.

Key areas of uncertainty:

- Long-term outcomes from RCTs are seldom reported so it has not been possible to externally validate the predicted survival differences between regimens.

- RCTs identified in the systematic review have not provided sufficient evidence to support subgroup analyses.

- The costs for diabetes are highly uncertain, especially as the costs relate to the general diabetic population rather than transplant recipients with NODAT.

- 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).

1.6.3. Generalisability of the findings

1.6.3.1. PenTAG economic model

The PenTAG economic model adheres to the NICE reference case where possible and is expected to generalise well to the NHS in England and Wales. Costs in the model are all from recent UK sources. Baselines of key drivers of health effects (graft survival, death with functioning graft, mortality following graft loss) are estimated from UK sources. Relative

effectiveness estimates will include non-UK studies but there is little to suggest that these would result in a biased estimate of relative effectiveness in England and Wales.

The model should be generalisable to additional interventions if these are to be considered in the future.

While some aspects of the PenTAG economic model would be expected to generalise to health care systems in other countries it is unlikely that cost-effectiveness results can be directly generalised without reparameterisation of the model.

1.7. Conclusions

The systematic review and meta-analyses of the clinical effectiveness of the two induction agents found both ATG and BAS were more effective than placebo/no induction at reducing BPAR, with ATG being more effective than BAS. However, the review found no evidence to suggest either BAS or ATG were more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality.

Overall, the systematic review and meta-analyses of the clinical effectiveness of the maintenance agents found that none of the maintenance regimens were consistently better on all four outcomes: mortality, graft loss, graft function and BPAR. However, for a number of pair-wise comparisons of different regimens, the one containing TAC had lower odds of BPAR and reduced loss of graft function than the other regimen.

The cost-effectiveness analyses suggest that only a regimen of basiliximab induction followed by maintenance with immediate-release tacrolimus and mycophenolate mofetil would be cost-effective at £20,000 to £30,000 per QALY.

1.7.1. Implications for service provision

The immunosuppressive regimen of basiliximab induction followed by maintenance with immediate-release tacrolimus, mycophenolate mofetil (with or without corticosteroids) is in common usage within most of the NHS at present.

If only these interventions were to be recommended then there would probably be little implication for service provision.

1.7.2. Suggested research priorities

New research in the following areas could reduce the uncertainty noted:

- Good quality longer term RCTs to include HRQoL as an outcome and sufficiently powered for subgroup analysis by sex, donor type, and HLA matching
- Improved reporting of trials would be beneficial, in particular, reporting of randomization methods and withdrawal, drop-outs and loss to follow-up

2. Background

2.1. Description of the health problem

2.1.1. End stage renal disease

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. ESRD 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. Chronic kidney disease is common, frequently unrecognised and often exists together with other conditions (for example, cardiovascular disease and diabetes). An estimated 4% of people in the UK with CKD progress to ESRD over a 5.5 year follow-up period.[1]

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.[2]

2.1.1.1. Transplantation: patient survival, acute rejection and graft loss

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 donors 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)). Most kidneys are primarily obtained from DBD donors, with the donor pool being extended by using DCD donors, and extended criteria donors (ECD; people who are over the age of 60 without co-morbidities, over the age of 50 years with hypertension or death from cerebrovascular accident, or donors with terminal serum creatinine >1.5 mg/dL).

Following kidney transplantation, major clinical concerns are acute kidney rejection and graft loss. Acute kidney rejection occurs when the immune response of the host attempts to destroy the graft as the graft is deemed foreign tissue. [2] Following renal transplantation, immunosuppressive therapy is implemented to reduce the risk of kidney rejection and prolong survival of the graft.

2.1.2. Aetiology, pathology and prognosis

2.1.2.1. Renal disease

Most diseases that cause renal failure fall into five categories: systemic disease, glomerulonephritis, hypertension, obstruction and genetic disease (Table 1) with diabetes mellitus causing around 20% of all renal disease.[3]

Table 1. Renal disease aetiology

Category	Description
Systemic disease	Diabetes mellitus, auto-immune conditions (e.g. systemic lupus erythematous and vasculitis), amyloidosis and multiple myeloma
Glomerulonephritis	There are many different causes of glomerulonephritis. Some types are relatively benign and unlikely to progress to established renal failure; other forms are more aggressive and can have an impact on disease progression and the development of established renal failure.
Hypertension	Accelerated hypertension causes chronic kidney disease, however early recognition and treatment of high blood pressure can have a positive effect on the disease. Hypertension is a common cause of renal failure in people of African origin.
Obstruction	Any pathology that obstructs the free flow of urine through the urinary system can cause chronic kidney disease. Most often obstruction is secondary to enlargement of the prostate gland in elderly men, but other causes include kidney stones, bladder tumours, and congenital abnormalities of the renal tract.
Genetic disease	Genetic disease accounts for about 8% of all kidney failure in the UK. Polycystic kidney disease is the most common genetic disease causing chronic kidney disease.

Source: UK Renal Registry 16th Annual Report[3]

When established renal failure is reached people become tired, nauseated, lose their appetite and cope less well both physically and mentally. The signs of established renal failure include fluid retention (shown as swollen ankles or breathlessness), itching, pallor and raised blood pressure. These symptoms are accompanied by falling haemoglobin levels and abnormality of biochemical markers e.g. serum urea, serum creatinine and potassium. When someone reaches this point they will need RRT within weeks or months to prevent death. Treatment will continue for the rest of their lives.

2.1.2.2. Survival, acute rejection and graft loss following transplantation

Various factors may influence patient survival following kidney transplantation (including factors related to the donor and to the patient). For example, the type of donor can influence patient survival, with recipients of a kidney transplant from an ECD having inferior survival outcomes compared with recipients of standard criteria donor kidneys. However, those from ECD will still have significantly better survival outcomes than people on waiting lists who remain on haemodialysis.[4 5]

In people who survive transplantation, acute rejection may occur when the immune response of the host attempts to destroy the graft as the graft is deemed foreign tissue.[2] Acute rejection is treated using changes to 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.[2] Acute rejection is primarily measured following a biopsy and graded according to Banff criteria (grade I to III). The gradings are as follows: Banff grade I moderate to severe mononuclear cell interstitial infiltrate and moderate tubulitis, grade II severe tubulitis and/or intimal arteritis, grade III transmural arteritis.[6] Incidences of acute rejections following a transplant are included in this appraisal; however the treatment for acute rejection is outside the scope of this appraisal.

In addition to acute rejections affecting the survival of the graft, other reasons which may facilitate graft loss include; blood clots, narrowing of an artery, fluid retention around the kidney, side effects of other medications and recurrent kidney disease (www.kidney.org). A major cause of long-term graft loss is chronic allograft nephropathy, an ill-defined process characterised clinically by progressive deterioration in graft function, proteinuria and hypertension and pathologically by changes on biopsy. Chronic allograft nephropathy is a consequence of immunological and non-immunological injury. Immunological factors include human leukocyte antigen (HLA) matching, episodes of acute rejection and suboptimal immunosuppression. Important non-immunological factors implicated are donor organ characteristics, delayed graft function, recipient related factors, hypertension and hyperlipidaemia. Recently the acute and chronic toxicity of calcineurin inhibitors has also been implicated.[7] People with high titres of pre-formed circulating anti-HLA antibodies, which may come about as a result of underlying illness, previous transplantation, previous pregnancy or multiple blood transfusions are at high risk of chronic rejection.[8]

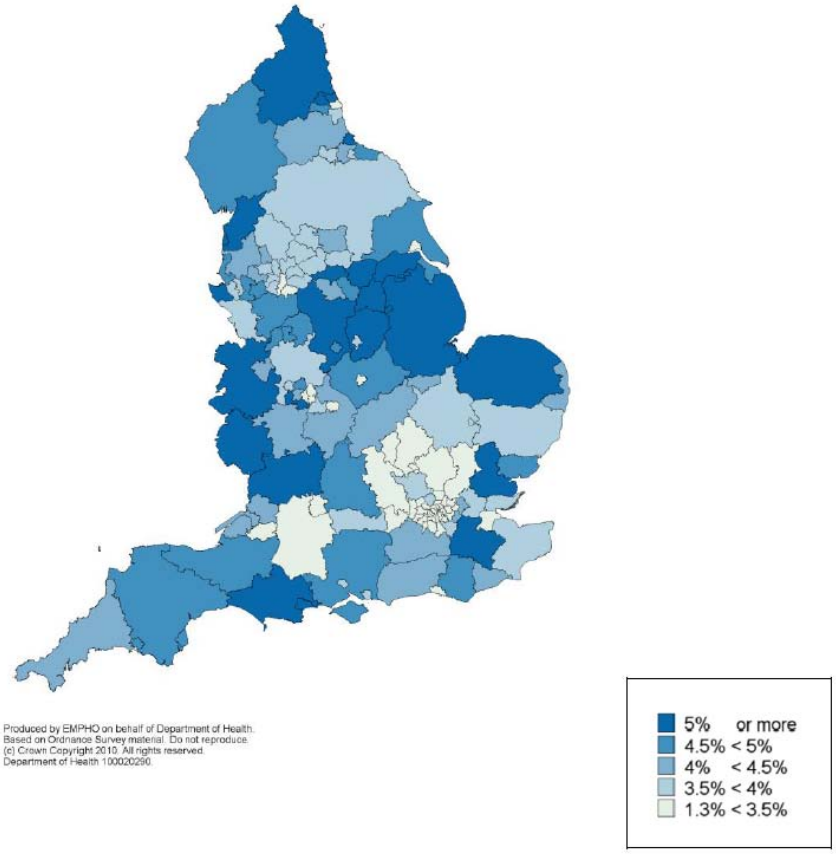
It is important to note that failing to adhere (or comply) with the immunosuppression regime prescribed following a kidney transplant will also significantly increase the risk of an acute

rejections and/or graft loss.[9] If the kidney is lost, ultimately the patient will need to return to dialysis where quality of life is lower and overall costs are higher.[2]

2.1.3. Incidence and prevalence in the UK

The most recent report by the NHS into Kidney disease stated that there were 1,739,443 people aged 18 and over in England in 2008/09 who were registered with CKD (stages 3-5). This represents an overall crude (not adjusted for age) proportion of 4.1% of the UK population in the 18 and over age group.[10] Figure 1 presents the prevalence of people who have detected and registered CKD around England in 2008/2009.[10] The actual prevalence which would include those undetected and unregistered would be much higher.

Figure 1. Chronic Kidney Disease prevalence % recorded from GP Quality and Outcomes Framework by PCT, England 2008/2009



Source: Kidney Disease: Key Facts and Figures, NHS Kidney Care, September 2010 [10]

In 2013 the incidence rate of renal replacement therapy (RRT) in the UK was stable at 109 per million population reflecting RRT initiation for 7,006 new cases per year.[3] There were

56,940 adults receiving RRT in the UK on 31st December 2013, an absolute increase of 4.0 % from 2012. Whilst the number of people with a functioning transplant increased to 7.1%. The UK adult only prevalence of RRT was 888 per million population (pmp).[3] Table 2 displays the prevalence of adults in the UK who are receiving haemodialysis (HD), peritoneal dialysis (PD) or living with a transplant split for age (over and under 65 years).

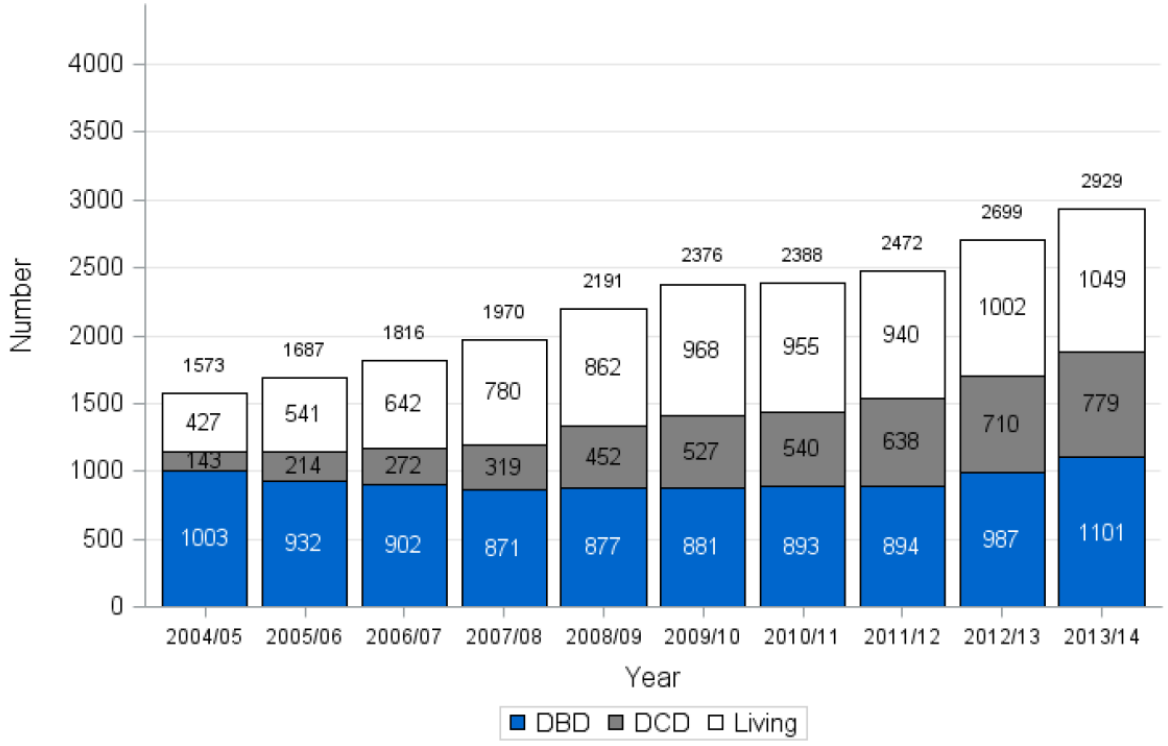
Table 2. Number of prevalent renal replacement adults by age and treatment modality, in the UK in 2013

	≤ 65 years old			≥ 65 years old		
	HD	**PD**	**Transplant**	**HD**	**PD**	**Transplant**
England	9,121	1,720	19,766	10,952	1,457	5,016
Northern Ireland	261	38	676	389	43	139
Scotland	888	115	2,050	972	111	428
Wales	430	91	1,158	648	91	359
UK	10,700	1,964	23,650	12,961	1,702	5,942

Key: HD, haemodialysis; PD, peritoneal dialysis

Between April 2013 and March 2014, 2,464 adult kidney transplant operations were performed in England, 97 in Northern Ireland, 112 in Wales and 242 in Scotland.[11] Figure 2 shows the total number of adult kidney only transplants performed in the last ten years, by type of donor. However, it should be noted that the total number of transplants for the year 2013/14 given in Figure 2 as 2,929 appears to be 14 transplants more than the total number of tranplants performed around the UK given (2,464 for England, 91 for NI, 112 for Wales and 242 for Scotland) from the same resource.[11] The number of adult transplants from donors after circulatory death (DCD) has been steadily increasing over the time period to 779 in the last financial year. The number of adult transplants from donors after brain death (DBD) has increased in the last couple of years to 1,101 in 2013/2014 after remaining fairly constant for the previous four financial years. The number of adult living kidney transplants performed has also increased over the time period and 1,049 were performed in the last financial year.[11]

Figure 2. Kidney transplant rates in the UK



Key: DBD, donation after brain death; DCD, donation after cardiac death; living, living donor.
Source: Annual Report on Kidney Transplantation Report for 2013/2014, NHS Blood and Transplant[11]

The NHS Blood and Transplant Annual Report on Kidney Transplantation reported kidney and patient survival following a kidney transplant over one and five years split for deceased and living donors (Table 3).

Table 3. Kidney and patient survival 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 (93-94)	86 (85-87)	96 (95-96)	89 (88-90)
Living Donors	97 (96-97)	91 (89-92)	99 (98-99)	95 (95-96)

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 Report for 2013/2014, NHS Blood and Transplant[11]

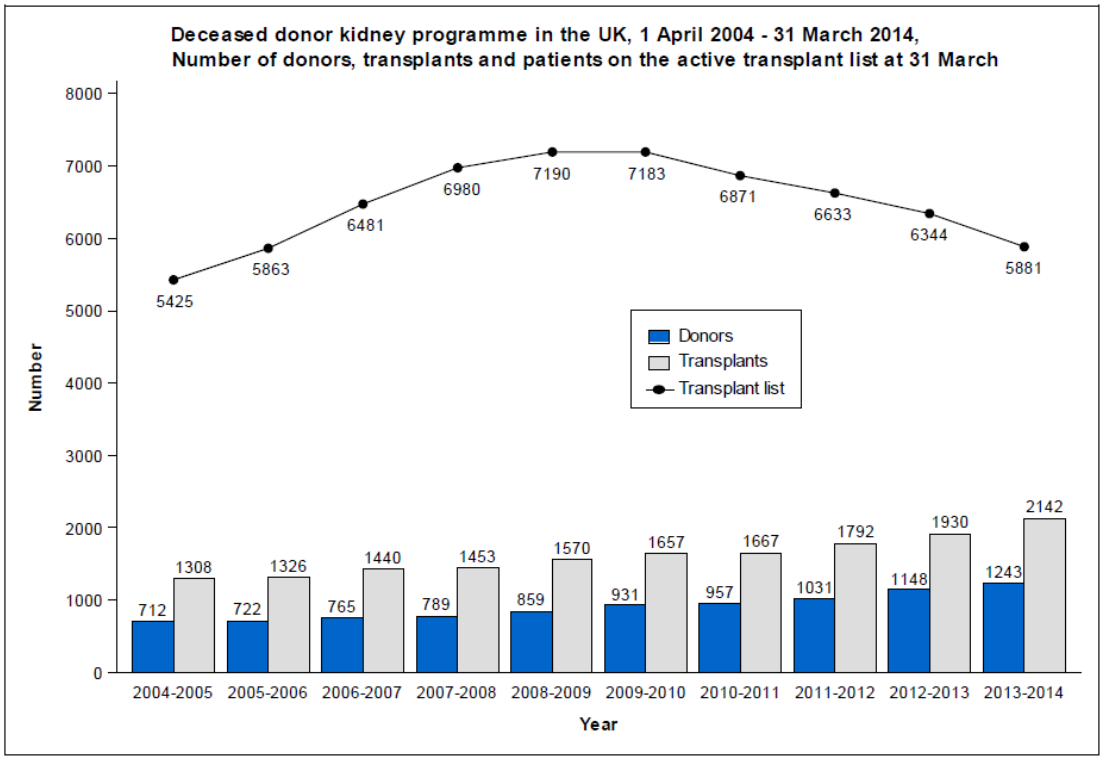
Acute rejection following a kidney transplant is likely to be reported in approximately a third of recipients (www.kidney.org). However, the incidences are variable depending on both patient and donor characteristics as well as the immunosuppression regime allocated.

2.1.4. Impact of health problem

2.1.4.1. Significance for patients

To a person suffering from end-stage renal disease the opportunity to have a kidney transplant is literally a matter of life or death. In the year 2013-2014, in the UK, 239 people died while on the active and suspended waiting lists for kidney transplantation; 518 people were removed from the list because they were no longer fit enough, most of whom would go on to die.[12] Encouragingly, over the last 5 years there has been a decline in the number of people waiting for a kidney transplant (Figure 3). This decline has primarily been attributed to an increase in the number of transplants being performed each year, as the number of people joining the list each year has remained relatively stable.[12] Although this is encouraging, figures from people registered between April 2007 – March 2011 indicated that the median wait time for a kidney only transplant in the UK was over 3 years (1,114 days) with a 95 % CI of 1,091-1,137.[13]

Figure 3. Number of donors, transplants and people on the active transplant list from 2004 to 31 March 2014



Source: Organ Donation and Transplantation Activity Report 2013/2014, NHS Blood and Transplant[12]

Whilst kidney transplantation relieves the person with ESRD from lengthy dialysis, the strict regimen of immunosuppressant medication required may produce unpleasant side effects, including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain.[14] Nevertheless, a large number of studies have similarly documented, using a variety of instruments, the clear quality of life improvements of having a functioning kidney transplant compared with being on dialysis.[15-27] Overbeck et al. 2005, for example, compared the quality of life of those who had received a kidney transplant with those dialysing and on the waiting list, they found that, when measured with the SF-36, people who had received a transplant reported better physical functioning, perception of general health, social functioning and overall physical component than those still dialysing, although these scores did not match those of the general population.[26] See Table 4 below.

Table 4. SF-36 mean scores comparing the quality of life of those on dialysis or transplanted with the general population

	Physical functioning	Bodily pain	General health	Social functioning	Physical well-being summary
	($p \leq 0.001$)	($p = 0.062$)	($p \leq 0.01$)	($p \leq 0.01$)	($p \leq 0.001$)
Dialysis (n = 65)	62.7	62.8	39.7	71.0	38.9
Transplant (n = 76)	77.0	73.5	51.0	83.9	45.6
General Population	84.8	77.7	68.5	89.0	50.2

Source: Overbeck et al. 2005.[26]

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 unpleasant side-effects. The treatment for actue rejection is outside the scope of this appraisial. Should a graft be lost, people face another wait for transplantation (if appropriate) and need to undergo dialysis whilst waiting for transplantation or need to undergo dialysis for life where transplantation is not possible. This, in effect, means that people are back to where they started with their treatment, but with the added psychological and physical burden from having undergone transplantation. Indeed, many people will develop depression following the loss of a graft. [28]

The impact on people of returning to dialysis (with regards psychological burden of graft failure and going back to a previous treatment modality) is scarcely documented, but necessarily includes the impact of being on dialysis per se: dialysis is time-consuming and may affect employment, education, normal family life and require changes in diet and fluid intake. Common side effects to dialysis (either hemodialysis or peritoneal dialysis) include fatigue, low blood pressure, invasive staphloccoccal infections, muscle cramps, itchy skin, peritonitis, hernia and weight gain (www.nhs.uk). Quality of life is lower on dialysis than the general population[29] and declines over time as the patient remains on dialysis.[30]

2.1.4.2. Significance for the NHS

Treatment for ESRD has been deemed resource intensive for the NHS, since current costs have been estimated to utilise 1-2 % of the total NHS budget to treat 0.05% of the population.[10] 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 people.[31]

It is projected that with an increasingly elderly and overweight population the demand for RRT will increase, with a consequent pressure on services providing 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.[32]

Data from the NHS standard contract for Adult Kidney Transplant Service indicated that the costs for the first year of care following a kidney transplant are approximately £17,000 and then £5,000 for every subsequent year. Conversely, the costs of dialysis are approximately £30,800 per year.[33] However, should a graft be lost following a transplant, the NHS would incur increased costs from either the patient returning to dialysis or requiring a replacement renal transplant (in comparison to successful maintenance of the kidney graft). Similarly, each acute rejection episode would incur increased costs due to the changes made to the immunosuppression regimen to treat the rejection.

2.1.5. 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

- 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 (Table 5). Measuring serum creatinine concentrations is a simple method for estimating glomerular filtration rate (GFR). Estimated glomerular filtration rate (eGFR) is calculated from serum creatinine levels, age, sex and race and provides information on creatinine clearance. There are various methods used to calculate eGFR (Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault, Nankivell) although no formula has been shown to be consistently more superior to another (White et al. 2008).[34]

Table 5. GFR categories (NICE guidelines CG182).

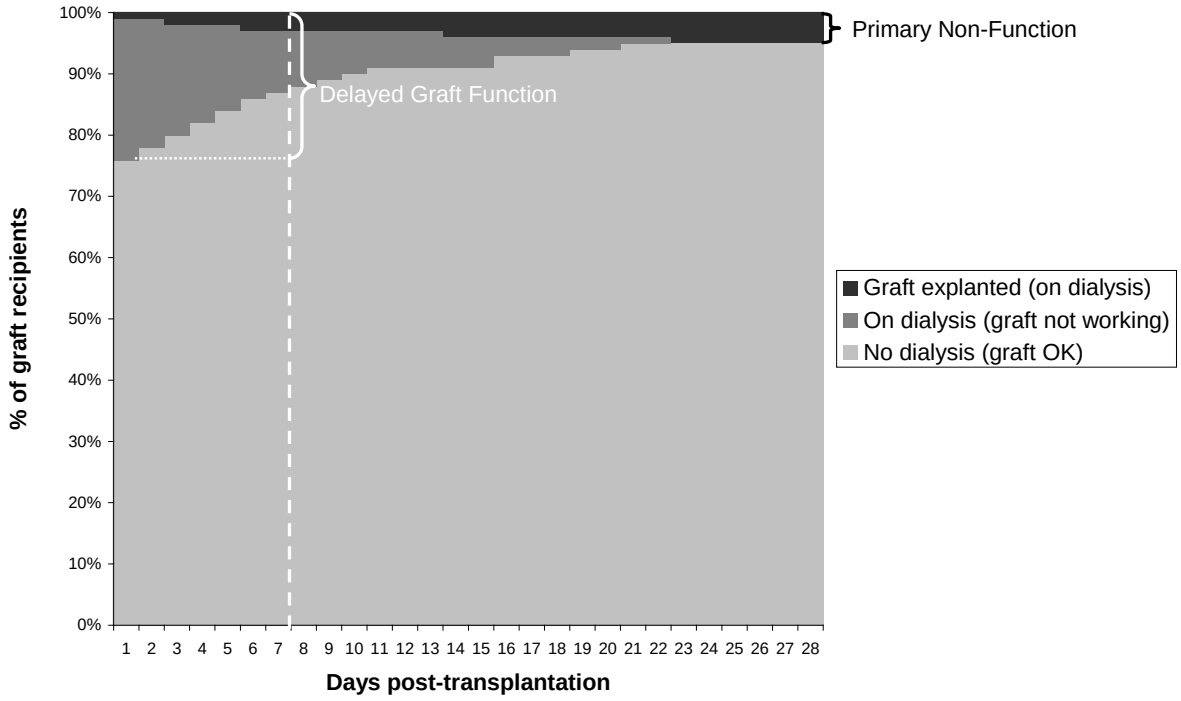
GFR category	GFR (ml/min/1.73m^2)	Terms
1	> 90	Normal or high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severely decreased
4	12-29	Severely decreased
5	<15	Kidney failure

- Rejection rates: The percentage of grafts that are rejected by the recipients' bodies, these can be acute or chronic.

- Patient survival: How long the recipient survives with the transplanted kidney
- Quality of life: How a person's well-being is affected by the transplant.

Figure 4 shows a hypothetical graph to explain the relationship between DGF and PNF. At seven days post-transplant some of the people who have needed to dialyse and whose grafts are therefore classified as DGF will in fact have grafts that never function. When this has been established these grafts are classified as PNF.

Figure 4. Hypothetical graph to explain the relationship between DGF and PNF



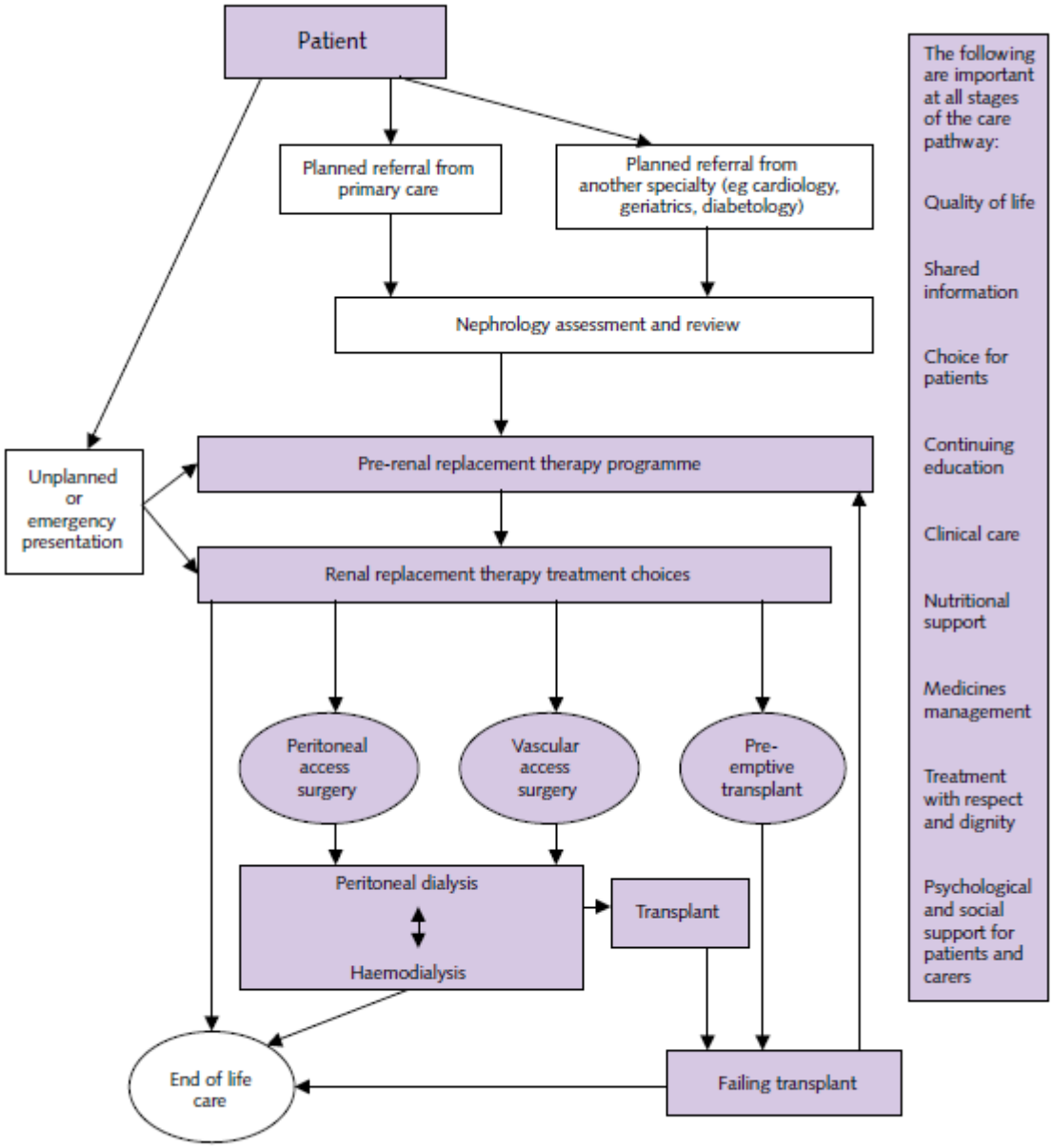
2.2. Current service provision

2.2.1. Management of disease

2.2.1.1. Management of end-stage kidney disease

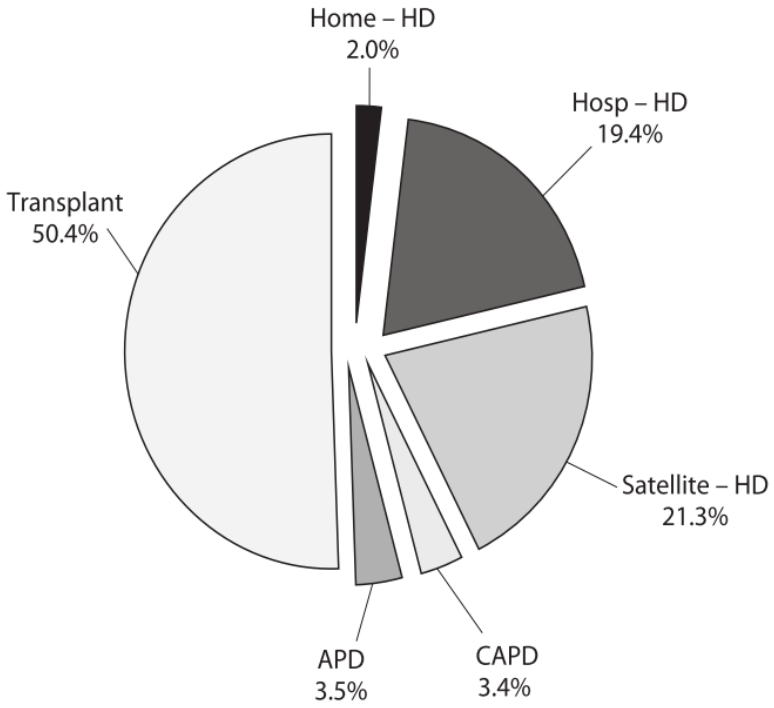
End-stage renal disease is primarily managed by RRT. The patient pathway leading to RRT for those with ESRD can be seen in Figure 5. The distribution of people on differing RRT in the UK as of 31/12/2012 is shown in Figure 6.

Figure 5. The care pathway for renal replacement therapy



Source: The National Service Framework for Renal Services – Part 1: Dialysis and Transplantation[35]

Figure 6. Treatment modality in prevalent renal replacement therapy adults on 31/12/2012 in the UK



Source: The sixteenth Annual report from the UK Renal Registry[3].
Key: HD, Haemodialysis; APD, automated peritoneal dialysis; CAPD, Continuous ambulatory peritoneal dialysis.

2.2.1.2. Management of kidney transplant

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

The first of these steps is organ procurement which includes the identification of potential donors, assessment of donor suitability, determination of donor brain death (where applicable) and medical management of the donor. The cross-matching for donor-recipient compatibility will include an assessment on HLA matching. HLA anitgens 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 2 mismatches at each loci.[11] However, it should be noted that due to improvements in immunosuppressants, the significance of HLA matching has diminished.[36]

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 immunosuppressive drugs can be divided into induction and maintenance drugs. Induction drugs are powerful antirejection drugs that are taken at the time of transplantation, and close 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.

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/or other complications. Complications fall into three categories:

1. Medical follow ups to to monitor for and treat rejections, nephrotoxicity of calcineruin inhibitors and recurrence of the native kidney diseases

2. 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

3. Other complications include, infection, malignancy, new onset of diabetes, liver disease, hypertension, cardiovascular disease

2.2.1.3. Management of graft loss

As the kidney loses its function, many of the physiological changes that occur mimic those seen with progressive renal diseases from other aetiologies. 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.[28]

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. Success rates of a subsequent kidney transplant have reported equovical findings. Some report that a subsequent transplant

will generally be as good as for the first [28] whilst others report inferior graft survival for those receiving their second[37] or third[38] transplant in comparison to those receiving their first.

Management of graft loss will also include management of the psychological impact of the loss; due to an increased risk for depression following the loss of a graft, it is recommended that depressive symptoms should be actively investigated and managed according to conventional lines.[28]

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.[39] 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.

2.2.3. Variation in services

Currently, 71 adult renal centres are operating in the UK (five renal centres in Wales, five in Northern Ireland, nine in Scotland, 52 in England) offering various levels of renal care. This includes 23 adult transplant centres in the UK (one Wales, one in Northern Ireland, two in Scotland, 19 in England). There is some variation across the services provided between these 71 centres, however, information describing how the services differ is not readily available.

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 following frequency of clinic appointments is suggested for an uncomplicated patient.[40]

- 2-3 times weekly for the first month after transplantation
- 1-2 times weekly for months 2-3 after transplantation
- Every 1-2 weeks for months 4-6 after transplantation
- Every 4-6 weeks for months 6-12 after transplantation
- 3-6 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.[41]

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). People 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, all people should have the following:[40]

- 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 adults” (NICE technology appraisal guidance, TA85) have the following recommendations for induction and maintenance therapy:[42]

2.2.4.1. Induction therapy

- Basiliximab or daclizumab, used as part of a calcineurin-inhibitor-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in adults undergoing renal transplantation. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used.[42]

2.2.4.2. Maintenance therapy

- Tacrolimus is an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual people.[42]

- Mycophenolate mofetil is recommended for adults as an option as part of an immunosuppressive regimen only:

    - where there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or

    - in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor.[42]

- Sirolimus is recommended for adults as an option as part of an immunosuppressive regimen only in cases of proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitating complete withdrawal of these treatments.[42]

As a consequence of following this guidance, some medicines may be prescribed outside the terms of their UK marketing authorisation. Clinicians prescribing these drugs should ensure that people are aware of this, and that they consent to their use in such circumstances .[42]

Since the publication of the current guidance in 2004 [42], the marketing authorisation for daclizumab has been withdrawn. Also, new technologies have received marketing

authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (belatacept, a prolonged-release formulation of tacrolimus, and an oral suspension of immediate-release tacrolimus). In addition, another new technology (everolimus) has been studied as an immunosuppressant in renal transplantation. Everolimus received UK marketing authorisation in this therapy area in November 2014.

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.

2.3.1.1. 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 the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adults. The summary of product characteristics states it is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in people 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. Higher panel reactive antibody scores indicate higher immunological risk. Basiliximab is administered intravenously.

Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline® [Sanofi]) is a gamma immune globulin, generated by immunising rabbits with human thymocytes. 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, and is administered intravenously.

2.3.1.2. Maintenance therapy

Tacrolimus is a calcineurin inhibitor. It is available in a prolonged-release formulation (Advagraf® [Astellas Pharma]) and immediate-release formulations (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]). All of these formulations have UK marketing authorisations for the prophylaxis of transplant rejection in adults undergoing kidney transplantation, and all are administered orally. Prograf can also be administered intravenously. The Commission on Human Medicines advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only.

Belatacept (Nulojix® [Bristol-Myers Squibb]) is a soluble fusion protein 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 is added to this belatacept-based regimen. Belatacept is administered intravenously.

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).

Mycophenolate sodium. MMF is also available as an enteric-coated formulation mycophenolate sodium (MPS) (Myfortic®, [Novartis Pharmaceuticals]).

Mycophenolate mofetil and mycophenolate sodium have UK marketing authorisations for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. Both drugs can be administered orally; mycophenolate mofetil can also be administered intravenously.

Sirolimus (Rapamune® [Pfizer]) is a non-calcineurin inhibiting immunosuppressant and acts as an antiproliferative. It has a UK marketing authorisation for the prophylaxis of organ rejection in adults at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2 to 3 months. It may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued. It is administered orally.

Everolimus (Certican ® [Novartis Pharmaceuticals]) is a proliferation signal inhibitor and is an analogue of sirolimus. Everolimus has recently (November 2014) received UK marketing

authorisation for immunosuppressive treatment in kidney transplantation. It has been studied in clinical trials in numerous regimens containing one or more additional immunosuppressant (including ciclosporin, tacrolimus, anti-thymocyte immunoglobulin, mycophenolate, corticosteroids and basiliximab), and compared with various alternative immunosuppressive regimens, in adults undergoing kidney transplantation. Everolimus is administered orally.

2.3.2. Important prognostic factors

A number of important factors have been identified which may influence both patient and graft survival.

- Age – both the age of the recipient and the age of the donor will influence the survival of the transplant. Graft survival decreases as the age of the recipient or the donor increases[43]

- Sex – women have a better graft survival rate than men, whereas men have better patient survival than women[43]

- Recipient ethnicity – Black people have worse graft function, shorter graft survival and higher rates of chronic allograft nephropathy when compared with White people[43]

- Waiting time to transplant – the longer a patient is on dialysis waiting for a kidney transplant, the poorer their outcomes post transplantation[44]

- Cold Ischaemia Time – the shorter this time (20 hrs or under), the better the immediate and long term outcomes[11]

- Donor Type – adults receiving donated kidneys from live donors have a better outcome than those receiving kidneys from deceased donors[43]. Similarly, people 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 parients receiving a standard donated kidney[45].

- 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[43]

- 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[46].

There is also evidence to suggest that African Americans people will require a higher dose of tacrolimus [47], MMF[48] and sirolimus[49] to achieve the target levels when compared to White people. However, how the prescription of the immunosuppression regime offered in the UK differs between subgroups is not readily available.

2.3.3. Current usage in the NHS

Although the combination of tacrolimus + mycophenolate (MMF or Myfortic) + prednisolone is widely used, immunosuppressive regimens tend to vary according to renal centre (thus the use of the drugs under consideration varies across centres). Some examples of immunosuppressive regimens in the UK are given below in Table 6 but this is by no means exhaustive as there are so many possible combinations of treatments.

Table 6. Current immunosupression prescriptions used in UK hospitals

Hospital	Treatment
Royal Devon & Exeter Hospital, Exeter[a]	Variable baseline immunosuppression depending on transplant centre. Typically, all kidney alone transplant patients should have basiliximab on days 1 and 4 in the transplant centre. Everyone will receive a combination of prednisolone, calcineurin inhibitor (either ciclosporine or tacrolimus) and/or antiproliferative agent (either azathioprine or mycophenolate). As an alternative people may be offered an mTOR inhibitor (either sirolimus or everolimus).
Derriford Hospital, Plymouth[a]	'Symphony study' regimen using triple therapy irrespective of immunological risk or delayed graft function risk with: tacrolimus; mycophenolate mofetil or mycopehnolate sodium and a reducing course of prednisolone
Nottingham University Hospitals NHS Trust[50]	Standard immunological risk: Basiliximab induction therapy. Tacrolimus azathioprine and prednisolone maintenance therapy
Oxford transplant centre[51]	Recipients receive alemtuzumab induction. Maintenance immunosuppression is steroid free with prolonged release tacrolimus and mycophenolate mofetil or mycophenolate sodium.
Royal Infirmary of Edinburgh[52]	Methyl Prednisolone 500 mg IV just prior to releasing clamps and again at 24 hours Standard immunosuppression is tacrolimus led triple therapy with prednisolone and azathioprine

Notes:alemtuzumab is outside the scope of the present technology appraisal.

Source: [a]Direct communication with clinical experts

2.3.4. Anticipated costs associated with the interventions

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.

Table 7. Indicative cost per week for different immunosuppressive agents

Compound	Unit cost	Estimated weekly dosage for 70 kg patient	Estimated weekly cost for 70 kg patient
Ciclosporin	Hospital pharmacy: 1.65p per mg[1] Community pharmacy: 2.55p per mg[2]	4 mg/kg per day[2] = 1,960 mg	Hospital pharmacy: £32.28 Community pharmacy: £49.95
Immediate-release tacrolimus	Hospital pharmacy: 52.0p per mg[1] Community pharmacy: 118.6p per mg[2,3]	0.2 mg/kg per day[5] = 98 mg	Hospital pharmacy: £50.98 Community pharmacy: £116.26
Prolonged-release tacrolimus	106.8p per mg[2]	0.2 mg/kg per day[5] = 98 mg	£52.31
Azathioprine	Hospital pharmacy: 0.1p per mg[1] Community pharmacy: 0.1p per mg[3]	1.75 mg/kg per day[2] = 858 mg	Hospital pharmacy: £0.92 Community pharmacy: £0.98
Mycophenolate mofetil	Hospital pharmacy: 37.7p per g[1] Community pharmacy: 40.4p per g[3]	2 g per day[2] = 14 g	Hospital pharmacy: £5.28 Community pharmacy: £5.66
Mycophenolate sodium	0.5p per mg[2]	1,440 mg per day[2] = 705,600 mg	£45.14
Sirolimus	288.3p per mg[2,3]	2 mg per day[2] = 14 mg	£40.36
Everolimus	990.0p per mg[4]	2 mg per day[4] = 14 mg	£138.60
Belatacept	141.8p per mg[2]	5 mg/kg per 4 weeks[6,7] = 125 mg	£177.25
Corticosteroids	Hospital pharmacy: 0.3p per mg[1] Community pharmacy: 0.9p per mg[3]	15 mg/day[2] = 105 mg	Hospital pharmacy: £0.35 Community pharmacy: £0.92

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).

1 Commercial Medicines Unit. Drug and pharmaceutical electronic market information (eMit), 2014

2 BNF 68

3 NHS Business Services Authority. NHS Drug Tariff for England and Wales. February 2015

4 Novartis submission

5 Kramer et al. (2010) [53]

6 BENEFIT (Vincenti 2010[54], Larsen 2010[55], Vincenti 2012[56], Rostaing 2013[57])

7 Belatacept comes in 250 mg vials, therefore dosage rounded up to 500 mg per 4 weeks

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 people 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 [58] to £320.[59] Costs are considered in greater detail in section 7.

3. Definition of the Decision Problem

3.1. Decision problem

3.1.1. Interventions

A total of nine interventions are being 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 summarised in the section 2.3.1. The maintenance treatments will be appraised as part of combination regimens where appropriate. 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 studies that used drugs outside the terms of their marketing authorisations.

3.1.2. Populations

The population being assessed is adults undergoing kidney transplantation from a living-related, living-unrelated or deceased donor. People receiving multi-organ transplants and those who have received transplants and immunosuppression previously will be excluded. Where data allows, the following subgroups will be considered: level of immunological risk (including human leukocyte antigen compatibility and blood group compatibility), people at high risk of rejection within the first 6 months, people who have had a re-transplant within 2 years, previous acute rejection, people at high risk of complications from immunosuppression (including new-onset 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 report are:

- Patient survival
- Graft survival
- Graft function (estimated glomerular filtration rate (eGFR), which is a measure of the kidney's ability to filter and remove waste products)
- Time to and incidence of acute rejection
- Severity of acute rejection
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

3.1.5. Key issues

A number of factors may influence the survival and function of a donated 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.

3.2. Overall aims and objectives of assessment

The aim of this assessment is to review and update the evidence for the clinical and cost-effectiveness of immunosuppressive therapies in adult 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 (TA85).[42] The current guidance was primarily based on research evidence presented to NICE in the assessment report by Woodroffe et al. 2005.[60] 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

The project was undertaken in accordance with a predefined protocol.There were no major departures from this protocol.

The aim was to systematically review the effectiveness of immunosuppressive therapies in adult renal transplantation and to determine the effect on patient survival, graft survival, graft function, time to and incidence of acute rejection, severity of acute rejection, the effectiveness in improving health related quality of life and the impact of adverse events.The review was undertaken following the principles published by the NHS Centre for Reviews and dissemination.[61]

4.1.1. Identification of studies

Bibliographic literature searching was conducted on April 14th 2014. The effectiveness 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 study design limit to RCTs or controlled trials). The search was date limited 2002-current in line with the previous assessment and the searches were updated on November 18th 2014. The search was not limited by language or human only studies to ensure records were not missed in error. Instead, these exclusion criteria were implemented during the screening process.

The following databases were searched for RCTs: Medline (OVID), Embase (OVID), CENTRAL (Wiley) and Web of Science (ISI – including conference proceedings). The following trials registries were hand-searched: Clinical Trails.Gov (https://clinicaltrials.gov/) and Controlled Trials (http://www.controlled-trials.com/). The search strategies (including web-searching) are recorded in Appendix 1.

A separate search was undertaken to identify systematic reviews. 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 (OVID), Embase (OVID), CDSR, DARE and HTA (The Cochrane Library via Wiley) and HMIC (OVID). The search was not limited by language and it was not limited to human only studies. The search strategies are recorded in Appendix 1.

In addition, 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/

The database search results were exported to, and de-duplicated using Endnote (X5).De-duplication was also performed using manual checking. The search strategies and the numbers retrieved for each database are detailed in Appendix 1. After the reviewers completed the screening process, the bibliographies of included papers were scrutinised for further potentially includable studies.

Studies included in the previous adult and child HTA reviews (Woodroffe et al. 2005 and Yao et al. 2006) were screened versus the inclusion criteria for the PenTAG review for includable studies. Reference lists of included guidelines, systematic reviews, and clinical trials were scrutinised for additional studies.

4.1.2. Ongoing studies

A search for ongoing trials was also undertaken. The terms used to search the ClinicalTrials.gov and Controlled Trials (ISRCTN) trial registers for the interventions are included in Appendix 1.

Trials that did not relate to immunosuppressive therapies for kidney transplantation in adults were removed by hand-sorting. Finally, duplicates, identified via their study identification numbers where possible, were removed. Searches were carried out on 19 September 2014.

4.1.3. Inclusion and exclusion criteria

4.1.3.1. Study design

Only randomised controlled trials (RCTs) were included or systematic reviews of RCTs.

4.1.3.2. Population

Adults undergoing kidney transplantation only and receiving immunosuppressive therapy were included in this review. Multi-organ transplantation, the treatment of episodes of acute rejection and individuals who have previously received a renal transplant and immunosuppression (i.e., individuals not undergoing the process of a new renal transplant) are outside the scope of this appraisal.

4.1.3.3. Interventions

Studies evaluating the use of the following immunosuppressive therapies for renal transplantation were included (further details in sections 2.3.1.1 and 2.3.1.2)

Induction therapy regimens containing:

- basiliximab (Simulect® [Novartis])
- rabbit anti-human thymocyte immunoglobulin (Thymoglobuline® [Sanofi-Aventis])

Maintenance therapy regimens containing:

- mycophenolate mofetil (non-proprietary [Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, Wockhardt] CellCept® [Roche], Arzip [Zentiva], Myfenax [TEVA UK])

- mycophenolate sodium (Myfortic® [Novartis]) - an enteric coated formulation of mycophenolic acid (Myfortic® [Novartis]).
- immediate-release tacrolimus (Adoport® [Sandoz], Prograf® [Astellas], Capexion® [Generics], Tacni® [TEVA UK], Vivadex® [Dexcel], Perixis® [Accord Healthcare], Modigraf® [Astellas])
- prolonged-release tacrolimus (Advagraf® [Astellas])
- belatacept (Nulojix® [Bristol-Myers Squibb])
- sirolimus (Rapamune® [Pfizer])
- everolimus (Certican® [Novartis])

Under an exceptional directive from the Department of Health, these interventions can be assessed outside their existing marketing authorisation (to reflect their use in clinical practice) where there was compelling evidence of safety and effectiveness.

4.1.3.4. 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.

4.1.3.5. Outcomes

Outcomes sought from the studies fell into four main categories: mortality, graft-related outcomes, adverse events data and health related quality of life outcomes. Due to the variability in evidence available and in order to ensure consistency with the modelling, measurements were restricted as follows:

- Mortality
- Graft-related outcomes:
    - Graft survival – where graft loss is defined as return to chronic dialysis, retransplant, graft removal or death,

  - Graft function – (estimated) glomerular filtration rate (eGFR), which is an estimate of actual glomerula filtration rate, using a formula involving age, weight, gender, and serum creatinine.
  - Time to and incidence of biopsy proven acute rejection
  - Severity of acute rejection according to Banff classification (Grade I, II, III).

- Adverse events (AEs):
  - cardiovascular complications,
  - malignancies,
  - diabetes,
  - infections
  - nephrotoxicity.

- Health-related quality of life (HRQoL), including data on validated quality of life measures, e.g. EQ-5D, SF-36, KTQ-25.

4.1.4. Selection of studies

Studies retrieved from the searches were selected for inclusion according to the inclusion/exclusion criteria specified in section 4.1.3. Initially, titles and abstracts returned by the search strategy were screened for inclusion independently by two researchers, with TJ-H as first reviewer and LC, MHa, MB or HC as second reviewer. Disagreements were resolved by discussion, with involvement of a third reviewer (MHa or HC). Full texts of identified studies were obtained and screened in the same way.

In addition, studies included in the reviews conducted by Woodroffe et al. 2005 and Yao et al. 2006, were screened for inclusion against the eligibility criteria for this review.

4.1.5. Data extraction strategy

Included full papers were split between five reviewers, with TJH as first reviewer (MHa, LC, MB and HC) for the purposes of data extraction using a standardised data extraction form, and checked independently by another reviewer. Discrepancies were resolved by discussion with the involvement of an additional review team member (MHa or HC) if necessary.

Information extracted and tabulated included details of the study's design and methodology, baseline characteristics of participants, and results including HRQoL and any AEs if reported.

If several publications were identified for one study, the data was extracted from the most recent publication and supplemented with information from other publications.

For studies comparing both induction and maintenance, we assigned a separate reference for each study arm with the author and publication year of the main publication and added the suffixes a; b.

4.1.6. Critical appraisal strategy

Four reviewers (TJH, MHa, MB and HC) independently assessed quality for the newly identified studies (2002 onwards) according to criteria based on CRD guidance (Table 8).[61]

Table 8. Quality assessment

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?
Completeness of trial	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

4.1.7. Methods of data synthesis

Where data permitted the results of individual studies were pooled using the methods described below for:

- Estimation of overall treatment effect
- Assessment of heterogeneity
- Subgroup analysis

- Assessment of publication bias

Due to the heterogeneity of population and study characteristics, a random-effects model was assumed for all meta-analyses. For binary data, odds ratio (OR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling. For continuous data (eGFR), mean differences were calculated if the outcome was measured on the same scale in all trials.

A narrative synthesis accompanies all included data.

4.1.8. Network meta-analysis

Network meta-analyses were undertaken within a Bayesian framework in WinBUGS (version 1.4.3). Where prior distributions were required they were intended to be vague.

For all network meta-analyses assessing the effectiveness of induction therapy, the reference treatment was no induction/placebo. For networks evaluating the effectiveness of maintenance therapy, the reference treatment was CSA+AZA. For the outcomes graft loss, mortality and BPAR fixed and random effects model having a binomial likelihood with logit link were used (see code in Appendix 6). For the outcome of graft function, models with a normal likelihood and identify link were used (see code in Appendix 6). All models account for the fact that some RCTs have more than 2-arms.[62]

Trials reporting zero events for all arms for a particular outcome were excluded from the analysis as these trials would not contribute information to the network. Where a trial had a zero event in at least one, but not all, treatment arms, 0.5 was added to all cells to allow the model to run within WinBUGS.[62]

Analyses were run with 3 chains, a burn-in of 40,000 iterations followed by an additional 100,000 iterations with thinning of every 5th iteration to help convergence. Convergence of the models was assessed by visual inspection of autocorrelation and trace plots for all monitored variables.

Fixed and random effects network meta-analyses were analysed and compared using the Deviance Information Criteria (DIC). Models with the lowest DIC were assumed to have a better fit to the data. The posterior medians and 95% credibility intervals (CrIs) are reported.

To assess inconsistency in the network, the inconsistency degrees of freedom (ICDF) were calculated (reflecting the number of independent loops in the network), and inconsistency networks (where only direct evidence for a comparison between treatments is used) were

modelled.[63] Results from the inconsistency models were compared to those from the consistency models (where direct and indirect evidence were combined) to help identify inconsistencies within the network. The model with the lowest DIC was assumed to be a better fit to the data.

The network meta-analyses that have been conducted to satisfy relevant items on the Decision Support Units Evidence Synthesis Checklist.[64]

4.2. Systematic review results

Due to the number of regimens for both the interventions and comparators, the assessment of effectiveness will be reported separately for induction and maintenance. All RCT evidence identified for each intervention is presented.

4.2.1. Identified research for induction and maintenance therapies

We screened the titles and abstracts of 5079 unique references identified by the searches, with 750 papers retrieved for detailed consideration. As highlighted in Figure 7, 619 papers were excluded, (a list of these, with reasons for their exclusion, can be found in Appendix 3). One hundred and seven studies met the inclusion criteria. At both stages, initial disagreements were easily resolved by consensus.

We then re-assessed included studies from the review conducted by Woodroffe et al. 2005 (43 studies) (TA85).[60 65] Of these, 21 studies were considered eligible for inclusion in the update review. The scope for the adult review by Woodroffe et al. 2005 differed from the final scope issued by NICE; the induction therapy originally included daclizumab (EU marketing authorization withdrawn Jan 2009) and not rATG, the maintenance therapy did not include belatacept or everolimus and treatment of acute rejection was included but is outside the scope of this appraisal. Reasons for exclusion from this review included: data only available in abstract format, population (either participants receiving multi-organ transplant or mixed population of age groups), or duplicate (studies also retrieved in the update searches).

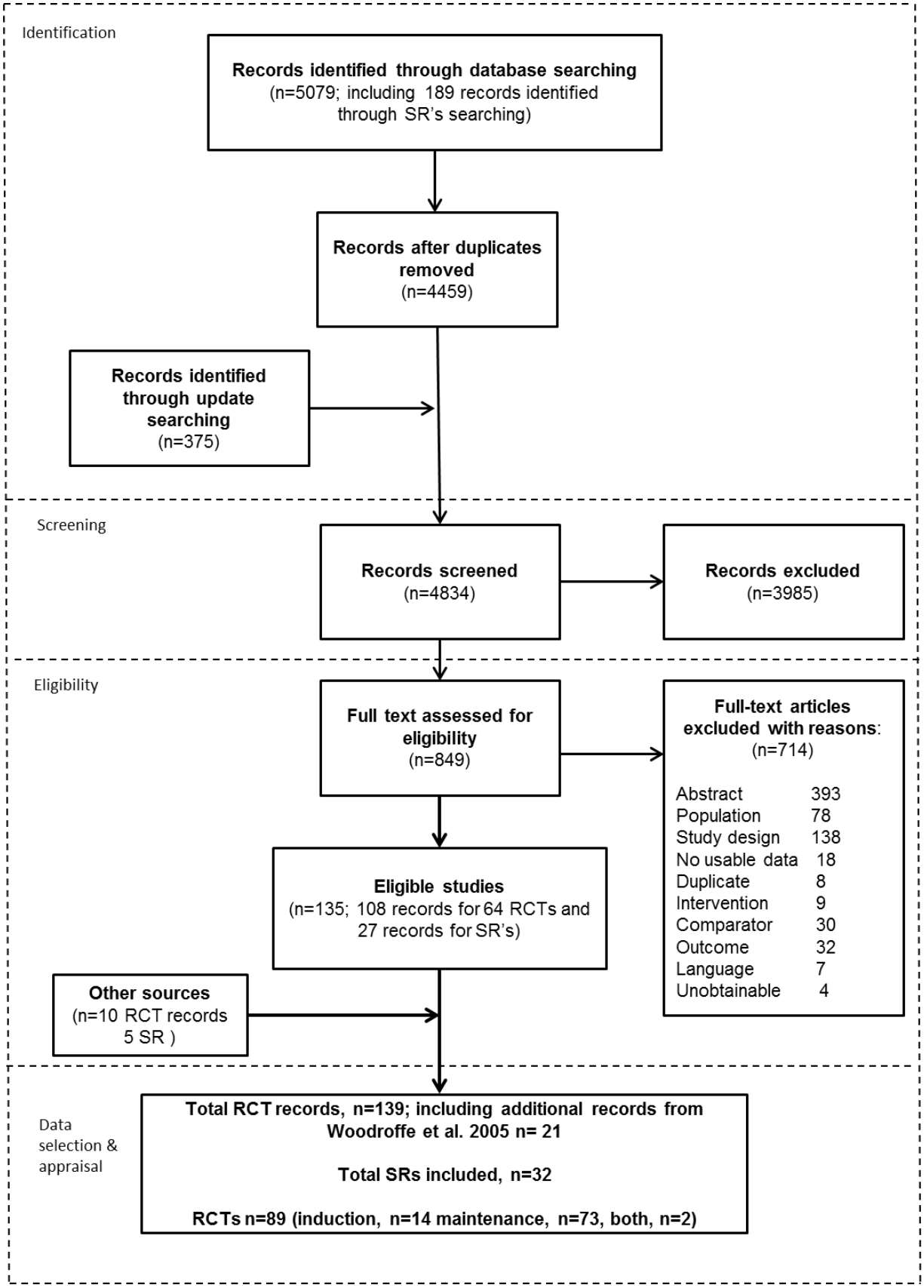
Citations of the includable systematic reviews were also searched by two reviewers (HC and MHa). This process revealed an additional 2 papers.

Update searches were conducted on 18th November 2014 using the same methodology as described earlier. Three hundred and seventy five records were screened by three reviewers (TJH, HC and MHa) with 99 records were selected for full-text retrieval. Four papers were

judged eligible on full-text appraisal. A list of these items with reasons for their exclusion can be found in Appendix 3.

The process is illustrated in detail in Figure 7.

Figure 7. Flowchart: clinical effectiveness review



Key: DX, data extraction; SRs, systematic reviews; RCTs, randomised controlled trials

4.2.2. Quality of included studies

We appraised both newly identified trials and those included in the previous HTA review. The reason for reappraising trials from the previous HTA review were twofold: first, to ensure consistency with appraisal of the newer studies, and second, because we have access to new information from papers published after the inclusion date for the previous review. Only primary studies were appraised. Secondary analyses of previously published data were not assessed. Similarly, 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). In total, 89 trials were assessed (14 induction studies, 73 maintenance studies, and two studies of both induction and maintenance treatment). Quality assessments of included trials are presented in Appendix 4. The two trials of both induction and maintenance treatment are repeated in both of these tables.

4.2.2.1. Overall assessment

The 89 included RCTs were of variable quality, but all appear to be flawed. However, due to reporting omissions, for most of the trials it was difficult to make a general assessment regarding quality. The quality appraisal should, therefore, be noted with caution. In fact, eight of the 14 induction trials, 41 of the 73 maintenance trials, and one of the two trials of both induction and maintenance either did not report, or lacked clarity on, at least five of the ten items constituting the quality appraisal assessment (see Appendix 4).

Only four induction studies (Nashan et al. 1997; Kahan et al. 1999; Ponticelli et al. 2001; Lawen et al. 2003)[66-69] and three maintenance studies (Salvadori et al. 2004; Vincenti et al. 2005; Kramer et al. 2010)[70-72] adequately addressed five or more of the ten items of the quality appraisal assessment. However, even the reports of these trials omitted important information relating to quality, with six of the seven failing to clearly describe the procedure used for allocation concealment and one failing to include an ITT analysis.

Eight of the maintenance studies (van Duijnhoven et al. 2002; Waller et al. 2002; Sollinger et al.1995; Tuncer et al. 2002; Soleimani et al. 2013; Schaefer et al. 2006; Welberry Smith et al. 2008; Vitko et al. 2006)[73-80] and two of the induction studies (Bingyi et al. 2003; Charpentier et al. 2001)[81 82] did not adequately address any of the items in the quality appraisal assessment. Further details of the quality of included studies, according to individual quality appraisal items, are described as follows.

4.2.2.2. Treatment allocation

Random allocation: The method of random allocation, including the method of sequence generation, was clearly stated and adequate in only two induction studies and 18 maintenance studies, while 68 studies (12 induction, 54 maintenance and both of the studies of induction and maintenance treatment) did not clearly specify the method used (Appendix 4). The remaining maintenance study used a minimisation technique that included a random element.

Concealment of allocation: The method of concealment of allocation was clearly reported in 13 trials (three induction studies, 9 maintenance studies, and one study of both induction and maintenance treatment). Fifty-six trials did not report any information on allocation concealment, while 20 trials provided some information pertaining to allocation concealment but lacked sufficient detail or clarity to demonstrate that allocation was adequately concealed.

4.2.2.3. Similarity of groups

Baseline characteristics: Forty-one trials (33 maintenance and eight induction studies) fully reported baseline characteristics and provided evidence, including statistical information, that treatment groups were adequately similar at baseline on a range of prognostic indicators (Appendix 4). Nine trials (eight maintenance studies and one study of both induction and maintenance) reported significant baseline between-group differences for key factors, including PRA grade, number of previous transplants, patient age, pre-transplant diabetes, HLA mismatches, and ECD donor kidneys. A further six maintenance studies were rated as ‘partial’ because they reported a baseline difference in patient sex.

The remaining trials (six induction studies, 26 maintenance studies and one study of both induction and maintenance) did not provide sufficient information for a judgement to be made about baseline similarity of groups, either by omitting to report sufficient statistical information, by reporting on a very limited range of patient baseline characteristics, or by not reporting any patient baseline characteristics.

4.2.2.4. Implementation of masking

Treatment allocation masked from participants: Eight induction studies, 47 maintenance studies and both of the studies of induction and maintenance treatment did not blind participants to treatment allocation (Appendix 3). Only two maintenance studies and four induction studies made clear that the participants were blinded to treatment allocation. A

further four maintenance studies were rated as ‘partial’ because it was reported that participants were blinded for a limited period of time only (until 24 weeks for one study and until 12 months for the other three studies). One further induction study was rated as ‘unclear’ because, despite being placebo-controlled, no further details were reported about blinding. The remaining trials (one induction study and 20 maintenance studies) did not report any information about blinding participants to treatment allocation.

Treatment allocation masked from clinicians: All of the trials that did not blind participants from treatment allocation also failed to mask treatment allocation from clinicians. An additional induction study also stated that treatment allocation was not masked from clinicians (participant blinding was not reported). Similarly, the four induction studies and two maintenance studies which reported blinding participants to treatment allocation also masked treatment allocation from clinicians. Again, four maintenance studies were rated as ‘partial’ for clinician blinding because blinded occurred for a limited time only, and one induction study was rated as ‘unclear’ because, although it was a placebo-controlled trial, no further details were reported about blinding. The other 20 maintenance studies did not report any details about clinician blinding.

Treatment allocation masked from outcome assessors: The majority of trials (52 maintenance studies, 12 induction studies, and both of the studies of induction and maintenance treatment) did not report whether outcome assessors were blind to treatment allocation. One induction study and five maintenance studies made it clear that the outcome assessors were not blinded to treatment allocation. For fifteen trials (one induction study and 14 maintenance studies) it was clear that outcome assessors were blinded for at least one outcome and a further two maintenance studies were given a ‘partial’ rating because the outcome assessors were blinded for the first 12 months of the study.

4.2.2.5. Completeness of trials

Reporting of all a priori outcomes: All trials were rated as ‘unclear’ with regards reporting of a priori outcomes (Appendix 4). This was because the trial reports failed to explicitly state whether all outcomes defined in the study protocol were reported.

Reporting of loss to follow-up, withdrawals and dropouts: 57 trials adequately reported loss to follow-up, withdrawals and dropouts (by providing numbers and reasons by treatment group). Of these, 45 were maintenance studies, 11 were induction studies, and one was a study of both induction and maintenance treatment. In 22 trials (20 maintenance studies and two induction studies) the reporting of loss to follow-up, withdrawals and dropouts was

inadequate, with key information omitted. A further four trials (one induction study, two maintenance studies, and one study of both induction and maintenance treatment) were rated as 'unclear'. For the study of both induction and maintenance this was because, despite all the relevant information being provided, the numbers did not appear to tally. For the other three trials, this was due to the fact that all participants appeared to complete the study but this was not explicitly stated. For the remaining six maintenance studies, information regarding loss to follow-up, withdrawals and dropouts was not reported.

ITT analysis: A strict definition of ITT was used (all randomised and transplanted participants). According to this definition, 49 trials (eight induction studies and 41 maintenance studies) were rated as adequately performing an ITT analysis, with 19 trials (three induction studies, 14 maintenance studies, and both studies of induction and maintenance treatment) not performing an adequate ITT analysis. In 16 cases there was a lack of clarity regarding whether an ITT analysis had been conducted (two induction studies and 14 maintenance studies) and the other five trials (one induction and four maintenance studies) did not report any relevant information regarding whether an ITT analysis had been conducted.

4.2.2.6. Applicability of trials to the NHS

Applicability to the current NHS in England: Only 11 trials (one induction study, 9 maintenance studies, and one study of both induction and maintenance) were adequately applicable to the current NHS in England (Appendix 4). The majority of trials (nine induction studies, 41 maintenance studies, and one study of both induction and maintenance) were limited in some way with regards to applicability to the current NHS in England. In all except one of these trials this was primarily due to the fact that patients, donors or organ characteristics were not representative of the current NHS in England (e.g. >90% deceased donors, or 'suboptimal transplants', or 'high risk of rejection population). In the other trial this was primarily due to a lack of statistical power.

The remaining four induction studies and 23 maintenance studies were rated as 'unclear' with regards applicability to the current NHS in England. The primary reason for this was as follows: the study lacked clarity regarding key demographic or patient/donor characteristics (two induction studies, 10 maintenance studies); the study was based on a non-EU population (two induction studies; 13 maintenance studies).

4.2.3. Study characteristics

4.2.3.1. Induction therapies

Sixteen studies were identified focusing on induction therapies. Details of study characteristics can be found in Appendix 5.

The majority of trials report outcomes up to one year, with the period of induction therapy generally continued for up to 14 days, however, this was occasionally unclear since length of treatment varied according to participant trough levels. No data for HRQoL was identified.

A follow-up of ten years is provided by Sheashaa et al. 2003 investigating BAS vs no induction, a follow-up to five years is provided by Sheashaa et al. (2008) for rATG vs no induction, Samsel et al. 2008 for rATG vs no induction and Kyllonen et al. 2007 for BAS vs rATG vs no induction.[83 84,85 86]

Overall, no new evidence has been identified for BAS vs PBO and additional data has been added to both rATG vs no induction and BAS vs no induction (Table 9). All Data for the rATG vs no induction comparison has been identified by the PenTAG search.

Table 9. Overview of included studies for induction therapies

Study id	Induction therapy	Included in TA85	Update review	n	Maintenance used
Bingyi 2003[81]	BAS vs PBO	✓ [b]		12	CSA +AZA + CCS
Kahan 1999[67]		✓		346	CSA + CCS
Lawen 2003[69]		✓[a]		123	CSA + MMF + CCS
Nashan 1997[66]		✓		380	CSA + CCS
Ponticelli 2001[68]		✓		340	CSA + Aza+ CCS.
Albano 2013[87]	BAS vs no induction		✓	1251	CSA + MMF + CCS
Sheashaa 2003[83]		✓[b]		100	CSA +AZA+ CCS
Charpentier 2001[82]	ATG vs no induction		✓	309	TAC + AZA + CCS
Samsel 2008[84]			✓	79	CSA + MMF (converted to AZA) + CCS
Sheashaa 2008[85]			✓	80	CNI + prolif + CCSen.
Charpentier 2003[88]			✓	555	TAC + AZA + CCS
Brennan 2006[89]	BAS vs rATG		✓	278	CSA + MMF + CCS
Lebranchu 2002[90]		✓ [a]		100	CSA + MMF + CCS
Mourad 2004[91]			✓	105	CSA + MMF + CCS
Sollinger 2001[92]		✓		135	CSA + MMF + CCS.
Kyllonen 2007[86]	BAS vs rATG vs no induction		✓	155	CSA + AZA + CCS

Key: (a) abstract, (b) identified in TA99[65]

4.2.3.2. Maintenance therapies

Seventy five studies were identified focusing on a combination of 30 maintenance therapy comparisons (Table 10). Details of study characteristics can be found in Appendix 5.

Outcomes are reported up to a maximum of five years, although the majority of data available is reported at one year. No data for HRQoL was identified.

Other than for the TAC+AZA vs CSA+AZA combination, the majority of data was identified by the PenTAG search.

Table 10. Studies identified for maintenance therapy

Study (multiple publications)	Maintenance therapy	Included in TA85	Update review	n
Schleibner 1995[93]	Tac + Aza vs CsA + Aza	✓		47
Laskow 1996[94] (Vincenti 1996)[95]		✓		120
Mayer 1997[96] (Mayer 2002, 1999)[97 98]		✓		448
Radermacher 1998[99]		✓		41
Jarzembowski 2005[100]			✓	35
Baboolal 2002[101]		✓		51
Campos 2002[102]		✓		166
Margreiter 2002[103] (Kramer 2005[104] & Kramer 2008[105])		✓		560
Van Duijnhoven 2002[73]		✓		23
Waller 2002[74] (Murphy 2003)[106]		✓		102
Charpentier 2003[88]			✓	555
Toz 2004[107]		✓		35
Hardinger 2005[108] (Brennan 2005)[109]			✓	200
Sollinger 1995[75]	CsA + MMF low vs CsA + AZA vs CsA + MMF	✓		499
Tricontinental MMF renal study 1996[110] (Mathew 1998,[111] Clayton 2012[112])		✓		497
Sadek 2002[113]	CsA + MMF vs CsA + AZA	✓		477
Tuncer 2002[76]		✓		76
Merville 2004[114]			✓	71
Remuzzi 2007[115] (The MYSS trial, Remuzzi 2004[116])			✓	336
Wlodarczyk 2005[117] (Wlodarczyk 2002[118])	TAC + MMF vs CsA + AZA		✓	489
Vacher-Coponat 2012[119]			✓	289
Zadrazil 2012[120]	TAC + MMF vs CsA + MMF		✓	53
Hernandez 2007[121]			✓	240
Rowshani 2006[122]			✓	126
Yang 1999[123] (Ulsh 1999[124])		✓		60

Study (multiple publications)	Maintenance therapy	Included in TA85	Update review	n
Weimer 2006[125] (Weimer 2005[126])	TAC + AZA vs CsA + AZA vs CsA + MMF		✓	81
Wlodarczyk 2009[127]	TAC + MMF vs TAC PR + MMF		✓	122
Kramer 2010[53] (NCT00189839)			✓	667
Tsuchiya 2013[128]			✓	102
Oh 2014[129]			✓	104
Albano 2013[87] (NCT00717470) OSAKA Trial	TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3		✓	1251
Ciancio 2008[130] (Ciancio 2011[131]), R01DK25243-25)	MMF + TAC vs MPS + TAC		✓	150
Salvadori 2004[132]	MMF + CsA vs MPS + CsA		✓	423
Vincenti 2005[133] (Vincenti 2010[134])	BEL low+ MMF vs BEL high + MMF vs CsA + MMF		✓	218
BENEFIT (Vincenti 2010[54], Larsen 2010[55], Vincenti 2012[56], Rostaing 2013[57])			✓	686
BENEFIT EXT (Durrbach 2010[135] Medina Pestana 2012[136], Charpentier 2013[137] Larsen 2010[55])			✓	578
Ferguson 2011[138]	BEL+MMF vs BEL+SIR vs TAC+MMF		✓	89
Lorber 2005[139]	EVL low + CsA vs EVL high + CsA vs MMF+CsA		✓	583
ATLAS Vitko 2005[140] (Vitko 2004[141] & 2005b[142])			✓	588
Takahashi 2013[143]			✓	122
Chadban 2013 (SOCRATES)[144]	EVL vs EVL +CsA vs CsA + MPS		✓	126
Tedesco Silva 2010[145]	EVL low + CsA vs EVL high + CsA vs MPA + CsA		✓	783
Bertoni 2011[146]	EVL + CsA vs MPS + CsA		✓	106
Budde 2011[147] (Budde 2012[148] , Liefeldt 2012[149], NCT00154310)	EVL + MPS vs CsA + MPS		✓	300
Mjornstedt 2012[150] (NCT00634920)			✓	202
Barsoum 2007[151]	SRL + CsA vs MMF + CsA		✓	113
Stallone 2003[152]			✓	90
Anil Kumar 2005[153]	SRL + TAC vs MMF + TAC		✓	150
Mendez 2005[154] (Gonwa 2003[155])			✓	361
Sampaio 2008[156]			✓	100

Study (multiple publications)	Maintenance therapy	Included in TA85	Update review	n
Gelens 2006[157]	SRL + MMF vs CsA + MMF		✓	54
Gallon 2006[158] (Chhabra 2012[159])			✓	83
Van Gurp 2010[160]			✓	634
Flechner 2002 (Flechner 2004, 2007)			✓	61
Noris 2007[161] (Ruggenenti 2007[162])			✓	21
Lebranchu 2009[163] (Servais 2009[164], Lebranchu 2011[165], Joannides 2011[166], 2004-002987-62)			✓	192
Büchler 2007[167] (Lebranchu 2012[168], Joannides 2010[169])			✓	145
Soleimani 2013[77]			✓	88
Durrbach 2008[170] (0468E1 – 100969)			✓	69
Kreis (2000)[171] - Identified from Campistol 2005[172]			✓	78
Guba 2010[173]			✓	140
Martinez-Mier 2006[174]			✓	41
Nafar 2012[175] (IRCT138804333049N7)			✓	100
Larson 2006[176] (Stegall 2003[177])	TAC + MMF vs SRL + MMF		✓	162
Schaefer 2006[78]			✓	80
Heilman 2011[178] (Heilman, 2012[179]; NCT00170053)			✓	122
Welberry Smith 2008[79]			✓	51
Silva 2013[180] (NCT01802268)	TAC + MPS vs SRL + MPS		✓	204
Hamdy 2005[181] (Hamdy 2008[182], Hamdy 2010[183])	TAC + SRL vs MMF + SRL		✓	132
Charpentier 2003[184] (Groth 1999[185])	SRL + AZA vs CsA + AZA	✓		83
Chen 2008[186]	TAC + SRL vs CsA + SRL		✓	41
Vitko 2006[80]	SRL low + TAC vs SRL high + TAC vs MMF + TAC		✓	977
Flechner 2011[187] (ORION study, NCT00266123)	SRL + TAC vs SRL + MMF vs MMF + TAC		✓	450
Grinyo 2009[188], (SYMPHONY study Ekberg 2009[189], Demirbas	MMF + CsA vs MMF + low CsA vs MMF + low		✓	1529

Study (multiple publications)	Maintenance therapy	Included in TA85	Update review	n
2009[190], Ekberg 2010[191], Frei 2010[192], Claes 2012[193])	TAC vs MMF low SRL (1 study)			
Anil Kumar 2008[194] (Anil Kumar 2005[153]; CRG110600009)	TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL		✓	200

4.2.4. Population characteristics

4.2.4.1. Induction therapies

Baseline characteristics of trial participants for induction therapy are summarised in Table 11.

Mean age across studies ranges from 30.3 years to 51.3 years. Men generally represented a higher proportion of the participants (57.5% to 76.3%) other than for the study reported by Mourad et al. 2004, where men were 28.6% and 30.5% in either treatment arm.[91]

Earlier papers tended to record cadaveric donors, with no further details, however, newer trials report deceased donors as DCD, DBD and ECD. Thirteen studies used only cadaveric donors and four used only living. For the remainder of the studies, the donors were either mixed or not reported.

The majority of studies had a high proportion of white participants, 60.3% to 96.2%. Brennan et al. 2006 and Kahan et al. 1999 report a comparatively high percentage of black participants (28.5% and 29.1%; 27% and 34%, respectively).[67 109]

The mismatching of HLA antigens ranges from 2.13 to 4 (section 2.2.1.2). Although a close antigen match is no longer considered as critical due to the more effective immunosuppressive therapy, a better HLA match may lead to longer the graft survival.

Table 11. Population baseline characteristics for induction therapies

Study id	Maintenance therapy	Arm	n	Mean age, yrs (sd)	Male (%)	Donor type (%)					Race (%)	Mean HLA mismatches (sd)
						Living	DBD	DCD	ECD	Cadaveric		
Bas v Pbo (5 studies)												
Bingyi 2003	CSA+AZA+CCS	BAS	6	35-59 (range)	4 (67)	NR	NR	NR	NR	NR	NR	NR
		PBO	6	36-54 (range)	5 (83)	NR	NR	NR	NR	NR	NR	NR
Kahan 1999	CSA+CCS	BAS	173	44.9 (11.79)	111 (64)	54 (31)	0	0	0	119 (69)	Caucasian 117 (68) African-American 47 (27) Asian 0 (0) Other 9 (5)	4.0 (1.44)
		PBO	173	46.2 (12.0)	108 (62)	51 (29)	0	0	0	122 (71)	Caucasian 106 (61) African-American 59 (34) Asian 5 (3) Other 3 (52)	3.9 (1.37)
Lawen 2003	CSA+MMF+CCS	BAS	59	45.4 (13.1)	45 (76.3)	16 (27.1)	0	0	0	43 (72.9)	White 52 (88.1) Black 6 (10.2) Asian 1 (1.7)	3.0 (1.5)
		PBO	64	45.9 (12.1)	41 (64.1)	14 (21.9)	0	0	0	50 (78.1)	White 58 (90.6) Black 6 (4.7) Asian 1 (4.7)	3.3 (1.5)
Nashan 1997	CSA+CCS	BAS	193	49.0 (median) 18-74	126 (66.3)	NR	NR	NR	NR	193 (100)	White 179 (94.2) Black 3 (1.6) Other 8 (4.2)	3.2 (1.2)
		PBO	186	48.0 (median) 18-73	118 (63.4)	NR	NR	NR	NR	186 (100)	White 179 (96.2) Black 1 (0.5) Other 6 (3.2)	3.0 (1.2)
Ponticelli 2001	CSA+AZA+CCS	BAS	168	44.2 (13.5)	110 (65.5)	27 (16.1)	0	0	0	141 (83.9)	Caucasian 146 (86.9) Black 1 (0.6%) Oriental 1 (0.6%) Other 20 (11.9%)	2.9 (1.4)
		PBO	172	44.2 (13.0)	118 (68.8)	32 (18.6)	0	0	0	140 (81.4)	Caucasian 150 (87.2) Black 2 (1.2%) Oriental 2 (1.2%) Other 18 (10.5%)	2.9 (1.4)
Bas v no induction (2 studies)												

Study id	Maintenance therapy	Arm	n	Mean age, yrs (sd)	Male (%)	Donor type (%)					Race (%)	Mean HLA mismatches (sd)
						Living	DBD	DCD	ECD	Cadaveric		
Albano 2013	TAC+MMF+CCS	BAS	283	49.3 (13.5)	185 (65.4)	36 (12.7)	0	5 (1.8)	158 (55.8)	247 (87.3)	White 265 (93.6) Black 11 (3.9) Asian, other 7 (2.5)	3.0
		No ind	302	50.7 (13.0)	206 (68.2)	34 (11.3)	0	3 (1.0)	155 (51.3)	268 (88.7)	White 284 (94.0) Black 14 (4.6) Asian, other 4 (1.3)	3.1
Sheashaa 2003	CSA+AZA+CCS	BAS	50	32.9 (9.9)	44 (88)	50 (100)	0	0	0	0	NR	<3; n= 9 3; n= 34 ≥4; n= 7
		No ind	50	32.5 (10.8)	41 (82)	50 (100)	0	0	0	0	NR	<3; n= 9 3; n= 31 ≥4; n= 10
rATG vs no induction (4 studies)												
Charpentier 2001	TAC+AZA+CCS	rATG	151	NR	NR	NR	NR	NR	NR	NR	NR	NR
		No ind	158	NR	NR	NR	NR	NR	NR	NR	NR	NR
Samsel 2008	CSA + MMF (converted to AZA) + CCS	rATG	29	43.0 (10.0)	23 (57.5)	0	NR	NR	NR	29 (100)	NR	3.29 (1.27)
		No ind	33	40.0 (12.0)	25 (64.1)	0	NR	NR	NR	33 (100)	NR	3.05 (0.9)
Sheashaa 2008	CNI+Antiproliferative+CS	rATG	40	30.3 (13.1)	33 (83)	40 (100)	0	0	0	0	NR	<3; n= 10 3; n= 20 ≥4; n= 10
		No ind	40	31.7 (10.45)	33 (83)	40 (100)	0	0	0	0	NR	<3; 8% 3; 24% ≥4; 8%
Charpentier 2003	TAC + AZA + CCS	rATG	186	44.7 (11.4)	118 (63.4)	0	NR	NR	NR	186 (100)	White 169 (90.9) Black 7 (3.8) Other 10 (5.4)	2.8
		No ind	185	44.5 (11.0	121 (65.4)	0	NR	NR	NR	185 (100)	White 170 (91.9) Black 5 (2.7) Other 10 (5.4)	2.9
BAS vs ATG (4 studies)												
Brennan 2006	CSA + MMF + CCS	BAS	137	49.7 (13.0)	82 (59.9)	0	NR	6 (4.4)	NR	82 (100)	White 89 (65.0) Black 39 (28.5) American Indian 0 Asian 3 (2.2) Other 6 (4.4)	NR
		rATG	141	51.3 (13.1)	79 (56.0)	0	NR	7 (5.0)	NR	79 (100)	White 85 (60.3) Black 41 (29.1) American Indian 1 (0.7) Asian 4 (2.8)	NR

Study id	Maintenance therapy	Arm	n	Mean age, yrs (sd)	Male (%)	Donor type (%)					Race (%)	Mean HLA mismatches (sd)
						Living	DBD	DCD	ECD	Cadaveric		
											Other 10 (7.1)	
Lebranchu 2002	CSA + MMF + CCS	BAS	50	44.1 (11.5)	36 (72.0)	0	NR	NR	NR	50 (100)	Caucasian 46 (92.0) Other 4 (8.0%)	3.5
		rATG	50	45.8 (10.8)	32 (64.0)	0	NR	NR	NR	50 (100)	Caucasian 47 (94.0%) Other 3 (6.0%)	3.5
Mourad 2004	CSA + MMF + CCS	BAS	52	45.3 (12.4)	30 (28.6)	2 (3.8)	NR	NR	NR	50 (96.2)	NR	NR
		rATG	53	45.4 (12.7)	32 (30.5)	1 (1.8)	NR	NR	NR	52 (98.2)	NR	NR
Sollinger 2001	CSA + MMF + CCS	BAS	70	44.5 (13.7)	37 (53.0)	28 (40)	NR	NR	NR	42 (60)	White 55 (79) African-American 12 (17%) Asian 1 (1%) Other 2 (3%)	<3; n= 28 3; n= 22 ≥4; n= 20
		rATG	65	49.8 (11.9)	42 (65.0)	23 (35)	NR	NR	NR	42 (65)	White 55 (85) African-American 9 (14%) Asian 0 Other 1 (2%)	<3; n= 21 3; n= 21 ≥4; n= 23
BAS vs ATG vs no induction (1 studies)												
Kyllonen 2007	CSA + AZA + CCS	rATG	53	47.8 (22-64)	14 (26)	0	NR	NR	NR	53 (100)	NR	2.13
		BAS	58	45.5 (22-65)	27 (46)	0	NR	NR	NR	58 (100)	NR	2.19
		No ind	44	47.5 (28-64)	15 (34)	0	NR	NR	NR	44 (100)	NR	2.48

Key: DBD, donor after brain death; DCD, donation after cardiac death, ECD; extended criteria donor

4.2.4.2. Maintenance therapies

Baseline characteristics of trial participants for maintenance therapy are summarised in Table 12.

Mean age across studies ranges from 29.6 years to 57.1 years. Men represented 50% to 80% of participants for the bulk of the studies. Baboolal et al. 2002 and Campos et al. 2002 fell slightly below this with men at 48 to 49%,[101 102] whereas Chen et al. 2008 recruited only 24% and 35% in treatment arms and Grinyo et al. 2009 recruited 33% and 38%.[186 188]

As for induction therapies, earlier papers tended to record cadaveric donors, with no further details. Seventeen studies used only cadaveric donors and two used only living. For the remainder of the studies, the donors were either mixed or not reported.

The majority of studies had a high proportion of white participants, however, Jarzembowski et al. 2005 recruited all African American participants[100], Ciancio et al. 2008 recruited Hispanic (29.3% and 30.7%) and African American (26.7% and 32.0%)[130], Chadban et al. 2013 reported Asian participants to be 38.8%[195], 46.7% and 40.4% in each arm, Kumar et al. 2005 recruited 59% and 60% African American and Kumar et al. (2008) recuited 50 to 54% African Americans in each arm.[153 194]

For the maintenance studies, HLA is reported in a variety of formats, making any comparisons between studies difficult. As previously mentioned, the matching of HLA antigens is no longer considered as critical, but may have an impact on graft survival.

Table 12. Population baseline characteristics for maintenance therapies

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
Tac + Aza vs CsA + Aza (13 studies)													
Schleibner 1995	✓	CCS	TAC	31	46.1	NR	NR	NR	NR	NR	NR	NR	NR
			CSA	16	45.1	NR	NR	NR	NR	NR	NR	NR	NR
Laskow 1996	×	ATG+CCS	Low TAC	33	44.0	24 (73)	0	0	0	0	33 (100)	Caucasian 17 (51.5) African American 7 (21.2) Asian 6 (18.2) Hispanic 3 (9.1) Other 0	NR
			Med TAC	30	44.3	15 (50)	0	0	0	0	30 (100)	Caucasian 11 (36.7) African American 11 (36.7) Asian 4 (13.3) Hispanic 4 (13.3) Other 0	NR
			High TAC	29	44.1	21 (72)	0	0	0	0	29 (100)	Caucasian 19 (65.5) African American 6 (20.7) Asian 1 (3.4) Hispanic 1 (3.4) Other 2 (6.9)	NR
			CSA	28	46.6	22 (79)	0	0	0	0	28 (100)	Caucasian 15 (53.6) African American 6 (21.4) Asian 2 (7.1) Hispanic 3 (17.9) Other 0	NR
Mayer 1997 (Mayer 2002, 1999)	✓	CCS	TAC	303	46.6	196 (64.7)	0	0	0	0	303 (100)	NR	NR
			CSA	145	45.8	92 (63.4)	0	0	0	0	145 (100)	NR	NR
Radermacher 1998	✓	CCS	TAC	28	41.3	63	0	0	0	0	28 (100)	NR	HLA(A) Match 0.81 HLA(B) Match 0.89 HLA (DR) Match 0.35

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
			CSA	13	47.1	50	0	0	0	0	13 (100)	NR	HLA(A) Match 0.85 HLA(B) Match 0.77 HLA (DR) Match 0.39
Jarzembowski 2005	×	OKT3+CCS	TAC	14	44	8 (57.1)	0	0	0	0	14 (100)	African American: 14 (100)	3.8
			CSA	21	46	16 (76.2)	0	0	0	0	21 (100)	African American: 21 (100)	4.5
Baboolal 2002	✓	CCS	TAC	27	41	49	0	0	0	0	27 (100)	NR	2.4
			CSA	24	42	48	0	0	0	0	24 (100)	NR	2.5
Campos 2002	✓	CCS	TAC	85	40.5	41 (48)	46 (54)	0	0	0	39 (46)	NR	NR
			CSA	81	40.9	45 (56)	39 (48)	0	0	0	42 (52)	NR	NR
Margreiter 2002 (Kramer 2005 & Kramer 2008)	✓	CCS	TAC	287	42.4	200 (69.9)	13 (4.5)	0	0	0	273 (95.5)	White 283 (99.0) Black 0 (0) Oriental 3 (1.0)	A (0.83) B (0.99) DR (0.66)
			CSA	273	43.8	171 (63.1)	8 (3.0)	0	0	0	263 (97.0)	White 270 (99.6) Black 1 (0.4) Oriental 0 (0)	A (0.86) B (1.00) DR (0.68)
Van Duijnhoven 2002	✓	CCS	TAC	11	45.4	8 (72.7)	0	0	0	0	11 (100)	White 11 (100)	NR
			CSA	12	46.8	9 (75.0)	0	0	0	0	12 (100)	White 12 (100)	NR
Waller 2002 (Murphy 2003)	✓	CCS	TAC	52	45	32 (61.5)	9 (17.3)	0	21 (40.4)	0	22 (42.3)	NR	(A, B, DR) 0: 4 (8%) 1: 4 (8) 2: 10 (20) 3: 16 (32) 4: 13 (26) 5: 3 (6) 6: 0 (0)
			CSA	50	45	35 (70)	8 (16)	0	21 (42)	0	21 (42)	NR	(A, B, DR) 0: 7 (13%) 1: 2 (4)

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
													2: 8 (15) 3: 16 (31) 4: 16 (31) 5: 3 (6) 6: 0 (0)
Charpentier 2003	×	rATG+CCS	TAC	186	44.7	118 (63.4)	0	0	0	0	186 (100)	White 169 (90.9) Black 7 (3.8) Other 10 (5.4)	2.8
			CSA	184	43.6	116 (63.0)	0	0	0	0	184 (100)	White 162 (88.8) Black 11 (6.0) Other 11 (6.0)	2.7
		CCS	TAC	185	44.5	121 (65.4)	0	0	0	0	185 (100)	White 170 (91.9) Black 5 (2.7) Other 10 (5.4)	2.9
Toz 2004	✓	CCS	TAC	17	35	10 (58.8)	12 (70.6)	0	0	0	5 (29.4)	NR	NR
			CSA	18	30	12 (66.7)	14 (77.8)	0	0	0	4 (22.2)	NR	NR
Hardinger 2005 (Brennan 2005)	×	ATG+CCS	TAC	134	44	86 (64)	55 (41)	0	0	0	79 (59)	Caucasian 106 (79) African American 24 (18) Other 4 (3)	2.28
			CSA	66	46	40 (61)	32 (48)	0	0	0	34 (52)	Caucasian 52 (79) African American 12 (18) Other 2 (3)	2.48
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)													
Sollinger 1995	✓	ATG+CCS	MMF low	167	45.1	95 (57)	0	0	0	0	167 (100)	Caucasian 101 (60.5) Black 44 (26.3) Hispanic 15 (9.0) Asian 2 (1.2) Other 5 (3.0)	0: 11 (7) 1: 4 (2) 2: 17 (10) 3: 35 (21) 4: 48 (29) 5: 31 (19) 6: 1
			MMF high	166	46.1	98 (59)	0	0	0	0	166 (100)	Caucasian 118 (71.1) Black 33 (19.9) Hispanic 11 (6.6) Asian 3 (1.8) Other 1 (0.6)	0: 10 (6) 1: 5 (3) 2: 17 (10) 3: 39 (23) 4: 49 (30) 5: 34 (20) 6: 0

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
			AZA	166	45.9	95 (57)	0	0	0	0	100	Caucasian 103 (62.0) Black 40 (24.1) Hispanic 14 (8.4) Asian 6 (3.6) Other 3(1.8)	0: 14 (8) 1: 6 (4) 2: 12 (7) 3: 40 (24) 4: 42 (25) 5: 40 (24) 6: 11 (7)
Tricontinental MMF renal study 1996 (Matthew 1998, Clayton 2012)	✓	CCS	MMF low	173	46	93 (53.8)	0	0	0	0	173 (100)	NR	NR
			MMF high	164	46	98 (59.8)	0	0	0	0	164 (100)	NR	NR
			AZA	166	47	111 (66.9)	0	0	0	0	166 (100)	NR	NR
CsA + MMF vs CsA + AZA (4 studies)													
Sadek 2002	✓	CCS	MMF	162	43.9	115 (71)	NR	NR	NR	NR	139 (86)	Caucasian 148 (91.4) Black 3 (1.2) Asian 4 (2.5) Other 8 (4.9)	NR
			AZA	157	43.9	94 (59.9)	NR	NR	NR	NR	137 (87)	Caucasian 142 (90.4) Black 5 (3.2) Asian 5 (3.2) Other 5 (3.2)	NR
			MMF/ AZA	158	44.7	102 (64.6)	NR	NR	NR	NR	136 (86)	Caucasian 142 (89.9) Black 7 (4.4) Asian 6 (3.8) Other 3 (1.9)	NR
Tuncer 2002	✓	ATG+CCS	MMF	38	34.8	27 (71.1)	32 (84.2)	0	0	0	6 (15.8)	NR	2.5
			AZA	38	41.4	28 (73.7)	29 (76.3)	0	0	0	9 (23.7)	NR	2.7
Merville 2004	×	ATG+CCS	MMF	37	44	26 (78.4)	0	0	0	0	37 (100)	NR	2.7

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
			AZA	34	47	23 (58.8)	0	0	0	0	34 (100)	NR	2.8
Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	×	CCS	MMF	168	43.3	119 (71)	0	0	0	0	168 (100)	NR	0: 3 (2%) 1: 42 (25) 2: 71 (42) 3: 45 (27) Missing: 7 (4)
			AZA	168	45.9	100 (60)	0	0	0	0	168 (100)	NR	0: 6 (4%) 1: 40 (24) 2: 82 (49) 3: 33 (20) Missing: 7 (4)
TAC + MMF vs CsA + AZA (2 studies)													
Wlodarczyk 2005 (Wlodarczyk 2002)	×	CCS	TAC+ MMF	243	43.8	156 (64.2)	9 (3.7)	0	0	0	234 (96.3)	NR	2.8
			TAC+ AZA	246	42.1	157 (63.8)	11 (4.5)	0	0	0	235 (95.5)	NR	2.6
Vacher-Coponat 2012	×	rATG+CCS	TAC+ MMF	143	46	87 (61)	0	0	0	0	143 (100)	NR	2.83
			CSA+ AZA	146	47	89 (61)	0	0	0	0	146 (100)	NR	2.84
TAC + MMF vs CsA + MMF (4 studies)													
Zadrazil 2012	×	CCS	TAC	24	52.9	18 (75.0)	NR	NR	NR	NR	NR	NR	NR
			CSA	29	54.4	16 (55.2)	NR	NR	NR	NR	NR	NR	NR
Hernandez 2007	×	BAS+rATG+ CCS	TAC+ MMF	80	47	44 (55)	0	0	0	0	80 (100)	White (100)	3.8
			CSA+ MMF	80	48	50 (62.5)	0	0	0	0	80 (100)	White (100)	3.7
			CSA+ AZA	80	47	59 (73.8)	0	0	0	0	80 (100)	White (100)	3.4

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
Rowshani 2006	×	BAS+CCS	TAC	63	NR	NR	NR	NR	NR	NR	NR	NR	NR
			CSA	63	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yang 1999 (Ulsh 1999)	✓	CCS	TAC	30	46.5	16 (52)	NR	NR	NR	NR	19 (62.9)	White 24 (81)	DR 19% A/B 21/23
			CSA	30	46.8	21 (69)	NR	NR	NR	NR	23 (76.9)	White 28 (92)	DR 16% A/B 19/22
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)													
Weimer 2006 (Weimer 2005)	×	ATG	TAC+ AZA	28	45	18 (64.3)	7 (25)	0	0	0	21 (75)	NR	HLA-A, B, DR: 2.5 HLA-B, DR: 1.6
			CSA+ AZA	25	50	13 (52.0)	4 (16)	0	0	0	21 (84)	NR	HLA-A, B, DR: 2.2 HLA-B, DR: 1.6
			CSA+ MMF	28	44	9 (29.0)	9 (32)	0	0	0	19 (68)	NR	HLA-A, B, DR: 2.7 HLA-B, DR: 2.1
TAC + MMF vs TAC PR + MMF (4 studies)													
Wlodarczyk 2009	×	CCS	TAC	59	43.6	44 (74.6)	NR	NR	NR	NR	NR	White 59 (100)	NR
			TAC PR	63	44.0	36 (56.7)	NR	NR	NR	NR	NR	White 61 (96.7) Black (0) Asian (0) Other 2 (3.3)	NR
Kramer 2010 (NCT00189839)	×	CCS	TAC	336	45.5	215 (64)	92 (27.4)	0	0	0	244 (72.6)	White 273 (81.6) Black 19 (5.7) Asian 7 (2.1) Other 37 (11)	Mean A: 1.0 Mean B: 1.2 Mean BR: 0.8
			TAC PR	331	44.9	204 (61.6)	89 (26.9)	0	0	0	242 (73.1)	White 277 (83.7) Black 14 (4.2) Asian 5 (1.5) Other 35 (10.6)	Mean A: 1.0 Mean B: 1.1 Mean BR: 0.9
Tsuchiya 2013	×	BAS+CCS	TAC	52	46.1	35 (67.3)	NR	NR	NR	NR	NR	NR	2.6

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
			TAC PR	50	47.5	34 (68.0)	NR	NR	NR	NR	NR	NR	2.9
Oh 2014	×	BAS+CCS	TAC	31	46.9	16 (57.1)	16 (51.6)	0	0	0	15 (48.4)	NR	0-2: 6 (19.4%) 3-4: 16 (51.6) 5-6: 9 (29.0)
			TAC PR	29	44.5	17 (58.6)	17 (58.6)	0	0	0	12 (41.4)	NR	0-2: 6 (20.7%) 3-4: 13 (44.8) 5-6: 10 (34.5)
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)													
Albano 2013: (NCT00717470) OSAKA Trial	×	CCS	TAC	320 (309)	50.8	211 (68.3)	41 (13.3)	0	0	0	268 (86.7)	White 296 (95.8) Black 7 (2.3) Other 6 (1.9)	3.1
			TAC PR low	316 (302)	50.7	206 (68.2)	34 (11.3)	0	0	0	268 (88.7)	White 284 (94.0) Black 14 (4.6) Other 4 (1.3)	3.1
			TAC PR high	317 (304)	50.2	204 (67.1)	33 (10.9)	0	0	0	271 (89.1)	White 291 (95.7) Black 7 (2.3) Other 6 (2.0)	3.2
			TAC PR low+ BAS	298 (283)	49.3	185 (65.4)	36 (12.7)	0	0	0	247 (87.3)	White 265 (93.6) Black 11 (3.9) Other 7 (2.5)	3.0
MMF + TAC vs MPS + TAC (1 study)													
Ciancio 2008 / (Ciancio 2011 (3016), R01DK25243-25)	×	ATG+DAC+ CCS	MMF	75	49.7	50 (66.7)	14 (18.7)	0	2 (2.7)	1 (1.3)	65.3 (+ 2 (2.7) paediatric en bloc and 7 (9.3) double kidneys)	White 30 (40.0) Hispanic 22 (29.3) African American 20 (26.7) Other 3 (4.0)	3.87
			MPS	75	51.1	25 (74.7)	8 (10.7)	0	3 (4.0)	4 (6.7)	65.3 (+ 2 (2.7) paediatric en bloc and 8 (10.7) double kidneys)	White 24 (32.0) Hispanic 23 (30.7) African American 24 (32.0) Other 4 (5.3)	3.95
MMF + CsA vs MPS + CsA (1 study)													
Salvadori 2004	×	CCS	MMF	210	47.2	142 (67.6)	37 (17.6)	0	0	0	173 (82.4)	White 187 (89.0) Black 13 (6.2) Oriental 2 (1.0) Other 8 (3.8)	0-3: 60.0 4-6: 38.6
			MPS	213	47.1	137 (64.3)	32 (15)	0	0	0	181 (85)	White 187 (87.8) Black 17 (8.0) Oriental 3 (1.4)	0-3: 62.0 4-6: 37.1

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
												Other 6 (2.8)	
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)													
Vincenti 2005 (Vincenti 2010)	×	BAS+CCS	BEL low	71	42.1	48 (68)	NR	NR	NR	NR	52 (73)	White 57 (80) Black 6 (9) Other 8 (11)	>3: 41%
			BEL high	74	46.5	54 (73)	NR	NR	NR	NR	51 (69)	White 64 (86) Black 6 (8) Other 6 (6)	>3: 42%
			CSA	73	46.1	57 (78)	NR	NR	NR	NR	57 (78)	White 59 (81) Black 6 (8) Other 8 (11)	>3: 40%
BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	×	BAS+CCS	BEL low	226	42.6	65	NR	NR	NR	NR	NR	White (59) Black (10) Asian (13) Other (18)	NR
			BEL high	219	43.6	69	NR	NR	NR	NR	NR	White (60) Black (7) Asian (12) Other (21)	NR
			CSA	221	43.5	75	NR	NR	NR	NR	NR	White (63) Black (8) Asian (12) Other (17)	NR
BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	×	BAS+CCS	BEL low	175	56.1	74	0	0	0	175 (100)	0	White (77) Black (14) Other (10)	>3: 50%
			BEL high	184	56.7	65	0	0	0	184 (100)	0	White (75) Black (14) Other (12)	>3: 51%
			CSA	184	55.7	63	0	0	0	184 (100)	0	White (75) Black (12) Other (14)	>3: 58%
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)													
Ferguson 2011		×	ATG+CCS	BEL+ MMF	33	49.2	25 (76)	16 (48)	0	0	0	17 (52)	White 24 (73) Black 8 (24) Other 1 (3)	NR
				BEL+ SRL	26	52.7	20 (77)	15 (57)	0	0	0	11 (42)	White 23 (89) Black 3 (12) Other 0 (0)	NR

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
				TAC+ MMF	30	53.6	22 (73)	13 (43)	0	0	0	17 (57)	White 23 (77) Black 5 (17) Other 2 (7)	NR
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)														
Lorber 2005		×	CCS	EVL low	193	43.3	110 (57.0)	94 (48.7)	94 (48.7)	5 (2.6)	0	0	White 133 (70.5) Black 29 (15.0) Hispanic 20 (10.4) Asian 3 (3.7) Other 8 (4.1)	<3: 23.8% ≥3: 76.2
				EVL high	194	43.7	123 (63.4)	94 (48.4)	93 (47.9)	7 (3.6)	0	0	White 123 (63.4) Black 36 (18.6) Hispanic 14 (7.2) Asian 6 (3.1) Other 15 (7.7)	<3: 27.8% ≥3: 72.2
				MMF	196	43.4	132 (67.3)	106 (54.1)	85 (43.4)	5 (2.6)	0	0	White 129 (65.8) Black 33 (16.8) Hispanic 24 (12.2) Asian 2 (1.0) Other 8 (4.1)	<3: 28.6% ≥3: 71.4
ATLAS Vitko 2005 (Vitko 2004 & 2005b)		×	CCS	EVL low	194	45.2	114 (58.8)	NR	NR	NR	NR	>90	Caucasian 181 (93.3) Black 4 (2.1) Oriental 4 (2.1) Other 5 (2.6)	NR
				EVL high	198	44.1	127 (64.1)	NR	NR	NR	NR	>90	Caucasian 177 (89.4) Black 9 (4.5) Oriental 5 (2.5) Other 7 (3.5)	NR
				MMF	196	46.1	139 (70.9)	NR	NR	NR	NR	>90	Caucasian 171 (87.2) Black 11 (5.6) Oriental 6 (3.1) Other 8 (4.1)	NR
Takahashi 2013		×	BAS+CCS	EVL	61	42.5	46 (75.4)	60 (98.3)	1 (1.6)	0	0	0	NR	1: 11.5% 2: 14.8 3: 41.0 <3: 26.2 ≥3: 73.8
				MMF	61	38.6	37 (60.7)	60 (98.4)	0	1 (1.6)	0	0	NR	1: 3.3% 2: 26.2 3: 39.5

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
													<3: 29.5 ≥3: 70.5
EVL vs CsA vs MPS (1 study)													
Bemelman 2009	×	BAS+CCS		EVL	38	49	23 (60)	16 (42)	NR	NR	NR	NR	Caucasian 30 (78.9) Asian 6 (15.8) North African 2 (5.3) Afrocaribbean 0 (0)	2.8
				CSA	39	55	20 (51)	19 (48)	NR	NR	NR	NR	Caucasian 36 (92.3) Asian 2 (5.1) North African 1 (2.6) Afrocaribbean 0 (0)	2.5
				MPS	36	52	22 (61)	15 (41)	NR	NR	NR	NR	Caucasian 31 (86.1) Asian 1 (2.8) North African 1 (2.9) Afrocaribbean 9 (8.3)	2.8
EVL vs EVL +CsA vs CsA + MPS (1 study)													
Chadban 2013 (SOCRATES)	×	BAS+CCS		EVL	49	48.8	32 (65.3)	27 (55.1)	20 (40.8)	2 (4.1)	0	0	Caucasian 26 (53.1) Black 0 Asian 19 (38.8) Pacific Islander 0 Other 4 (8.2)	0: 3 (6.1) 1: 8 (16.3) 2: 9 (18.4) >2: 27 (55.1) Missing: 2 (4.1)
				EVL+ CSA	30	43.5	24 (80)	16 (53.3)	13 (43.3)	1 (3.3)	0	0	Caucasian 13 (43.3) Black 1 (3.3) Asian 14 (46.7) Pacific Islander 1 (3.3) Other 1 (3.3)	0: 2 (6.7) 1: 0 (0) 2: 3 (10.0) >2: 24 (80.0) Missing: 1 (3.3)
				CSA+ MPS	47	45.8	34 (72.3)	31 (65.9)	15 (31.9)	1 (2.1)	0	0	Caucasian 25 (53.2) Black 0	0: 6 (12.8) 1: 5 (10.6) 2: 6 (12.8)

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
													Asian 19 (40.4) Pacific Islander 3 (6.4) Other 0	>2: 27 (57.4) Missing: 3 (6.4)
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)														
Tedesco Silva 2010	×	BAS+CCS	EVL low	277	45.7		176 (63.5)	147 (53)	128 (46.2)	2 (0.7)	0	(Missing 1 (0.4))	Caucasian 193 (69.7)	0 Match 10 (3.0) 1 Match 19 (6.9) 2 Match 37 (13.4) ≥3 Match 210 (75.8)
			EVL high	279	45.3		191 (68.5)	151 (54.1)	126 (45.2)	0	0		Caucasian 180 (64.5)	0 Match 15 (5.4) 1 Match 18 (6.5) 2 Match 51 (18.3) ≥3 Match 194 (69.5)
			MPA	277	47.2		189 (68.6)	148 (53.5)	127 (45.8)	1 (0.4)	0	(Missing 1 (0.4))	Caucasian 190 (68.6)	0 Match 15 (5.4) 1 Match 19 (6.9) 2 Match 40 (14.4) ≥3 Match 202 (72.9)
EVL + CsA vs MPS + CsA (1 study)														
Bertoni 2011	×	BAS+CS	EVL	56	45.7		NR	NR	NR	NR	NR	NR	NR	3.364
			MPS	50	49.75		NR	NR	NR	NR	NR	NR	NR	3.5
EVL + MPS vs CsA + MPS (2 studies)														
Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	×	BAS+CCS	EVL+ CSA	155	46.9		102 (66)	32 (27)	0	0	0	113 (73)	White 152 (98.1) Asian 2 (1.3) Other 1 (0.6)	DR 0 59 (38) 1 68 (44) 2 28 (18)
			CSA	145	46.7		86 (59)	38 (27)	0	0	0	107 (74)	White 152 (98.1) Asian 2 (1.3) Other 1 (0.6)	DR 0 59 (38) 1 68 (44) 2 28 (18)
Mjornstedt 2012 (NCT00634920)	×	BAS+CCS	EVL	102	55.5		70 (68.6)	NR	NR	NR	NR	73 (71.6)	Caucasian 99 (97.1)	A 14/100 (14) B 11/100 (11) DR 26/99 (26.3)
			CSA	100	53.8		74 (74)	NR	NR	NR	NR	71 (71.0)	Caucasian 100 (100)	A 24/99 (24.2) B 14/99 (14.1) DR 23/99 (23.3)
SRL + CsA vs MMF + CsA (2 studies)														

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
Barsoum 2007		×	CCS	SRL	76	45	47 (61.8)	NR	NR	NR	NR	NR	NR	3.1
				MMF	37	44	27 (73.0)	NR	NR	NR	NR	NR	NR	2.8
Stallone 2003		×	BAS+CCS	SRL	42	50.4	NR	NR	NR	NR	NR	NR	NR	3.25
				MMF	48	51.8	NR	NR	NR	NR	NR	NR	NR	3.14
SRL + TAC vs MMF + TAC (6 studies)														
Anil Kumar 2005		×	BAS+CCS	SRL	75	55	54 (72)	NR	NR	NR	NR	65 (87)	African-American 44 (59)	4.8
				MMF	75	49	51 (68)	NR	NR	NR	NR	67 (89)	African-American 45 (60)	4.3
Mendez 2005 / (Gonwa 2003)		×	CCS	SRL	185	45.3	123 (66.5)	68 (36.8)	0	0	0	117 (63.2)	White 94 (50.8) African American 51 (27.6) Hispanic 28 (15.1) Other 12 (6.5)	3.4
				MMF	176	47.8	123 (69.9)	63 (35.8)	0	0	0	113 (64.2)	White 95 (54.0) African American 43 (24.4) Hispanic 24 (13.6) Other 14 (8.0)	3.6
Sampaio 2008		×	CCS	SRL	50	37.4	31 (62)	38 (76)	0	0	0	12 (24)	White 21 (42) Black 23 (46) Other 6 (12)	3.4
				MMF	50	42.6	38 (76)	38 (76)	0	0	0	12 (24)	White 27 (54) Black 16 (32) Other 7 (14)	3.3
Gelens 2006		×	CCS	SRL+ Tac	18	59.3	12 (67)	3 (17)	4 (22)	11 (61)	0	0	NR	No A mismatches 11 (61) No B Mismatches 6 (33) No DR mismatches 9 (50)

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
				SRL+ MMF	18	57.1	12 (67)	3 (17)	6 (33)	9 (50)	0	0	NR	No A mismatches 6 (33) No B Mismatches 6 (33) No DR mismatches 6 (33)
				MMF+ TAC	18	47.6	13 (72)	3 (17)	10 (56)	5 (28)	0	0	NR	No A mismatches 5 (28) No B Mismatches 4 (22) No DR mismatches 5 (28)
Gallon 2006 (Chhabra 2012)	×		BAS+CCS	SRL	37	45.7	22 (59.5)	27 (73)	0	0	0	10 (27.0)	White 25 (67.6) African American 10 (27.0) Hispanic 1 (2.7) Asian 1 (2.7)	3.1
				MMF	46	42.3	28 (62.2)	30 (66.7)	0	0	0	15 (33.3)	White 30 (66.7) African American 11 (24.4) Hispanic 1 (2.2) Asian 3 (6.7)	3.6
Van Gurp 2010	×		CCS	SRL	318	44.3	204 (64.2)	41 (12.9)	0	0	0	277 (87.1)	White 299 (94) Black 10 (3.1) Oriental 7 (2.2) Other 2 (0.6)	2.9
				MMF	316	44.9	204 (64.6)	32 (10.1)	0	0	0	284 (89.9)	White 303 (95.9) Black 7 (2.2) Oriental 4 (1.3) Other 2 (0.6)	3.0
SRL + MMF vs CsA + MMF (10 studies)														
Flechner 2002 (Flechner 2004, 2007)	×		BAS+CCS	SRL	31	48.4	21 (67.7)	11 (35.5)	0	0	0	20 (64.5)	White 20 (64.5) Black 8 (25.8) Asian 3 (9.7)	3.04
				CsA	30	46.7	19 (63.3)	10 (33.3)	0	0	0	20 (66.7)	White 21 (70.0) Black 7 (23.3) Asian 2 (6.7)	2.82
Noris 2007 (Ruggenenti 2007)	×		Alemtuzumab+CCS	SRL	11	51	6 (70)	0 (0)	0	0	0	11 (100)	NR	4.0

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
				CSA	10	47	7 (70)	2 (20)	0	0	0	8 (80)	NR	4.0
Lebranchu 2009 (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)		×	DAC+CCS	SRL+ CSA	95	46.5	67 (70.5)	0	25 (26.3)	46 (48.4)	24 (25.3)	0	NR	3.9
				CSA	97	47.3	70 (72.2)	0	22 (22.7)	43 (44.3)	32 (33.0)	0	NR	3.7
Büchler 2007 (Lebranchu 2012, Joannides 2010)		×	rATG+CCS	SRL	71	45.6	44 (62.0)	0	0	0	0	71 (100)	Caucasian 67 (94.4)	3.52
				CSA	74	41.3	45 (60.80)	0	0	0	0	74 (100)	Caucasian 71 (95.9)	3.39
Soleimani 2013		×	CCS	SRL	29	46.72	24 (82.8)	NR	NR	NR	NR	NR	NR	NR
				CSA	59	41.93	32 (54.2)	NR	NR	NR	NR	NR	NR	NR
Durrbach 2008 : (0468E1 – 100969)		×	CCS	SRL	33	52.6	NR	NR	NR	NR	NR	NR	NR	3.68
				CSA	36	57.1	NR	NR	NR	NR	NR	NR	NR	3.5
Kreis (2000) - Identified from Campistol 2005		×	CCS	SRL	40	43.5	28 (70)	0	0	0	0	40 (100)	White 38 (95) Black 1 (3) Oriental 1 (3) Other 0	Match 0: 1 (3) 1: 5 (13) 2: 10 (25) 3: 13 (33) 4: 8 (20) 5: 3 (8) 6: 0
				CSA	38	42.9	27 (71)	0	0	0	0	38 (100)	White 35 (92) Black 0 Oriental 1 (3) Other 2 (5)	Match 0: 2 (5) 1: 6 (16) 2: 11 (29) 3: 11 (29) 4: 5 (13) 5: 2 (5) 6: 1 (3)

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
Guba 2010		×	ATG+CCS	SRL+ CSA	69	47.0	45 (65.2)	8 (11.6)	61 (88.4)	0	0	0	White 68 (98.6) Asian 1 (1.4)	2.8
				CSA	71	47.1	50 (70.4)	7 (9.9)	64 (90.1)	0	0	0	White 70 (98.6) Asian 1 (1.4)	2.9
Martinez-Mier 2006		×	BAS+CCS	SRL	21	29.6	12 (57)	21 (100)	0	0	0	0	NR	2.7
				CSA	20	31.2	12 (60)	20 (100)	0	0	0	0	NR	2.9
Nafar 2012 : (IRCT138804333049N7)		×	CCS	SRL+ CSA/ MMF	50	38.5	29 (58)	NR	NR	NR	NR	NR	NR	NR
				CSA+ MMF	50	42.5	26 (52)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs SRL + MMF (4 studies)														
Larson 2006 (Stegall 2003)		×	rATG+CCS	TAC	82	48	44 (53.7)	71 (85)	0	0	0	0	Caucasian 79 (94)	NR
				SRL	80	50	45 (56.3)	65 (81)	0	0	0	0	Caucasian 78 (98)	NR
Schaefer 2006		×	rATG	TAC	39	NR	NR	NR	NR	NR	NR	NR	NR	3.4
				SRL	41	NR	NR	NR	NR	NR	NR	NR	NR	3.8
				TAC	39	NR	NR	NR	NR	NR	NR	NR	NR	2.7
Heilman 2011 (Heilman, 2012; NCT00170053)		×	ATG+CCS	SRL+ TAC	62	51.7	40 (65)	NR	NR	NR	1 (1.6)	29 (46.8)	African American 6 (10) Hispanic 9 (15)	3.4
				TAC	60	54.1	36 (60)	NR	NR	NR	1 (1.7)	33 (55)	African American 5 (8) Hispanic 7 (12)	3.2
Welberry Smith 2008		×	BAS	TAC→ SRL	10	42	7	1 (10)	9 (90)	0	0	0	White 9 (90) Other 1 (10)	Mean Mismatch A: 0.8 B: 1.3 DR: 0.2

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)						Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric			
				TAC→ SRL	13	49	10	4 (30.8)	8 (61.5)	0	0	0	White 13 (100) Other 0	Mean Mismatch A: 0.8 B: 0.9 DR: 0.5
				TAC	28	50	19	4 (14.3)	23 (82.1)	0	0	0	White 28 (100) Other 0	Mean Mismatch A: 1.0 B: 0.9 DR: 0.5
TAC + MPS vs SRL + MPS (1 study)														
Silva 2013 (NCT01802268)		×	CCS	SRL	97	44.5	66 (68)	50 (52)	47 (48)	0	0	0	Caucasian 52 (54) Black 11 (11) Mixed 29 (30) Other 5 (5)	A: 1.2 B: 1.2 DR: 0.9
				TAC	107	43.9	72 (67)	61 (57)	46 (43)	0	0	0	Caucasian 60 (56) Black 11 (10) Mixed 28 (26) Other 8 (8)	A: 1.2 B: 1.1 DR: 0.9
TAC + SRL vs MMF + SRL (1 study)														
Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)		×	CCS	SRL+ TAC	65	32	52 (80)	65 (100)	0	0	0	0	NR	4: 2 3: 8 2: 36 1: 8 0: 11
				SRL+ MMF	67	31.8	47 (70.1)	67 (100)	0	0	0	0	NR	4: 2 3: 7 2: 43 1: 8 0: 7
SRL + AZA vs CsA + AZA (1 study)														
Charpentier 2003 (Groth 1999)		✓	CCS	SRL	41	47.54	29 (71)	0	0	0	0	42 (100)	White 40 (98) Black 0 Oriental 0 Other 1 (2)	Matches 0: 6 (15) 1: 7 (17) 2: 11 (27) 3: 7 (17) 4: 6 (15) 5: 4 (10) 6: 0
				CSA	42	41.67	25 (60)	0	0	0	0	42 (100)	White 37 (88) Black 1 (2) Oriental 3 (7) Other 1 (2)	Matches 0: 5 (12) 1: 7 (17) 2: 9 (21)

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
													3: 15 (36) 4: 2 (5) 5: 3 (7) 6: 1 (2)
TAC + SRL vs CsA + SRL (1 study)													
Chen 2008		× CCS	TAC	21	42.7	5 (23.8)	8 (38.1)	0	0	0	13 (61.9)	NR	3.3
			CSA	20	40.2	7 (35)	7 (35)	0	0	0	13 (65)	NR	2.8
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)													
Vitko 2006		× CCS	SRL low	325	44.6	210 (64.6)	30 (9.2)	NR	NR	NR	NR	Caucasian 316 (97.2) Black 4 (1.2) Oriental 3 (0.9) Other 2 (0.6)	2.8
			SRL high	325	47.3	196 (60.3)	36 (11.1)	NR	NR	NR	NR	Caucasian 317 (97.5) Black 2 (0.6) Oriental 2 (0.6) Other 4 (1.2)	2.9
			MMF	327	46.0	218 (66.7)	27 (8.3)	NR	NR	NR	NR	Caucasian 319 (97.6) Black 3 (0.9) Oriental 3 (0.9) Other 2 (0.6)	2.9
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)													
Flechner 2011 / (the ORION study, NCT00266123)		× DAC+ CCS	SRL+ TAC	155	47.9	109 (71.7)	60 (40)	0	0	0	92 (60)	White 114 (75) Black 14 (9) Asian 6 (4) Other 18 (11.8)	3.38
			SRL+ MMF	155	50.4	110 (72.4)	56 (37)	0	0	0	96 (63)	White 117 (77) Black 17 (11) Asian 4 (2.6) Other 14 (9.2)	3.36
			TAC+ MMF	140	48.4	81 (58.3)	50 (36)	0	0	0	89 (64)	White 102 (73) Black 15 (11) Asian 5 (3.6) Other 17 (12.2)	3.32
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)													

Study id (multiple publications)	Included in TA85	Induction therapy	Arm	n	Age (yrs)	Male (%)	Donor type (%)					Race	HLA mismatches
							Living	DBD	DCD	ECD	Cadaveric		
Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	×	DAC+ CCS	CSA	390	45.9	148 (38)	134 (34.4)	0	0	0	256 (65.6)	White 359 (92.1) Black 8 (2.1) Asian 5 (1.3) Other 18 (4.6)	2: 70 (18)
			Low CSA	339	47.2	115 (34)	121 (35.6)	0	0	0	218 (64.2)	White 312 (92.2) Black 8 (2.3) Asian 3 (0.8) Other 16 (4.8)	2: 64 (19)
			Low TAC	401	45.5	136 (34)	148 (36.9)	0	0	0	252 (62.8)	White 377 (94.0) Black 4 (1.0) Asian 3 (0.7) Other 17 (4.2)	2: 72 (18)
			Low SRL	399	44.8	132 (33)	143 (35.9)	0	0	0	256 (64.2)	White 376 (94.2) Black 5 (1.3) Asian 2 (0.5) Other 16 (4.0)	2: 64 (16)
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)													
Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	×	BAS+ CCS	CSA+ MMF	50	51	35 (70)	0	0	0	12 (24)	41 (82)	African American 25 (50)	4.0
			CSA+ SRL	50	56	37 (74)	0	0	0	11 (22)	43 (86)	African American 25 (50)	4.1
			TAC+ MMF	50	48	34 (68)	0	0	0	11 (22)	44 (88)	African American 27 (54)	4.0
			TAC+ SRL	50	59	34 (68)	0	0	0	13 (26)	43 (86)	African American 26 (52)	4.1

Key: DBD, donor after brain death; DCD, donation after cardiac death, ECD; extended criteria donor

4.3. Study results

The following outcomes have been addressed for each combination of therapies for both induction and maintenance, with meta-analysis performed where possible:

- Mortality
- Graft loss
- Biopsy proven acute rejection
- Graft function
- Time to biopsy proven acute rejection
- Severity of biopsy proven acute rejection
- Adverse effects of treatment
- HRQoL

We also sought HRQoL outcome data from included RCTs. However, none was reported, so we do not have a section for this outcome.

Furthermore, due to an insufficient number of RCTs within each comparison for induction and maintenance therapies (i.e., 10 or more, as recommended by the Cochrane Handbook), publication bias has not been investigated with funnel plots.[196]

4.3.1. Induction therapies

4.3.1.1. BAS vs PBO/no induction

The 2005 review identified four RCTs investigating the effectiveness of basiliximab compared with placebo or no induction, those reported by Albano et al. 2013, Kahan et al. 1999, Lawen et al. 2003, Kyllonen et al. 2007, Nashan et al. 1997, and Ponticelli et al. 2001.[66-69 86 87] One further RCT identified in the review by Yao et al. 2006 was by Bingyi et al. 2003.[81 197] All studies included CSA and CCS as maintenance therapy. The studies reported by Bingyi et al. 2003 and Ponticelli et al. 2001 also included AZA and the study reported by Lawen et al. 2003 included MMF.[68 69 81] No additional studies were identified in the PenTAG search. No data was identified for HRQoL and time to BPAR.

For BAS vs no induction, one RCT was identified in TA99 (Sheashaa et al. 2003) where a combination of CSA, AZA and CCS was used as maintenance therapy.[83] A second RCT reported by Albano et al. 2013 was identified by the PenTAG search using CSA, MMF and CCS as maintenance therapy.[87]

Mortality

Participant mortality was recorded at 6 months by three studies; Lawen et al. 2003, Ponticelli et al. 2001 and Albano et al. 2013.[69,68,87]. Six studies report mortality at 1 year. [66-69 83 86]

As displayed in Table 13 and Figure 8, the OR at 0.5 years for Ponticelli et al. 2001 and Albano et al. 2013 indicates that BAS is associated with lower odds of mortality, although the results are not statistically significant (OR 0.36, 95% CI 0.13 to 1.01).[68 87] Pooled results at one year for Lawen et al. 2003, and Sheashaa et al. 2003 also display no statistically significant difference (OR 0.95, 95% CI 0.49 to 1.87).[69 83] Therefore, BAS did not improve mortality when compared to placebo or no induction up to 1 year, which is in agreement with the previous HTA.

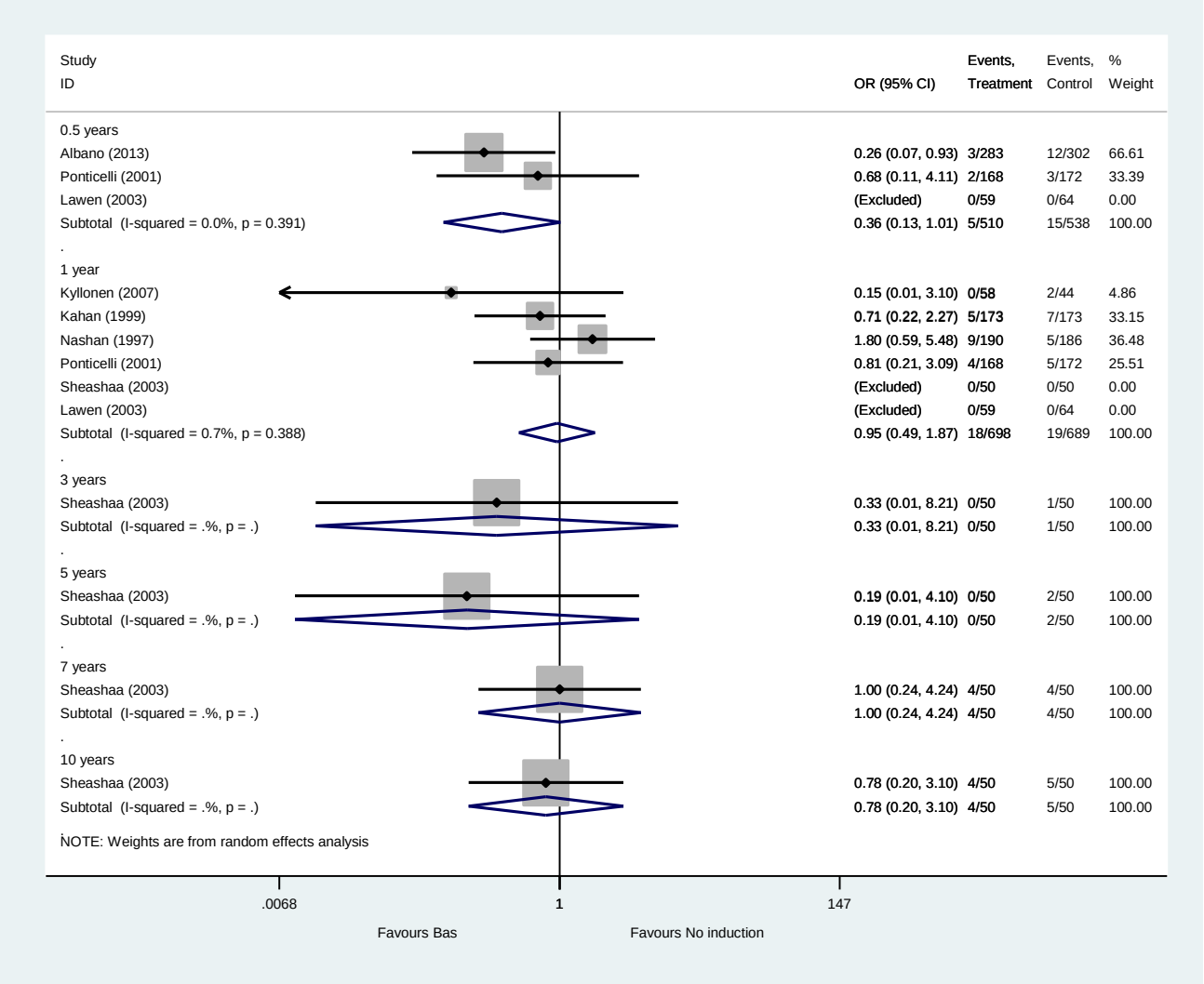
The effect estimate for Sheashaa et al. 2003 at years three, five, seven and 10 years also shows no difference between arms.[83]

Table 13. Mortality for BAS vs PBO/no induction

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Albano, 2013; Ponticelli, 2001; Lawen, 2003	0.5 years	3[a]	0.36	0.13 – 1.01	0.0%	0
Kyllonen, 2007; Kahan, 1999; Nashan, 1997; Ponticelli, 2001; Lawen, 2003; Sheashaa, 2003	1 year	6[b]	0.95	0.49 – 1.87	0.0%	0
Sheashaa, 2003	3 years	1	0.33	0.01 – 8.21	NA	
	5 years		0.19	0.01 – 4.10		
	7 years		1.00	0.24 – 4.24		
	10 years		0.78	0.20 – 3.10		

Key: NA, not applicable; a, one trial excluded from pooled analysis due to no deaths in either arm; b,two trials excluded from pooled analysis due to no deaths in either arm

Figure 8. Forest plot – mortality for BAS vs PBO/ no induction



Graft loss

Of the seven studies in this group[66-69 86 87], three recorded graft loss at 6 months[68 69 87] and six at one year (Table 14; Figure 9).[66-69 83 86]

At both time points the OR indicate some benefit of BAS as compared to PBO or no induction in reducing graft loss (0.5 years OR 0.78, 95% CI 0.50 to 1.22; 1 year OR 0.82, 95% CI 0.56-1.21). However, this estimate must be treated with caution due to the wide confidence intervals indicating a lack of statistical significance.

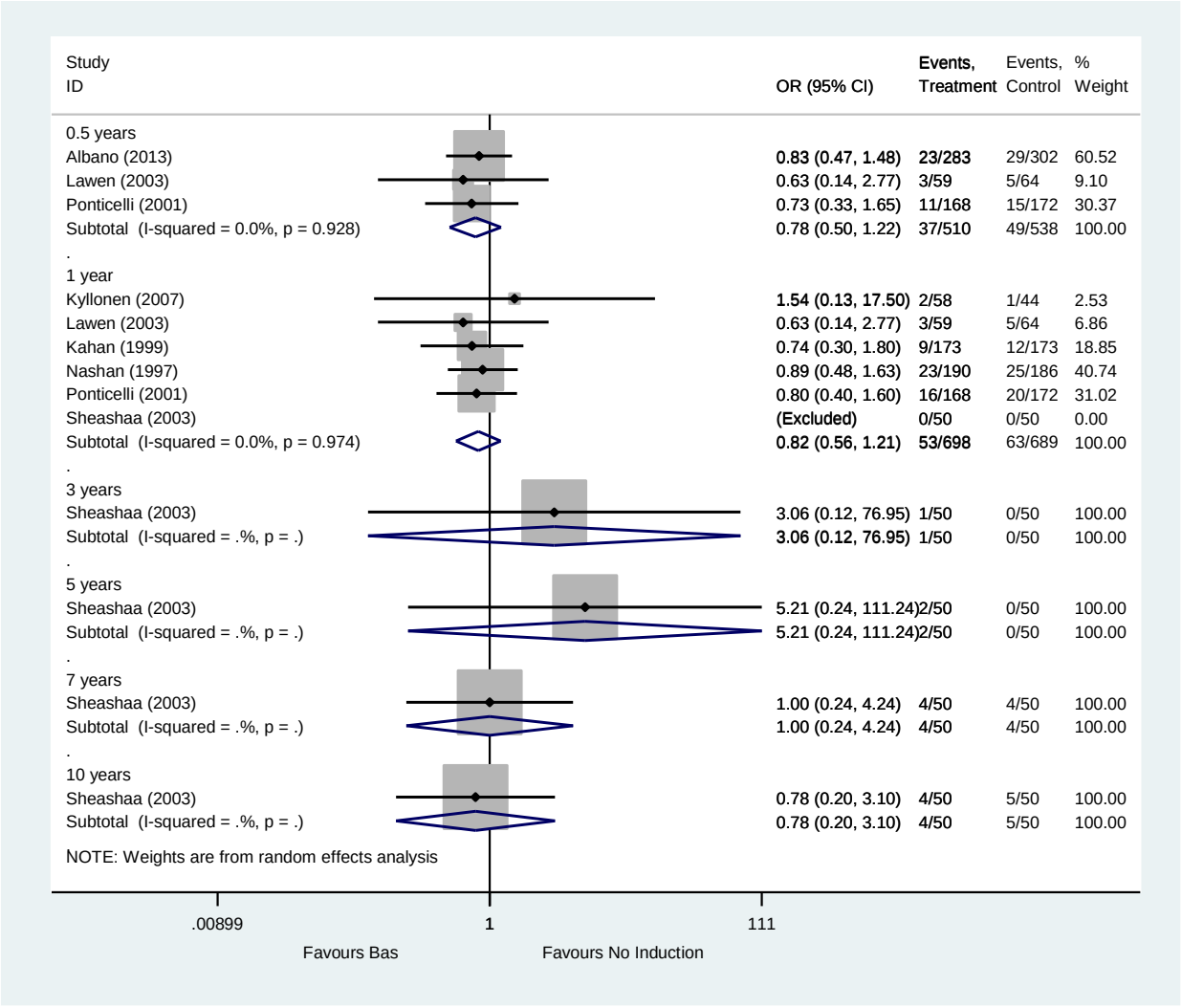
No induction is slightly favoured at years three and five for one study, however, the confidence intervals are extremely wide, indicating a lack of precision as well as no statistical significance.[83] This effect is contrast to the results at the seven and 10 year time points.

Table 14. Graft loss for BAS v PBO

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Albano, 2013; Ponticelli, 2001; Lawen, 2003	0.5 years	3	0.78	0.50 – 1.22	0.0%	0.0
Kyllonen, 2007; Kahan, 1999; Nashan, 1997; Ponticelli, 2001; Lawen, 2003; Sheashaa, 2013	1 year	6[a]	0.82	0.56 – 1.21	0.0%	0.0
Sheashaa, 2003	3 years	1	3.06	0.12 – 76.95	NA	
	5 years		5.21	0.24 – 111.24		
	7 years		1.00	0.24 – 4.24		
	10 years		0.78	0.20 – 3.10		

Key:a, one trial excluded due to no graft loss in either arm

Figure 9. Forest plot – graft loss for BAS vs PBO/no induction



Biopsy Proven Acute Rejection

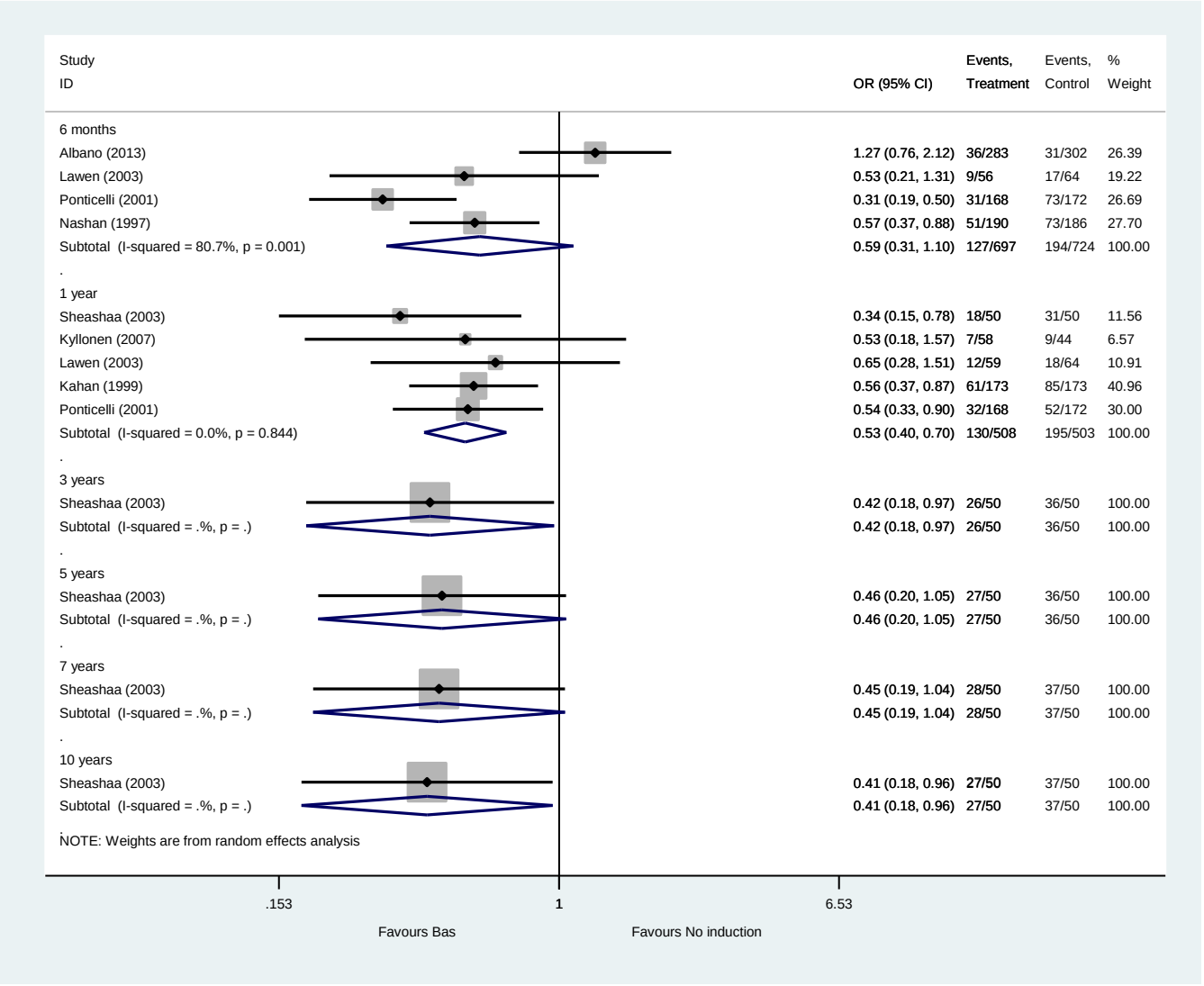
The results of BPAR at 0.5 years are inconclusive due to the substantial heterogeneity across studies (I^2 80.7%).[66 68 69 87 196] In contrast, at one year, BAS statistically significantly reduced BPAR as compared to PBO/no induction (OR 0.53, 95% CI 0.40 to 0.70, I^2 0.0%) (Table 15;

Figure 10).[67-69 83 86] Furthermore, the report by Sheashaa et al. 2003 indicates this effect is maintained up to 10 years (OR 0.41, 95% CI 0.18 to 0.96).[83]

Table 15. Pooled analysis for BAS v PBO - BPAR

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Albano, 2013 Ponticelli, 2001; Lawen, 2003; Nashan, 1997	0.5 years	4	0.59	0.31 – 1.10	80.7%	0.064
Sheashaa, 2003; Kyllonen, 2007; Ponticelli, 2001; Lawen, 2003; Kahan, 1999	1 year	5	0.53	0.40 – 0.70	0.0%	0.0

Figure 10. Forest plot – BPAR for BAS vs PBO



Graft function

Pooled analysis for graft function measured as CrCL implies no beneficial effect of BAS as compared to PBO (0.5 years WMD-1.56 ml/min, 95% CI -6.72 to 3.60; 1 year 1.93, 95% CI -0.97 to 4.83) (Table 16 and Table 17; Figure 11).[66-68 83 87] In particular, results for 0.5 years must be treated with caution due to the substantial heterogeneity across studies (I^2 83.4%). Furthermore, the study reported by Kahan et al. 1999, which indicates an improved graft function for participants on BAS, had a higher percentage of African-American participants (34% and 27%) who generally exhibit poor long-term graft survival compared with other ethnic groups.[67]

Table 16. Pooled analysis for BAS vs PBO/no induction - graft function

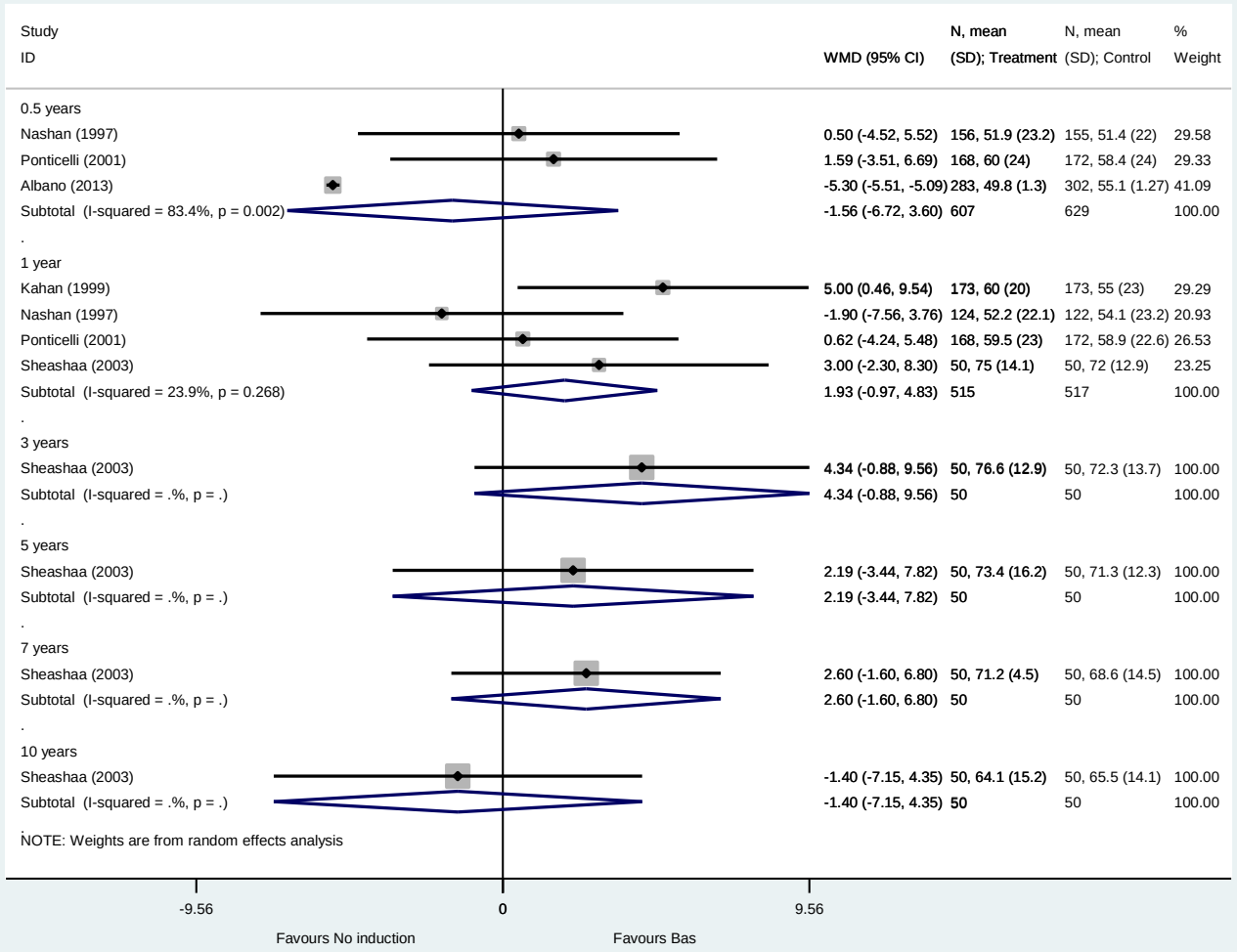
Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Albano, 2013; Nashan, 1997; Ponticelli, 2001	0.5 years	3	-1.56	-6.72 – 3.60	83.4%	0.06
Kahan, 1999; Nashan, 1997; Ponticelli, 2001; Sheashaa, 2003	1 year	4	1.93	-0.97 – 4.83	23.9%	5.75

Table 17. Graft function for BAS vs no induction (unpooled)

Study id	Time point	BAS, mean ml/min (sd)	No ind, mean ml/min (sd)	Mean difference	95% CI	P value (*t*-Test)
Sheashaa, 2003	1 year	75.0 (14.1)	72.0 (12.9)	3.00	-2.30 – 8.30	0.2697
	3 years	76.6 (12.9)	72.3 (13.7)	4.34	-0.88 – 9.56	0.1094
	5 years	73.4 (16.2)	71.3 (12.3)	2.19	-3.44 – 7.82	0.4671
	7 years	71.2 (14.5)	68.6 (14.4)	2.60	-3.06 – 8.26	0.3705
	10 years	64.1 (15.2)	65.5 (15.1)	-1.40	-7.15 – 4.35	0.6451

Notes: All methods either reported as CrCl or Cockcroft gault unless otherwise stated

Figure 11. Forest plot – graft function for BAS vs PBO/ no induction



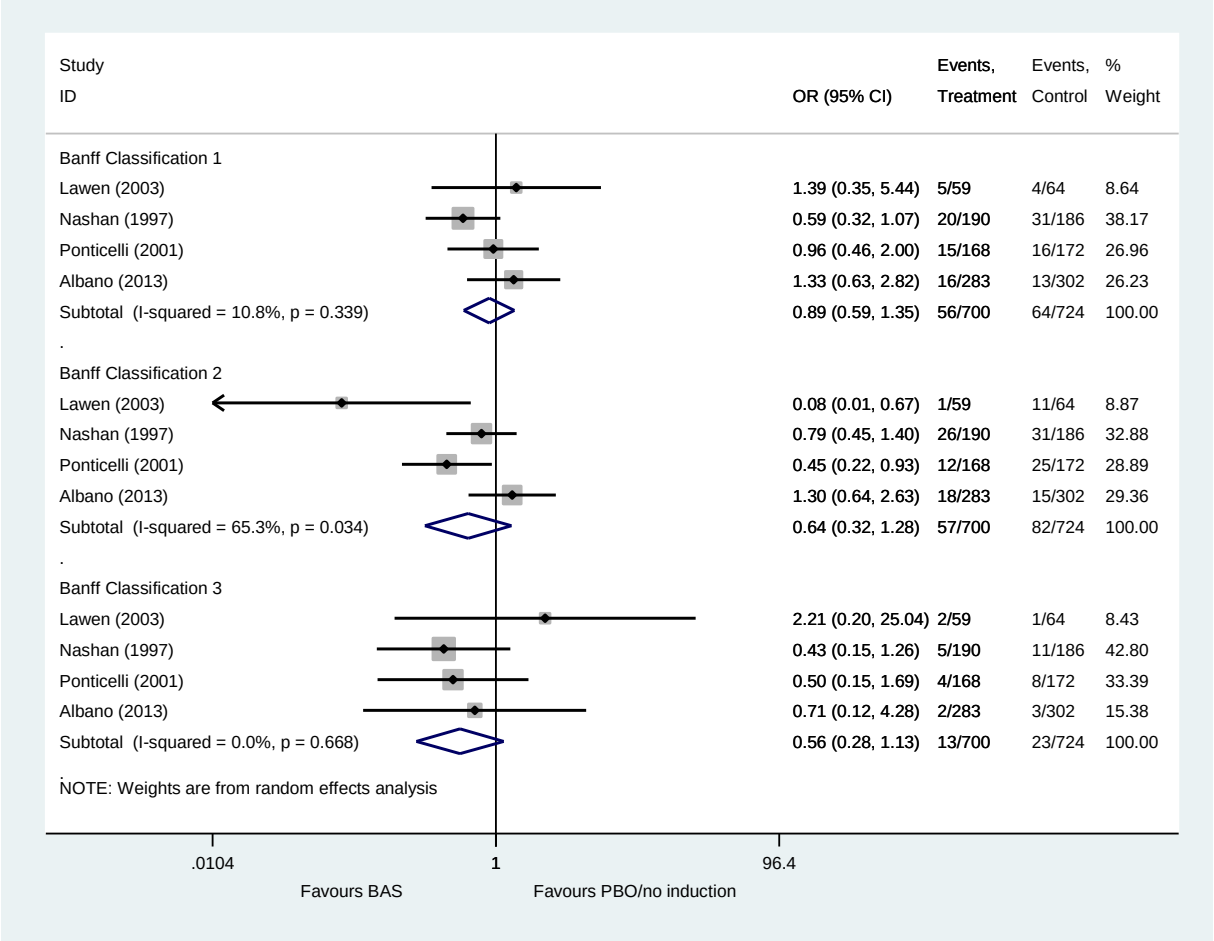
Severity of biopsy proven acute rejection

Results are pooled for four trials at 0.5 years.[69 87,66,68] OR for Banff classifications three is less than one, indicating that BAS may be associated less severe exacerbations of BPAR (Table 18; Figure 12). However, confidence intervals are wide, pointing to a lack of statistical significance. The results for Kahan et al. 1997 at one year display a similar trend.[67] Sheashaa et al. 2003 do not report any episodes of Banff 3 classifications.[83]

Table 18. Severity of BPAR for BAS vs PBO

Study id	Time point	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Albano, 2013; Lawen, 2003; Nashan, 1997; Ponticelli, 2001	0.5 years	1	3	0.89	0.59 – 1.35	10.8%	0.02
		2		0.64	0.32 – 1.28	65.3%	0.30
		3		0.56	0.28 – 1.13	0.0%	0.0
Kahan, 1999	1 year	1	1	0.63	0.36 – 1.09	NA	NA
		2		0.80	0.47 – 1.37		
		3		0.38	0.12 – 1.25		
Sheashaa, 2003	1 year	1	1	0.50	0.22 – 1.14		
		2		0.17	0.03 – 0.81		
	5 years	1		0.92	0.42 – 2.02		
		2		0.23	0.06 – 0.87		
	7 years	1		1.60	0.52 – 4.92		
		2		0.23	0.06 – 0.87		
	10 years	1		1.60	0.52 – 4.92		
		2		0.23	0.06 – 0.87		

Figure 12. Forest plot – severity of BPAR for BAS vs PBO/no induction at 0.5 years



Summary of results for BAS vs PBO/no induction

Pooled results indicate no statistically significant difference between BAS and PBO/no induction for mortality up to one year (6 studies) (OR 0.95, 95% CI 0.49 to 1.87).[69 83] The effect estimate for Sheashaa et al. 2003 at years three, five, seven and 10 years also shows no difference between arms.[83]

No statistically significant difference is found between BAS and PBO/no induction for graft loss (6 studies) (0.5 years OR 0.78, 95% CI 0.50 to 1.22; 1 year OR 0.82, 95% CI 0.56-1.21). This is also the case for the single study where follow-up continues up to 10 years. [83]

The results of BPAR at 0.5 years are inconclusive due to the substantial heterogeneity across studies (I^2 80.7%).[66 68 69 87 196] In contrast, at one year, BAS statistically significantly reduced BPAR as compared to PBO/no induction (OR 0.53, 95% CI 0.40 to 0.70, I^2 0.0%)).[67-69 83 86] Furthermore, the report by Sheashaa et al. 2003 indicates this effect is maintained up to 10 years (OR 0.41, 95% CI 0.18 to 0.96).[83]

Pooled analysis for graft function measured as CrCL implies no beneficial effect of BAS as compared to PBO (0.5 years WMD-1.56 ml/min, 95% CI -6.72 to 3.60; 1 year 1.93, 95% CI -0.97 to 4.83).[66-68 83 87]

4.3.1.2. rATG vs no induction

All four RCTs for this comparison were identified via the PenTAG search. Charpentier et al. 2001 and Charpentier et al. 2003 both used TAC, AZA and CCS as maintenance therapy.[82 88] The study reported by Samsel et al. 2008) describes an initial maintenance therapy of CSA, MMF and CCS, however at 4 months the MMF was switched to AZA.[84] The final study reported by Sheashaa et al. 2008 does not give details of the maintenance therapy, other than the use of a CNI, antiproliferative and steroids.[85]

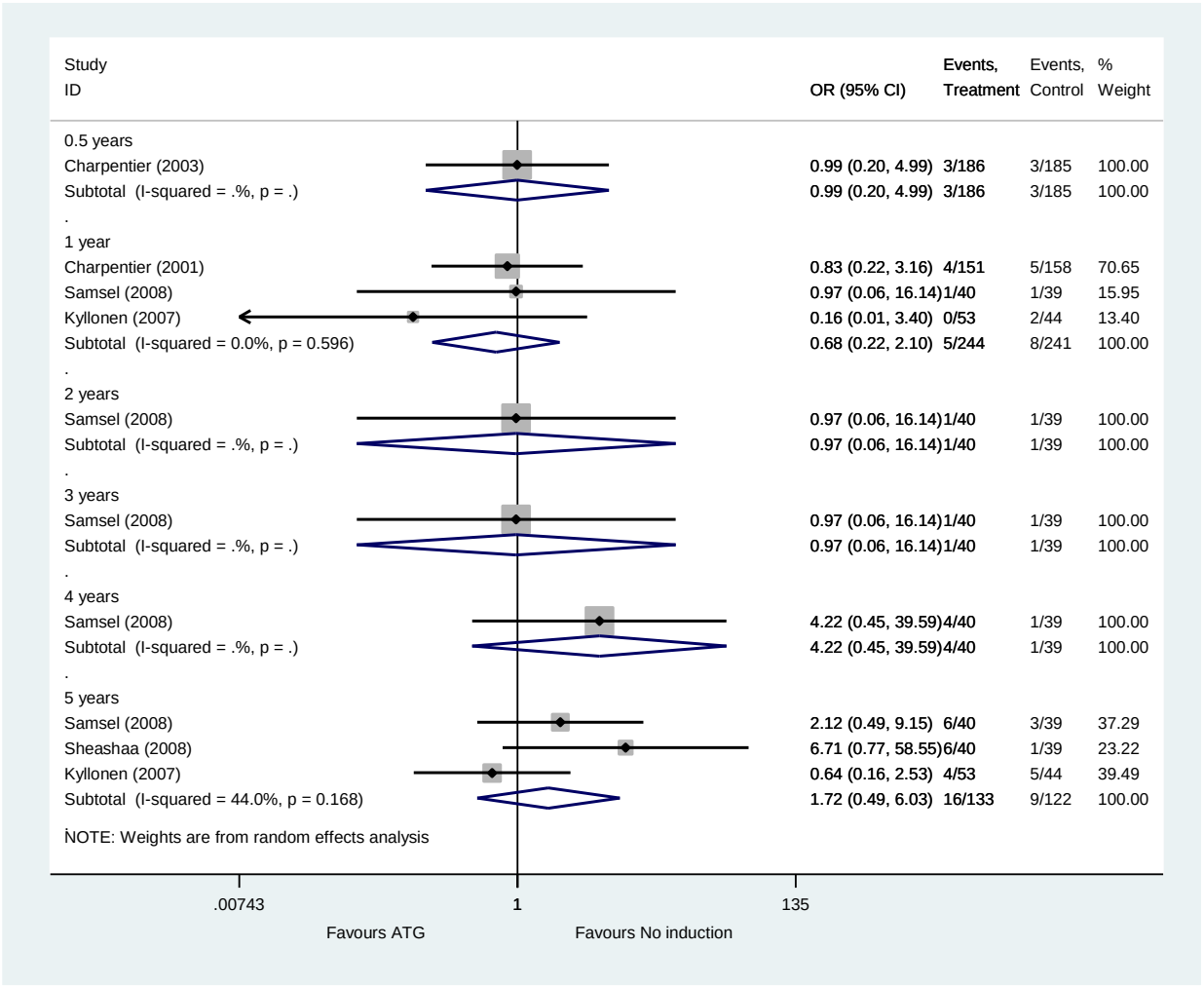
Mortality

Five trials provided data on mortality for rATG vs no induction (Table 19; Figure 13).[82 84-86 88] Follow up data is provided for 5 years by three RCTs.[84-86] No clear evidence of a difference between arms is visible for 0.5 years to 3 years, since the OR is close to one and the confidence intervals are wide. Moderate heterogeneity across studies is noted at five years (I^2 44.0%), again with no statistical difference between arms.[198]

Table 19. Mortality for rATG vs induction

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Charpentier, 2003	0.5 years	1	0.99	0.20 – 4.99	NA	NA
Charpentier, 2001; Samsel, 2008; Kyllonen, 2007	1 year	3	0.68	0.22 – 2.10	0.0%	0.0
Samsel, 2008	2 years	1	0.97	0.06 – 16.14	NA	NA
Samsel, 2008	3 years	1	0.97	0.06 – 16.14	NA	NA
Samsel, 2008	4 years	1	4.22	0.45 – 39.59	NA	NA
Samsel, 2008; Sheashaa, 2008; Kyllonen, 2007	5 years	3	1.72	0.49 – 6.03	44.0%	0.5403

Figure 13. Forest plot – mortality for rATG vs no induction



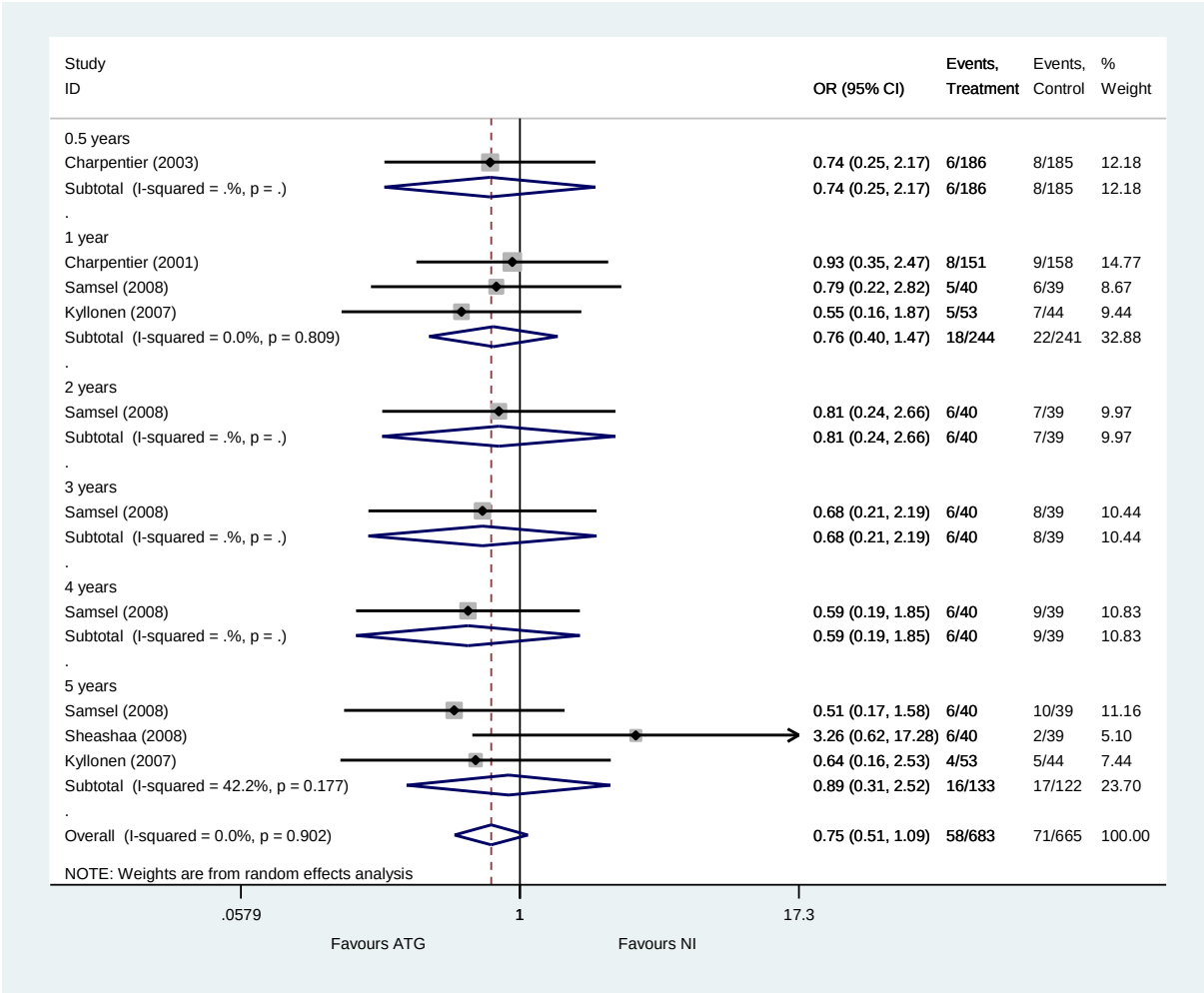
Graft loss

Five trials provide graft loss data for rATG vs no induction (Table 20; Figure 14).[82 84-86 88] Sheashaa et al. 2008 appears to stand out in the forest plot as having an effect estimate which indicates rATG to be beneficial (OR 3.26, 95% CI0.62 to 17.28). However, the population is relatively small and confidence intervals are extremely wide, crossing an OR of 1, indicating no statistical difference between arms.

Table 20. Graft loss for rATG vs no induction

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Charpentier, 2003	0.5 years	1	0.74	0.25 – 2.17	NA	NA
Charpentier, 2001; Samsel, 2008; Kyllonen, 2007	1 year	3	0.76	0.40 – 1.47	0.0%	0.0
Samsel, 2008	2 years	1	0.81	0.24 – 2.66	NA	NA
	3 years		0.68	0.21 – 2.19	NA	NA
	4 years		0.59	0.19 – 1.85	NA	NA
Samsel, 2008; Sheashaa, 2008; Kyllonen, 2007	5 years	3	0.89	0.31 – 2.52	42.2%	0.543

Figure 14. Forest plot – graft loss for rATG vs no induction



Biopsy proven acute rejection

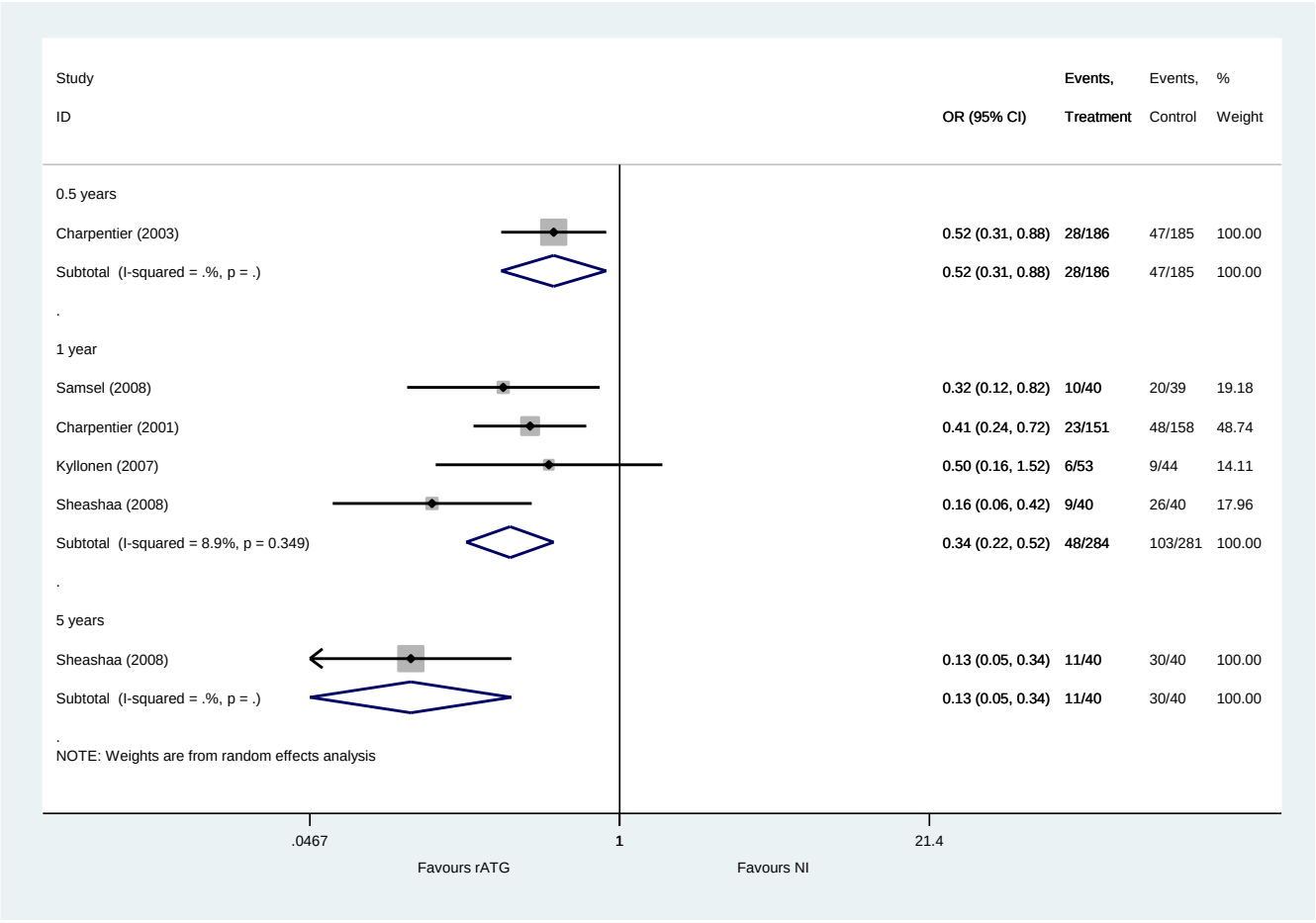
Five studies report on BPAR for rATG vs no induction from 0.5 years to five years (Table 21; Figure 15)Table 21. BPAR for rATG vs no induction.[82 84-86 88] The pooled data of four studies at one year investigating BPAR for rATG vs no induction suggest a statistically significant beneficial effect for rATG (OR 0.34, 95% CI 0.22 to 0.52). (Table 21. BPAR for rATG vs no induction).[82 84-86] There is low evidence of heterogeneity across studies (I^2 8.9%).The single studies at 0.5 years and five years are consistent with the pooled results.[85 88]

Table 21. BPAR for rATG vs no induction

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Charpentier, 2003	0.5 years	1	0.52	0.31 – 0.88	NA	NA
Samsel, 2008; Sheashaa, 2008; Charpentier, 2001; Kyllonen, 2007;	1 year	4	0.34	0.22 – 0.52	8.9%	0.02
Sheashaa, 2008	5 years	1	0.13	0.05 – 0.34	NA	NA

Key: NA, not applicable

Figure 15. Forest plot – BPAR for rATG vs no induction



Graft function

Only Sheashaa et al. 2008 reports graft function at one year as CrCl (Table 22). [85] Despite a mean difference of 3.04 ml/min, in favour of rATG, this result is not statistically significant (p=0.3171).

Table 22. Graft function for rATG vs no induction

Study id	Time point	rATG, mean ml/min (sd)	No induction, mean ml/min (sd)	Mean difference	95% CI	P value (*t*-Test)
Sheashaa, 2008	1 year	75.04 (14.08)	72.00 (12.90)	3.04	-2.97 – 9.05	0.3171

Time to biopsy proven acute rejection

Time to BPAR is reported in various ways by three studies (Table 23).[82 84 86] The only study to note a statistically significant difference is Samsel et al. (2008), where first mean time to BPAR was 20.78 days (sd 14.78) for rATG and 9.21 days (sd 3.91) for no induction (p<0.0001).[84]

Table 23. Time to BPAR for rATG vs no induction

Study	Mean time to BPAR, days (sd)		P value (t-Test)[a]
	rATG	No induction	
Charpentier, 2001	7 pts, 0-14d 10 pts , 15-28d 6 pts, 29-365d	30 pts, 0-14d 10 pts,15-28d 8 pts, 29-365d	NA
Samsel, 2008	20.78 (14.78)	9.21 (3.91)	<0.0001
Kyllonen, 2007	16 (range 7-29)	101 (range 10 - 364)	

Key: NA, not applicable; NR, not reported, (a) calculated by PenTAG

Severity of biopsy proven acute rejection

Two studies report severity of BPAR; Charpentier et al. 2003 at 0.5 years and Sheashaa et al. 2008) at one year (Table 24). [85 88] For the most severe classification of BPAR there is no statistical difference (0.5 years; OR 0.99, 95% CI 0.20 – 5.00). For Banff classification 2, there are greater odds of association with no induction (1 year; OR 0.09; 95% CI 0.01 to 0.73)

Table 24. BPAR for rATG vs no induction

Study id	Time point	Banff classification	BAS, n/N (%)	No induction, n/N (%)	Odds ratio	95% CI
Charpentier, 2003	0.5 years	1	18/186 (9.60)	27/185 (14.59)	0.63	0.33 – 1.18
		2	7/186 (3.76)	17/185 (9.19)	0.39	0.16 – 0.95
		3	3/186 (1.61)	3/185 (1.62)	0.99	0.20 – 5.00
Sheashaa, 2008	1 year	1	8/40 (20)	17/40 (43)	0.34	0.12 – 0.92
		2	1/40 (2.5)	9/40 (22.5)	0.09	0.01 – 0.73

Summary of results for rATG vs no induction

- Five trials provided data on mortality for rATG vs no induction.[82 84 86 88 85] Follow up data is provided for 5 years.[84-86] No clear evidence of a difference between arms is visible for 0.5 years to 3 years, since the OR is close to one and the confidence intervals are wide. Moderate heterogeneity across studies is noted at five years (I^2 44.0%), again with no statistical difference between arms. [198]

- Five trials provide graft loss data for rATG vs no induction.[82 84-86 88] Sheashaa et al. 2008) appears to stand out in the forest plot as having an effect estimate which indicates rATG to be beneficial (OR 3.26, 95% CI0.62 to 17.28). However, the population is relatively small and confidence intervals are wide, crossing an OR of 1, indicating no statistical difference between arms.

- The pooled data of three studies at one year investigating BPAR for rATG vs no induction suggest a statistically significant beneficial effect for rATG (OR 0.34, 95% CI 0.22 to 0.52).)Table 21. BPAR for rATG vs no induction.[82 84-86] There is low evidence of heterogeneity across studies (I^2 8.9%).The single studies at 0.5 years and five years are consistent with the pooled results.[85 88]

- Only Sheashaa et al. 2008) reports graft function at one year.[85] Despite a mean difference of 3.04 ml/min, in favour of rATG, this result is not statistically significant (p=0.3171).

- Time to BPAR is reported in various ways by three studies.[86 90 92 199] The only study to note a statistically significant difference is Samsel et al. 2008), where first mean time

to BPAR was 20.78 days (sd 14.78) for rATG and 9.21 days (sd 3.91) for no induction (p<0.0001).{Samsel 2008)

- Two studies report severity of BPAR; Charpentier et al. 2003) at 0.5 years and Sheashaa et al. 2008) at one year. {Charpentier 2003}[85] In all cases, there are lower odds of association with BPAR for all Banff classifications for BAS. This effect is statistically significant for all results, except Banff classification 3 at 0.5 years (OR 0.99, 95% CI 0.20 – 5.00).

4.3.1.3. Basiliximab vs rATG

The RCTs reported by Lebranchu et al. 2002 and Sollinger et al. 2001 were identified in the 2005 review.[90 92] The PenTAG search retrieved a further three RCTs; Brennan et al. 2006, Kyllonen et al. 2007 and Mourad et al. 2004.[86 89 199] All five RCTs had a maintenance therapy comprising of CSA, MMF and CS.

Mortality

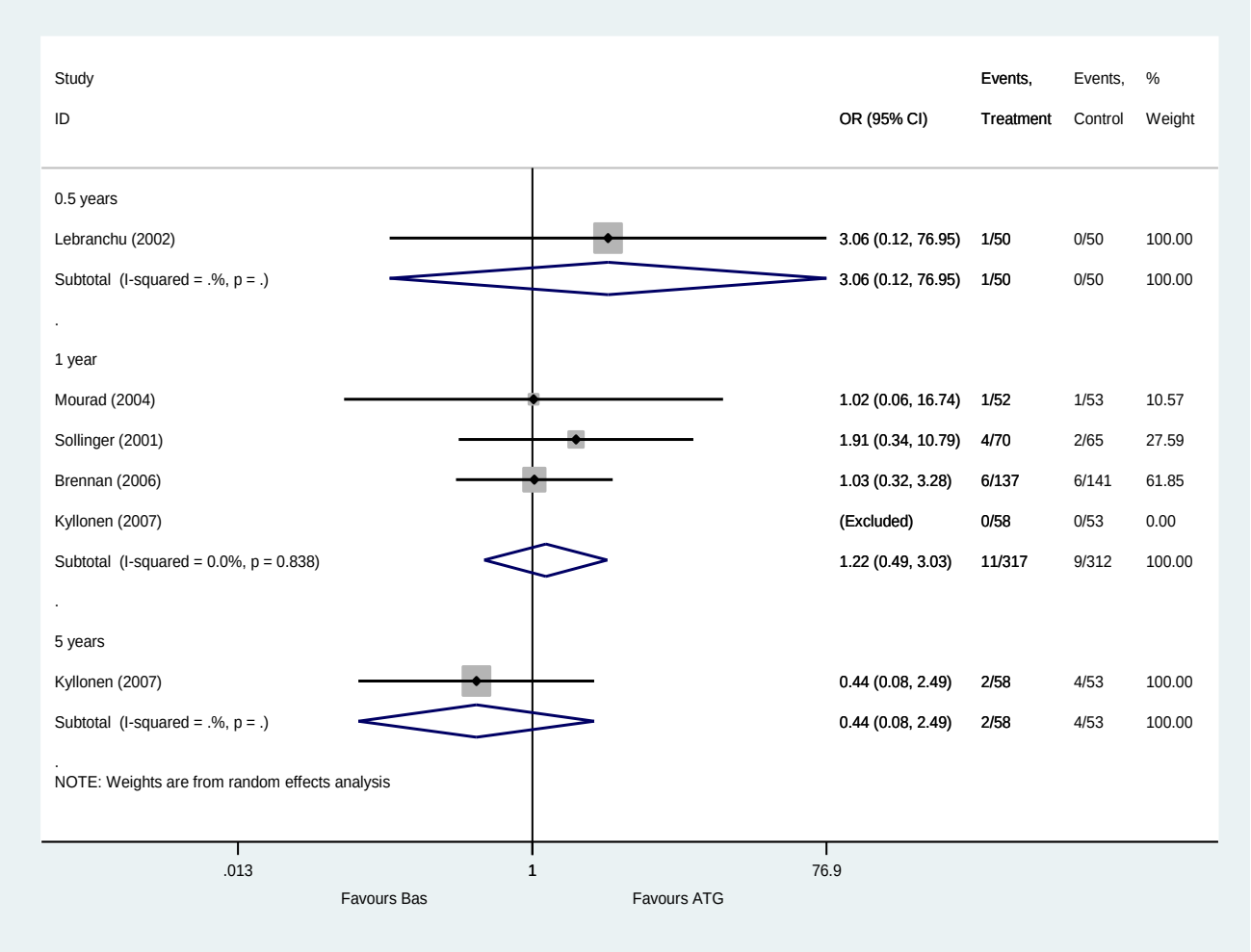
The comparison between BAS and rATG for mortality is reported by five studies (Table 25; Figure 16).[86 89 90 92 199] Four studies are pooled with one year results where no statistically significant effect is seen between arms (OR 1.22, 95% CI 0.49 to 3.03).[86 89 92 199] The 0.5 years and five years results for individual studies are also not statistically significant.

Table 25. Mortality for BAS vs rATG

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Lebranchu, 2002	0.5 years	1	3.06	0.12 – 76.95	NA	NA
Mourad, 2004; Sollinger, 2001; Brennan, 2006: Kyllonen, 2007	1 year	4[a]	1.22	0.49 – 3.03	0.0%	0.0
Kyllonen, 2007	5 years	1	0.44	0.08 – 2.49	NA	NA

Notes: NA, not applicable; (a) One trial excluded from pooled analysis due to no deaths in either arm

Figure 16. Forest plot – mortality for BAS vs rATG



Graft loss

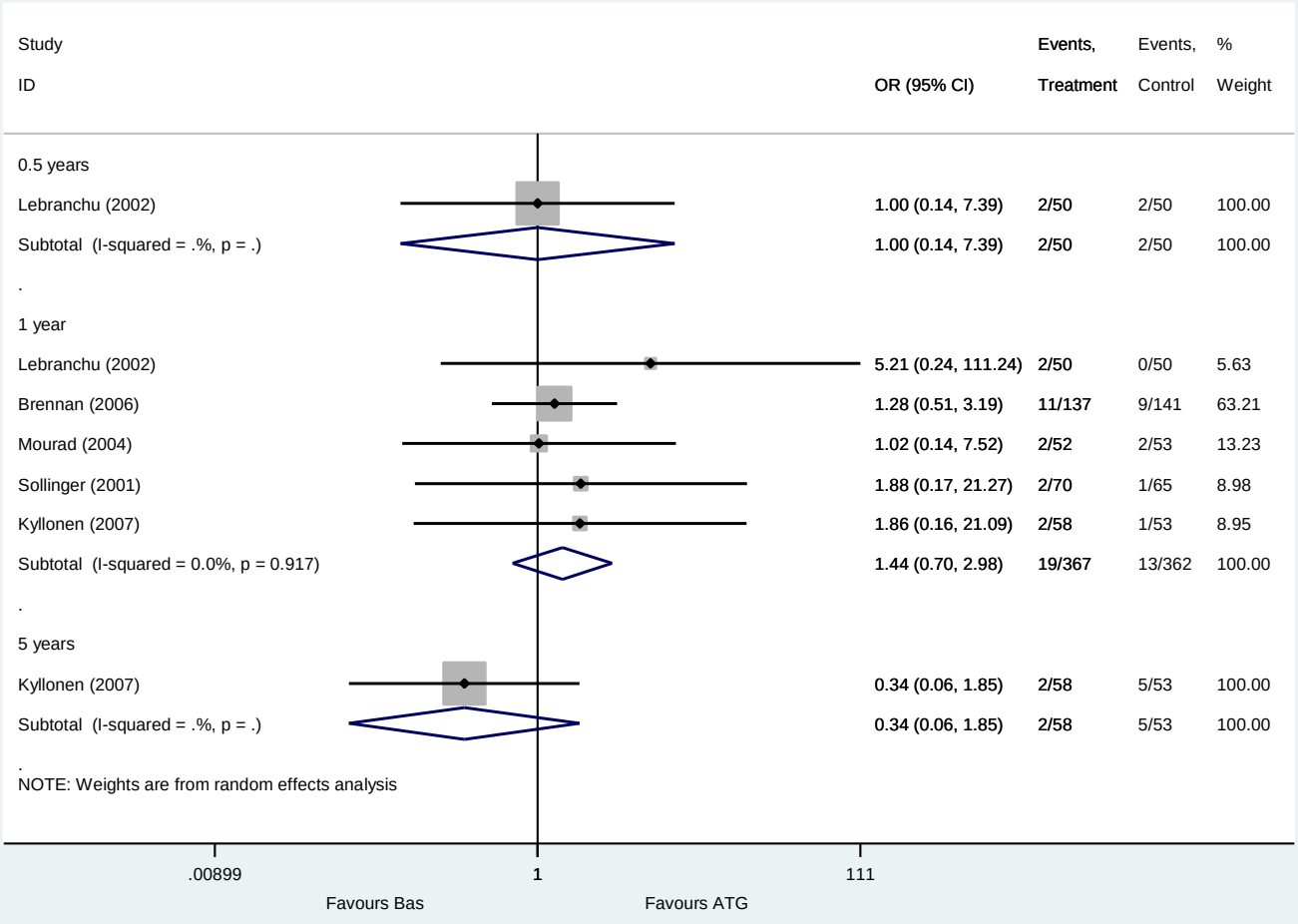
Data from five trials pooled was pooled at the one year time point (Table 26, Figure 17).[86 89 90 92 199] Although the OR indicates lower odds of graft loss associated with rATG, the effect is not statistically significant (OR 1.44, 95% CI 0.70 to 2.98). There was no evidence of heterogeneity across studies. For the individual studies at 0.5 years and five years, there was no statistically significant effect for BAS or rATG.

Table 26. Graft loss for Bas vs rATG

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Lebranchu, 2002	0.5 years	1	1.00	0.14 – 7.39	NA	NA
Lebranchu, 2002; Mourad, 2004; Sollinger, 2001; Brennan, 2006: Kyllonen, 2007	1 year	5	1.44	0.70 – 2.98	0.0%	0.0
Kyllonen, 2007	5 years	1	0.34	0.06 – 1.85	NA	NA

Key: NA, not applicable

Figure 17. Forest plot – graft loss for BAS vs rATG



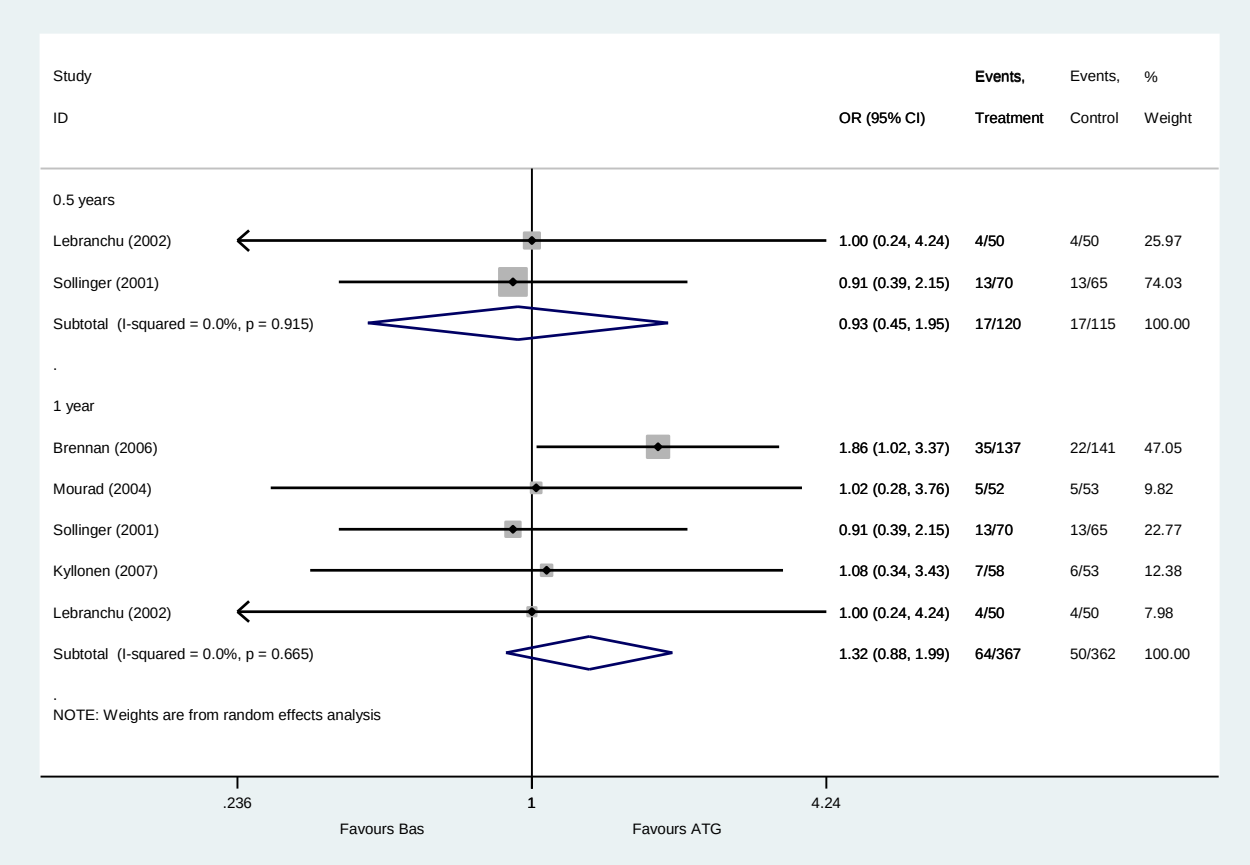
Biopsy proven acute rejection

A total of five studies report on BPAR for BAS vs rATG (Table 27; Figure 18).[86 89 90 92 199] At both 0.5 years and one year, the OR is relatively close to one and both sets of 95% CI imply a lack of statistically significant difference between treatments (0.5 years, OR 0.93, 95%CI 0.45 to 1,95; 1 year, OR1.32, 95% CI 0.88 to 1.99) .

Table 27. BPAR for BAS vs rATG

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Lebranchu, 2002; Sollinger, 2001	0.5 years	2	0.93	0.45 – 1.95	0.0%	0.0
Lebranchu, 2002; Mourad, 2004; Sollinger, 2001; Brennan, 2006: Kyllonen, 2007	1 year	5	1.32	0.88 – 1.99	0.0%	0.0

Figure 18. Forest plot – BPAR for BAS vs rATG



Graft function

Only Lebranchu et al. 2002 reports graft function, with results at 0.5 years and one year (Table 28). [90] Despite a mean difference for CrCl of 6.10 ml/min at one year, in favour of BAS, this result is not statistically significant (p=0.1103).

Table 28. Graft function for BAS vs rATG

Study id	Time point	BAS, mean ml/min (sd)	rATG, mean ml/min (sd)	Mean difference	95% CI	P value (*t*-Test)
Lebranchu, 2002	0.5 years	63 (14.7)	59.1 (20.3)	3.90	-3.13 – 10.93	0.2739
	1 year	66.5 (17.9)	60.4 (19.9)	6.10	-1.42 – 13.612	0.1103

Time to BPAR

Time to BPAR is reported in various ways by four studies (Table 29).[86 90 92 199] None of the studies revealed a statistically significant difference between BAS and rATG, despite the study by Mourad et al., 2004, reporting a mean time for BAS of 155 days (sd 196.27) and for rATG of 35 days (30.19).

Table 29. Time to BPAR for BAS vs no rATG

Study	Mean time to BPAR, days (sd)		P value (*t*-Test)[a]
	BAS	rATG	
Lebranchu, 2002[a]	48.50 (29.83)	35.00 (29.70)	0.5449
Mourad, 2004[a]	155 (196.27)	35 (30.19)	0.2316
Sollinger, 2001	62 (NR)	25 (NR)	NA
Kyllonen, 2007	97 (NR)	16 (NR)	NA

Key: NA, not applicable; NR, not reported, (a) calculated by PenTAG

Severity of biopsy proven acute rejection

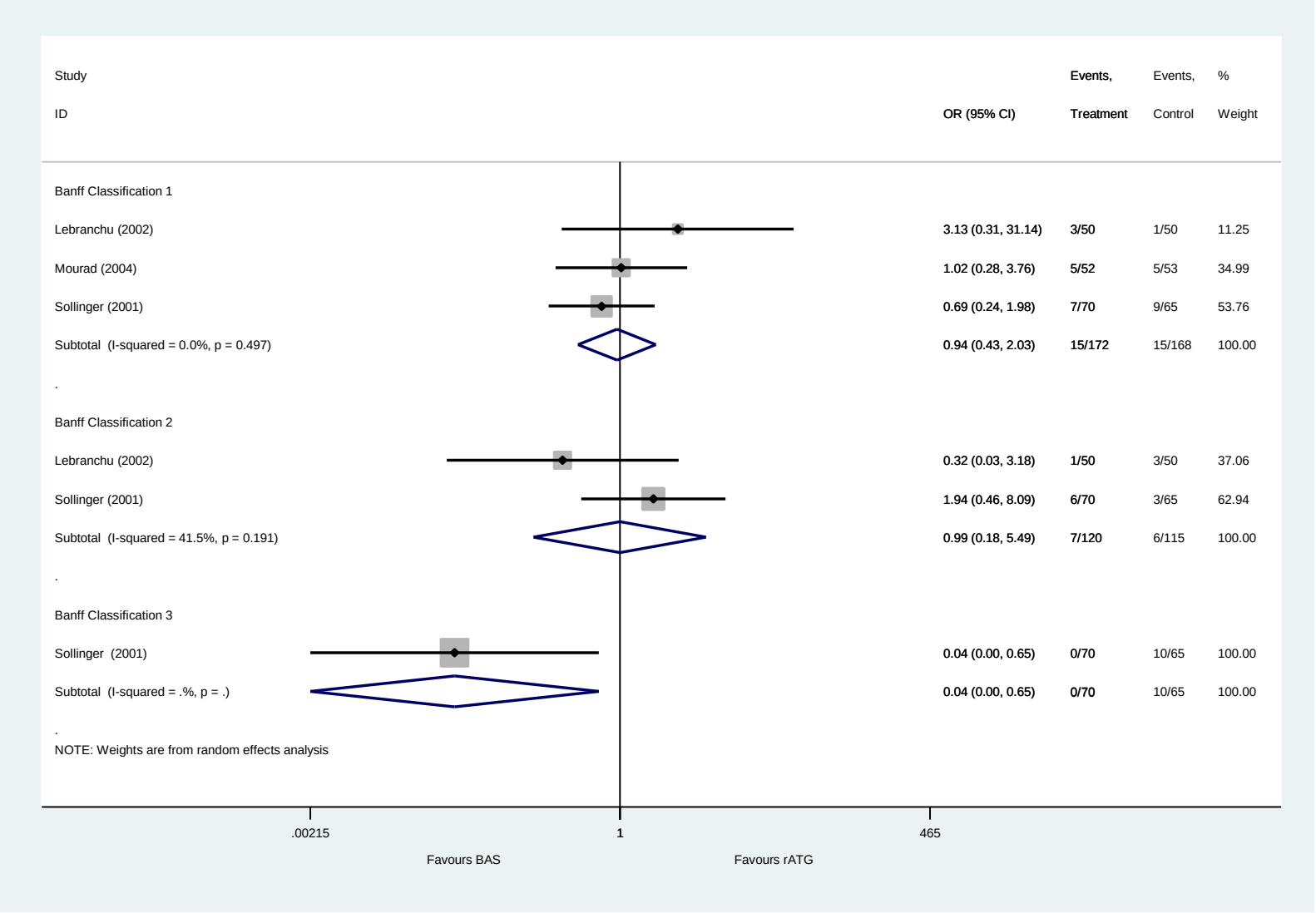
Three studies report on severity of BPAR, although results are not provided for all Banff classifications (Table 30;

Figure 19).[88 90 103] A statistically significant difference is seen for the most severe Banff classification 3 in favour of BAS (OR 0.04, 95%CI 0.00 to 0.65), which is reported by Sollinger et al. (2001).[92]

Table 30. Severity of BPAR for BAS vs rATG

Study id	Time point	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Lebranchu, 2002	0.5 years	1	1	3.13	0.31 – 31.14	NA	NA
		2		0.32	0.032 – 3.18	NA	NA
Margreiter, 2002; Charpentier, 2003	1 year	1	3	0.94	0.43 – 2.03	0.0%	0.0
		2	2	0.99	0.18 – 5.49	41.5%	0.68
		3	1	0.04	0.00 – 0.65	NA	NA

Figure 19. Forest plot – severity of BPAR for BAS vs rATG



Summary of results for BAS vs rATG

- The comparison between BAS and rATG for mortality is reported by five studies.[86 89 90 92 199] Four studies are pooled with one year results where no statistically significant effect is seen between arms (OR 1.22, 95% CI 0.49 to 3.03).[86 89 92 199] The 0.5 years and five years results for individual studies are also not statistically significant.

- Data from five trials pooled was pooled at the one year time point.[86 89 90 92 199] Although the OR indicates lower odds of graft loss associated with rATG, the effect is not statistically significant (OR 1.44, 95% CI 0.70 to 2.98). There was no evidence of heterogeneity across studies. For the individual studies at 0.5 years and five years, there was no statistically significant effect for BAS or rATG.

- A total of five studies report on BPAR for BAS vs rATG.[86 89 90 92 199]At both 0.5 years and one year, the OR is relatively close to one and both sets of 95% CI imply a lack of statistically significant difference between treatments (0.5 years, OR 0.93, 95%CI 0.45 to 1,95; 1 year, OR1.32, 95% CI 0.88 to 1.99) .

- Only Lebranchu et al. 2002) reports graft function, with results at 0.5 years and one year. [90] Despite a mean difference of 6.10 ml/min at one year, in favour of BAS, this result is not statistically significant (p=0.1103).

- Time to BPAR is reported in various ways by four studies (Table 29).[86 90 92 199] None of the studies revealed a statistically significant difference between BAS and rATG, despite the study by Mourad et al., 2004, reporting a mean time for BAS of 155 days (sd 196.27) and for rATG of 35 days (30.19).

- Three studies report on severity of BPAR, although results are not provided for all Banff classifications.[88 90 103]A statistically significant difference is only seen for Banff classification 3 in favour of BAS (OR 0.04, 95%CI 0.00 to 0.65), which is reported by Sollinger et al. 2001.[92]

4.3.2. Maintenance therapies

4.3.2.1. TAC+AZA vs CSA+AZA

Fourteen studies were identified using this combination. [73 74 88 93 94 96 99-103 107 108 125]. Where possible, meta-analysis has been performed. Results are presented for all outcomes, other than HRQoL where no evidence was reported.

Mortality

Ten studies report mortality, with meta-analysis possible at the 0.5 and 1 year time points (Table 31; Figure 20). [74 88 93 94 96 100 102 103 108 125]. All studies are presented graphically on the forest plot to provide a visual overview (Figure 20). At 0.5 years, pooled results of only two studies generates an OR of 0.54, 95% CI 0.18 to 1.62, indicating lower odds of mortality for TAC, however, the large confidence intervals indicate a low level of precision, and since they all overlap the null value (OR=1) there is unlikely to be a significant difference between treatments. Although the OR at one year, which includes eight studies, has shifted to 1.51, indicating reduced odds of mortality in the CSA arm, the 95% CI of 0.75 to 3.06 also suggest no significant difference between treatments.[74 94 96 100 102 103 108 125]. Heterogeneity across studies for the one year time point is low and may not be important at this level according to the Cochrane Handbook (I^2 14.8%).[198]

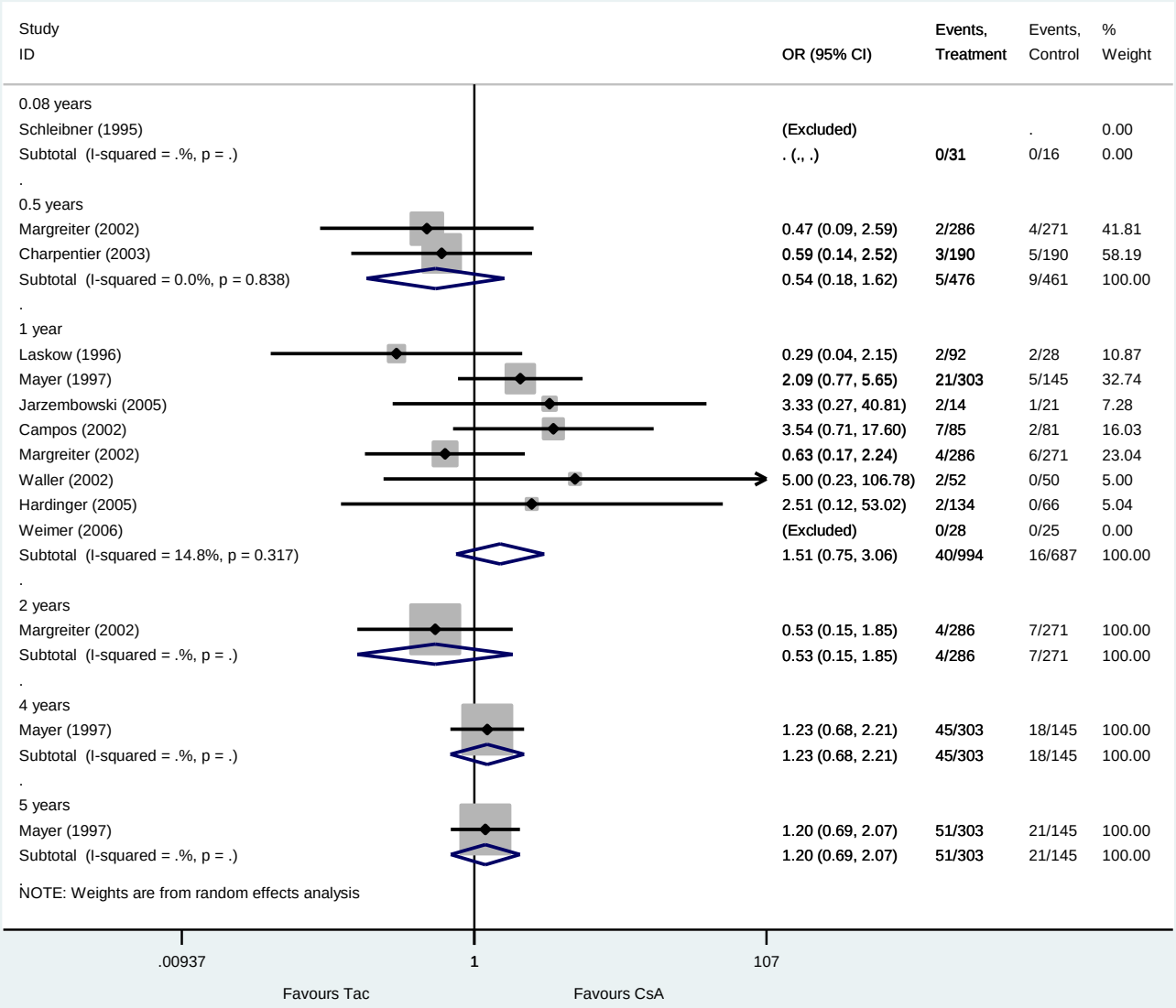
Mayer et al. 1997 report mortality up to five years, however, the results are consistent with earlier timepoints and indicate no difference between arms (OR 1.20, 95% CI 0.69 to 2.07).[96]

Table 31. Mortality for TAC+AZA vs CSA+AZA

Study id	Time point	Trials	Odds Ratio	95% CI	I^2	Tau^2
Schleibner, 2005	0.08 years	1[a]	NA	NA	NA	NA
Margreiter, 2002; Charpentier, 2003	0.5 years	2	0.54	0.18 – 1.62	0.0%	0.0
Laskow 1996, Mayer 1997, Jarzembowski 2005, Campos 2002, Margreiter 2002, Waller 2002, Hardinger 2005, Weimer 2006	1 year	8[b]	1.51	0.75 – 3.06	14.8%	0.13
Margreiter 2002	2 years	1	0.53	0.15 – 1.85	NA	NA
Mayer, 1997	4 years	1	1.23	0.68 – 2.21	NA	NA
Mayer, 1997	5 years	1	1.20	0.69 – 2.07	NA	NA

Key: (a) No deaths reported for either arm, (b) One trial excluded from pooled analysis due to no deaths in either arm

Figure 20. Forest plot - mortality for TAC+AZA vs CSA+AZA



Graft loss

Graft loss is reported for ten trials (Table 32; Figure 21). [74 88 93 94 96 100 102 103 108 125]. Results were pooled for the 0.5, 1 and 2 year time points. The pooling of trials reported by Margreiter et al. 2002 and Charpentier et al. 2003, at 0.5 years give an OR of 2.33 with 95% CI 0.04 to 129.96.[88 103] The wide confidence intervals and the I^2 of 86.1% indicate substantial heterogeneity and low precision. As such, no preference can be established in favour of either treatment. The one year time point is more reliable, where seven studies are pooled

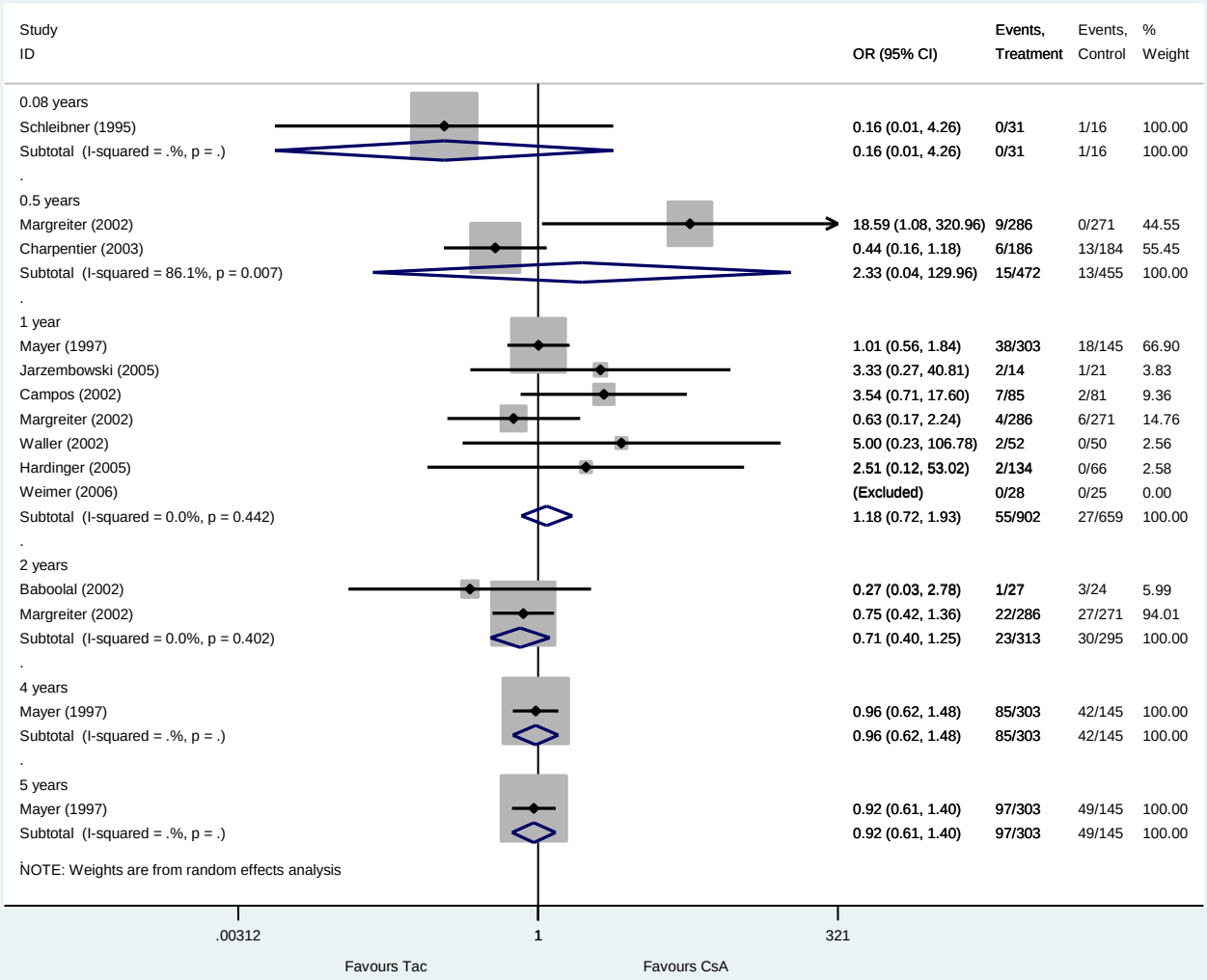
generating an OR of 1.18 and 95% CI 0.72 to 1.93. However, as with mortality, the results for graft loss suggest no difference between TAC and CSA. This lack of preference for either treatment remains at 5 years (OR 0.92, 95% CI 0.61 to 1.40).

Table 32. Graft loss for TAC+AZA vs CSA+AZA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Schleibner, 2005	0.08 years	1	0.16	0.01 – 4.26	NA	NA
Margreiter, 2002; Charpentier, 2003	0.5 years	2	2.33	0.04 – 129.96	86.1%	7.34
Mayer 1997, Jarzembowski 2005, Campos 2002, Margreiter 2002, Waller 2002, Hardinger 2005, Weimer 2006	1 year	7[a]	1.18	0.72 – 1.93	0.0%	0.0
Baboolal, 2002; Margreiter 2002	2 years	2	0.71	0.40 – 1.25	0.0%	0.0
Mayer, 1997	4 years	1	0.96	0.62 – 1.48	NA	NA
Mayer, 1997	5 years	1	0.92	0.61 – 1.40	NA	NA

Notes: (a) One trial excluded from pooled analysis due to no deaths in either arm

Figure 21. Forest plot - graft loss for TAC+AZA vs CSA+AZA



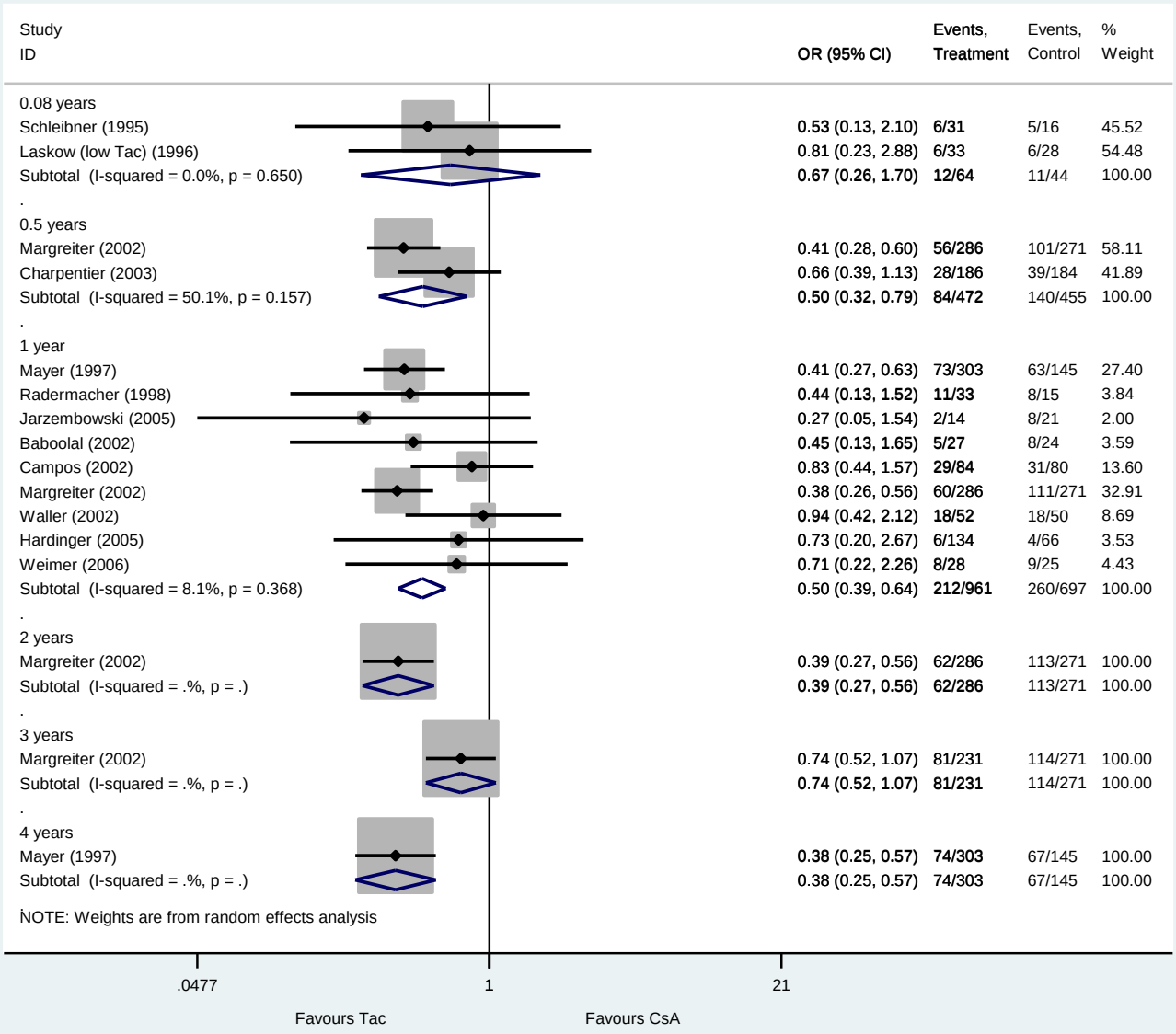
Biopsy proven acute rejection

All time points from 0.08 to 4 years reveal ORs below one for BPAR, indicating that TAC is more effective than CSA in reducing this outcome (Table 33; Figure 22).[74 88 93 94 96 99-103 108 125] BPAR outcomes were reported by nine studies at one year, where pooled analysis gives an OR of 0.50 and 95% CI 0.39 to 0.64. Minimal heterogeneity is indicated across the studies at year one (I^2= 8.1%). Mayer et al. 1997 report BPAR at 4 years, where the beneficial effect of TAC appears to be maintained (OR 0.38, 95% CI 0.25 to 0.57).[96]

Table 33. Biopsy proven acute rejection for TAC+AZA vs CSA+AZA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Schleibner, 2005; Laskow 1996	0.08 years	2	0.669	0.263 – 1.70	0.0%	0.00
Margreiter, 2002; Charpentier, 2003	0.5 years	2	0.50	0.32 – 0.79	50.1%	0.06
Mayer 1997, Radermacher, 1998, Jarzembowski 2005, Baboolal, 2002; Campos 2002, Margreiter 2002, Waller 2002, Hardinger 2005, Weimer 2006	1 year	9	0.50	0.39 – 0.64	8.1%	0.01
Baboolal, 2002; Margreiter 2002	2 years	1	0.39	0.27 – 0.56	NA	NA
Mayer, 1997	3 years	1	0.74	0.52 – 1.07	NA	NA
Mayer, 1997	4 years	1	0.38	0.25 – 0.57	NA	NA

Figure 22. Forest plot – BPAR for TAC+AZA vs CSA+AZA



Notes: Only the low dose TAC arm is used for Lorber et al. 1996), since this is closest to the dose used in practice

Graft function

Graft function was measured and reported by four studies, with effects measured from 0.08 to 3 years. No meta-analysis is provided for graft function, since the results are presented in a number of ways and not appropriate for pooling [73 74 93 103]. In general, Table 34 shows some variation between arms with large standard deviations, for example, results presented by Margreiter et al. 2002 at one year imply an improved graft function for TAC, as opposed to CSA (68.9 (sd 23.2) ml/min and 61.8 ml/min (sd 23.2), respectively), which is in contrast

to Van Duijnhoven et al. 2002 who report 60.2 ml/min (range 11.5 to 86.2) and 64.9 (range 29.5 to 84.5), respectively. This conflict between studies is seen at all time points.

Table 34. Graft function for TAC+AZA vs CSA+AZA

Study id	Time point	TAC, mean ml/min (sd)	CSA, mean ml/min (sd)	Mean difference	95% CI	P value (*t*-Test)
Schleibner, 1995[a]	0.08 years	50.3 (16.25)	48.52 (22.5)	0.0959	-0.5078 – 0.6995	0.3114
Van Duijnhoven, 2002	0.25 years	41.7 (13.5-100.2)	60.5 (26.8 – 74.5)	NA	NA	NA
Margreiter,2002	0.5 years	44.8 (13.6 – 106.1)	65.1 (29.6 – 84.2)	NA	NA	NA
Margreiter, 2002	1 year	68.9 (23.2)	61.8 (23.2)	0.3106	0.1434 – 0.4777	0.003
Van Duijnhoven, 2002		60.2 (11.5 – 86.2)	64.9 (29.5 – 84.5)	NA	NA	NA
Waller, 2002 [c]		47 (14)	47 (18)	0	-0.392 – 0.392	1.000
Margreiter, 2002	2 years	68.9 (23.2)	61.8 (23.2)	0.3106	0.1434 – 0.4777	0.003
Van Duijnhoven, 2002		60.6 (10.0 – 99.2)	57.1 (18.8 – 79.2)	NA	NA	NA
Margreiter,2002	3 years	67.3 (23.6)	64.0 (23.9)	0.139	-0.0274 – 0.3053	0.1017
Van Duijnhoven 2002		64.0 (38.9 – 97.9)	66.9 (9.5 – 94.2)	NA	NA	NA

Notes: All methods either reported as CrCl or Cockcroft gault unless otherwise stated
Key: (a) Iothalmate method; (b) median and range; (c) method of estimation unclear

Time to biopsy proven acute rejection

Time to first BPAR is reported by only two studies, with contrasting results (Table 35).[101 102] However, the difference between arms for Campos et al. 2002 is not statistically significant (p=0.6631).[102] The results reported by Baboolal et al. 2002) indicate that BPAR is achieved more quickly for participants receiving TAC (35 days, sd 13) rather than CSA (59 days, sd 38).[101]

Table 35. Time to BPAR for TAC+AZA vs CSA+AZA

Study	Mean time to BPAR, days (sd)		P value (*t*-Test)
	TAC	CSA	
Baboolal 2002	35 (13)	59 (38)	0.0033
Campos 2002	14.5 (47.3)	12.0 (21.0)	0.6631

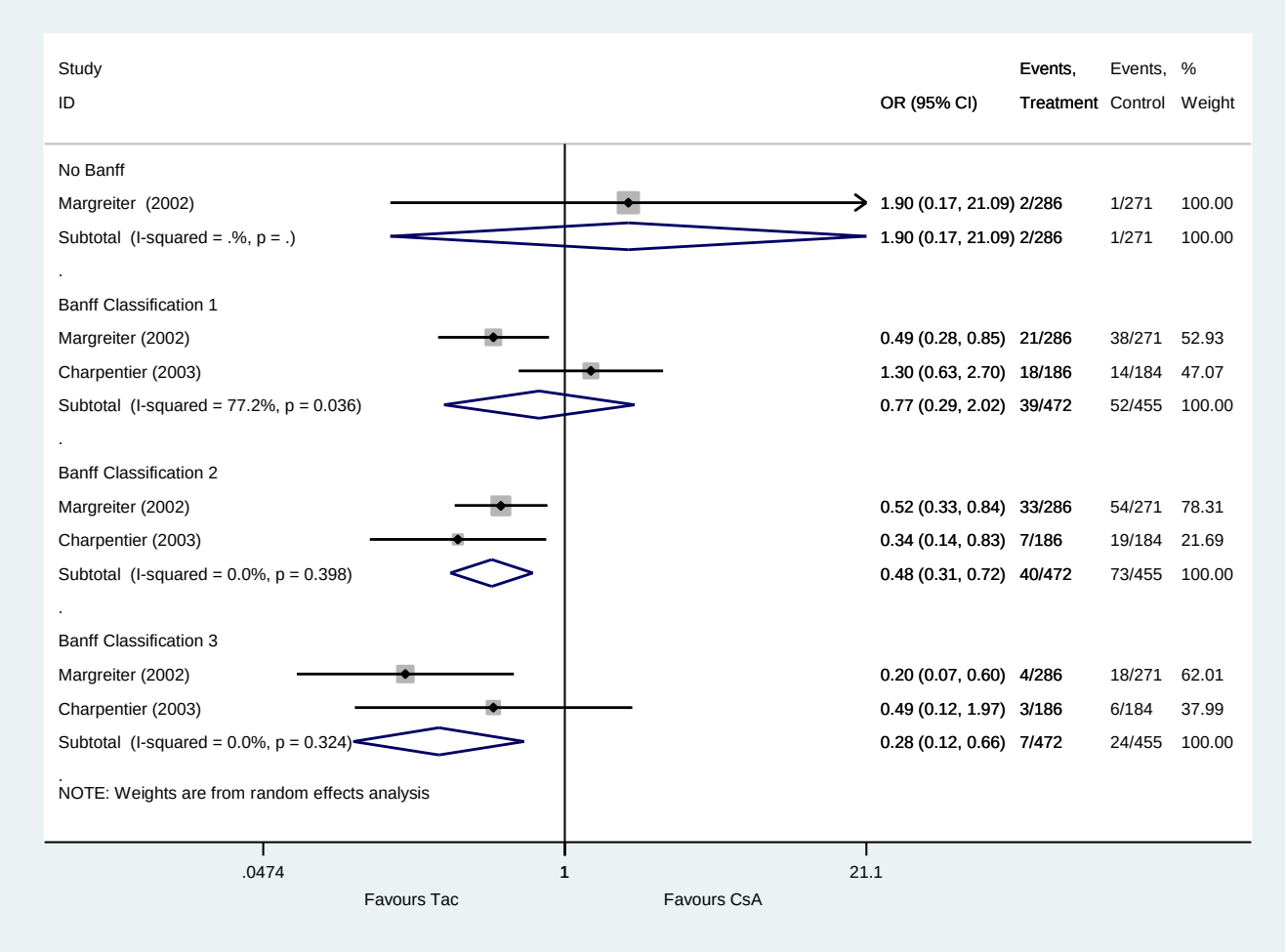
Severity of biopsy proven acute rejection

Severity of BPAR has been meta-analysed according to time point. Two trials report on the 0.5 year time point (Table 36; Figure 23).[88 103] The OR of <1 for indicate lower odds of all three Banff classifications (1 to 3) in the TAC arm, as opposed to CSA. These results must be treated with some caution due to the heterogeneity across studies for Banff 1 (I^2 77.2%).

Table 36. Severity of BPAR at 6 months for TAC+AZA vs CSA+AZA

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Margreiter, 2002	None	1	1.90	0.17 – 21.09	NA	NA
Margreiter, 2002; Charpentier, 2003	1	2	0.77	0.29 – 2.02	77.2%	0.3746
	2	2	0.48	0.31 – 0.72	0	0
	3	2	0.28	0.12 – 0.66	0	0

Figure 23. Forest plot – severity of BPAR at 0.5 years for TAC+AZA vs CSA+AZA



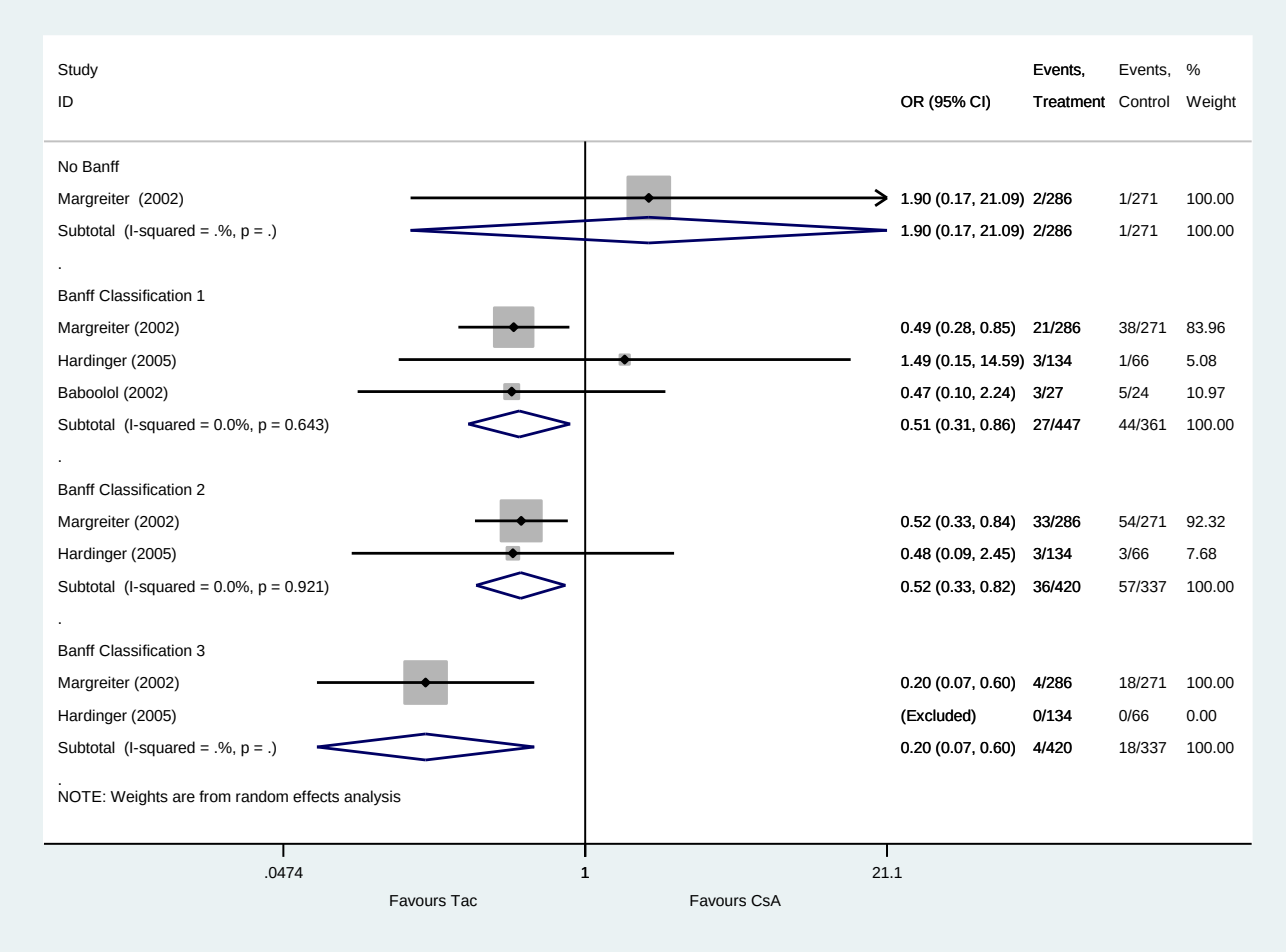
Three trials report on the one year time point.[101 103 108]. As for the 0.5 year timepoint, the OR of <1 for indicate lower odds of all three Banff classifications (1 to 3) in the TAC arm, as opposed to CSA (Table 37; Figure 24). Therefore, at this time point there is evidence of a lower severity of BPAR with TAC.

Table 37. Severity of BPAR at 1 year for TAC+AZA vs CSA+AZA

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Margreiter, 2002	None	1	1.90	0.17 – 21.09	NA	NA
Margreiter, 2002, Hardinger, 2005; Baboolol, 2002	1	3	0.51	0.31 – 0.86	0	0
Margreiter, 2002, Hardinger, 2005	2	2	0.52	0.33 – 0.82	0	0
Margreiter, 2002, Hardinger, 2005	3	2[a]	0.20	0.07 – 0.60	NA	NA

Notes: (a) One trial excluded due as there were no classifications at Banff 3

Figure 24. Forest plot – severity of BPAR at 1 year for TAC+AZA vs CSA+AZA

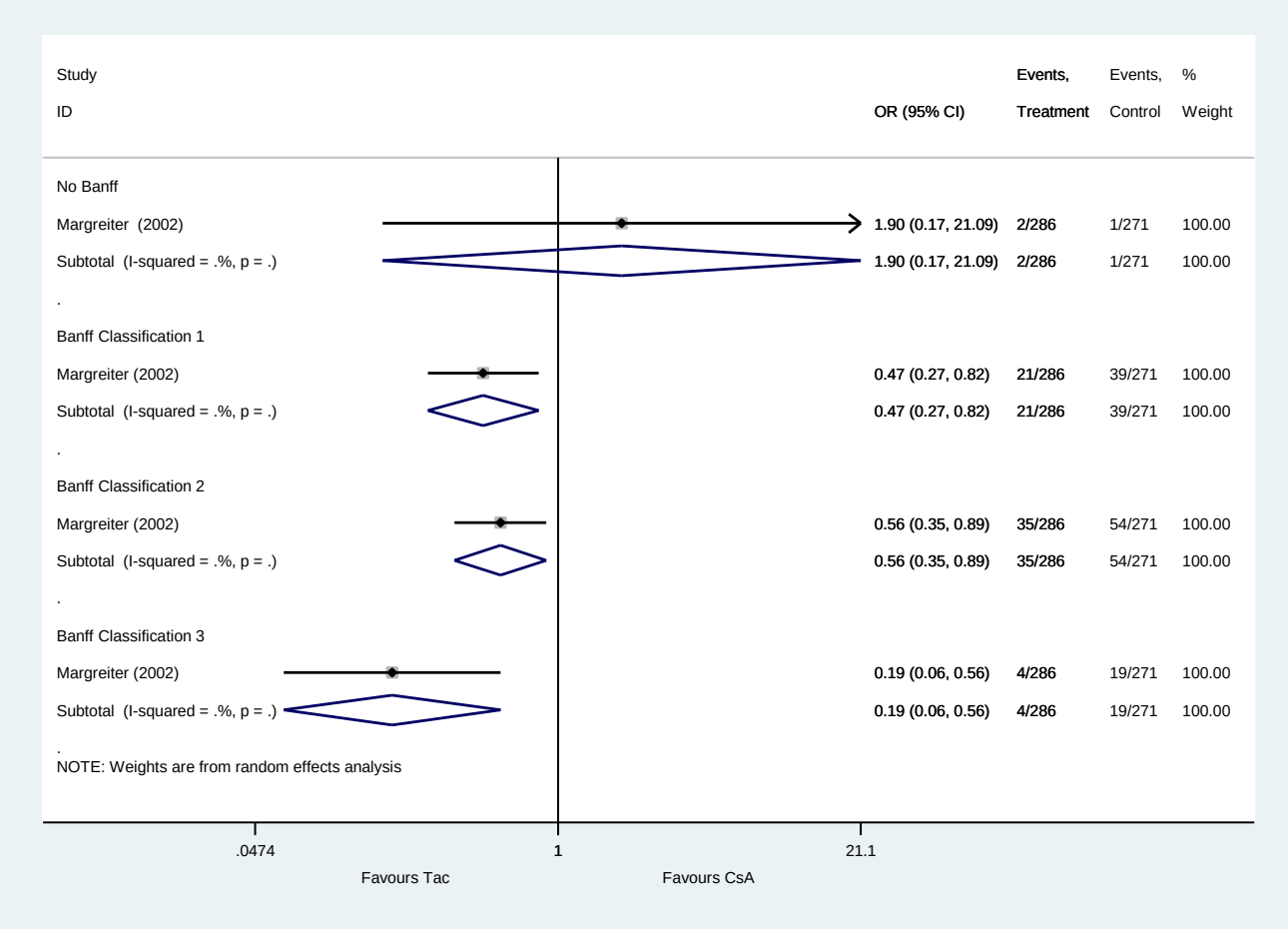


Only one trial reports at two years (Table 38; Figure 25) and results are consistent with the previous time points.[103]

Table 38. Severity of BPAR at 2 years forTAC+AZA vs CSA+AZA

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Margreiter, 2002	None	1	1.90	0.17 – 21.09	NA	NA
	1	1	0.47	0.27 – 0.82	NA	NA
	2	1	0.56	0.35 – 0.89	NA	NA
	3	1	0.19	0.06 – 0.56	NA	NA

Figure 25. Forest plot – severity of BPAR at 2 years for TAC+AZA vs CSA+AZA



Summary of results for TAC+AZA vs CSA+AZA

- Ten studies report mortality, with meta-analysis possible at the 0.5 and 1 year time points. [74 88 93 94 96 100 102 103 108 125]. At 0.5 years, pooled results of only two studies

generates an OR of 0.54, 95% CI 0.18 to 1.62, indicating lower odds of mortality for TAC, however, the large confidence intervals overlap the null value (OR=1) therefore there is unlikely to be a significant difference between treatments. Although the OR at one year, which includes eight studies, has shifted to 1.51, indicating reduced odds of mortality in the CSA arm, the 95% CI of 0.75 to 3.06 also suggest no significant difference between treatments.[74 94 96 100 102 103 108 125]. Heterogeneity across studies for the one year time point is low and may not be important at this level according to the Cochrane Handbook (I2 14.8%).[198]

- Graft loss is reported for ten trials). [74 88 93 94 96 100 102 103 108 125]. Results were pooled for the 0.5, 1 and 2 year time points. The pooling of trials reported by Margreiter et al. 2002) and Charpentier et al. 2003), at 0.5 years give an OR of 2.33 with 95% CI 0.04 to 129.96.[103] The wide confidence intervals and the I^2 of 86.1% indicate substantial heterogeneity and low precision. The one year time point is more reliable, where seven studies are pooled generating an OR of 1.18 and 95% CI 0.72 to 1.93. However, as with mortality, the results for graft loss suggest no difference between TAC and CSA. This lack of preference for either treatment remains at 5 years (OR 0.92, 95% CI 0.61 to 1.40).

- All time points from 0.08 to 4 years reveal ORs below one for BPAR, indicating that TAC is more effective than CSA in reducing this outcome. BPAR outcomes were reported by nine studies at one year, where pooled analysis gives an OR of 0.50 and 95% CI 0.39 to 0.64. Low heterogeneity is indicated across the studies at year one (I^2= 8.1%). Mayer et al. 1997) report BPAR at 4 years, where the beneficial effect of TAC appears to be maintained (OR 0.38, 95% CI 0.25 to 0.57).

- Graft function was measured and reported by four studies, with effects measured from 0.08 to 3 years. No meta-analysis is possible, since the results are presented in a number of ways and not appropriate for pooling. In general, there is some variation between arms with large standard deviations, for example, results presented by Margreiter et al. 2002) at one year imply an improved graft function for TAC, as opposed to CSA (68.9 (sd 23.2) ml/min and 61.8 ml/min (sd 23.2), respectively), which is in contrast to Van Duijnhoven et al. 2002) who report 60.2 ml/min (range 11.5 to 86.2) and 64.9 (range 29.5 to 84.5), respectively. This conflict between studies is seen at all time points.

- Time to first BPAR is reported by only two studies, with contrasting results. However, the difference between arms for Campos et al. 2002) is not statistically significant

(p=0.6631). The results reported by Baboolal et al. 2002) indicate that BPAR is achieved more quickly for participants receiving TAC (35 days, sd 13) rather than CSA (59 days, sd 38).

- Severity of BPAR has been meta-analysed according to time point. Two trials report on the 0.5 year time point.[88 103]. The OR of <1 for indicate lower odds of all three Banff classifications (1 to 3) in the TAC arm, as opposed to CSA. These results must be treated with some caution due to substantial heterogeneity across studies for Banff 1 (I^2 77.2%).

4.3.2.2. CSA+MMF vs CSA+AZA

Seven studies report on this combination of immunosuppressive therapies, with a follow-up of five years. [75 76 113-115 125 200] All outcomes have been reported other than HRQoL.

Mortality

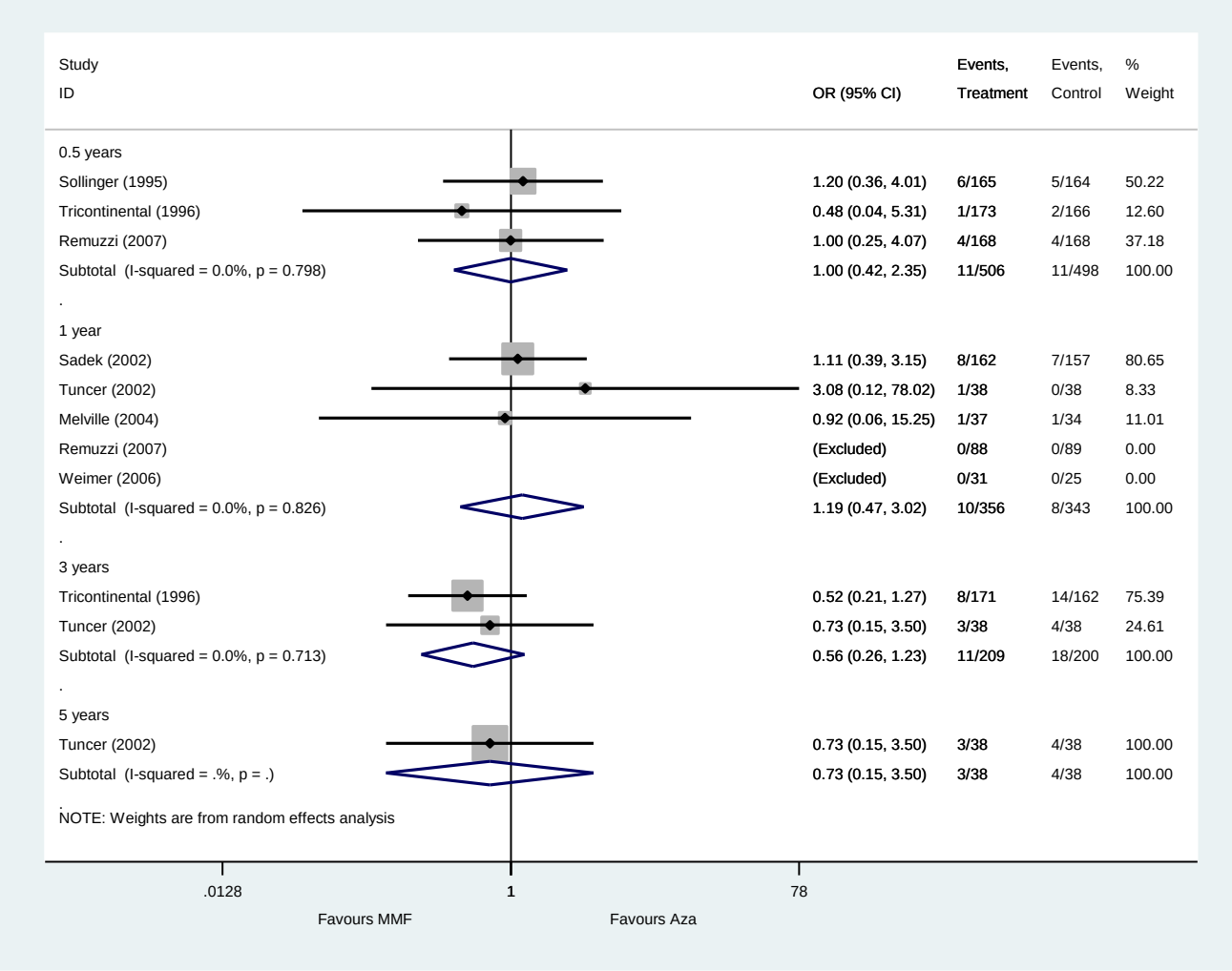
Seven studies report on mortality for CSA+MMF vs CSA+AZA. [75 76 113-115 125 200] Pooling results of five studies for this combination imply no difference between arms at one year, with no evidence of heterogeneity across studies (Table 39). [76 113-115 125]The ORs switch from >1 to <1, for the pooled results at 1 and 3 years, however, the confidence intervals cross OR=1 in both cases, suggesting there may be no difference betwee MMF and AZA (OR 1.19, 95% CI 0.47 to 3.02 and 0.56, 95% CI 0.26 to 1.23).The study reported by Tuncer et al. 2002 provides data at five years, which also indicates no preference for either MMF or AZA (OR 0.73, 95% CI 0.15 to 3.50).

Table 39. Mortality for CSA+MMF vs CSA+AZA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Sollinger, 1995; Tricontinental, 1996; Remuzzi, 2007	0.5 years	3	1.00	0.42 – 2.35	0	0
Sadek, 2002; Tuncer, 2002; Merville, 2004; Remuzzi, 2007; Weimer, 2006	1 year	5[a]	1.19	0.47 – 3.02	0	0
Tricontinental, 1996; Tuncer, 2002	3 years	2	0.56	0.26 – 1.23	0	0
Tuncer, 2002	5 years	1	0.73	0.15 – 3.50	NA	NA

Key: (a) 2 trials excluded from pooled analysis due to no deaths in both arms; NA, not applicable

Figure 26. Forest plot – mortality for CSA+MMF vs CSA+AZA



Graft loss

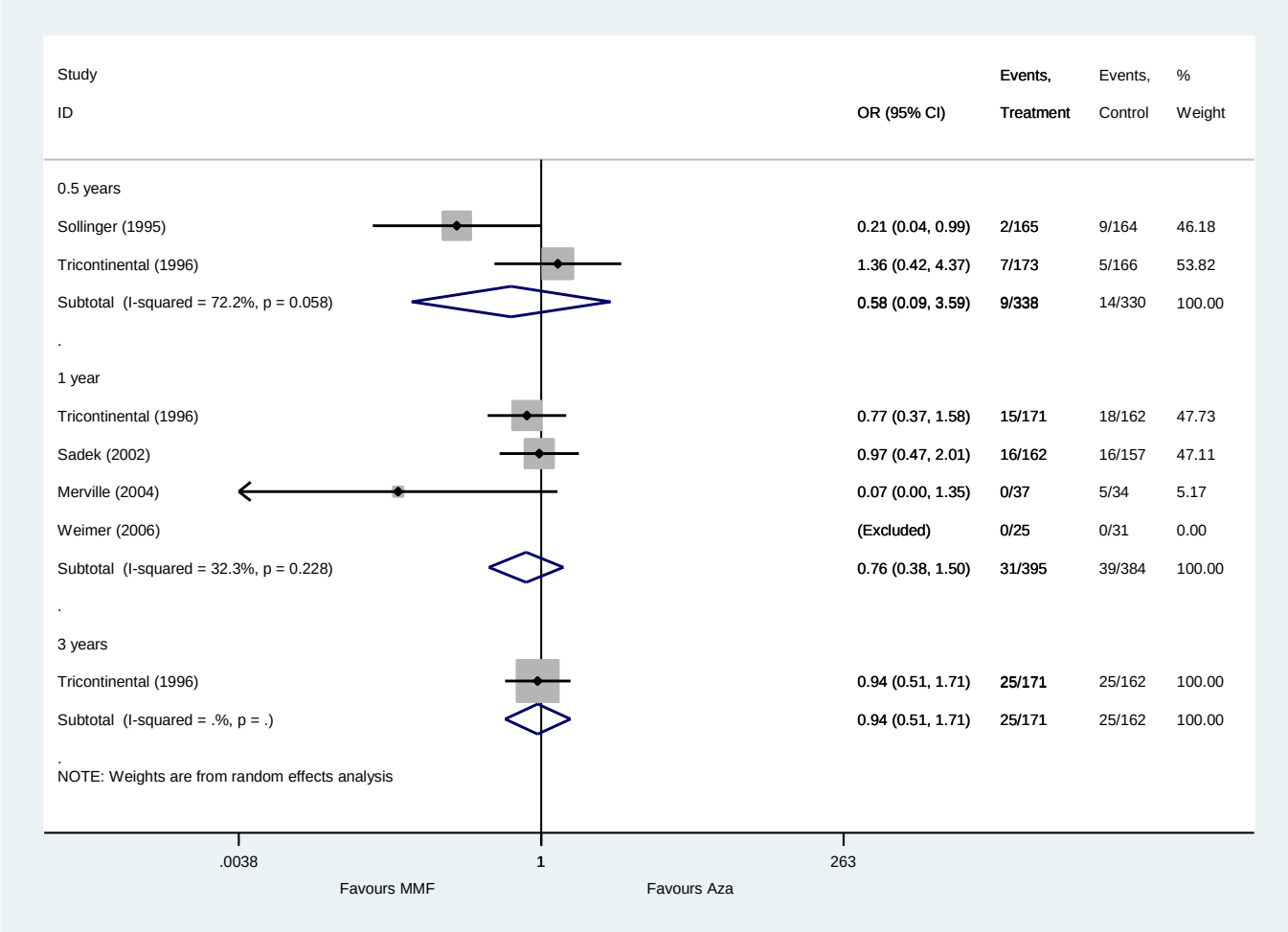
Five studies report on graft loss, with results pooled at 0.5 and 1 year time points (Table 40;Figure 27). [75 113 114 125 200] However, the 0.5 year timepoint only has two studies and a substantial level of heterogeneity (I^2 72.2%), therefore the OR of 0.58 and 95% CI 0.04 to 0.59, which indicates that MMF is more effective at reducing graft loss, must be treated with caution. [198]The results for 1 year suggest no difference between arms (OR 0.76, 95% CI 0.38 to 1.50). Merville et al. 2004) appears to show more of an effect in favour of MMF, however, the population is much smaller than that for the Tricontinental study 1996 and Sadek et al. 2002.[113 114 200] Weimer et al. 2006 found no evidence of graft loss in either arm. [125]

Table 40. Pooled results of graft loss for CSA+MMF vs CSA+AZA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Sollinger, 1995; Tricontinental, 1996	0.5 years	2	0.58	0.04 – 0.59	72.2%	1.2684
Tricontinental, 1996; Sadek, 2002; Merville, 2004; Weimer, 2006	1 year	4	0.76	0.38 – 1.50	32.3%	0.1203
Tricontinental, 1996	3 years	1	0.94	0.51 – 1.71	NA	NA

Key: NA, not applicable

Figure 27. Forest plot – graft loss for CSA+MMF vs CSA+AZA



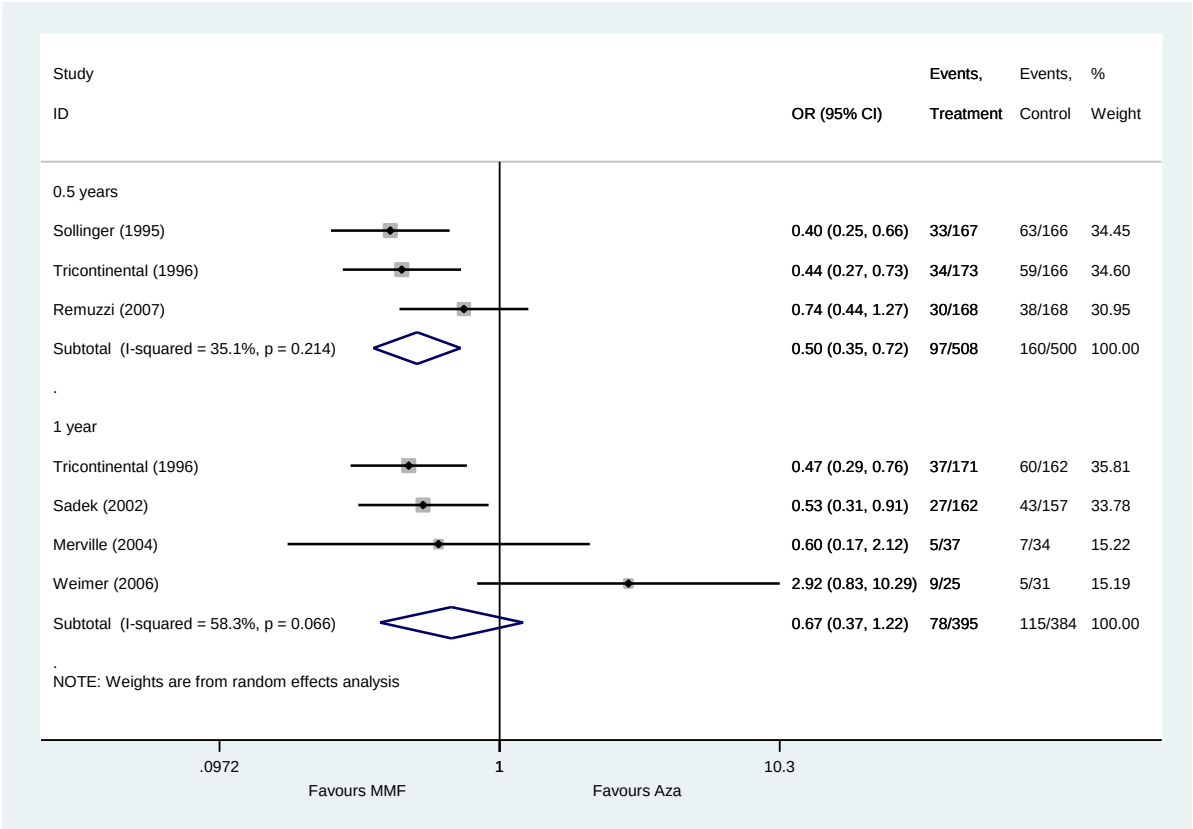
Biopsy proven acute rejection

Six studies report on BPAR. [75 113-115 125 200] Unlike mortality and graft loss, BPAR analysis reveals that MMF is more beneficial than AZA at 0.5 and 1 year (0.5 year OR 0.50, 95% CI 0.35 to 0.72; 1 year OR 0.67, 95% CI 0.37 to 1.22) (Table 41; Figure 28). The results for Weimer et al. 2006) appear to be in contrast, however, the recruited population is small (OR 2.92, 95%CI 0.83 to 10.29).[125]

Table 41. Pooled results of BPAR for CSA+MMF vs CSA+AZA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Sollinger, 1995; Tricontinental, 1996; Remuzzi 2007	0.5 years	3	0.50	0.35 – 0.72	35.1%	0.0361
Tricontinental, 1996; Sadek, 2002; Merville, 2004; Weimer, 2006	1 year	4	0.67	0.37 – 1.22	58.3%	0.1978

Figure 28. Forest plot – BPAR for CSA+MMF vs CSA+AZA



Graft function

Only Merville et al. 2004 reported on this outcome, where at 6 months mean graft function as CrCl was greater for the MMF arm, however, this was reversed at one year where AZA had greater graft function (Table 42).[114] There is no significant difference between arms (0.5 years, p=0.7236; 1 year, p=0.6584)

Table 42. Graft function for CSA+MMF vs CSA+AZA

Study	Time	MMF, mean (sd)	AZA, mean (sd)	Mean difference[a]	95% CI[a]	P value (*t*-Test)
Merville, 2004	0.5 years	60.4 (17.3)	58.5 (27.1)	0.08	-0.38 – 0.55	0.72
	1 year	61.3 (15.8)	63.1 (16.8)	-0.11	-0.58 - 0.35	0.66

Time to biopsy proven acute rejection

Insufficient data is provided for analysis on this outcome. Merville et al. 2004 report 48.5 days for MMF and 43.7 days for AZA.[114]

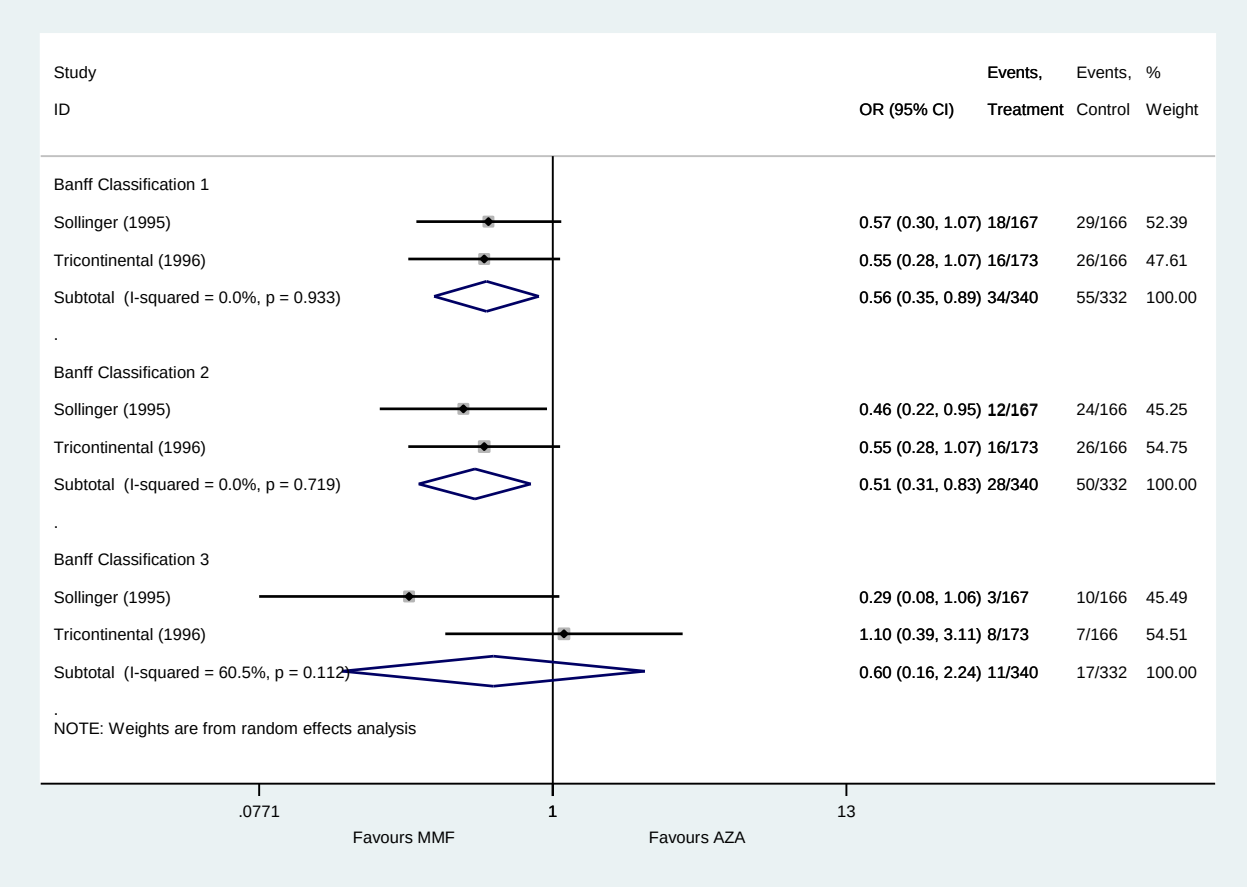
Severity of biopsy proven acute rejection

Two studies were available for 0.5 years, which enabled pooling (Table 43; Figure 29).[75 200] The odds ratio indicates a lower association with any Banff classification for CSA+MMF , however, there is substantial heterogeneity and a lack of statistical significance across the two studies for Banff classification 3, therefore there is no evidence for more severe BPAR (I^2 60.5%).

Table 43. Severity of BPAR at 6 months for CSA+MMF vs CSA+AZA

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Sollinger, 1995; Tricontinental, 1996	1	2	0.56	0.35 – 0.89	0.0%	0
	2	2	0.51	0.31 – 0.83	0.0%	0
	3	2	0.60	0.16 – 2.24	60.5%	0.5552

Figure 29. Forest plot – severity of BPAR at 0.5 years for CSA+MMF vs CSA+AZA

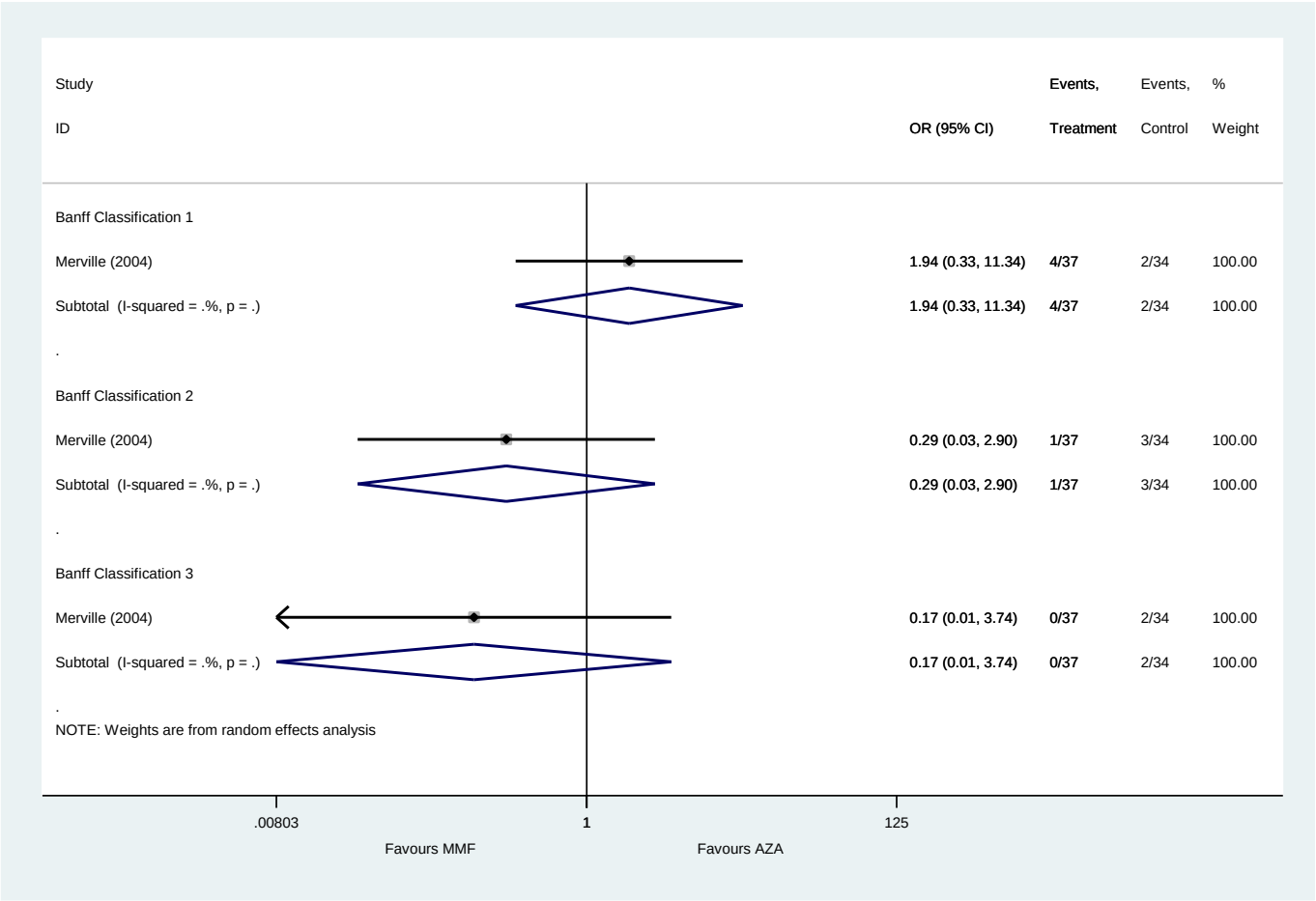


Only the study by Merville et al. 2004 provided data on severity of BPAR by one year (Table 44; Figure 30).[114] The recruitment numbers are low, therefore caution is required with interpretation of the results. Overall,the more severe classifications of Banff 2 and 3 appear to be more likely in the AZA arm, however, the confidence intervals cross OR=1 and therefore there may be no true difference between interventions.

Table 44. Severity of BPAR at 1 year for CSA+MMF vs CSA+AZA

Study id	Banff classification	CSA+MMF, n/N (%)	CSA+AZA, n/N (%)	Odds ratio	95% CI
Merville, 2004	1	4/37 (11)	2/34 (5)	1.94	0.33 – 11.34
	2	1/37 (3)	3/34 (9)	0.29	0.03 – 2.90
	3	0/37 (0)	2/34 (6)	0.17	0.01 – 3.74

Figure 30. Forest plot – severity of BPAR at one year for CSA+MMF vs CSA+AZA



Summary of results for CSA+MMF vs CSA+AZA

- Seven studies report on mortality for CSA+MMF vs CSA+AZA. [75 76 113-115 125 200] Pooling results of five studies for this combination imply no difference between arms at one year, with no evidence of heterogeneity across studies. [76 113-115 125]The ORs switch from >1 to <1, for the pooled results at 1 and 3 years, however, the confidence intervals cross OR=1 in both cases, suggesting there may be no difference betwee MMF and AZA (OR 1.19, 95% CI 0.47 to 3.02 and 0.56, 95% CI 0.26 to 1.23).The study reported by Tuncer et al. (2002) provides data at five years, which also indicates no preference for either MMF or AZA (OR 0.73, 95% CI 0.15 to 3.50).

- Five studies report on graft loss, with results pooled at 0.5 and 1 year time points. [75 113 114 125 200] However, the 0.5 year timepoint only has two studies and a substantial level of heterogeneity (I^2 72.2%), therefore the OR of 0.58 and 95% CI 0.04 to 0.59, which indicates that MMF is more effective at reducing graft loss, must be treated with caution. [198]The results for 1 year suggest no difference between arms (OR 0.76,

95% CI 0.38 to 1.50). Merville et al. (2004) appears to show more of an effect in favour of MMF, however, the population is much smaller than that for the Tricontinental study (1996) and Sadek and colleages (2002). }[113 114 200]

- Six studies report on BPAR. [75 113-115 125 200] Unlike mortality and graft loss, BPAR analysis reveals that MMF is more beneficial than AZA at 0.5 and 1 year (0.5 year OR 0.50, 95% CI 0.35 to 0.72; 1 year OR 0.67, 95% CI 0.37 to 1.22).

- Only Merville et al. (2004) reported on this outcome, where at 6 months mean graft function was greater for the MMF arm, however, this was reversed at one year where AZA had greater graft function. [114] There is no significant difference between arms (0.5 years, p=0.7236; 1 year, p=0.6584)

- Insufficient data is provided for analysis on time to BPAR. Merville et al. (2004) report a slightly more rapid rate of 48.5 days for MMF and 43.7 days for AZA.

- Two studies were available for 0.5 years, which enabled pooling.[75 200] The odds ratio indicates a lower association with any Banff classification for CSA+MMF , however, there is substantial heterogeneity and a lack of statistical significance across the two studies for Banff classification 3 (I^2 60.5%). Only the study by Merville et al. 2004 provided data on severity of BPAR by one year. [114] Overall,the more severe classifications of Banff 2 and 3 appear to be more likely in the AZA arm, however, the confidence intervals cross OR=1 and therefore there may be no true difference between interventions.

4.3.2.3. TAC+MMF vs CSA+AZA

Two studies compare these combinations, Wlodarczyk et al. 2005 and Vacher-Coponat et al. 2012.[117 119] Graft function and time to BPAR are not reported.

Mortality

Wlodarczyk et al. 2005 reports mortality at 0.5 years and Vacher-Caponat et al. 2012 report at 1 year (Table 45).[117 119] In both cases the OR is >1, indicating that TAC+MMF is associated with greater odds of mortality, however, the 95% CI cross OR=1, implying no statistical difference between arms.

Table 45. Mortality for TAC+MMF vs CSA+AZA

Study id	Time point	TAC+MMF, n/N (%)	CSA+AZA, n/N (%)	Odds ratio	95% CI
Wlodarczyk, 2005	0.5 years	239/243 (98)	242/246 (98)	1.0126	0.25 – 4.09
Vacher-Caponat, 2012	1 year	139/143 (97)	144/146 (99)	2.0719	0.37 – 11.49

Graft loss

As with mortality, there is only one study for each time point of 0.5 years and 1 year (Table 46).[117 119] The wide confidence intervals highlight the low precision and indicate no difference between arms.

Table 46. Graft loss for TAC+MMF vs CSA+AZA

Study	Time point	TAC+MMF, n/N (%)	CSA+AZA, n/N (%)	Odds ratio	95% CI
Wlodarczyk, 2005	0.5 years	231/243 (95)	230/246 (93)	0.75	0.35 – 1.61
Vacher-Caponat, 2012	1 year	133/143 (93)	140/146 (96)	1.75	0.62 – 4.96

Notes: All percentages calculated by PenTAG

Biopsy proven acute rejection for TAC+MMF vs CSA+AZA

Only two studies have reported BPAR, one at 0.5 years and one at the 1 year time point (Table 47).[117 119] In both cases the OR is <1, indicating that TAC+MMF is associated with lower odds of BPAR (OR 0.6368, 95% CI 0.4154 to 0.9763; OR 0.3527, 95% CI 0.1508 to 0.8252, respectively).

Table 47. BPAR for TAC+MMF vs CSA+AZA

Study id	Time point	TAC+MMF, n/N (%)	CSA+AZA, n/N (%)	Odds ratio	95% CI
Wlodarczyk, 2005	0.5 years	46/243 (19)	66/246 (27)	0.6368	0.41 – 0.98
Vacher-Caponat, 2012	1 year	8/143 (6)	21/146 (14)	0.3527	0.15 – 0.82

Notes: All precentages calculated by PenTAG

Severity of biopsy proven acute rejection

This outcome is only reported by Vacher-Caponat et al. 2012, with no participants experiencing Banff 2 and 3 in the TAC+MMF arm, but with 2% and 3 % reported in the CSA+AZA arm, respectively (Table 48).[119]

Table 48. Severity of BPAR at one year for TAC+MMF vs CSA+AZA

Study id	Banff classification	TAC+MMF, n/N (%)	CSA+AZA, n/N (%)	Odds ratio	95% CI
Vacher-Caponat, 2012	No Banff	3/143 (2)	5/146 (3)	0.6043	0.1417 – 2.577
	1	6/143 (4)	14/146 (10)	0.4129	0.1541 – 1.1066
	2	0/143 (0)	3/146 (2)	NA	NA
	3	0/143 (0)	1/146 (1)	NA	NA

Key: NA, not applicable

Summary for TAC+MMF vs CSA+AZA

- Wlodarczyk et al. 2005 reports mortality at 0.5 years and Vacher-Caponat et al. 2012 report at 1 year.[117 119] In both cases the OR is >1, indicating that TAC+MMF is associated with greater odds of mortality, however, the 95% CI cross OR=1, implying no statistical difference between arms.

- Only one study reporting on graft loss at 0.5 years and 1 year. No significant difference is evident between treatments

- Only two studies have reported BPAR, one at 0.5 years and one at the 1 year time point.[117 119] In both cases the OR is <1, indicating that TAC+MMF is associated with

lower odds of BPAR (OR 0.6368, 95% CI 0.4154 to 0.9763; OR 0.3527, 95% CI 0.1508 to 0.8252, respectively).

- Severity of BPAR is only reported by one study, with the greater proportion of people experiencing Banff 2 and 3 in the CSA+AZA arm.

4.3.2.4. TAC+MMF vs CSA+MMF

This combination of immunosuppressive therapy was identified in five RCTs, with all outcomes, other than HRQoL reported. [120-122 188 201] The RCT reported by Grinyo et al. 2009 is also known as the Symphony study.

Mortality

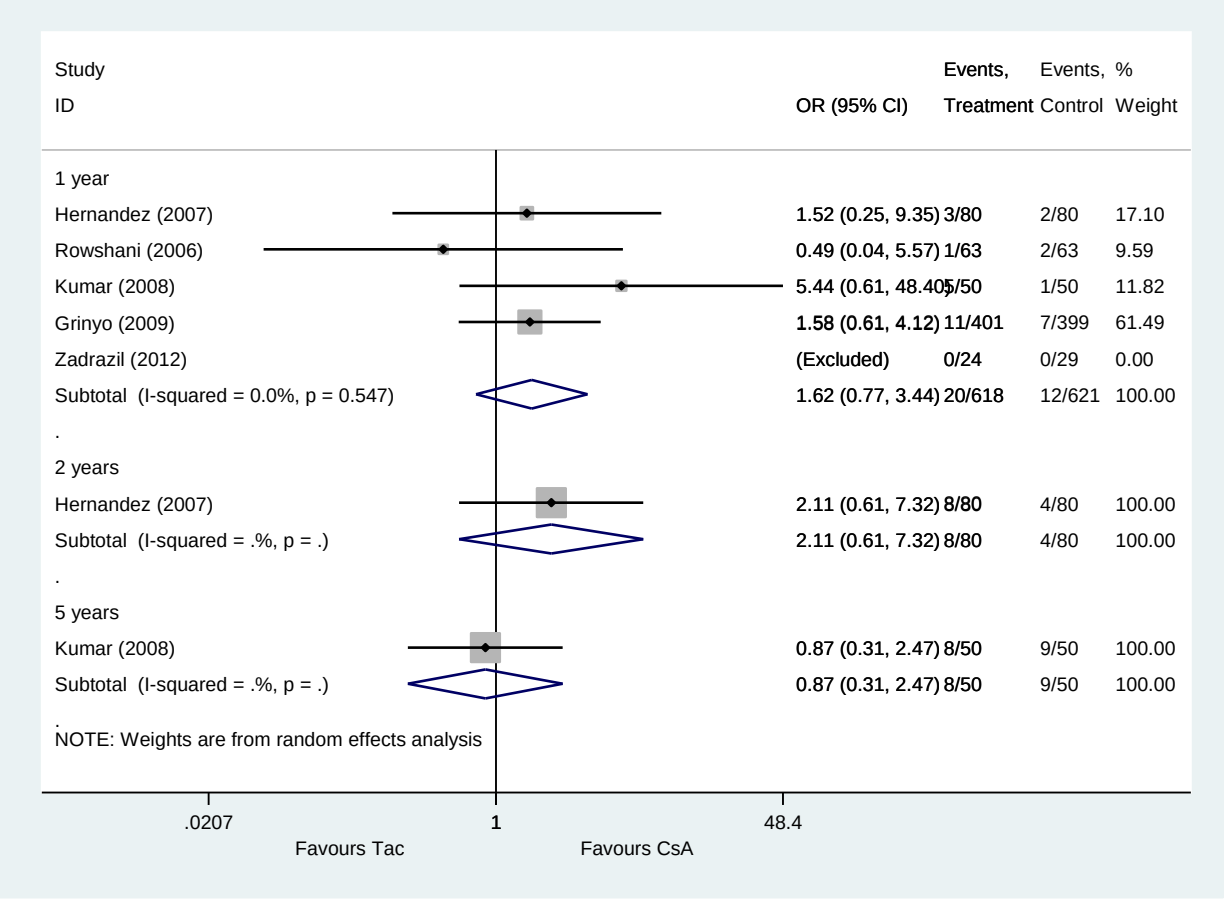
The effect estimate of five pooled studies at one year suggests TAC+MMF is associated with higher odds of mortality (OR 1.62; 95% CI 0.77 to 3.44) (Table 49; Figure 31). [120-122 188 201] However, although there is no evidence of hetereogeneity across studies (I^2 0.0%), the confidence intervals are wide and cross OR=1, indicating low precision and a lack of statistical significance. Results for two years and five years also demonstrate no statistically significant difference between treatments.

Table 49. Mortality for TAC+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Hernandez, 2007; Rowshani, 2006, Kumar, 2008; Grinyo, 2009; Zadrazil 2012	1 year	5[a]	1.62	0.77 – 3.44	0.0%	0.0
Hernandez, 2007;	2 years	1	2.11	0.61 – 7.32	NA	NA
Kumar, 2008	5 years	1	0.87	0.31 – 2.47	NA	NA

Notes: (a) One trial excluded from pooled analysis due to no deaths in either arm

Figure 31. Forest plot – mortality for TAC+MMF vs CSA+MMF



Graft loss

Graft loss is reported for five studies. [120-122 124 188 201] The OR for pooled results at one year and two years (1.43 and 1.63, respectively) imply greater odds of graft loss for TAC+MMF, however, the confidence intervals cross OR=1, indicating no difference between arms (Table 50; Figure 32).

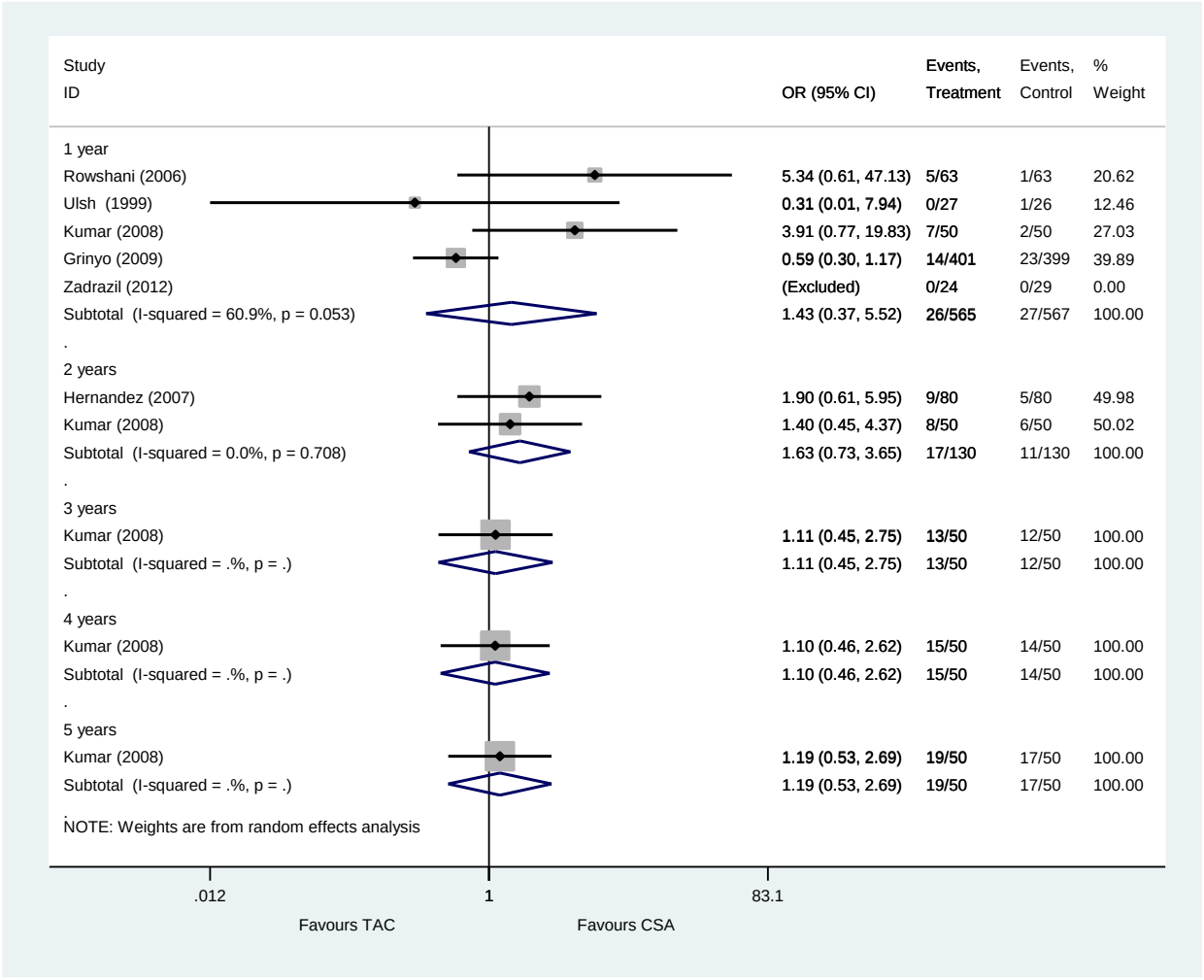
Kumar et al. 2008 report graft loss up to five years, with similar results of no difference between arms.[201]

Table 50. Graft loss for TAC+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Rowshani, 2006; Ulsh, 1999; Kumar, 2008; Grinyo, 2009; Zadrazil 2012	1 year	5[a]	1.43	0.37 – 5.52	11.4%	0.17
Hernandez, 2007; Kumar, 2008	2 years	2	1.63	0.73 – 3.65	0.0%	0.0
Kumar, 2008	3 years	1	1.11	0.45 – 2.75	NA	NA
	4 years	1	1.10	0.46 – 2.62	NA	NA
	5 years	1	1.19	0.53 – 2.69	NA	NA

Notes: (a) One trial excluded from pooled analysis due to no graft loss in either arm

Figure 32. Forest plot – graft loss for TAC+MMF vs CSA+MMF



Biopsy proven acute rejection for TAC+MMF vs CSA+MMF

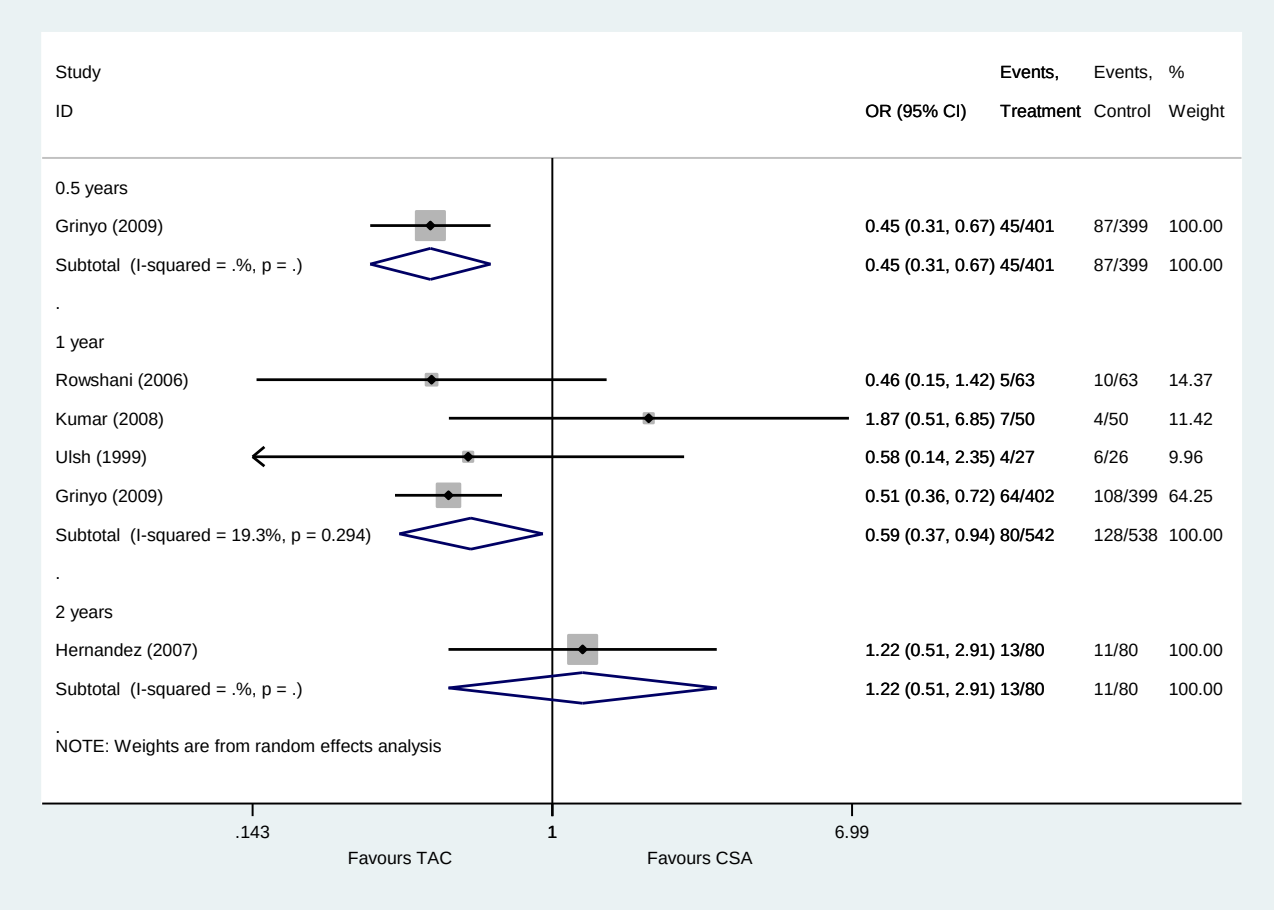
BPAR was reported by five studies, with four reporting at one year suitable for meta-analysis (Table 51; Figure 33). [120 122 124 188 201] The study at 0.5 years by Kumar et al. 2008 indicates that lower odds of BPAR are associated with TAC. This is in agreement with the pooled results at one year, although some heterogeneity is noted across studies (OR 0.59, 95% CI 0.37 to 0.94; I^2 19.3%). The study reported by Hernandez et al. 2007 at two years does not demonstrate a statistical difference between arms (OR 1.22; 95% CI 0.51 to 2.91). [121]

Table 51. BPAR for TAC+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Grinyo, 2009	0.5 years	1	0.45	0.31 – 0.67	NA	NA
Ulsh, 1999; Rowshani, 2006; Kumar, 2008; Grinyo, 2009	1 year	4	0.59	0.37 – 0.94	19.3%	0.06
Hernandez, 2007	2 years	1	1.22	0.51 – 2.91	NA	NA

Key: NA, not applicable

Figure 33. Forest plot – BPAR for TAC+MMF vs CSA+MMF



Graft function

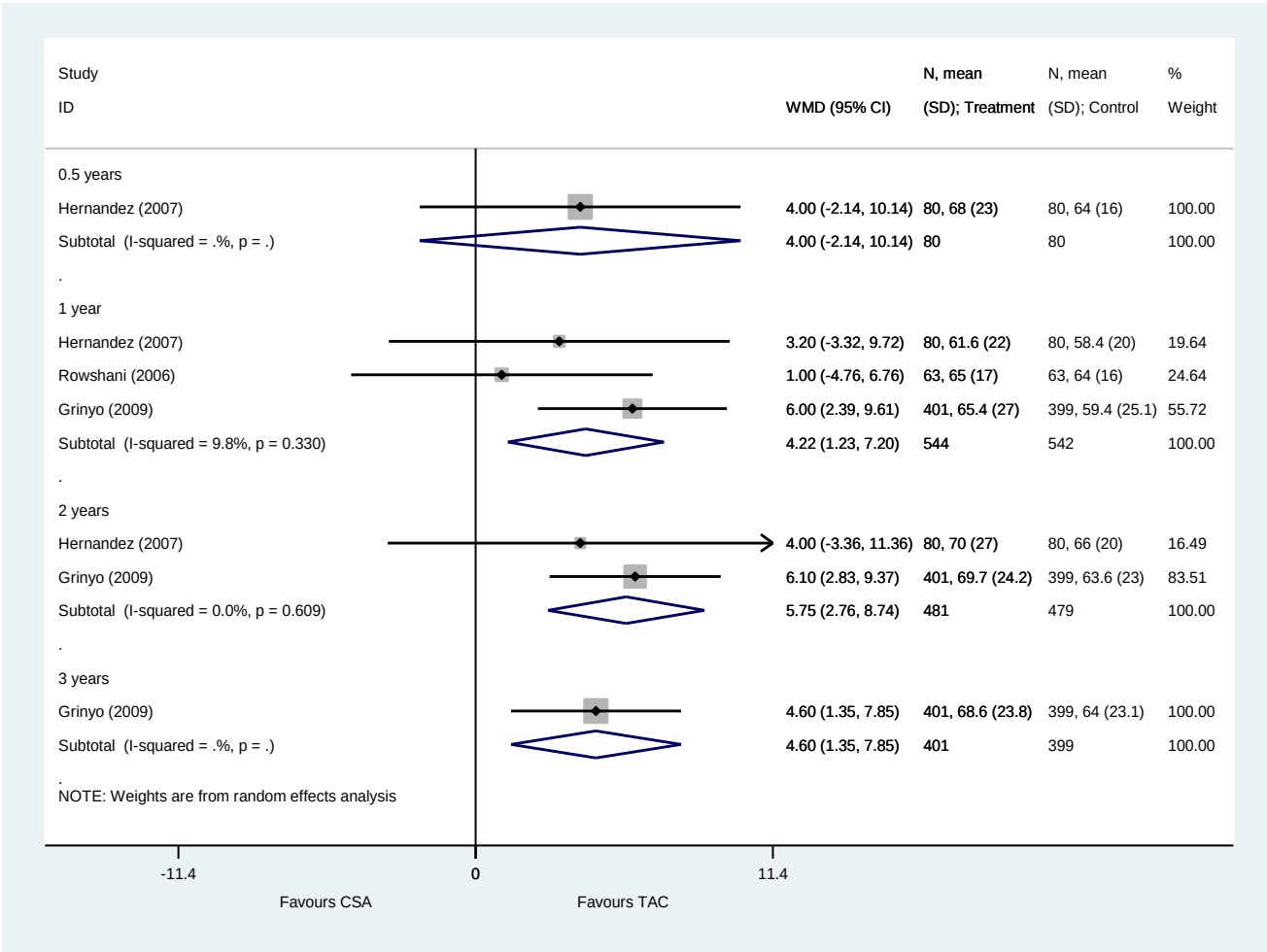
Graft function as CrCl is reported by three studies up to three years (Table 52; Figure 34). [121] [122] Pooling of results for year one and two year data demonstrated a statistically significant difference in graft function in favour of TAC (WMD 4.22 ml/min, 95% CI 1.23 to 7.20 and WMD 5.75, 95% CI 2.76 to 8.74, respectively). There is low evidence of heterogeneity across the one year studies (I^2 9.8%).

Table 52. Graft function for TAC+MMF vs CSA+MMF

Study id	Time point	Trials	Weighted mean difference	95% CI	I^2	Tau^2
Hernandez, 2007	0.5 years	1	4.00	-2.14 – 10.14	NA	NA
Hernandez, 2007; Rowshani, 2006, Grinyo, 2009	1 year	3	4.22	1.23 – 7.20	9.8%	0.77
Hernandez, 2007; Grinyo, 2009	2 years	2	5.75	2.76 – 8.74	0.0%	0.0
Grinyo, 2009	3 years	1	4.60	1.35 – 7.85	NA	NA

Key: NA, not applicable

Figure 34. Forest plot – graft function for TAC+MMF vs CSA+MMF



Time to biopsy proven acute rejection

Time to BPAR was reported by Ulsh et al. 1999, with a statistically significant difference in favour of TAC of 88.7 days (p value = 0.0001).[124]

Table 53. Time to BPAR for TAC+MMF vs CSA+MMF

Study id	Mean time to BPAR, days (sd)		P value (*t*-Test)[a]
	TAC	CSA	
Ulsh (1999)	88.7 (32.3)	42 (35.3)	<0.0001

Key: (a) Calculated by PenTAG

Severity of biopsy proven acute rejection

Two studies report severity of BPAR separately at one year and two years (Table 54).[121 188] For year one, results indicate that TAC+MMF is associated with increased odds of all three Banff classifications and this is statistically significant for Banff 1 and 2 (OR 2.51, 95% CI 1.52 to 4.15 and OR 2.79, 95% CI 1.51 to 5.14, respectively). [188] The study by Hernandez et al. 2007 indicates no significant difference for all three classifications.[121]

Table 54. Severity of BPAR at one year for TAC+MMF vs CSA+MMF

Study	Time point	Banff classification	TAC, n/N (%)	CSA, n/N (%)	Odds ratio	95% CI
Grinyo, 2009	1 year	1	55/399 (14)	24/401 (6)	2.51	1.52 - 4.15
		2	39/399 (10)	15/401 (4)	2.79	1.51 - 5.14
		3	8/399 (2)	3/401 (0.7)	2.71	0.71 – 10.28
Hernandez, 2007	2 years	1	7/80 (9)	6/80 (8)	1.1826	0.38 – 3.69
		2	4/80 (0.05)	4/80 (0.05)	NA	NA
		3	2/80 (0.03)	1/80 (0.01)	NA	NA

Notes: All precentages calculated by PenTAG

Summary of results for TAC+MMF vs CSA+MMF

- The effect estimate of five pooled studies at one year suggests TAC+MMF is associated with higher odds of mortality (OR 1.62; 95% CI 0.77 to 3.44). [120-122 188 201] However, although there is no evidence of hetereogeneity across studies (I^2 0.0%), the confidence intervals are wide and cross OR=1, indicating low precision and a

lack of statistical significance. Results for two years and five years also demonstrate no statistically significant difference between treatments.

- Graft loss is reported for five studies. [120 122 124 188 194] The OR for pooled results at one year and two years (1.43 and 1.63, respectively) imply greater odds of graft loss for TAC+MMF, however, the confidence intervals cross OR=1, indicating no statistically significant difference between arms. The lack of difference remains at five years for the study reported by Kumar et al. (2008)

- BPAR was reported by five studies, with four reporting at one year suitable for meta-analysis. [120 122 124 188 194]The study at 0.5 years by Kumar et al. (2008) indicates that lower odds of BPAR are associated with TAC. This is in agreement with the pooled results at one year, although some heterogeneity is noted across studies (OR 0.59, 95% CI 0.37 to 0.94; I^2 19.3%).

- Graft function is reported by three studies up to three years.[121 188] Pooling of results for year one and two year data demonstrated a statistically significant difference in graft function in favour of TAC (WMD 4.22, 95% CI 1.23 to 7.20 and WMD 5.75, 95% CI 2.76 to 8.74, respectively).

- Time to BPAR was reported by Ulsh et al. (1999), with a statistically significant difference in favour of TAC of 88.7 days (p value = 0.0001).

- Two studies report severity of BPAR separately at one year and two years.[121 188] For year one, results indicate that TAC+MMF is associated with increased odds of all three Banff classifications and this is statistically significant for Banff 1 and 2 (OR 2.51, 95% CI 1.52 to 4.15 and OR 2.79, 95% CI 1.51 to 5.14, respectively). [188] However, the study by Hernandez et al. 2007 indicates no significant difference for all three classifications. [121]

4.3.2.5. TAC+MMF vs TAC PR+MMF

Four studies are reported investigating all outcomes other than time to BPAR and HRQoL for TAC+MMF vs TAC PR+MMF. [72 87 128 129]

Mortality

Four studies report on mortality, two report at 0.5 years and two at one year (Table 55; Figure 35). [72 87 128 129]The pooled estimates for both time points imply TAC is more favourable

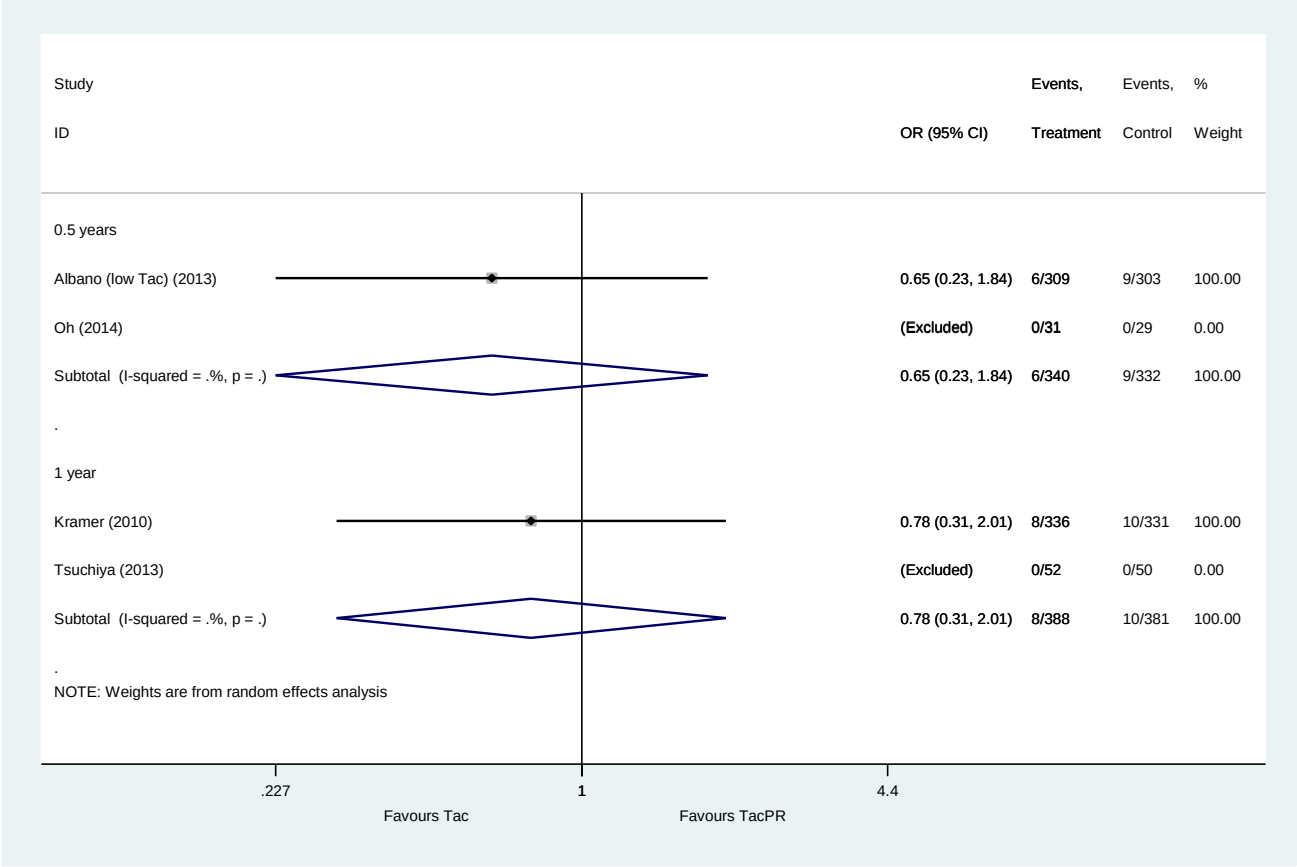
in reducing mortality than TAC PR, although two studies had no deaths in either arm and overall the effect is not statistically significant (1 year, OR 0.78, 95% CI 0.31 to 2.01).

Table 55. Mortality for TAC+MMF vs TAC PR+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Albano, 2013; Oh, 2014	0.5 years	2[a]	0.65	0.23 – 1.84	NA	NA
Kramer, 2010; Tsuchiya, 2013	1 year	2[a]	0.78	0.31 – 2.01	0.0%	0

Notes: (a) One trial excluded from pooled analysis due to no deaths in either arm

Figure 35. Forest plot – mortality for TAC+MMF vs TAC PR+MMF



Graft loss

Four studies report on graft loss, two report at 0.5 years and two at one year. [72 87 128 129] As revealed by the forest plot (Table 56; Figure 36), no clear benefit is seen for either immediate release or prolonged release TAC with regard to graft loss at six months and one

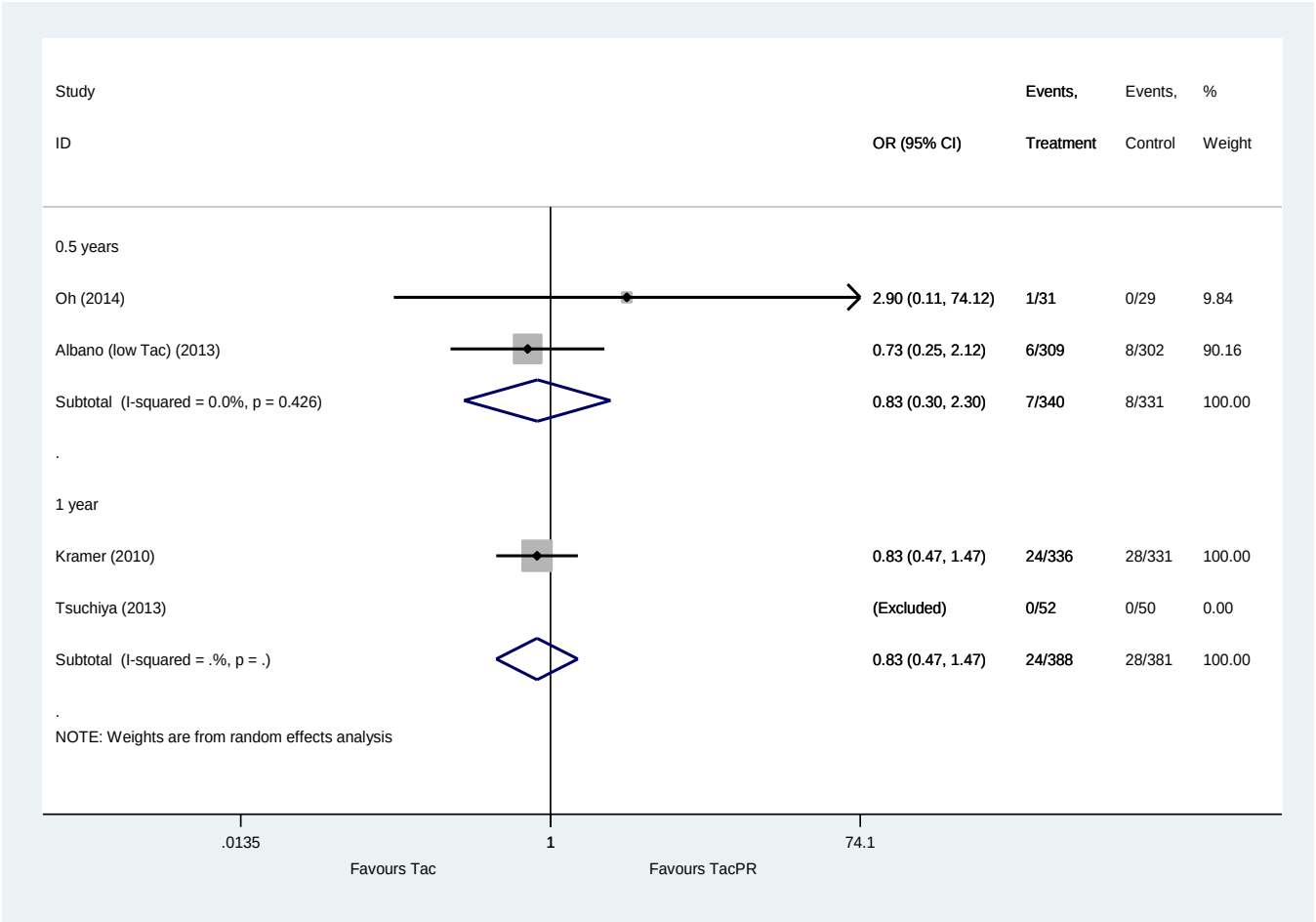
year. OR for both are identical and below 1, however, confidence intervals cross OR=1, indicating no statistical difference between arms (OR 0.83; 95% CI 0.30 to 2.30 and 0.47 to 1.47)

Table 56. Graft loss for TAC+MMF vs TAC PR+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Oh, 2014; Albano, 2013	0.5 years	2	0.83	0.30 – 2.30	0.0%	0
Kramer, 2010; Tsuchiay, 2013	1 year	2[a]	0.83	0.47 – 1.47	NA	NA

Notes: (a) One trial excluded from pooled analysis due to no graft loss in either arm

Figure 36. Forest plot – graft loss for TAC+MMF vs TAC PR+MMF



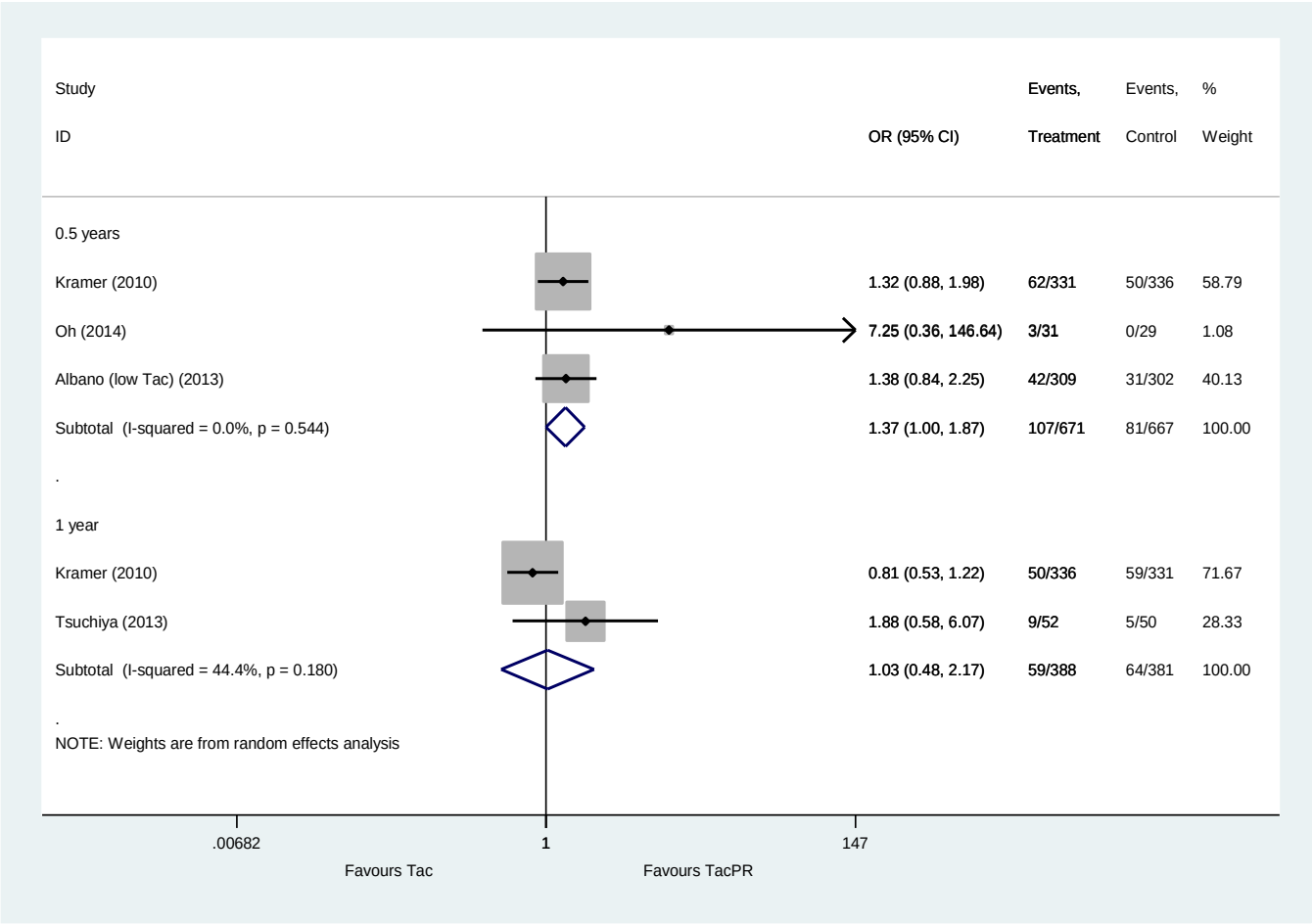
Biopsy proven acute rejection for TAC+MMF vs TAC PR+MMF

Three studies report BPAR at 0.5 years and two report at one year (Table 57; Figure 37). [72] [87] [128] [129] Pooling of results at both time points show no significant difference between arms (OR 1.37 95% CI 1.00 to 1.87; OR 1.03 95% CI 0.48 to 2.17). Furthermore, moderate heterogeneity exists across studies (I^2 34.8% and 44.4%). [198]

Table 57. BPAR for TAC+MMF vs TAC PR+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kramer, 2010; Oh, 2014; Albano, 2013	0.5 years	3	1.37	1.00 – 1.87	34.8%	0.04
Kramer, 2010; Tsuchiay, 2013	1 year	2	1.03	0.48 – 2.17	44.4%	0.16

Figure 37. Forest plot – BPAR for TAC+MMF vs TAC PR+MMF



Graft function

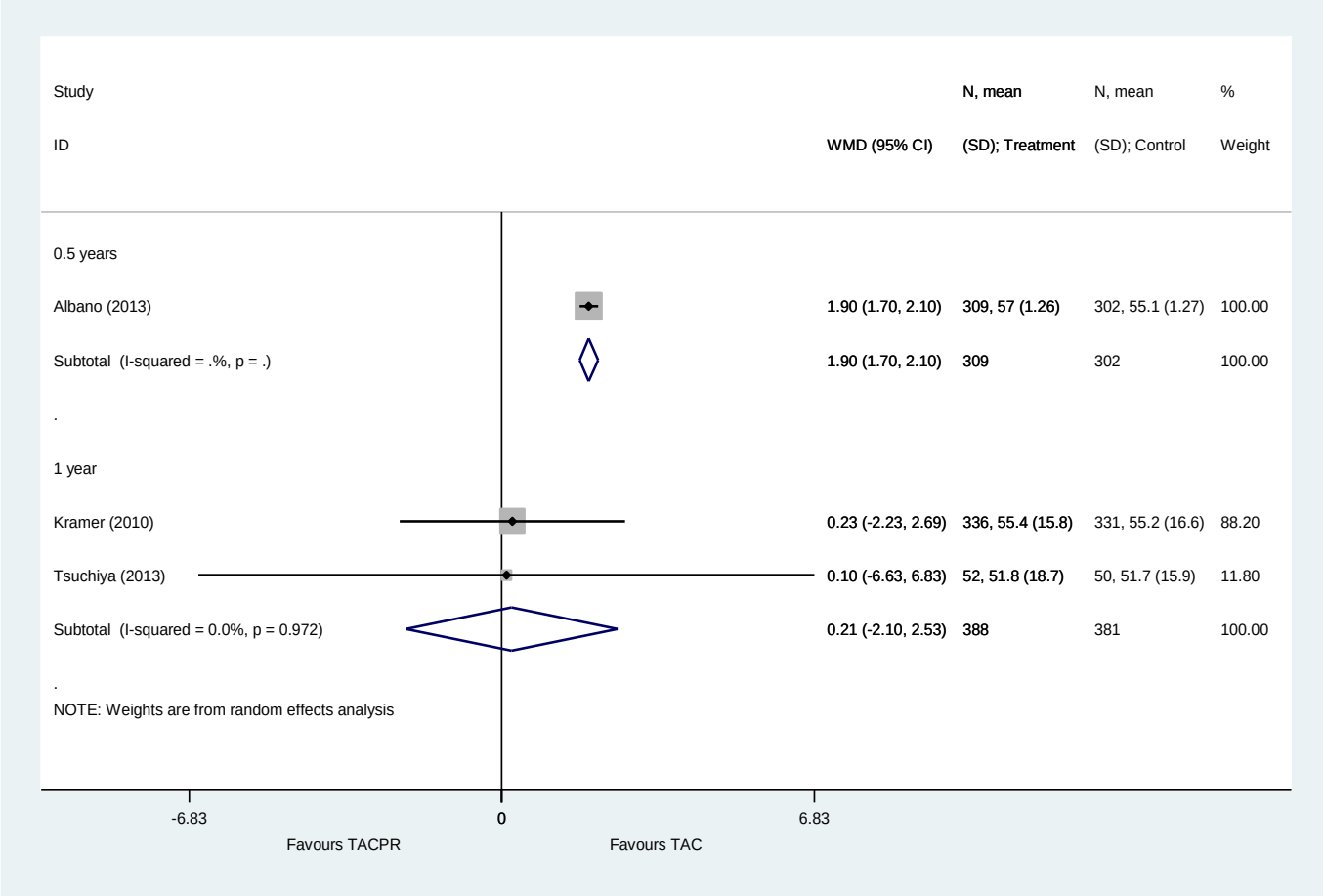
Graft function is reported by three studies, one for 0.5 years and two for one year (Table 58; Figure 36). [72 87 128] Pooling of results at one year demonstrated no statistically significant difference in graft function (WMD 0.21, 95% CI -2.10 to 2.53), however, the single study by Albano et al. (2013) suggests TAC to be more effective than TAC PR for graft function (WMD 1.90, 95% CI 1.70 – 2.10).

Table 58. Graft function for TAC+MMF vs TAC PR +MMF

Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Albano, 2013	0.5 years	1	1.90	1.70 – 2.10	NA	NA
Kramer, 2010; Tsuchiya, 2013	1 year	2	0.21	-2.10 – 2.53	0.0%	0.0

Key: NA, not applicable

Figure 38. Forest plot – graft function for TAC+MMF vs TAC PR+MMF



Severity of biopsy proven acute rejection

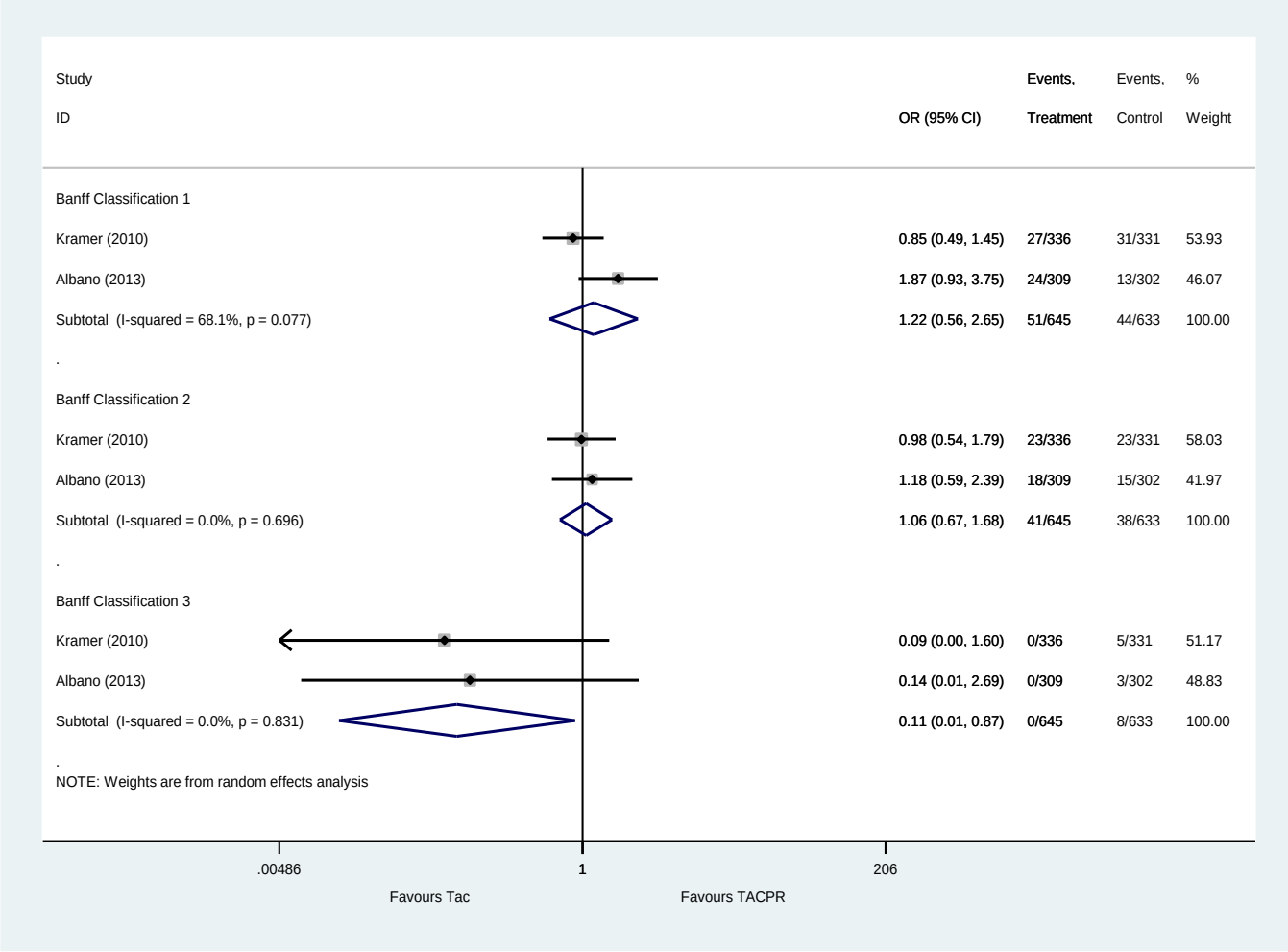
Meta-analysis of two studies indicates that TAC is associated with lower odds of Banff classification 3 (OR 0.11, 95% CI 0.01 to 0.87). [72 87] There is no statistically significant difference demonstrated for Banff classifications one and two (Table 59; Figure 39).

Furthermore, substantial heterogeneity is evident for Banff classification 1 (I^2 68.1%), therefore this result must be treated with caution.

Table 59. Severity of BPAR for TAC+MMF vs TAC PR+MMF

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Kramer, 2010; Albano, 2013	1	2	1.22	0.56 – 2.65	68.1%	0.2153
	2	2	1.06	0.67 – 1.68	0.0%	0
	3	2	0.11	0.01 – 0.87	0.0%	0

Figure 39. Forest plot – severity of BPAR for TAC+MMF vs TAC PR+MMF



Summary for TAC+MMF vs TAC PR+MMF

- Four studies report on mortality, two report at 0.5 years and two at one year. [72 87 128 129]The pooled estimates for both time points imply TAC is more favourable in reducing mortality than TAC PR, although two studies had no deaths in either arm and overall the effect is not statistically significant (1 year, OR 0.78, 95% CI 0.31 to 2.01).

- Four studies report on graft loss, two report at 0.5 years and two at one year. [72 87 128 129] No clear benefit is seen for either immediate release or prolonged release TAC with regard to graft loss at six months and one year. OR for both are identical and below 1, however, confidence intervals cross OR=1, indicating no statistical difference between arms (OR 0.83; 95% CI 0.30 to 2.30 and 0.47 to 1.47)

- Three studies report BPAR at 0.5 years and two report at one year [72 87 128 129]Pooling of results at both time points show no significant difference between arms (OR 1.37 95% CI 1.00 to 1.87; OR 1.03 95% CI 0.48 to 2.17).

- Graft function is reported by three studies, one for 0.5 years and two for one year.[87 128 202]Pooling of results at one year demonstrated no statistically significant difference in graft function (WMD 0.21, 95% CI -2.10 to 2.53), however, the single study by Albano et al. (2013) suggests TAC to be more effective than TAC PR for graft function (WMD 1.90, 95% CI 1.70 – 2.10).

- Meta-analysis of two studies indicates that TAC is associated with lower odds of Banff classification 3 (OR 0.11, 95% CI 0.01 to 0.87). [72 87] There is no statistically significant difference demonstrated for Banff classifications one and two.

4.3.2.6. MMF+TAC vs MPS+TAC

Since only one trial reports outcomes for this combination, results are presented in summary tables (Table 60; Table 61).[130]

In contrast to other outcomes, graft function displays a significant difference in favour of MPS at 0.5 years and 1 year (0.5 years, mean difference -1.317; 1 year, mean difference -1.9019. p<0.0001) (Table 61). This effect is lost at later time points.

Overall, there appears to be no discernible difference between arms, since all confidence intervals are wide and cross OR=1. Time to BPAR is not reported.

Table 60. Summary of outcomes for MMF+TAC vs MPS+TAC

Study id	Outcome	Time	MMF	MPS	Odds ratio	95% CI
Ciancio, 2008	Mortality, n/N (%)	1 year	0/75 (0)	1/75 (1)	NA	NA
		4 years	2/75 (3)	3/75 (4)	0.6575	0.1067 – 4.0524
	Graft loss, n/N (%)	1 year	2/75 (3)	2/75 (3)	NA	NA
		4 years	6/75 (8)	8/75 (11)	0.5059	0.1768 – 1.4476
	BPAR, n/N (%)	1 year	2/75 (3)	7/75 (9)	0.2661	0.0534 – 1.3259
		2 years	8/75 (11)	7/75 (9)	1.1599	0.3983 – 3.3783
		4 years	14/75 (19)	13/75 (17)	1.0946	0.4756 – 2.5192
	Banff Classification, n/N (%)					
	1	1 year	1/75 (1)	6/75 (8)	0.1554	0.0182 – 1.3238
	2		1/75 (1)	0/75 (0)	NA	NA
	3		0/75 (0)	1/75 (1)	NA	NA

Table 61. Graft function for MMF+TAC vs MPS+TAC

Study id	Time	MMF	MPS	Mean difference	95% CI	P value (*t*-Test)
Ciancio, 2008	0.5 years	63.3 (2.1)	66.0 (2.0)	-1.3167	-1.67 – 0.96	<0.0001
	1 year	62.10 (2.0)	66.0 (2.1)	-1.9019	-2.29 - 1.52	<0.0001
	2 years	63.7 (2.2)	64.10 (2.4)	-0.1737	-0.49 - 0.15	0.2891
	3 years	71.3 (3.0)	69.8 (2.7)	0.5256	0.20 - 0.85	0.0016

Summary for MMF+CSA vs MPS+TAC

- Only one study was identified for this combination.[130] No difference was identified between interventions, other than for graft function, where a statistically significant difference in favour of MPS at 0.5 years and 1 year (p<0.0001) was noted. This effect is lost at later time points.

4.3.2.7. MMF+CSA vs MPS+CSA

Only one trial is reported by Salvadori et al. 2004 using this combination, therefore all outcomes are included in a summary table up to one year (Table 62).[132] Overall, the OR indicates that MPS is associated with lower mortality (OR 4.1165, 95% CI 0.4563 to 37.1396), however the confidence intervals are wide and the effect is not statistically significant. Graft loss initially has better odds for MPS at 0.5 years, however, this reverses at one year. Again, confidence intervals imply no statistical significance. BPAR and severity of BPAR show no difference between interventions. Graft function and time to BPAR are not reported.

Table 62. Summary of outcomes for MMF+TAC vs MPS+TAC

Study id	Outcome	Time	MMF	MPS	Odds ratio	95% CI
Salvadori, 2004	Mortality, n/N (%)	0.5 years	2/210 (1)	1/213 (0)	2.0385	0.18 - 22.65
		1 year	4/210 (2)	1/213 (0)	4.1165	0.45 - 37.14
	Graft loss, n/N (%)	0.5 years	9/210 (4)	7/213 (3)	1.3177	0.48 - 3.61
		1 year	6/210 (3)	15/213 (7)	0.3882	0.15 - 1.02
	BPAR, n/N (%)	0.5 years	48/210 (23)	46/213 (22)	1.0757	0.68 - 1.70
		1 year	51/210 (24)	48/213 (22)	1.1026	0.70 - 1.73
	Banff Classification, n/N (%)					
	1	1 year	31/210 (15)	33/213 (15)	0.9446	0.55 - 1.61
	2		14/210 (7)	12/213 (6)	1.1964	0.54 - 2.65
	3		3/210 (1)	2/213 (1)	1.529	0.25 - 9.24

Summary for MMF+TAC vs MPS+TAC

- Only one trial reported by Salvadori et al. 2004 uses this combination. Graft function and time to BPAR are not reported. All other results indicate no significant difference between MMF and MPS.

4.3.2.8. BEL+MMF vs CSA+MMF

Three studies report on this combination of therapies.[55 71 203] Time to BPAR and HRQoL are not reported

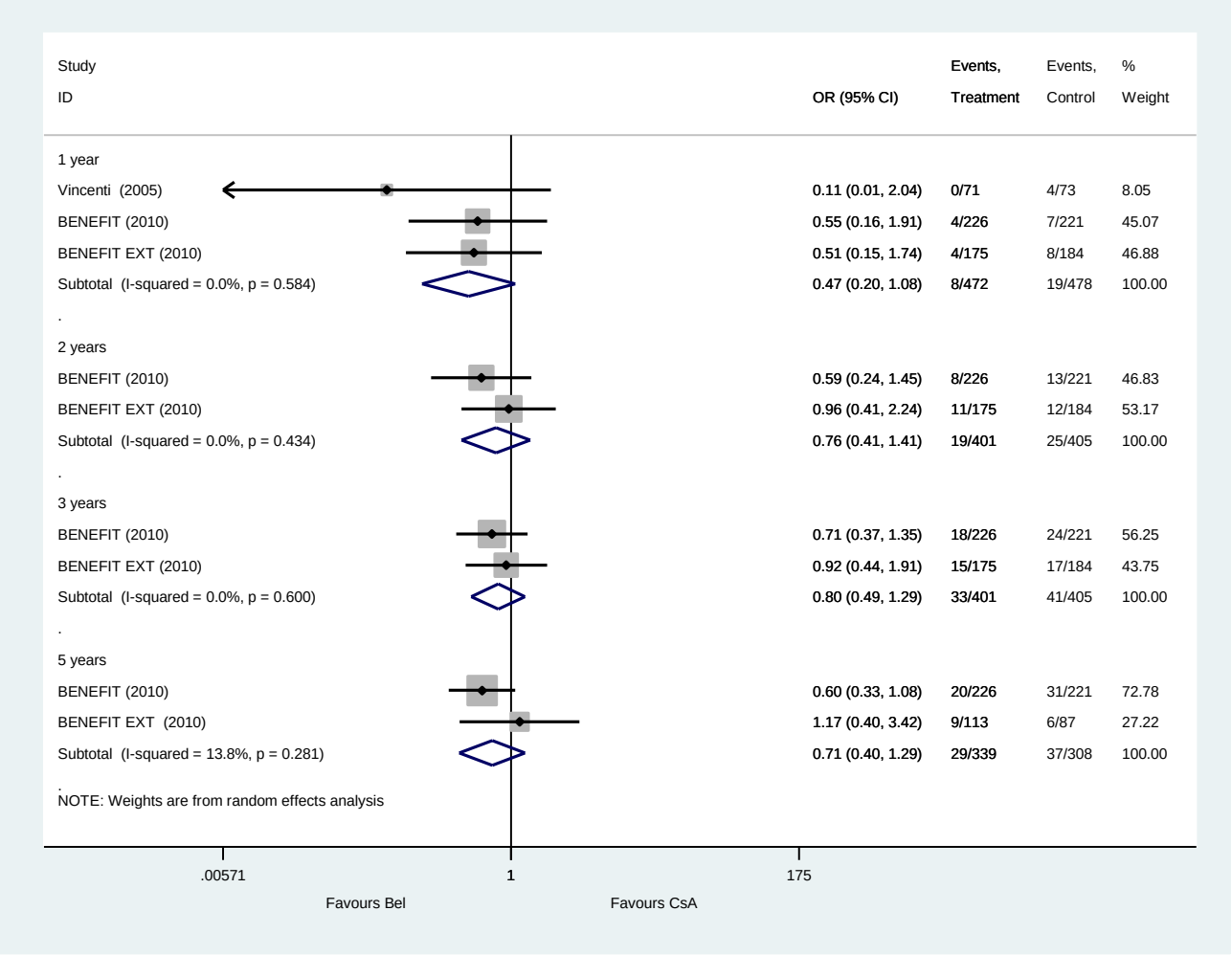
Mortality

Three studies report one year outcomes, with BENEFIT and BENEFIT-EXT providing data up to five years. [55 71 203] The odds ratios generally fall below one for all time points, indicating that BEL has a lower association with mortality than CSA (Table 63; Figure 40). However, the confidence intervals indicate that this is not statistically significant.

Table 63. Mortality for BEL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2
Vincenti, 2005; BENEFIT, 2010; BENEFIT-EXT, 2010	1 year	3	0.47	0.20 – 1.08	0.0%
BENEFIT, 2010; BENEFIT-EXT, 2010	2 years	2	0.76	0.41 – 1.41	0.0%
	3 years	2	0.80	0.49 – 1.29	0.0%
	5 years	2	0.71	0.40 – 1.29	13.85%

Figure 40. Forest plot – mortality for BEL+MMF vs CSA+MMF



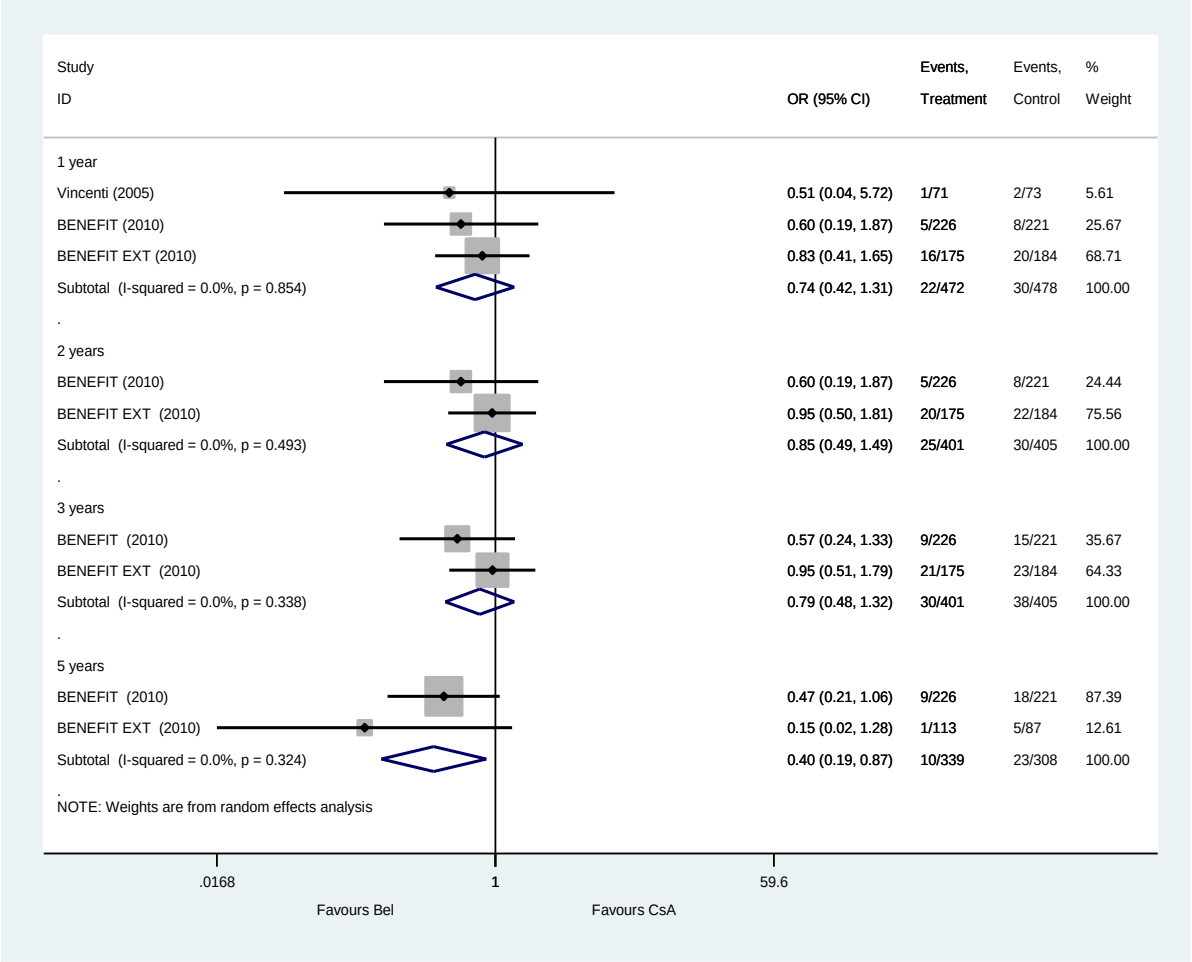
Graft loss

The OR for graft loss up is also reported by three studies up to five years. [55 71 203] Pooled results indicate that BEL may be preferable to CSA, although the results are not statistically significant (1 year, OR 0.74, 95% CI 0.42 to 1.31) (Table 64; Figure 41). However, at 5 years, there may be more confidence that this effect is true (OR 0.40, 95% CI 0.19 to 0.87).

Table 64. Graft loss for BEL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Vincenti, 2005; BENEFIT, 2010; BENEFIT-EXT, 2010	1 year	3	0.74	0.42 – 1.31	0.0%	0.0
BENEFIT, 2010; BENEFIT-EXT, 2010	2 years	2	0.85	0.49 – 1.49	0.0%	0.0
	3 years	2	0.79	0.48 – 1.32	0.0%	0.0
	5 years	2	0.40	0.19 – 0.87	0.0%	0.0

Figure 41. Forest plot – graft loss for BEL+MMF vs CSA+MMF



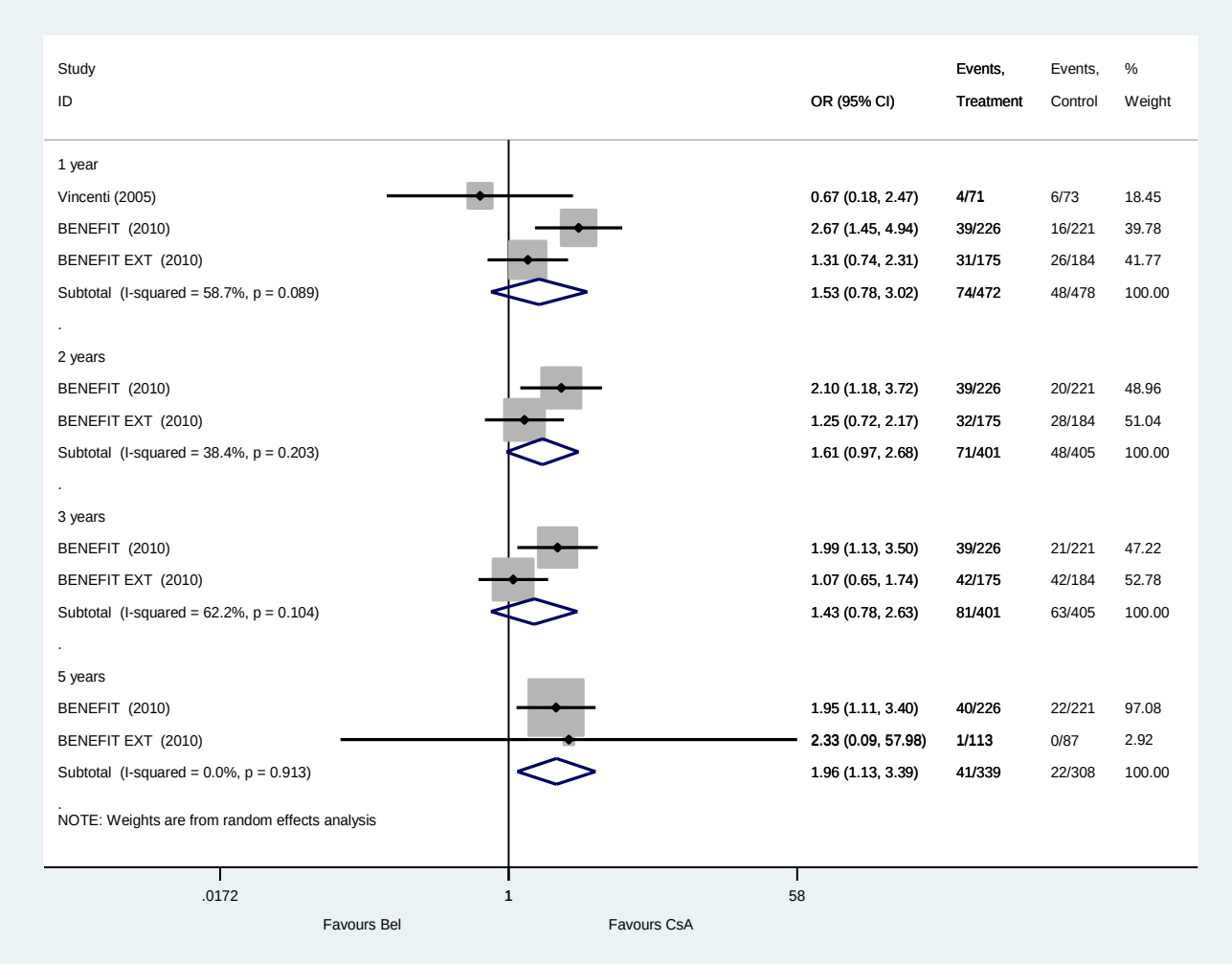
Biopsy proven acute rejection

In contrast to previous outcomes, results for BPAR are more clear for the three studies, however, there is substantial heterogeneity for the 1, 2 and 3 year time points (I^2 58.7%, 38.4% and 62.2%, respectively) (Table 65; Figure 42). [55] [203] [71] Overall, participants in the CSA arm appear to be less likely to experience BPAR between one and five years, as opposed to those in the BEL arm (1 year, OR 1.53, 95% CI 0.78 to 3.02).

Table 65. BPAR for BEL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Vincenti, 2005; BENEFIT, 2010; BENEFIT-EXT, 2010	1 year	3	1.53	0.78 – 3.02	58.7%	0.2030
BENEFIT, 2010; BENEFIT-EXT, 2010	2 years	2	1.61	0.97 – 2.68	38.4%	0.0518
	3 years	2	1.43	0.78 – 2.63	62.2%	0.1198
	5 years	2	1.96	1.13 – 3.39	0.0%	0.0

Figure 42. Forest plot – BPAR for BEL+MMF vs CSA+MMF



Graft function

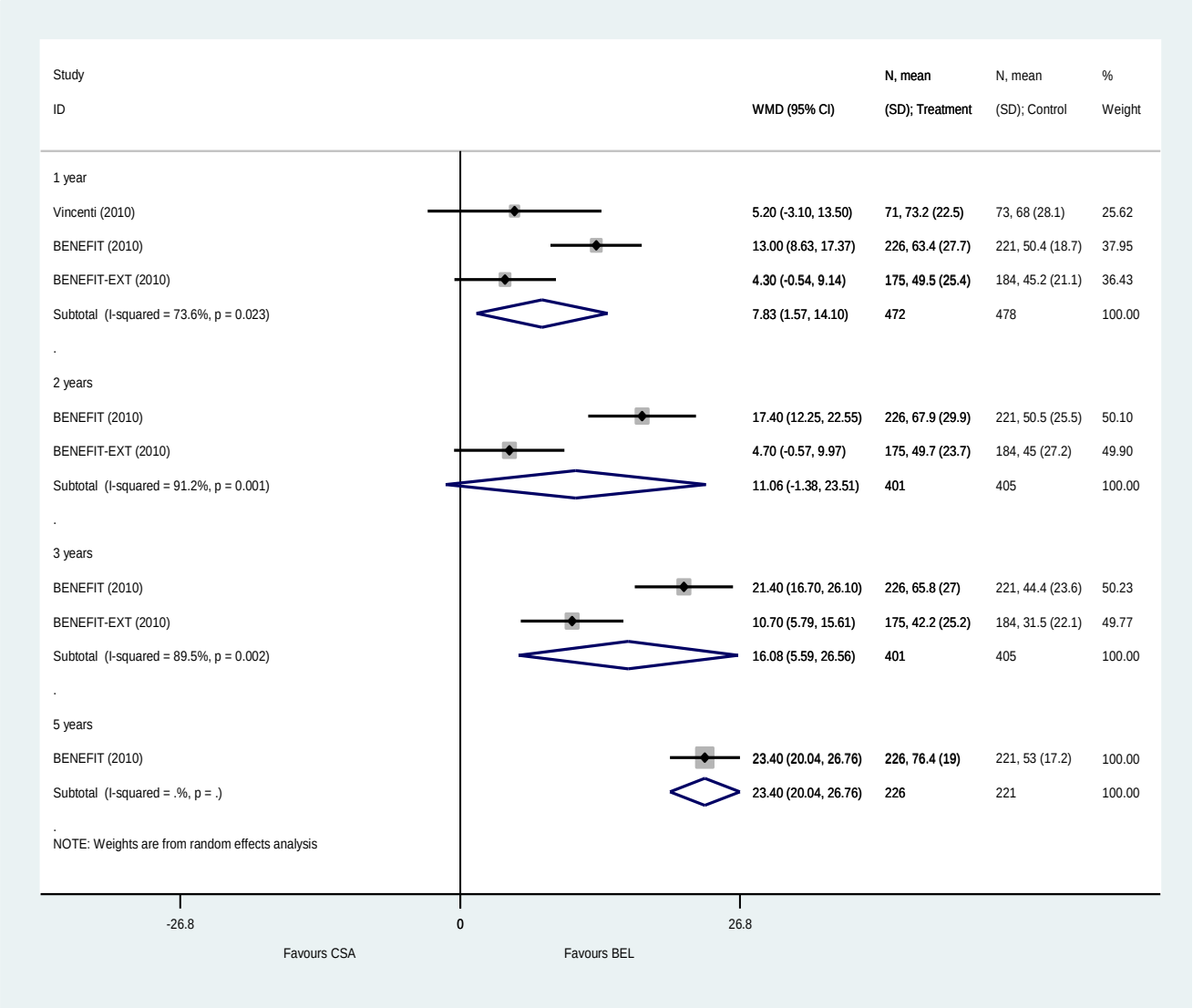
Graft function is reported by three studies up to five years (Table 66; Figure 43).[55 71 203] The results must be treated with caution due to substantial heterogeneity across studies, which may be due to variations in methods of calculation and measurement of graft function (I^2 73.6% to 91.2%). Pooling of results for year one and three year data demonstrated a statistically significant difference for graft function in favour of BEL (WMD 7.83, 95% CI 1.57 to 4.10 and WMD 16.08, 95% CI 5.59 to 26.56, respectively).

Table 66. Graft function for BEL+MMF vs CSA+MMF

Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Vincenti, 2005[a]; BENEFIT, 2010[b];	1 year	3	7.83	1.57 – 4.10	73.6%	21.96
BENEFIT 2010[b], BENEFIT-EXT, 2010[b]	2 years	2	11.06	-1.38 – 23.51	91.2%	73.58
	3 years	2	16.08	5.59 – 26.56	89.5	51.23
BENEFIT, 2010[b]	5 years	1	23.40	20.04 – 26.76	NA	NA

Key: NA, not applicable; (a) MDRD; (b) measured

Figure 43. Forest plot – graft function for BEL+MMF vs CSA+MMF



Severity of biopsy proven acute rejection

Only one study reports results for time points of 0.5 years and five years, where no difference is seen between interventions (Table 67; Figure 44). Pooled analysis was possible at one year (Table 67; Figure 44). [71] For all three Banff classifications, there are greater odds of association for BEL, but there is no statistically significant difference. It should be noted there is a moderate degree of heterogeneity across studies for Banff classification 2.[198]

Table 67. Severity of BPAR for BEL+ MMF vs CSA + MMF (unpooled results)

Study		Banff classification	BEL+MMF, n/N (%)	CSA+MMF, n/N (%)	Odds ratio	95% CI
Vincenti, 2005	0.5	1	0/71 (0)	2/73 (3)	0	NA
		2	4/71 (6)	4/73 (5)	1.03	0.25 - 4.29
BENEFIT-EXT	5 years	2	1/113 (1)	0/87 (0)	NA	NA
		3	0/104 (0)	0/87 (0)	NA	NA

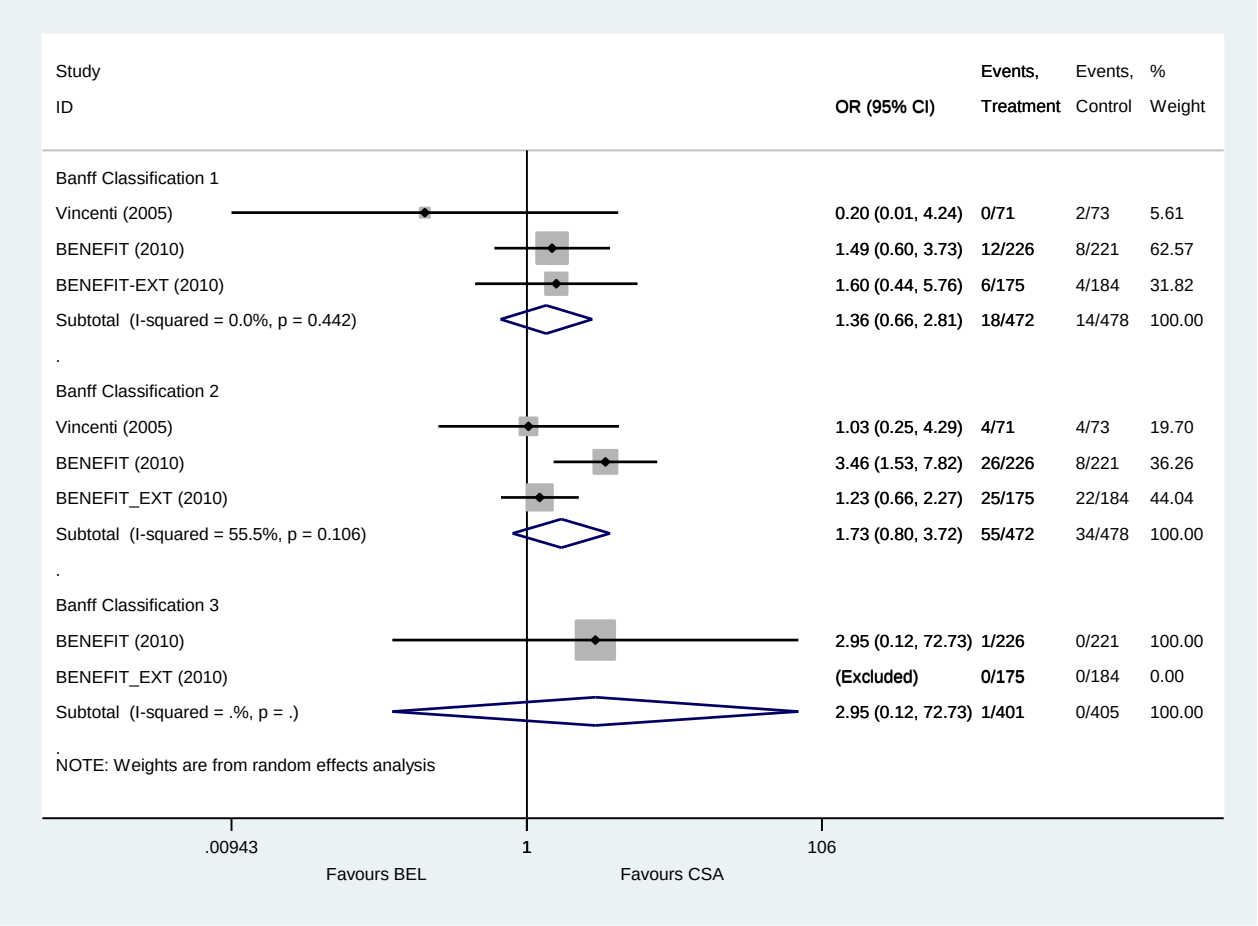
Key: NA, not applicable

Table 68. Severity of BPAR for BEL+MMF vs CSA+MMF (pooled results)

Study id	Time point	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Vincenti, 2005; BENEFIT 2010; BENEFIT-EXT 2010	1 year	1	3	1.36	0.66 – 2.81	0.0%	0.0
		2		1.73	0.80 – 3.72	55.5%	0.2153
		3		2.95	0.12 – 72.73	NA	NA

Key: NA, not applicable

Figure 44. Forest plot – severity of BPAR for BEL+MMF vs CSA+MMF



Summary for BEL+MMF vs CSA+MMF

- Three studies report one year outcomes, with two providing data up to five years. [55 71 203] The odds ratios generally fall below one for all time points, indicating that BEL has a lower association with mortality than CSA. However, the confidence intervals indicate that this is not statistically significant.The OR for graft loss up to four years indicates that BEL may be preferable to CSA, although the results are not statistically significant. However, at 5 years, there may be more confidence that this effect is true (OR 0.40, 95% CI 0.19 to 0.87).

- The OR for graft loss up is also reported by three studies up to four years. [55 71 203] Pooled results indicate that BEL may be preferable to CSA, although the results are not statistically significant (1 year, OR 0.74, 95% CI 0.42 to 1.31). However, at 5 years, there may be more confidence that this effect is true (OR 0.40, 95% CI 0.19 to 0.87).

- In contrast to previous outcomes, results for BPAR are more clear for the three studies. However, there is substantial heterogeneity across studies at the 1, 2 and 3 year time points (I^2 58.7%, 38.4% and 62.2%, respectively).[55 203 71] Overall, participants in the CSA arm appear to be less likely to experience BPAR between one and five years, as opposed to those in the BEL arm (1 year, OR 1.53, 95% CI 0.78 to 3.02).

- Graft function is reported by three studies up to five years. [55 71 203] The results must be treated with caution due to substantial heterogeneity across studies, which may be due to variations in methods of calculation and measurement of graft function (I^2 73.6% to 91.2%). Pooling of results for year one and three year data demonstrated a statistically significant difference for graft function in favour of BEL (WMD 7.83, 95% CI 1.57 to 4.10 and WMD 16.08, 95% CI 5.59 to 26.56, respectively).

- Pooled analysis of three studies was possible for severity of BPAR at one year. [55 71 203] For all three Banff classifications, there are greater odds of association for BEL. It should be noted there is some degree of heterogeneity across studies for Banff classification 2 and no statistically significant difference.

4.3.2.9. BEL+MMF vs BEL+SRL vs TAC+MMF

This combination is only reported Ferguson et al. 2011, therefore results are summarised in below (Table 69).[138] Time to BPAR is not reported. Analysis indicates no statistical difference between arms for any outcome, however, recruitment numbers are relatively low (n=26 and n=30).

Table 69. Summary of outcomes for BEL+MMF vs BEL+SRL vs TAC+MMF

Study id	Time point	Outcomes	BEL+MMF	BEL+SRL	TAC+MMF	Chi-squared
Ferguson, 2011	0.5 years	BPAR, n/N	4/33	1/26	1/30	2.0751, p=0.354
		Banff Classification 1, n/N	0/33	0/26	0/30	NA
		Banff Classification 2, n/N	4/33	1/26	1/30	2.0751, p=0.354
		Banff Classification 3, n/N	0/33	0/26	0/30	NA
	1 year	Mortality, n/N	1/33	0/26	0/30	1.6656, p=0.435
		Graft loss, n/N	2/33	2/26	0/30	2.0675, p=0.356
		BPAR, n/N	5/33	1/26	1/30	3.2067, p=0.201

4.3.2.10. EVL+CSA vs MMF+CSA

Three RCTs investigating this combination of immunosuppressive therapies was identified. All outcomes other than time to BPAR were reported.

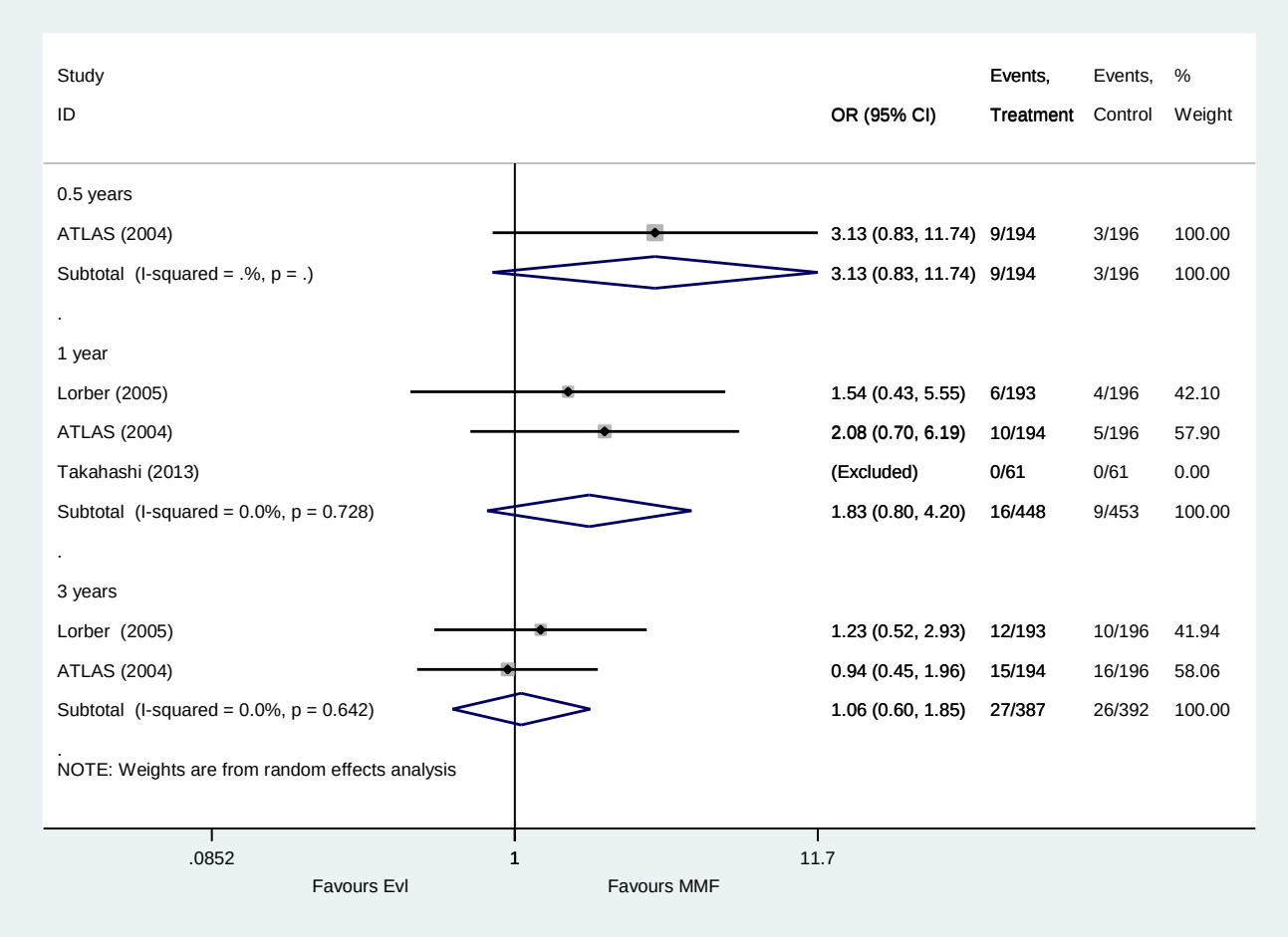
Mortality

Mortality is reported at 0.5 years, one year and three years (Table 70; Figure 48). [139 141 143] Results are pooled for the one year and two year time points, where the OR is >1, indicating a preference in favour of MMF, however, this is not statistically significant (OR 1.83, 95% CI 0.80 to 4.20; OR 1.06, 95% CI 0.60 to 1.85, respectively). This trend is reflected at 0.5 years and three years.

Table 70. Mortality for EVL+CSA vs MMF+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
ATLAS, 2004	0.5 years	1	3.13	0.83 – 11.74	NA	NA
Lorber, 2005; ATLAS, 2004; Takahashi, 2013	1 year	3	1.83	0.80 – 4.20	0.0%	0.0
Lorber, 2005; ATLAS, 2004	3 years	2	1.06	0.60 – 1.85	0.0%	0.0

Figure 45. Forest plot - mortality for EVL+CSA vs MMF+CSA



Graft loss

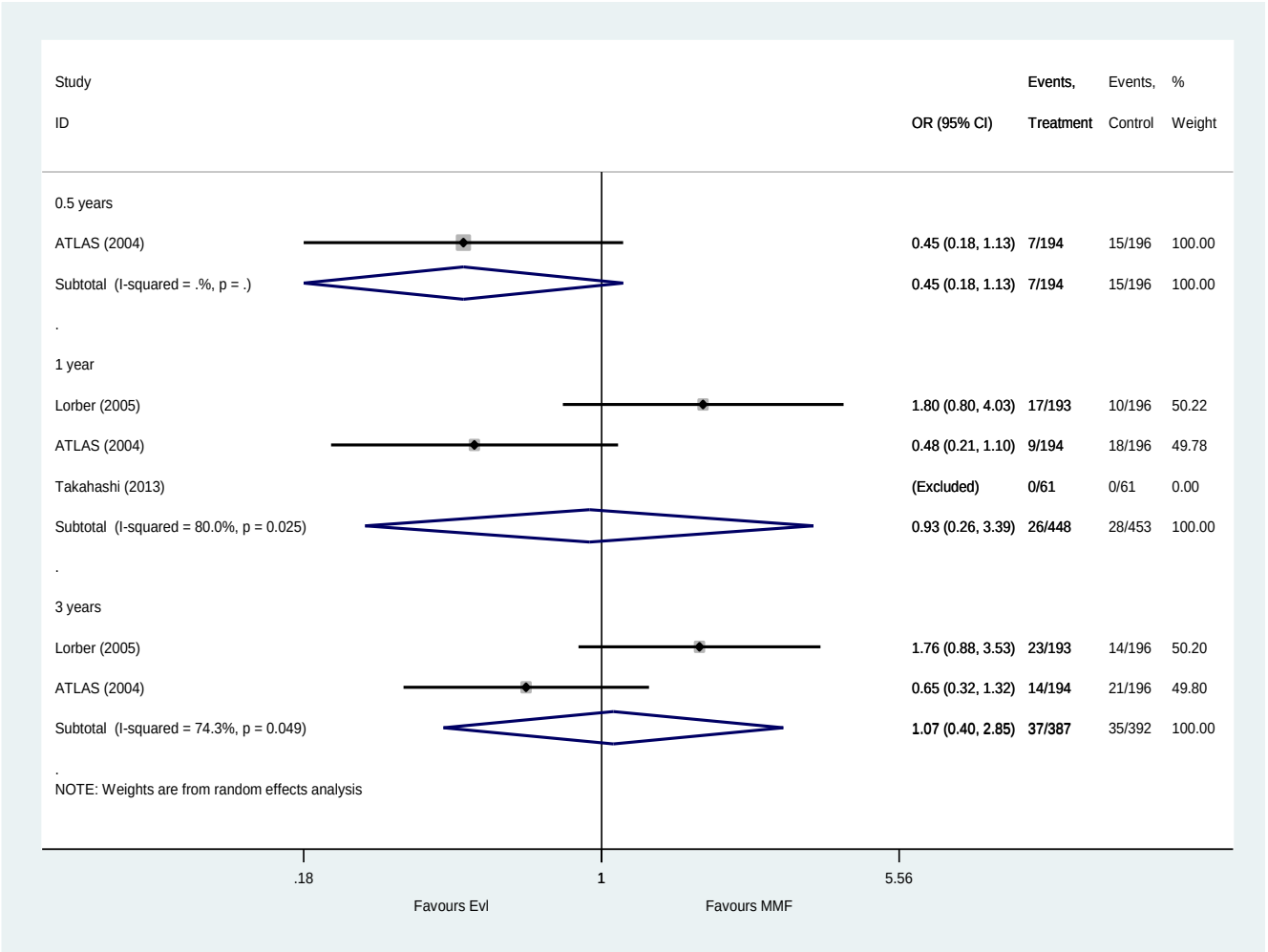
Three RCTs report graft loss for this combination (Table 71;Figure 46). [139 141 143] There is considerable heterogeneity across studies for one year and three years (I^2 80.0% and

74.3%, respectively), therefore results must be treated with caution. The study reported by Lorber et al. (2005), which favours MMF, appears to contrast the ATLAS study, however, there is no statistically significant difference between arms for either trial (Figure 46).

Table 71. Graft loss for EVL+CSA vs MMF+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
ATLAS, 2004	0.5 years	1	0.45	0.08 – 1.13	NA	NA
Lorber, 2005; ATLAS, 2004; Takahashi, 2013	1 year	3	0.93	0.26 – 3.39	80.0%	0.6944
Lorber, 2005; ATLAS, 2004	3 years	2	1.07	0.40 – 2.85	74.3%	0.3700

Figure 46. Forest plot – graft loss for EVL+CSA vs MMF+CSA



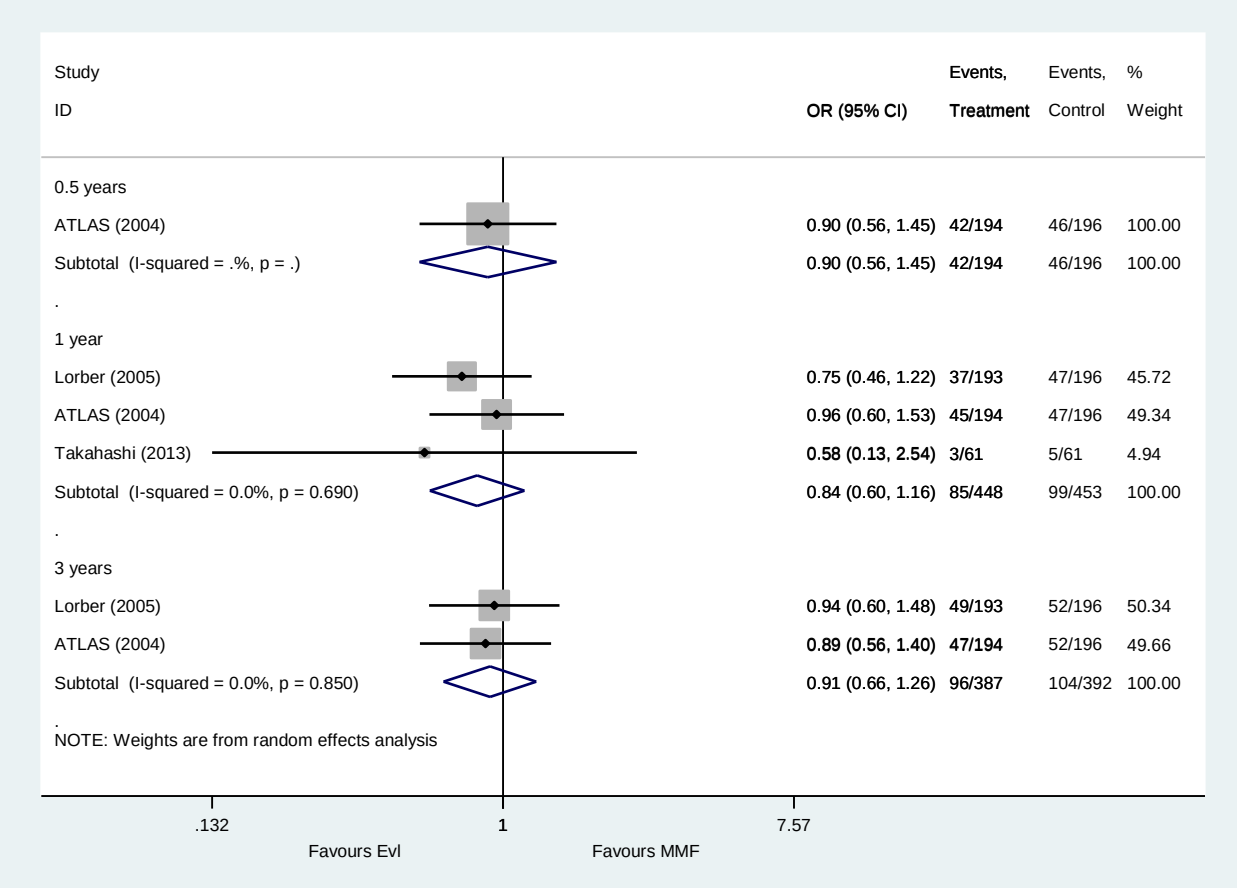
Biopsy proven acute rejection

The pooled and unpooled OR<1 for this outcome all suggest that EVL is associated with lower odds of BPAR, however, the confidence intervals indicate a lack of statistical significance (Table 72;Figure 47). [139 141 143] There is no evidence of heterogeneity across studies.

Table 72. BPAR for EVL+CSA vs MMF+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
ATLAS, 2004	0.5 years	1	0.90	0.56 – 1.45	NA	NA
Lorber, 2005; ATLAS, 2004; Takahashi, 2013	1 year	3	0.84	0.60 – 1.16	0.0%	0.0
Lorber, 2005; ATLAS, 2004	3 years	2	0.91	0.66 – 1.26	0.0%	0.0

Figure 47. Forest plot - BPAR for EVL+CSA vs MMF+CSA



Graft function

Lorber et al. 2005, provide a median and range for graft function, rather than a standard deviation; therefore results could not be pooled witht the ATLAS study (Table 73). [139 141] Overall, there is no significant difference in graft function between EVL+CSA and MMF+CSA (p=0.1989 to 0.3703)

Table 73. Graft function for EVL+CSA vs MMF+CSA

Study	Time point	EVL, mean ml/min (sd)	MMF, mean ml/min (sd)	Mean difference	95% CI	P value (*t*-Test)
Lorber, 2005[a]	1 year	58 (7-124)	69 (8-153)	NA	NA	NA
ATLAS, 2004		52 (21)	54 (18)	-0.1023	-0.30 - 0.10	0.3131
Lorber, 2005[a]	2 years	60 (5 – 141)	71 (6 – 412)	NA	NA	NA
ATLAS, 2004		55 (24)	58 (22)	-0.1303	-0.33 - 0.07	0.1989
Lorber, 2005[a]	3 years	57 (4 – 140)	70 (8 – 157)	NA	NA	NA
ATLAS, 2004		55 (23)	57 (21)	-0.0908	-0.29 - 0.11	0.3703

Notes: All methods either reported as CrCl or Cockcroft gault unless otherwise stated
Key: (a) Median and range

Severity of biopsy proven acute rejection

Severity of BPAR is only reported by Takahashi et al. 2013 at one year (Table 74).[143] For borderline and Banff classification 1, there is no significant difference between EVL and MMF. No other Banff classifications are reported.

Table 74. Severity of BPAR for EVL vs MMF

Study	Time point	Banff classification	EVL, n/N (%)	MMF, n/N (%)	Odds ratio	95% CI
Takahashi, 2013	1 year	None/borderline	2/61 (3)	3/61 (5)	0.6554	0.1056 - 4.0673
		1	1/61 (2)	2/61 (3)	0.4917	0.0434 - 5.5692

Notes: All precentages calculated by PenTAG

Summary for EVL+CSA vs MMF+CSA

- Results for mortality are pooled for three studies at the one year time point. [139 141 143] The OR is >1, indicating a preference in favour of MMF, however, this is not statistically significant (OR 1.83, 95% CI 0.80 to 4.20). This trend is reflected at 0.5 years and three years.

- Three RCTs report graft loss for this combination, however, there is significant heterogeneity across studies for one year and three years (I^2 80.0% and 74.3%, respectively). The study reported by Lorber et al. 2005, which favours MMF, appears to contrast the ATLAS study, which favours EVL, however, there is no statistical difference between arms for either trial.

- The pooled and unpooled OR<1 for BPAR all suggest that EVL is associated with lower odds, however, the confidence intervals indicate a lack of statistical significance (Table 72;Figure 47). [139 141 143] There is no evidence of heterogeneity across studies.

- Lorber et al. 2005, provide a median and range for graft function, rather than a standard deviation; therefore results could not be pooled witht the ATLAS study (Table 73).[139 141] Overall, there is no significant difference in graft function between EVL+CSA and MMF+CSA (p=0.1989 to 0.3703)

- Severity of BPAR is only reported by Takahashi et al. 2013 at one year. For borderline and Banff classification 1, there is no significant difference between EVL and MMF. No other Banff classifications are reported.

4.3.2.11. EVL+CSA vs MPS+CSA

Three RCTs were identified reporting on this combination. [144 145 146] All outcomes other than time to BPAR and HRQoL are reported.

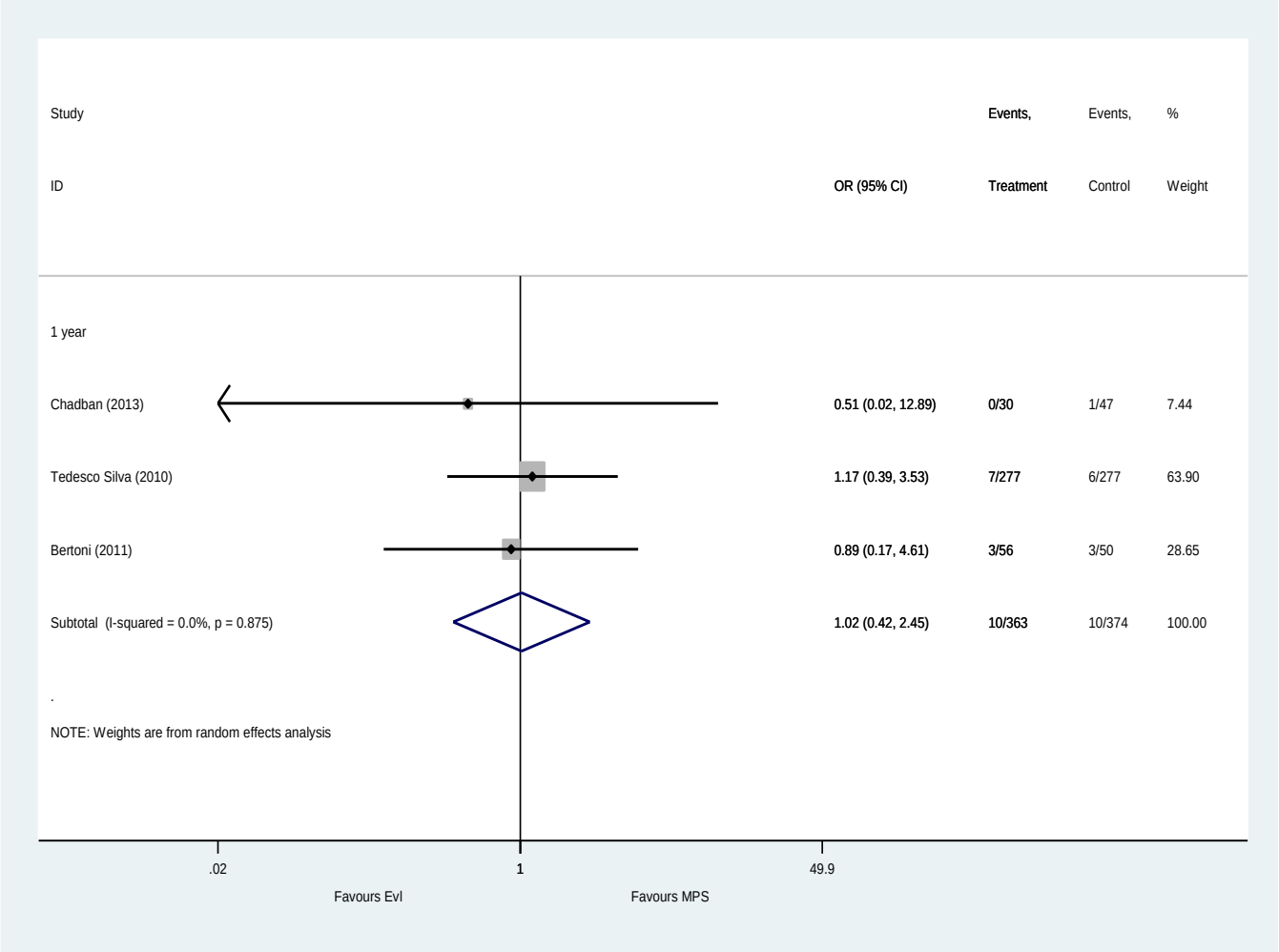
Mortality

Pooled analysis of four studies at one year for mortality indicates no significant difference between EVL+CSA and MPS+CSA (OR 1.02, 95% CI 0.42 to 2.45) (Table 75; Figure 48). [145 146 195] No heterogeneity was evident across studies.

Table 75. Mortality for EVL+CSA vs MPS+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Chadban , 2013; Tedesco Silva, 2010; Bertoni, 2011.	1 year	3	1.02	0.42 – 2.45	0.0%	0.0

Figure 48. Forest plot – mortality for EVL+CSA vs MPS+CSA



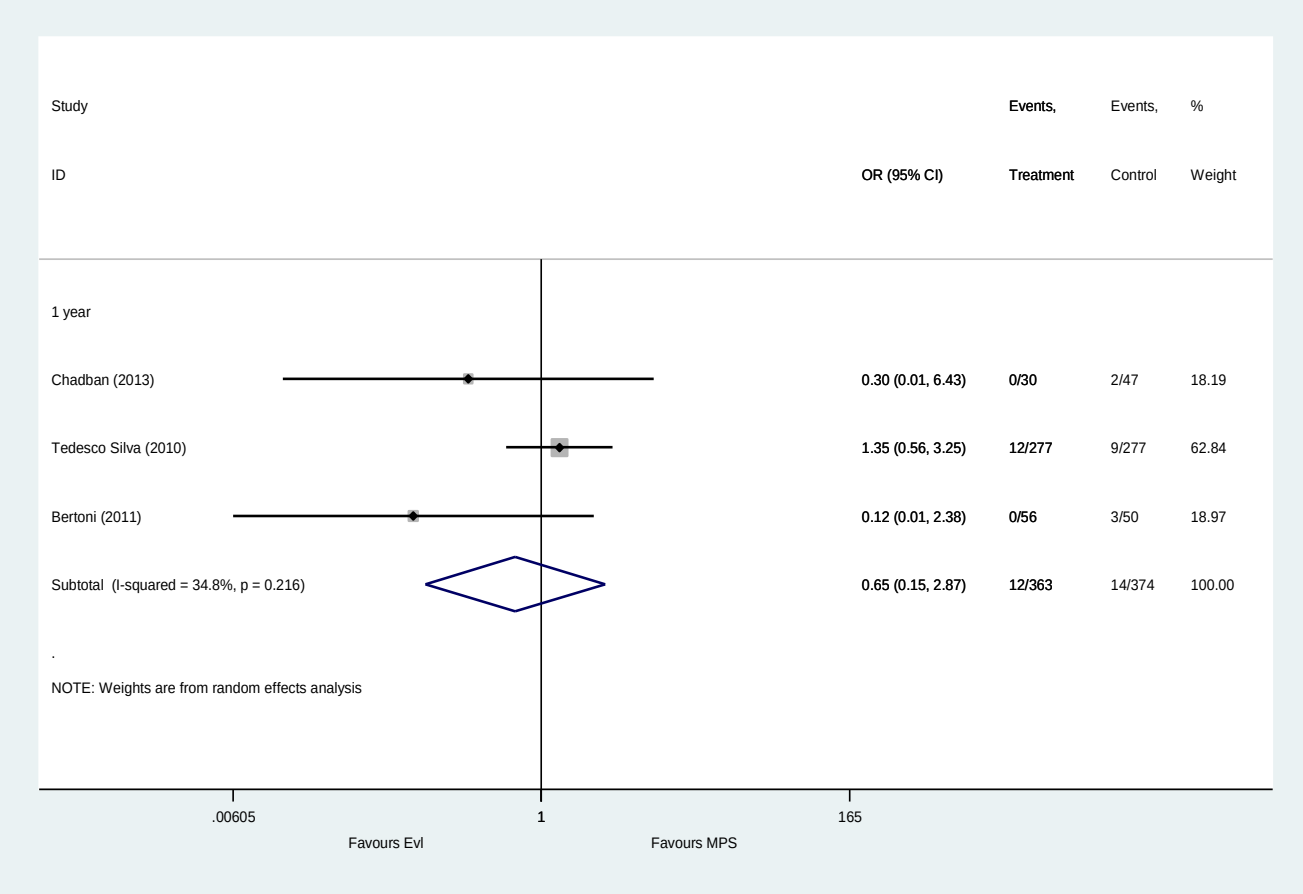
Graft loss

The OR for graft loss is generated from three pooled studies, which indicates that EVL may be preferable in reducing graft loss, however, this result is not statistically significant (OR 0.648, 95% CI 0.146 to 2.870) (Table 76; Figure 49). [145 146 195] Furthermore, moderate heterogeneity is noted across studies.

Table 76. Graft loss for EVL+CSA vs MPS+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Chadban , 2013; Tedesco Silva, 2010; Bertoni, 2011.	1 year	3	0.648	0.15 – 2.87	34.8%	0.7158

Figure 49. Forest plot - graft loss for EVL+CSA vs MPS+CSA



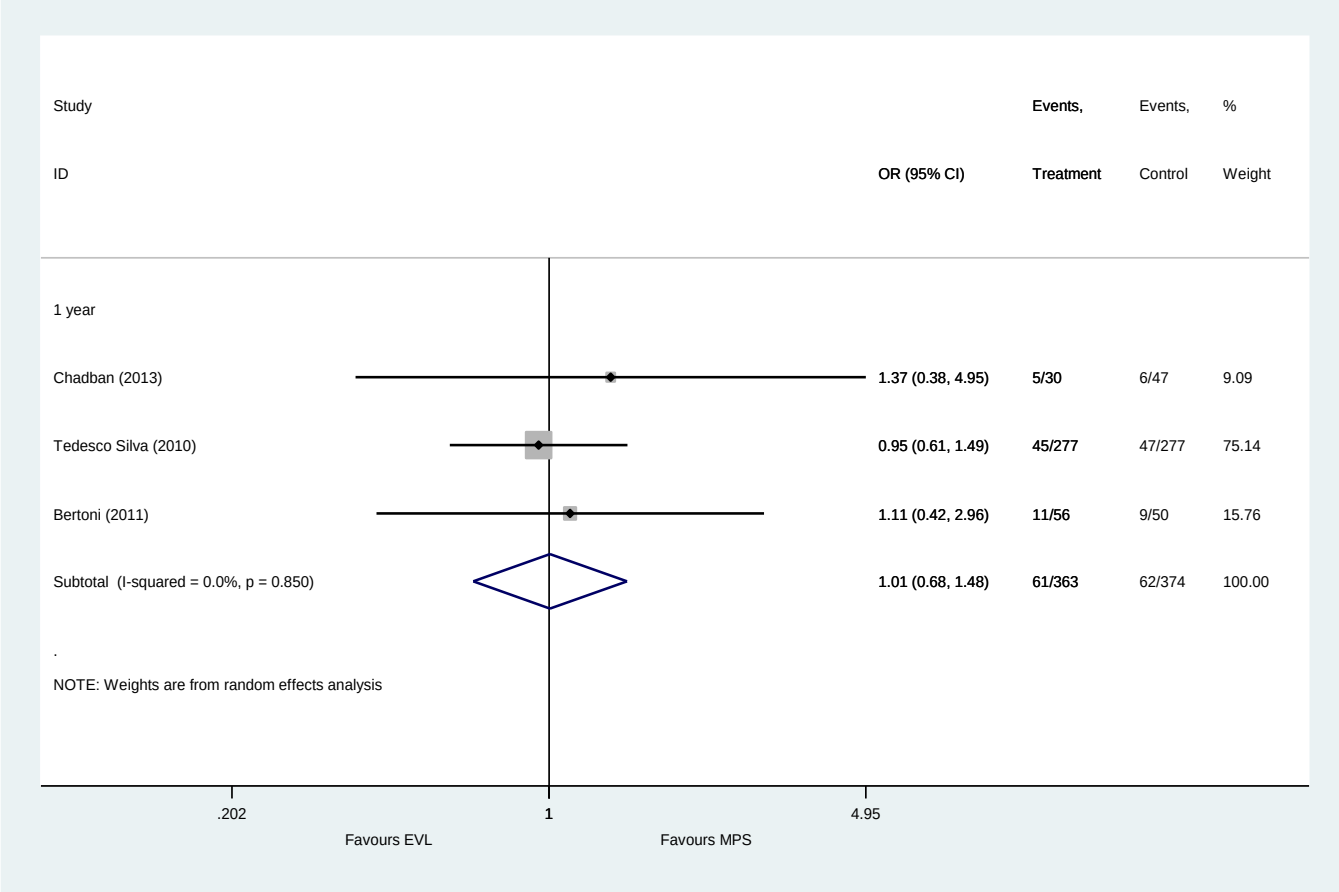
Biopsy proven acute rejection

Biopsy proven acute rejection is reported by three studies at one year. [145 146 195] Pooling of results indicates no statistically siginificant difference between EVL+CSA vs MPS+CSA (OR 1.01, 95% CI 0.68 to 1.48) (Table 77; Figure 47).

Table 77. BPAR for EVL+CSA vs MPS+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Chadban , 2013; Tedesco Silva, 2010; Bertoni, 2011.	1 year	3	1.01	0.68 – 1.48	0.0%	0.0

Figure 50. Forest plot – BPAR for EVL+CSA vs MPS+CSA



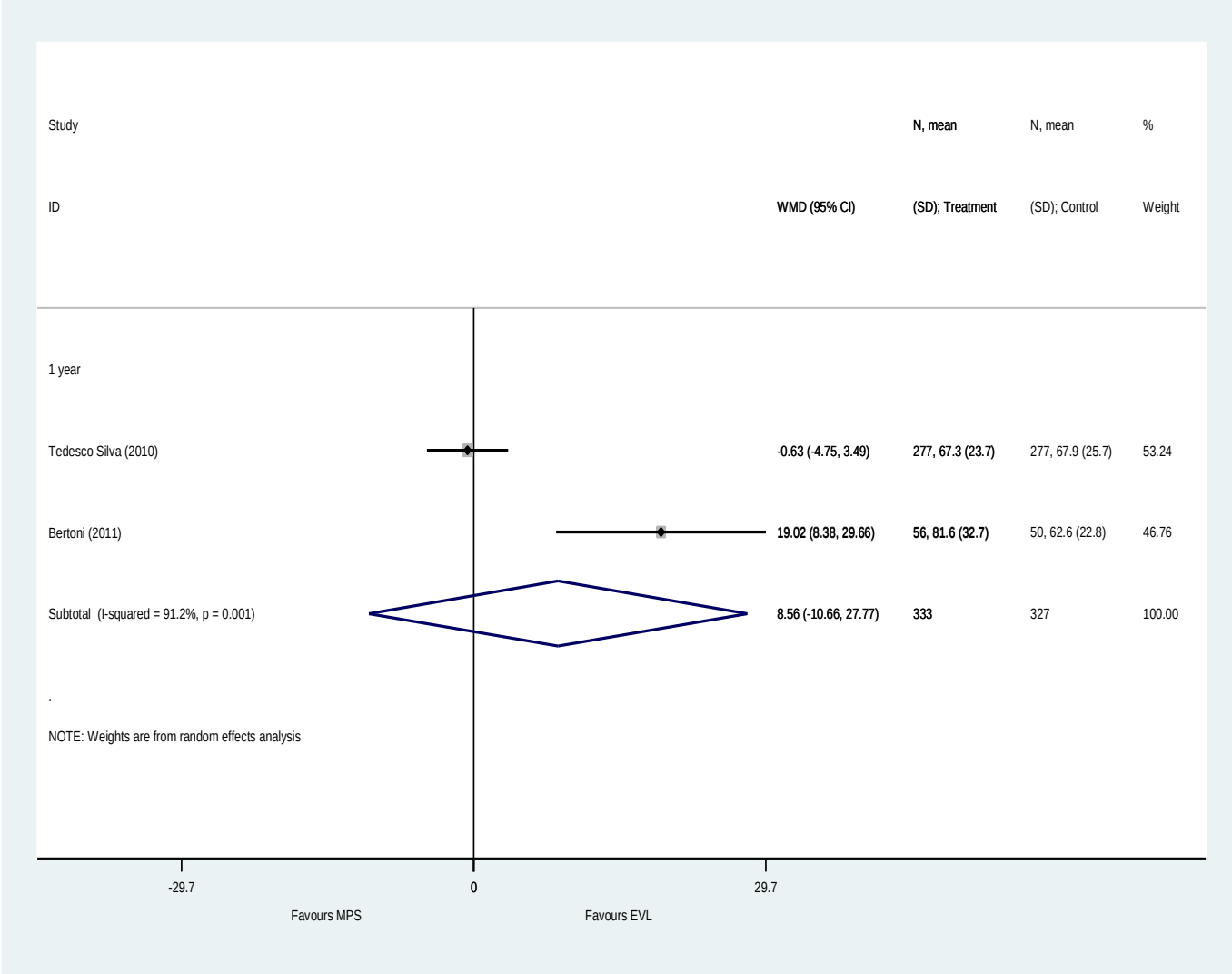
Graft function

Two studies report graft function, however, although results are pooled, the heterogeneity between them is extremely high (I^2 91.2%) (Table 78; Figure 51). [145 146] As such, the evidence is unclear as to which treatment may be beneficial.

Table 78. Graft function for EVL+CSA vs MPS+CSA

Study id	Time point	Trials	Weighted mean difference	95% CI	I^2	Tau^2
Tedesco Silva, 2010; Bertoni, 2011	1 year	2	8.56	-10.66 – 27.77	91.2%	176.12

Figure 51. Forest plot – graft function for EVL+CSA vs CSA+MPS



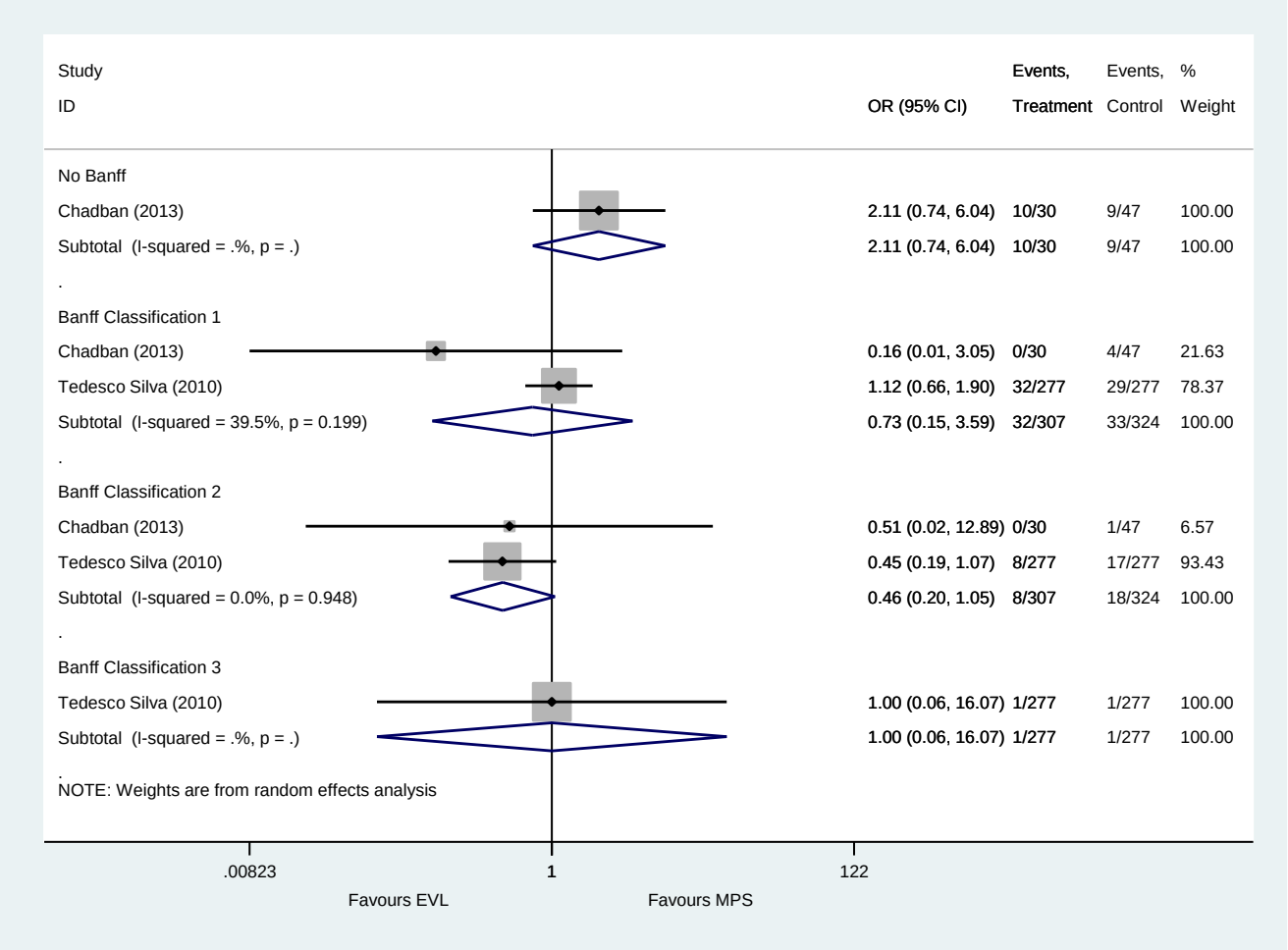
Severity of biopsy proven acute rejection

Two studies were pooled for Banff classification one and two, where the effect estimate suggests participants in the MPS arm are more likely to receive these results, although the effect is not statistically significant (Table 79; Figure 52).[145 195] There is no difference between arms for Banff classification three, which is only reported by Tedesco Silva et al. 2010. [145]

Table 79. Severity of BPAR for EVL+CSA vs MPS+CSA

Study id	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Chadban, 2013	None	1	2.11	0.74 – 6.04	NA	NA
Chadban, 2013; Tedesco Silva, 2010	1	2	0.73	0.15 – 3.59	39.5%	0.7666
	2	2	0.46	0.20 – 1.05	0.0%	0.0
Tedesco Silva, 2010	3	1	1.00	0.06 – 16.07	NA	NA

Figure 52. Forest plot – severity of BPAR for EVL+CSA vs CSA+MMF



Summary for EVL+CSA vs MPS+CSA

- Pooled analysis of four studies at one year indicates no significant difference between EVL+CSA and MPS+CSA (OR 1.02, 95% CI 0.42 to 2.45). No heterogeneity was evident across studies.

- The OR for graft loss is generated from three pooled studies, which indicates that EVL may be preferable in reducing graft loss, however, this result is not statistically significant (OR 0.648, 95% CI 0.146 to 2.870). Furthermore, moderate heterogeneity is noted across studies.

- Biopsy proven acute rejection is reported by three studies at one year. [145 146 195] Pooling of results indicates no statistically siginificant difference between EVL+CSA vs MPS+CSA (OR 1.01, 95% CI 0.68 to 1.48).

- Two studies were pooled for Banff classification one and two, where the effect estimate suggests participants in the MPS arm are more likely to receive these results, although the effect is not statistically significant. [145 195] There is no difference between arms for Banff classification three, which is only reported by Tedesco Silva et al. (2010).[145]

4.3.2.12. EVL+MPS vs CSA+MPS

Only the study reported by Mjornstedt et al. 2012 investigated this combination of therapies.[150] Therefore outcomes are summarised in Table 80. Time to BPAR not reported. Data is provided at one year, where there is no statistical difference between arms for mortality or graft loss. There is evidence to indicate greater odds of BPAR associated with EVL+MPS (OR 19.31, 95% CI 9.09 to 41.04). There is no significant difference in severity of BPAR.

Table 80. Summary of outcomes for EVL+MPS vs CSA+MPS at one year

Study id	Time point	Outcome	EVL+MPS	CSA+MPS	Odds ratio	95% CI
Mjornstedt, 2012	1 year	Mortality, n/N (%)	2/102 (98)	2/100 (98)	1	0.14 - 7.24
		Graft loss, n/N (%)	0/102 (0)	0/100 (0)	NA	NA
		BPAR, n/N (%)	28/102 (27)	11/100 (11)	19.31	9.09 – 41.04
		BPAR – no Banff, n/N (%)	31/102 (30)	6/100 (6)	6.84	2.71 – 17.28
		BPAR – Banff 1, n/N (%)	5/102 (5)	7/100 (7)	0.68	0.21 – 2.23
		BPAR – Banff 2, n/N (%)	0/102 (0)	0/100 (0)	NA	NA

4.3.2.13. SRL+CSA vs MMF+CSA

Three RCTs were identified for this combination of therapies.[151 152 194] No time to BPAR or severity of BPAR was reported.

Mortality

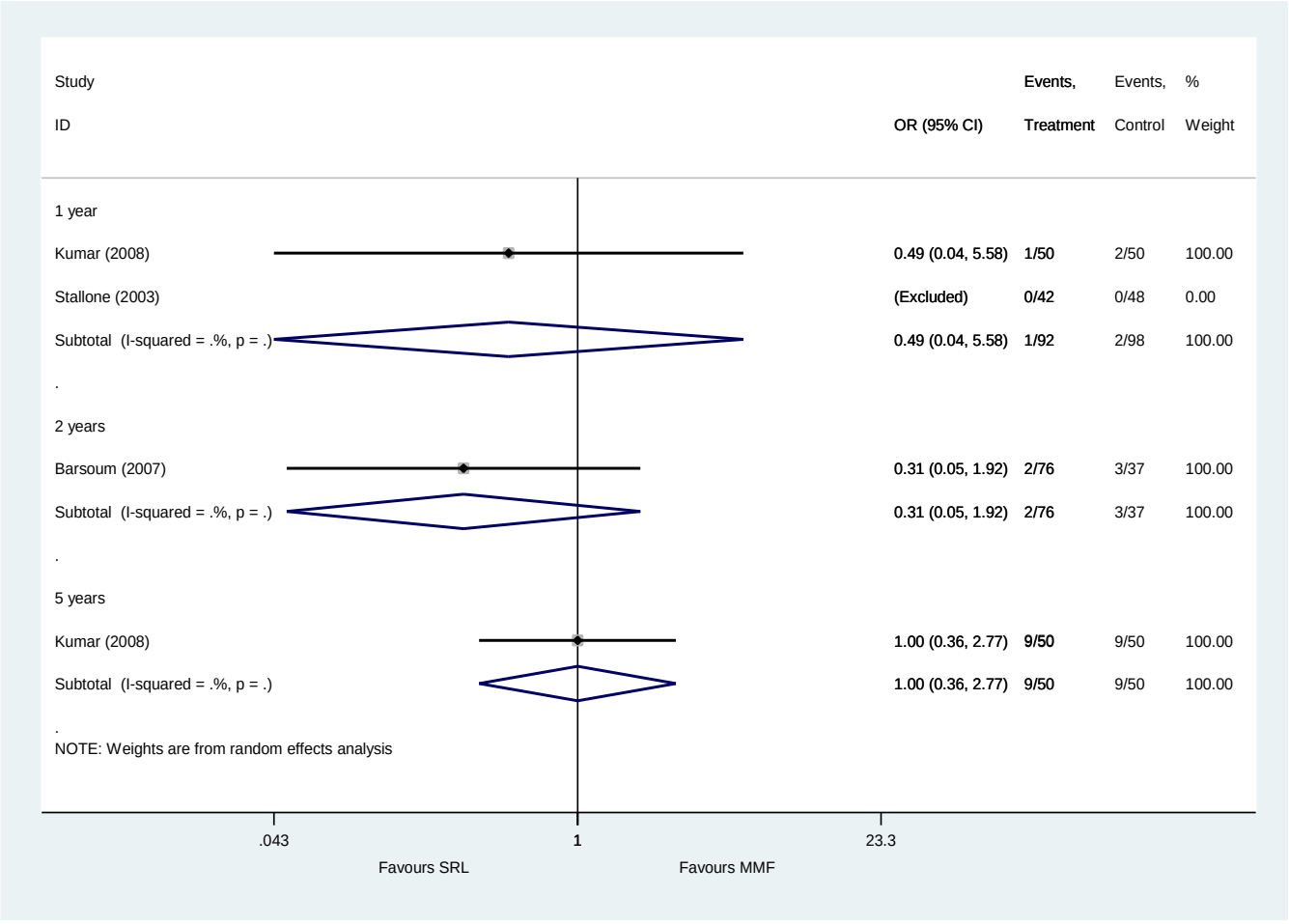
Two studies were available for pooling at one year, however, one of the studies had no deaths in either arm (Table 81; Figure 53).[151 152 194] The ORs appear to indicate lower odds associated with mortality for SRL, however this is not statistically significant (1 year OR 0.49, 95% CI 0.04 to 5.59).

Table 81. Mortality for SRL+CSA vs MMF+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kumar, 2008; Stallone, 2003[a]	1 year	2	0.49	0.04 – 5.59	NA	NA
Barsoum, 2007	2 years	1	0.31	0.05 – 1.92	NA	NA
Kumar, 2008	5 years	1	1.0	0.36 – 2.77	NA	NA

Key: (a) One study excluded due to no deaths in either arm

Figure 53. Forest plot – mortality for SRL+CSA vs MMF+CSA



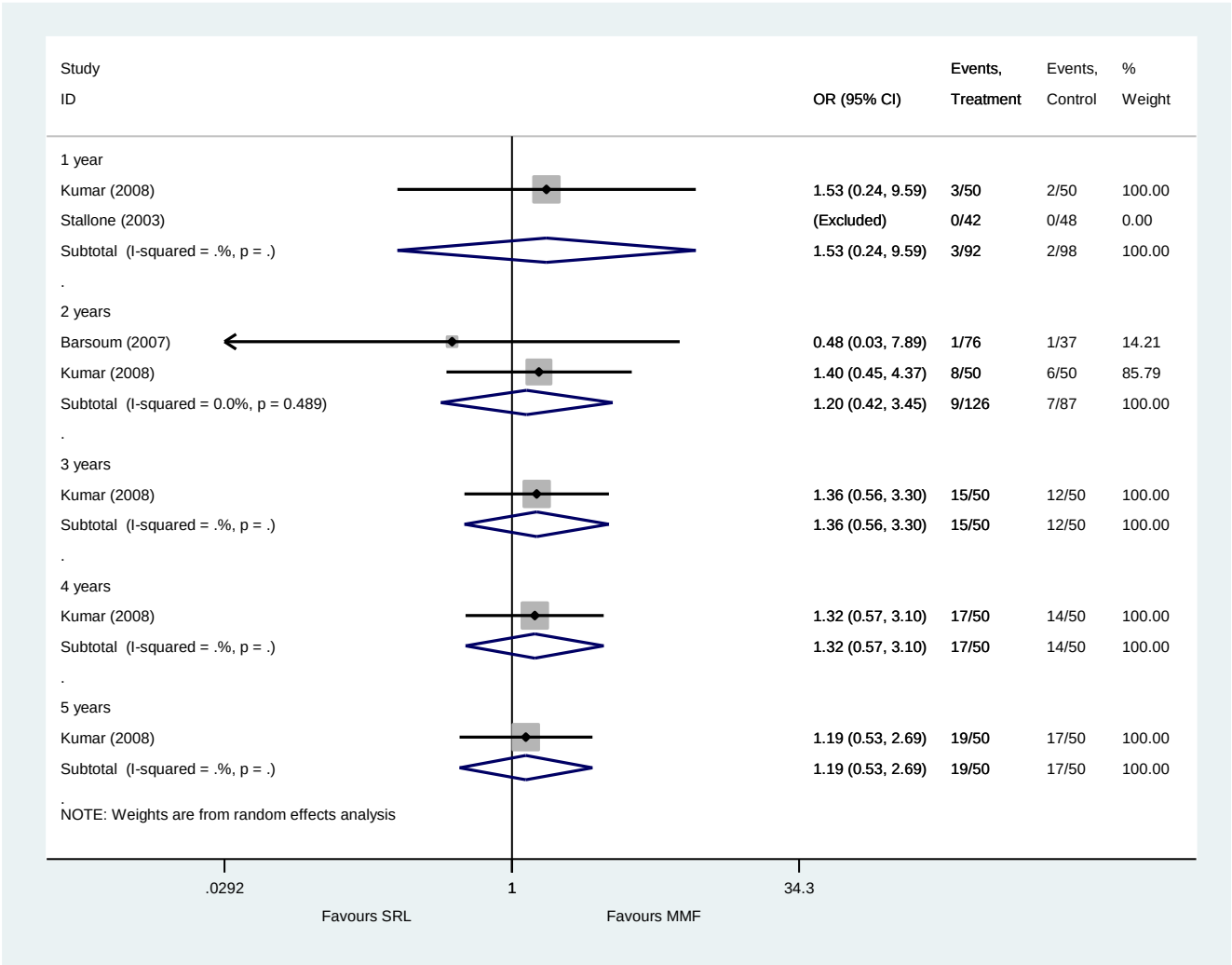
Graft loss

Three studies report on graft loss for SRL+CSA vs MMF+CSA from one to five years (Table 82; Figure 54). [151 152 194] Odds ratios slightly favour MMF, but the effect is not statistically significant (1 year, OR 1.53, 95%CI 0.24 to 9.59).

Table 82. Graft loss for SRL+CSA vs MMF+CSA

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kumar, 2008; Stallone, 2003	1 year	2	1.53	0.24 – 9.59	NA	NA
Barsoum, 2007; Kumar, 2008	2 years	2	1.20	0.42 – 3.45	0.0%	0.0
Kumar, 2008	3 years	1	1.36	0.56 – 3.30	NA	NA
	4 years	1	1.32	0.57 – 3.10	NA	NA
	5 years	1	1.0	0.36 – 2.77	NA	NA

Figure 54. Forest plot – graft loss for SRL+CSA vs MMF+CSA



Biopsy proven acute rejection

The study by Kumar et al. (2008) reporting on BPAR at one year had eight events in both arms and therefore no difference between treatments (Table 83).[194] At two years, Barsoum et al. (2007) report more favourable outcomes for SRL, however, this is not statistically significant (OR 0.65, 95% CI 0.22 to 1.87).[151]

Table 83. BPAR for SRL+CSA vs MMF+CSA

Study id	Time point	SRL	MMF	Odds ratio	95% CI
Kumar, 2008	1 year	4/50 (8)	4/50 (8)	NA	NA
Barsoum, 2007	2 years	10/76 (13)	7/37 (19)	0.65	0.22 – 1.87

Graft function

Graft function is monitored by one study (Stallone et al. 2003) at one year (Table 84).[152] No statistical difference is apparent between SRL and MMF (WMD 0.11, p=0.5708)

Table 84. Graft function for SRL+CSA vs MMF+CSA

Study id	SRL	MMF	Weighted mean difference (ml/min)	95% CI	P value (*t*-Test)
Stallone, 2003	61.5 (11)	60.3 (9)	0.11	-0.28 – 0.51	0.5708

Summary for SRL+CAS vs MMF+CSA

- Two studies were available for pooling at one year, however, one of the studies had no deaths in either arm. [151 152 194] The ORs appear to indicate lower odds associated with mortality for SRL, however this is not statistically significant (1 year OR 0.49, 95% CI 0.04 to 5.59).

- Three studies report on graft loss for SRL+CSA vs MMF+CSA from one to five years.[151 194 204] Odds ratios slightly favour MMF, but the effect is not statistically significant (1 year, OR 1.53, 95%CI 0.24 to 9.59).

- The study by Kumar et al. (2008) reporting on BPAR at one year had eight events in both arms and therefore no difference between treatment.[194] At two years, Barsoum et al. (2007) report more favourable outcomes for SRL, however, this is not statistically significant (OR 0.65, 95% CI 0.22 to 1.87).[151]

- Graft function is monitored by one study (Stallone et al., 2003) at one year. No statistical difference is apparent between SRL and MMF (WMD 0.11, p=0.5708).

4.3.2.14. SRL+TAC vs MMF+TAC

A total of eight RCTs were identified investigating SRL+TAC vs MMF+TAC with all outcomes other than HRQoL reported. [80 153 155 156 158 160 187 194]

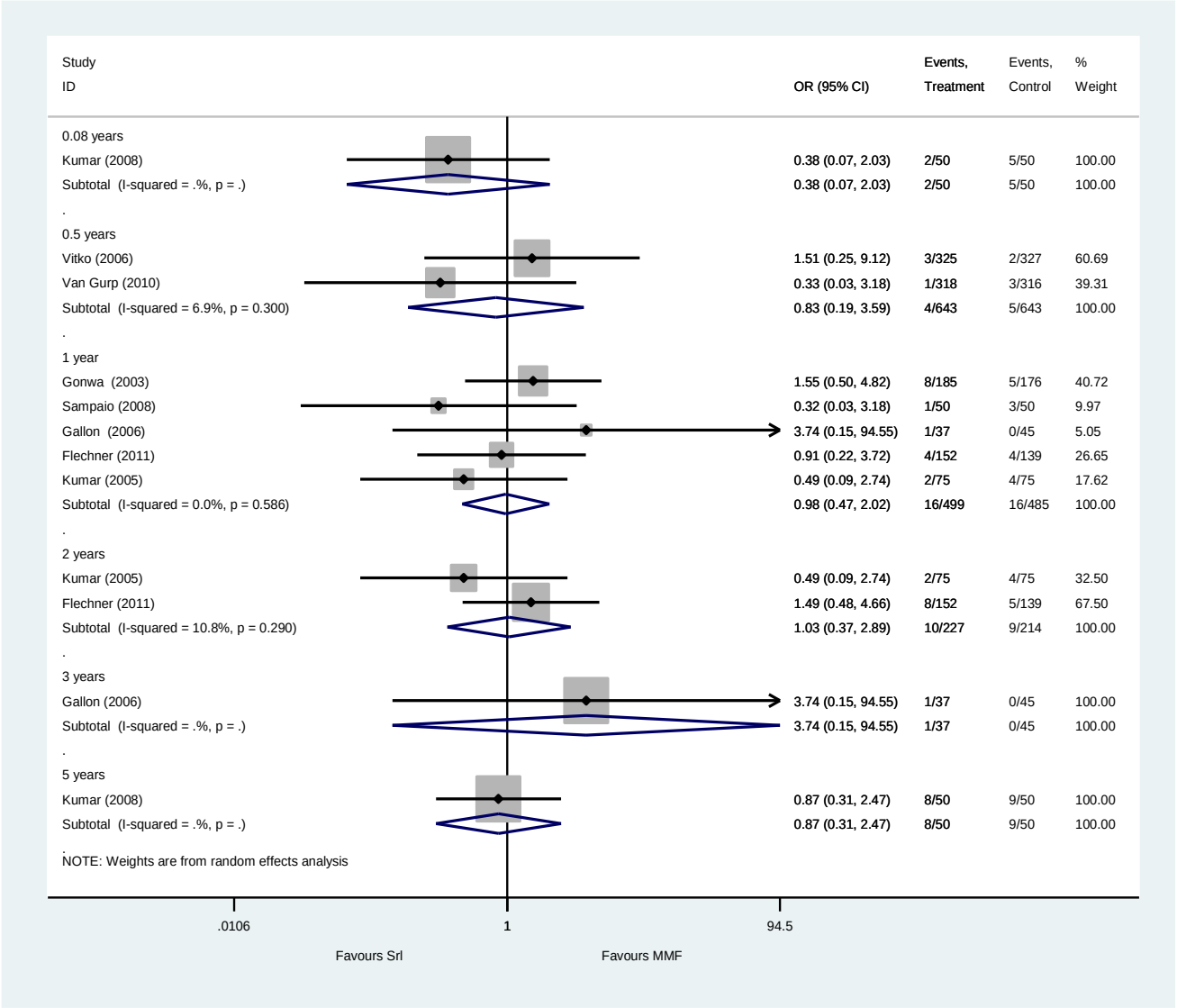
Mortality

Eight RCTs report mortality from 0.08 years to three years (Table 85; Figure 55).[80 153 155 156 158 160 187 194] The odds ratios vary from <1 at 0.08 years to >1 at 3 years, however the confidence intervals are wide and cross OR=1, indicating no statistical significance at any time point.

Table 85. Mortality for SRL+TAC vs MMF+TAC

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kumar, 2008	0.08 years	1	0.38	0.07 – 2.03	NA	NA
Van Gurp, 2010; Vitko, 2006	0.5 years	2	0.83	0.19 – 3.59	6.9%	0.08
Kumar, 2005; Gonwa, 2003; Sampaio, 2008; Gallon, 2006; Flechner, 2011	1 year	5	0.98	0.47 – 2.02	0.0%	0.0
Kumar, 2005; Flechner, 2011	2 years	2	1.03	0.37 – 2.89	10.8%	0.07
Gallon, 2006	3 years	1	3.74	0.15 – 94.55	NA	NA

Figure 55. Forest plot – mortality for SRL+TAC vs MMF+TAC



Graft loss

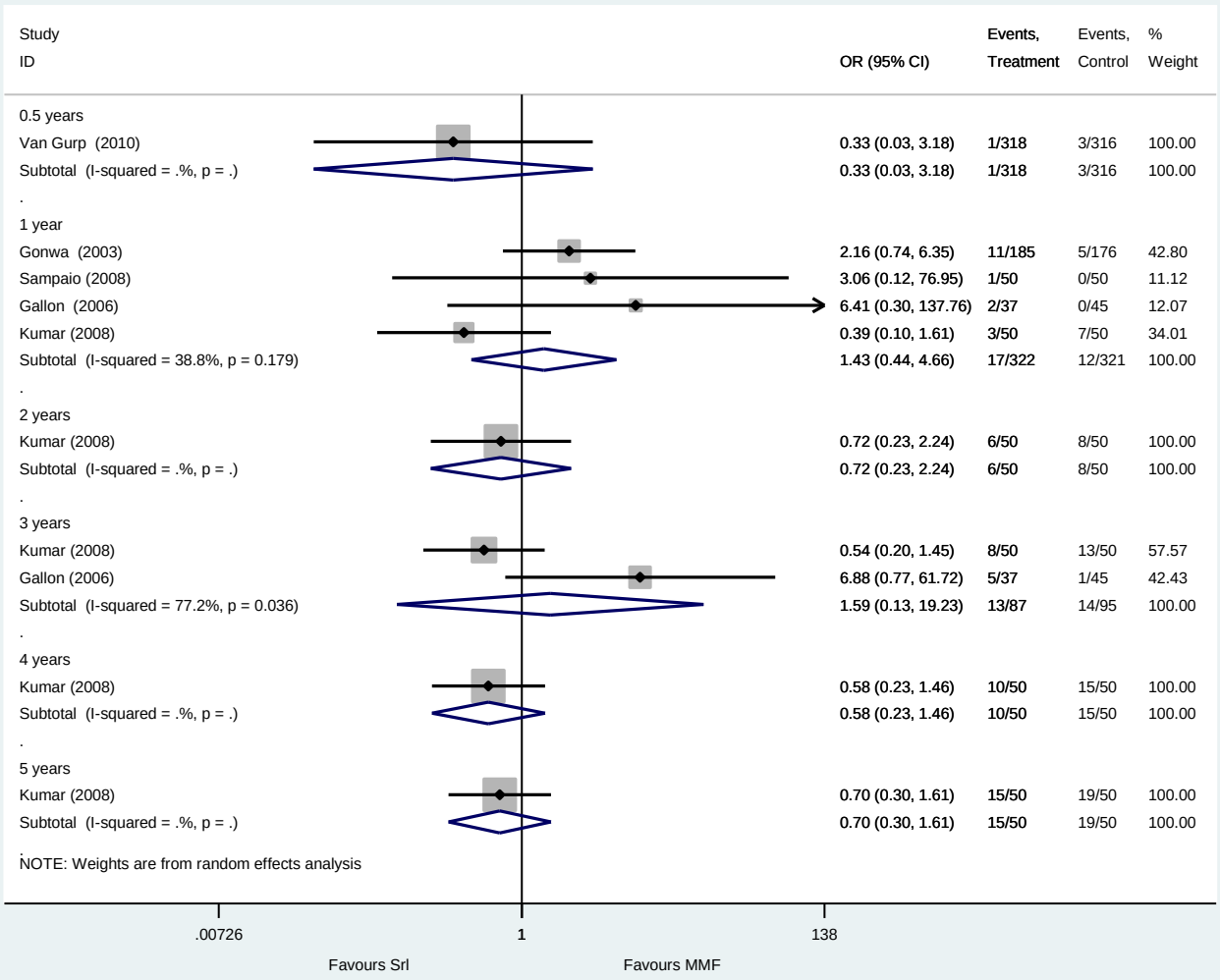
Five RCTs were identified reporting graft loss (Table 86; Figure 56). [155 156 158 160 194] Four RCTs are pooled at one year where increased odds of graft loss are associated with SRL. [194]Gonwa 2003}[156 158] however the effect is not statistically significant (OR 1.43, 95% CI 0.44 to 4.66). There may also be moderate heterogeneity across studies following pooling (I^2 38.8%). The study by Kumar et al. (2008) provides follow up to five years, where the OR<1favouring SRL, however, the results are not statistically significant.

Table 86. Graft loss for SRL+TAC vs MMF+TAC

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Van Gurp, 2010	0.5 years	1	0.33	0.03 – 3.18	NA	NA
Gonwa, 2003; Sampaio, 2008; Gallon, 2006; Kumar, 2008	1 year	4	1.43	0.44 – 4.66	38.8%	0.54
Kumar, 2008	2 years	1	0.72	0.23 – 2.24	NA	NA
Gallon, 2006; Kumar, 2008	3 years	2	1.59	0.13 – 19.23	77.2%	2.55
Kumar, 2008	4 years	1	0.58	0.23 – 1.46	NA	NA
Kumar, 2008	5 years	1	0.70	0.30 – 1.61	NA	NA

Notes: NA, not applicable

Figure 56. Forest plot – graft loss SRL+TAC vs MMF+TAC



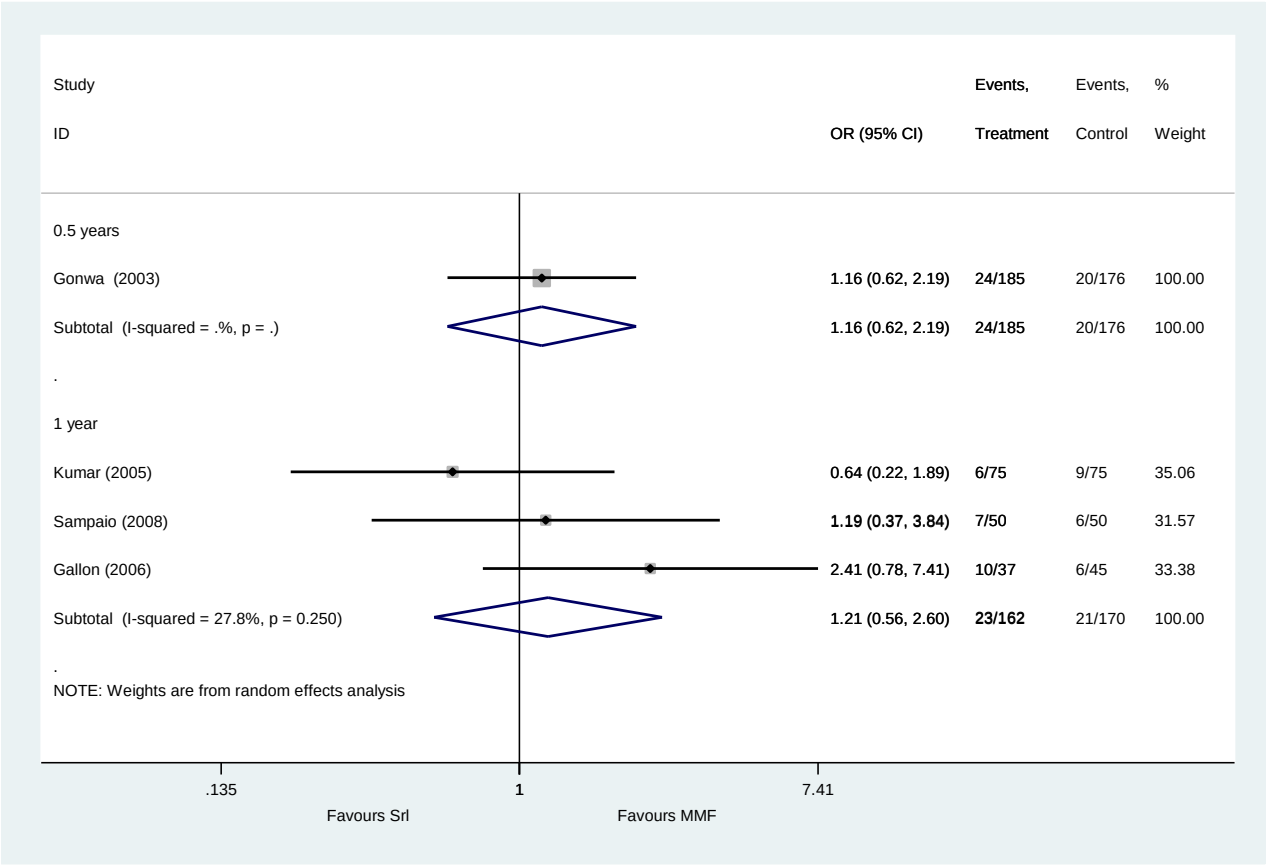
Biopsy proven acute rejection

BPAR is reported in four studies, with three pooled at one year (Table 87;Figure 57). [155 156 158 194] The odds ratios for 0.5 years and one year suggest MMF+TAC has lower odds of BPAR, however the effect is not statistically significant (1 year, OR 1.16, 95% CI 0.56 to 2.60). There is also a low level of heterogeneity (I^2 27.8%)

Table 87. BPAR for SRL+TAC vs MMF+TAC

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Gonwa, 2003	0.5 years	1	1.16	0.62 – 2.19	NA	NA
Kumar 2005; Sampaio, 2008; Gallon, 2006	1 year	3	1.21	0.56 – 2.60	27.8%	0.13

Figure 57. Forest plot – BPAR for SRL+TAC vs MMF+TAC



Graft function

Three RCTs were identified reporting graft function, however, due to the different time points, only two could be pooled at 0.5 years (Table 88; Table 89; Figure 58). [154 158 160] The results indicate no statistical difference between arms (WMD -1.875, 95% CI -8.425 to 4.675). Furthermore, substantial heterogeneity across studies is evident (I^2 81.6%)

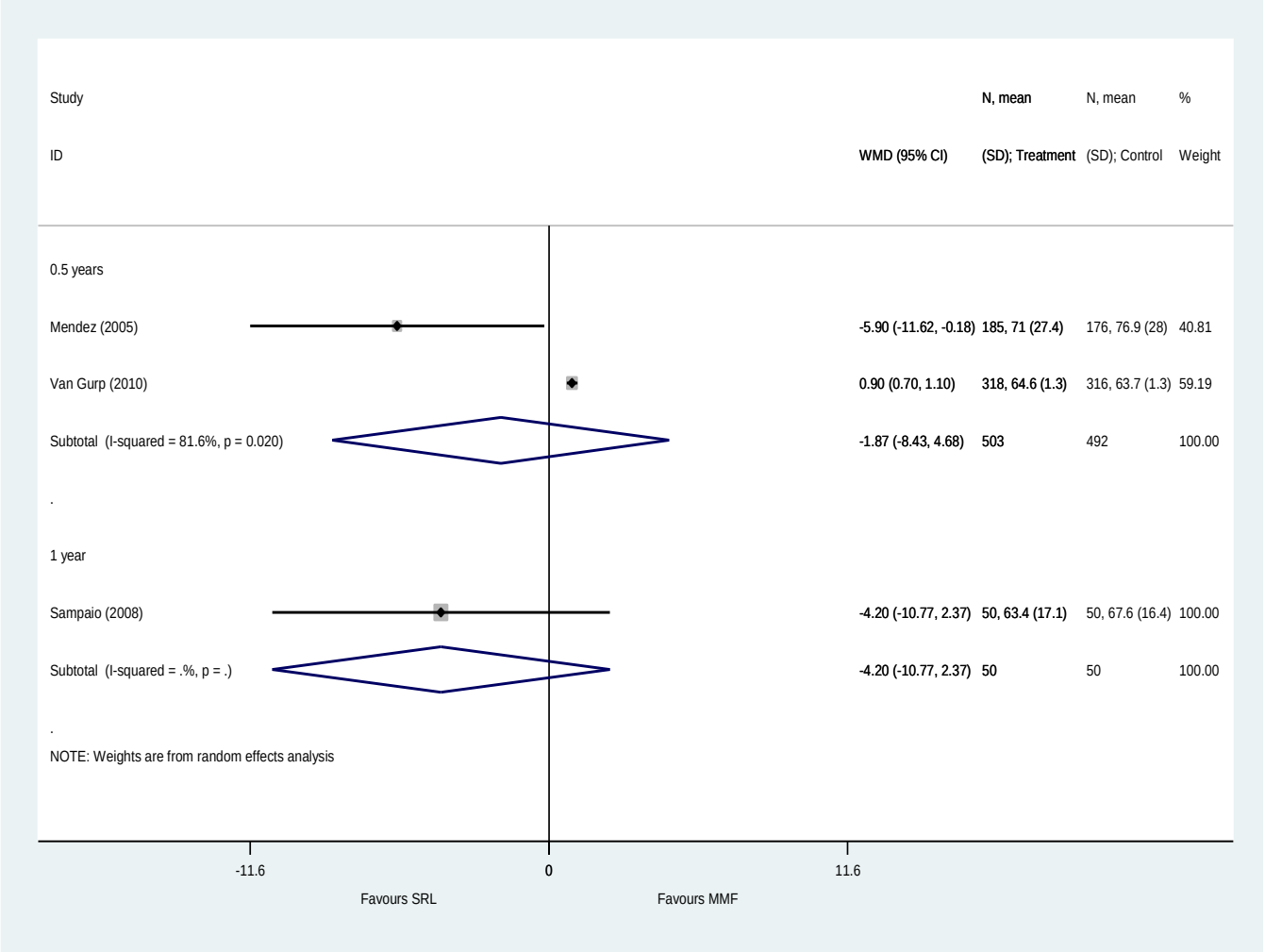
Table 88. Graft function for SRL+TAC vs MMF+TAC (pooled results)

Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Mendez, 2005; Van Gurp 2010	6 months	2	-1.875	-8.425 – 4.675	81.6%	18.86

Table 89. Graft function for SRL+TAC vs MMF+TAC (unpooled results)

Study id	Time point	Trials	Graft function, mean ml/min (sd)	
			SRL	MMF
Mendez, 2005	1 year	1	54.3 (NR)	58.4 (NR)
Gallon, 2006	3 years	1	36.9 (NR)	58.3 (NR)
	8.5 years		23.5 (NR)	54.1 (NR)

Figure 58. Forest plot – graft function for SRL+TAC vs MMF+TAC



Time to biopsy proven acute rejection

Time to BPAR is reported by Sampaio et al. 2008, where a statistically significant difference is demonstrated in favour of MMF (mean difference 48.6 days, p=0.0017) (Table 90).[156]

Table 90. Time to BPAR for SRL+TAC vs MMF+TAC

Study	Mean time to BPAR, days (sd)		P value (*t*-Test)[a]
	SRL	MMF	
Sampaio, 2008	**60.9 (104.5)**	**12.3 (19.4)**	**0.0017**

Key: (a) Calculated by PenTAG

Severity of biopsy proven acute rejection

Two studies report severity of BPAR; Van Gurp et al. 2010 at 0.5 years and Sampaio et al. (2008) at one year (Table 91).[156 160] No statistically significant difference is apparent at either time point for any Banff classification.

Table 91. Severity of BPAR for SRL+TAC vs MMF+TAC

Study id	Time point	Banff classification	SRL+TAC, n/N (%)	MMF+TAC, n/N (%)	Odds ratio	95% CI
Van Gurp, 2010	0.5 years	1	30/218 (14)	26/316 (8)	1.7799	1.0204 – 3.1045
		2	17/318 (5)	17/316 (5)	0.9934	0.4977 – 1.9825
		3	1/318 (0.3)	2/316 (0.6)	0.4953	0.0447 – 5.4897
Sampaio, 2008	1 year	1	4/50 (8)	2/50 (4)	2.087	0.3645 – 11.9484
		2	3/50 (6)	4/50 (8)	1.4681	0.3887 – 5.5445

Notes: All percentages calculated by PenTAG

Summary for SRL+TAC vs MMF+TAC

- Eight RCTs report mortality from 0.08 years to three years. [80 153 155 156 158 160 187 194] The odds ratios vary from <1 at 0.08 years to >1 at 3 years, however the confidence intervals are wide and cross OR=1, indicating no statistical significance at any time point.

- Five RCTs were identified reporting graft loss. [155 156 158 160 194] Four RCTs are pooled at one year where increased odds of graft loss are associated with SRL, however the effect is not statistically significant (OR 1.43, 95% CI 0.44 to 4.66). There may also be moderate heterogeneity across studies following pooling (I^2 38.8%). The study by Kumar et al. (2008) provides follow up to five years, where the OR<1favouring SRL, however, the results are not statistically significant.

- BPAR is reported in four studies, with three pooled at one year. [155 156 158 194] The odds ratios for 0.5 years and one year suggest MMF+TAC has lower odds of BPAR, however the effect is not statistically significant (1 year, OR 1.16, 95% CI 0.56 to 2.60). There is also a low level of heterogeneity (I^2 27.8%)

- Three RCTs were identified reporting graft function, however, due to the different time points, only two could be pooled at 0.5 years. [154 158 160] The results indicate no

statistical difference between arms (WMD -1.875, 95% CI -8.425 to 4.675). Furthermore, substantial heterogeneity across studies is evident (I^2 81.6%)

- Time to BPAR is reported by Sampaio et al. (2008), where a statistically significant difference is demonstrated in favour of MMF (mean difference 48.6 days, p=0.0017).[156]

- Two studies report severity of BPAR; Van Gurp et al. (2010) at 0.5 years and Sampaio et al. (2008) at one year. [156 160]No statistically significant difference is apparent at either time point for any Banff classification.

4.3.2.15. SRL+MMF vs CSA+MMF

Ten studies were identified investigating SRL+MMF vs CSA+MMF. [77 161 163 167 170 173-175 205 206]

Mortality

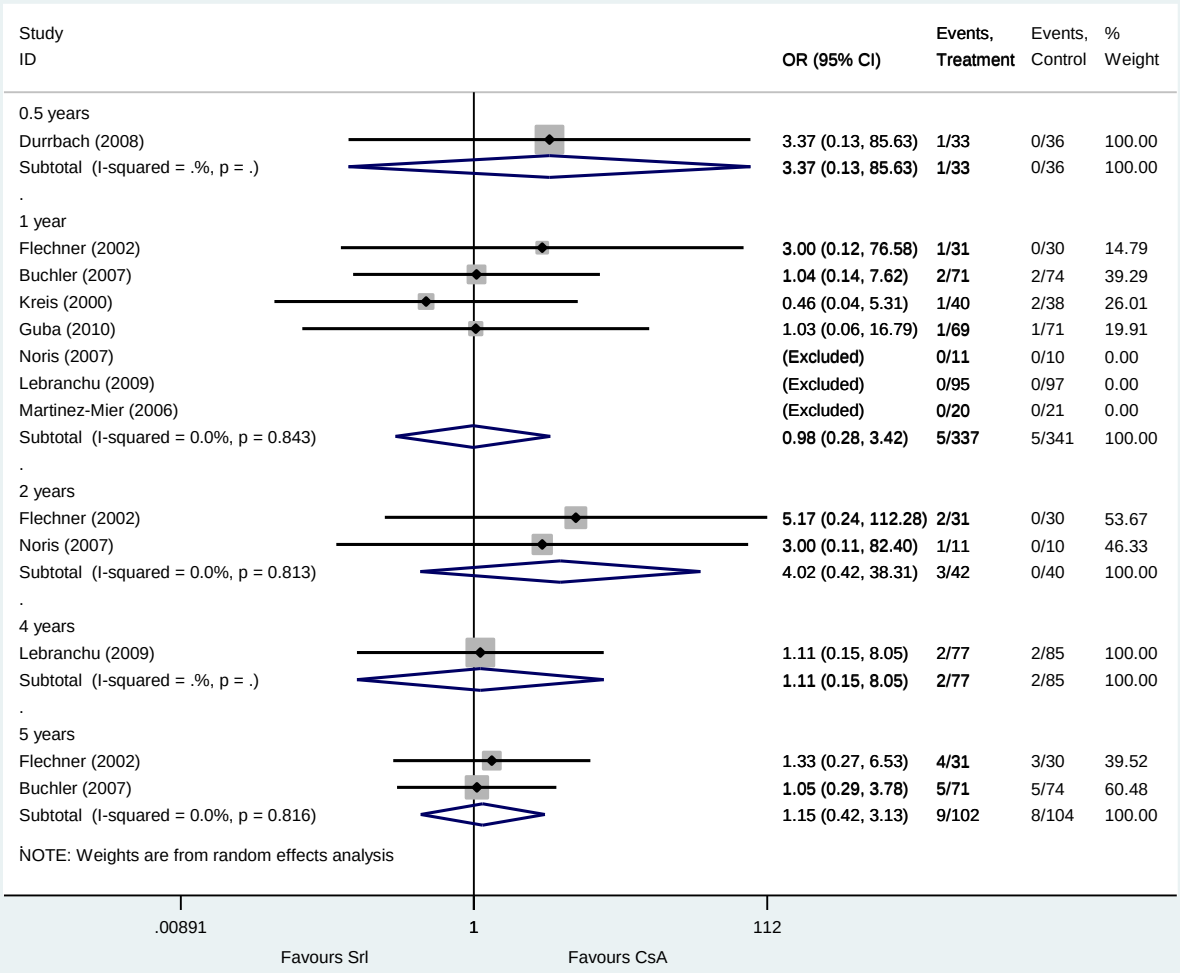
Eight studies report on mortality, with seven pooled at one year (Table 92; Figure 59). [161 163 167 170 173 174 205 206]No statistically significant difference was evident at this time point (1 year, OR 0.98, 95%CI 0.28 to 3.42). Data is available up to five years, however, although the OR is slightly in favour of CSA, the effect is also not statistically significant (5 years, OR 1.15, 95%CI 0.42 to 3.13). [161 207]

Table 92. Mortality for SRL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Durrbach, 2008	0.5 years	1	3.37	0.13 – 85.63	NA	NA
Flechner, 2002; Noris, 2007; Lebranchu, 2009; Büchler, 2007; Kreis, 2000; Guba, 2010; Martinez-Mier, 2006	1 year	7[a]	0.98	0.28 – 3.42	0.0%	0
Flechner, 2002; Noris, 2007	2 years	2	4.02	0.42 – 38.31	0.0%	0
Lebranchu, 2009	4 years	1	1.11	0.15 – 8.05	NA	NA
Flechner, 2002; Büchler, 2007	5 years	2	1.15	0.42 – 3.13	0.0%	0

Notes: (a) 3 trials excluded from pooled analysis due to no deaths in both arms

Figure 59. Forest plot – mortality for SRL+MMF vs CSA+MMF



Graft loss

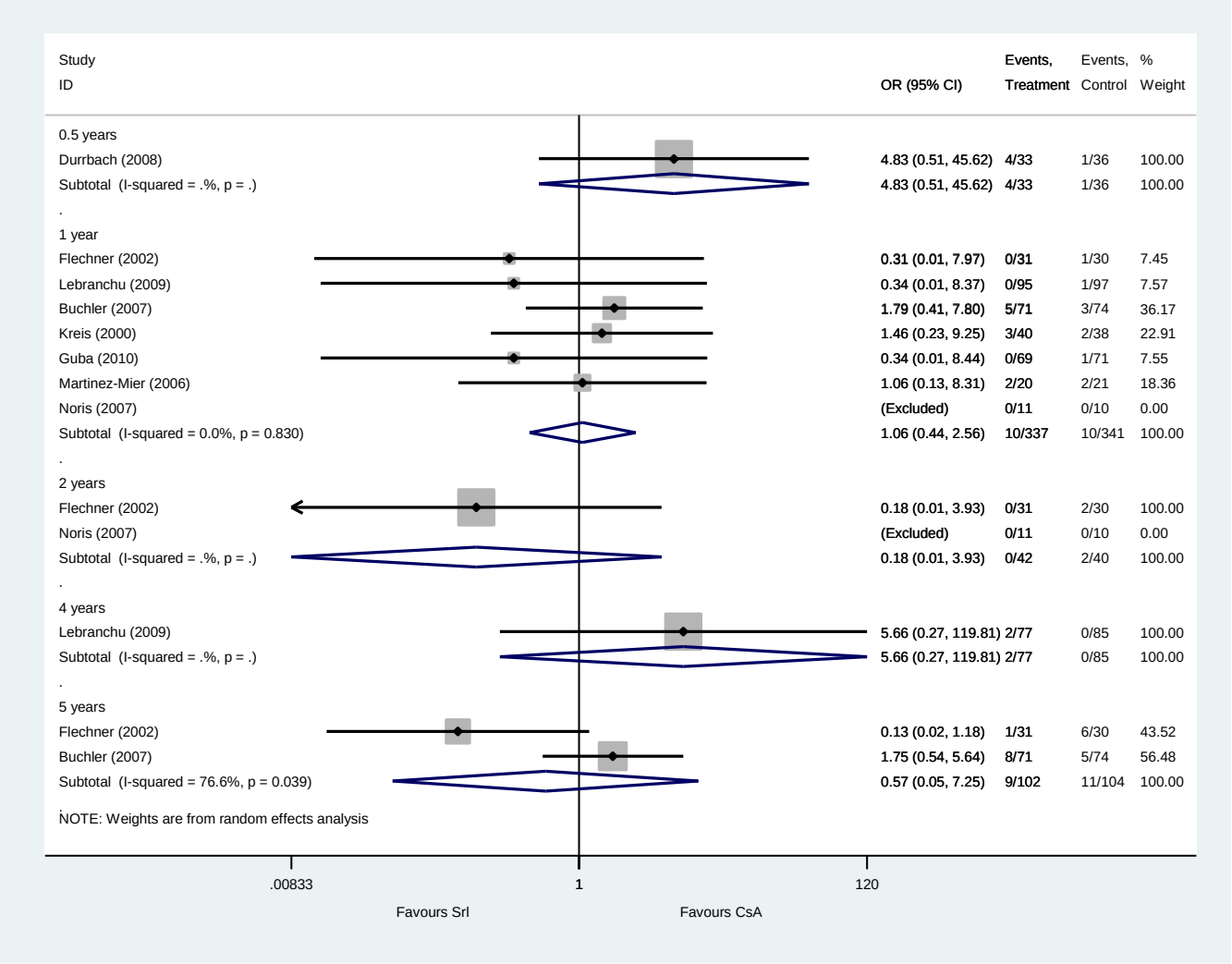
Eight studies report on graft loss from 0.5 years to five years (Table 93; Figure 60). [161 163 167 170 173 174 205 206]Seven studies are pooled at one year, however, there is no statistically significant difference between SRL+MMF and CSA+MMF (1 year, OR 1.06, 95%CI 0.44 to 2.56).[161 163 167 173 174 205 206]Flechner et al. 2002 and Buchler et al. 2007 report graft loss at five years, however, again, there is no statistically significant difference and heterogeneity across studies is substantial (5 years, OR 0.57, 95%CI 0.05 to 7.25, I^2 76.6%).[167 205]

Table 93. Graft loss for SRL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Durrbach, 2008	0.5 years	1	4.83	0.51 – 45.62	NA	NA
Flechner, 2002; Lebranchu, 2009; Büchler, 2007; Kreis, 2000; Guba, 2010; Martinez-Mier, 2006; Noris, 2007	1 year	7[a]	1.06	0.44 – 2.56	0.0%	0
Flechner, 2002; Noris, 2007	2 years	2	0.18	0.01 – 3.93	NA	NA
Lebranchu, 2009	4 years	1	5.66	0.27 – 119.81	NA	NA
Flechner, 2002; Büchler, 2007;	5 years	2	0.57	0.05 – 7.25	76.6%	2.6195

Key: (a) 1 trial excluded from pooled analysis due to no deaths in both arms

Figure 60. Forest plot – graft loss for SRL+MMF vs CSA+MMF



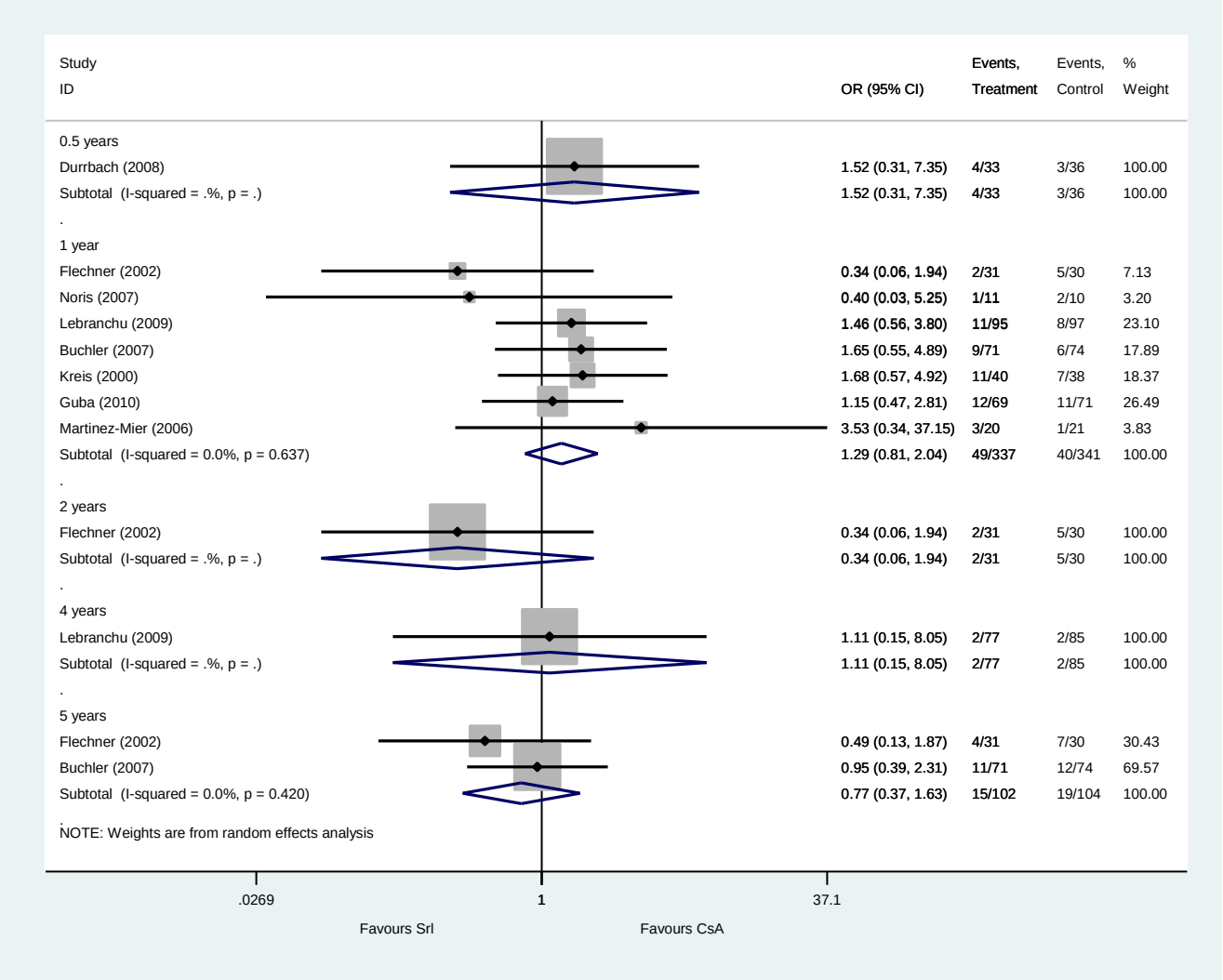
Biopsy proven acute rejection

Eight studies report on BPAR from 0.5 years to five years (Table 94; Figure 61).[161 163 167 170 173 174 205 206] Seven studies are pooled at one year, however, there is no statistically significant difference between arms, although the OR falls in favour of CSA+MMF (1 year, OR 1.29, 95%CI 0.81 to 2.04).[161 163 167 173 174 205 206] Flechner et al. 2002 and Buchler et al. 2007 report BPAR at five years, however, again, there is no statistically significant difference and heterogeneity across studies is substantial (5 years, OR 0.77, 95%CI 0.37 to 1.63).[167 205]

Table 94. BPAR for- SRL+MMF vs CSA+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Durrbach, 2008	0.5 years	1	1.52	0.31 – 7.35	NA	NA
Flechner, 2002; Lebranchu, 2009; Büchler, 2007; Kreis, 2000; Guba, 2010; Martinez-Mier, 2006; Noris, 2007	1 year	7	1.29	0.81 – 2.04	0.0%	0
Flechner, 2002	2 years	1	0.34	0.06 – 1.94	NA	NA
Lebranchu, 2009	4 years	1	1.11	0.15 – 8.05	NA	NA
Flechner, 2002; Büchler, 2007	5 years	2	0.77	0.37 – 1.63	0.0%	0

Figure 61. Forest plot – BPAR for SRL+MMF vs CSA+MMF



Graft function

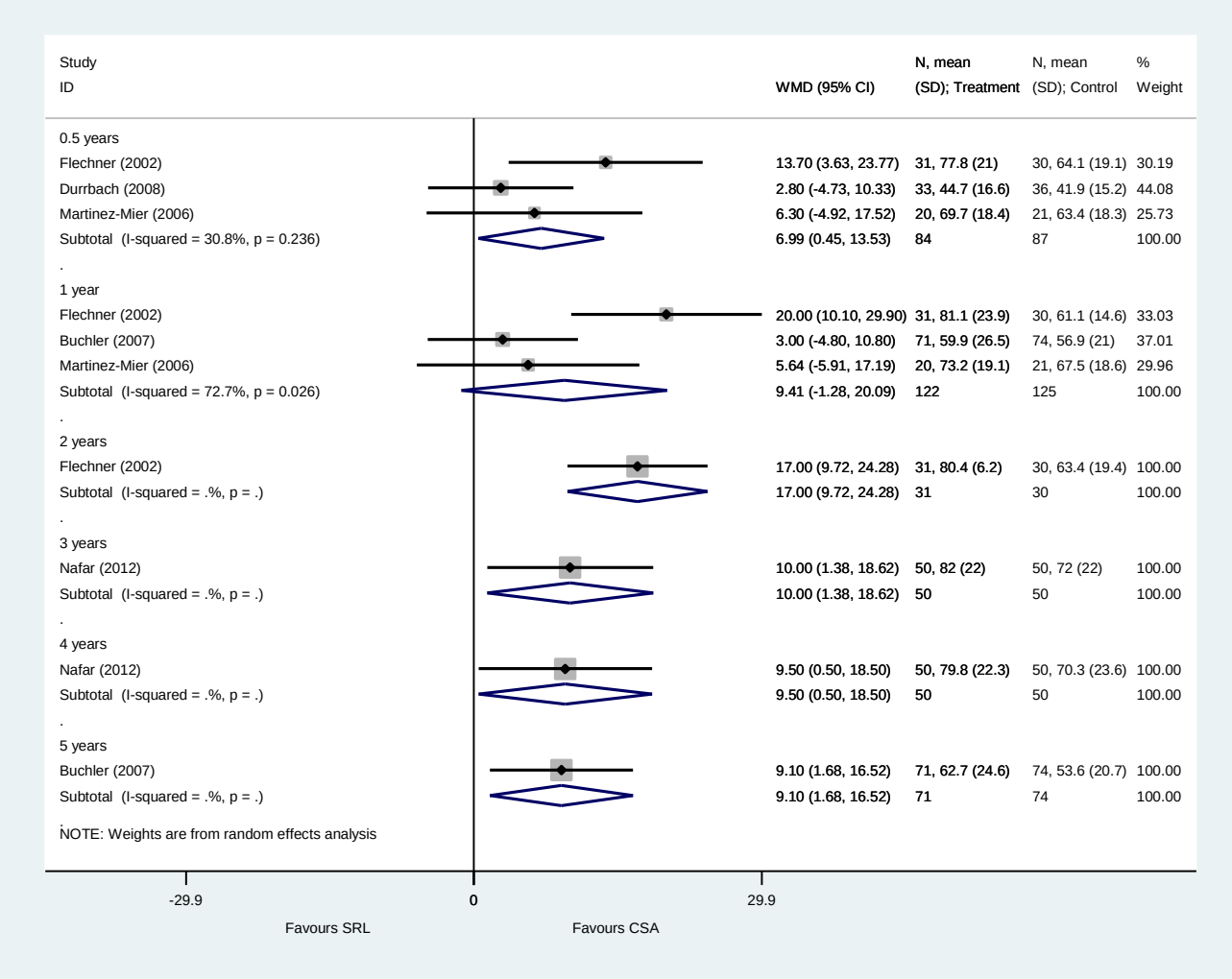
Six studies report graft function (note, this includes Lebranchu et al. 2009, with 68.9 ml/min for SRL and 64.4 ml/min for CSA, however a standard deviation is not provided). [163 167 170 174 175 205] Pooled analysis for 0.5 years and one year suggest that improved graft function is associated with CSA, although this effect is not statistically significant (0.5 year, WMD 6.99, 95%CI 0.45 to 13.53; 1 year, WMD 9.41, 95%CI -1.28 to 0.09). The individual studies for two, three, four and five years all have OR<1 and are statistically significant, therefore CSA appears beneficial in terms of graft function.

Table 95. Graft function for SRL+MMF vs CSA+MMF

Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Durrbach, 2008; Flechner, 2002; Martinez-Mier, 2006;	0.5 years	3	6.99	0.45 – 13.53	30.8%	10.47
Flechner, 2002; Büchler, 2007; Martinez-Mier, 2006;	1 year	3	9.41	-1.28 – 0.09	72.7%	64.39
Flechner, 2002	2 years	1	17.00	9.72 – 24.28	NA	NA
Nafar, 2012	3 years	1	10.00	1.38 – 18.62	NA	NA
	4 years	1	9.50	0.50 – 18.50	NA	NA
Büchler, 2007	5 years	1	9.10	1.68 – 16.52	NA	NA

Notes: The Cockcroft Gault formula was used for all graft function estimations, other than Büchler et al. (2007), where the Nankivell formula was used.

Figure 62. Forest plot – graft function for SRL+MMF vs CSA+MMF



Time to biopsy proven acute rejection

Time to BPAR is reported by three studies (Table 96). [167 170 205]A statistically significant difference is seen by Durrbach et al. 2008 (SRL 56 days, sd 57; CSA 94 days, sd 47; p=0.0035). [170] The studies reported by Buchler et al. 2007 and Flechner et al. 2002 show no statistical difference between treatments (p=0.3858 and p=0.982, respectively).

Table 96. Time to BPAR - SRL+MMF vs CSA+MMF

Study	Mean time to BPAR, days (sd)		P value (*t*-Test)[a]
	SRL	CSA	
Durrbach, 2008	56 (57)	94 (47)	0.0035
Büchler 2007	75 (82)	87 (84)	0.3858
Flechner, 2002	481 (507)	(471 (534)	0.982

Key: (a) Calculated by PenTAG

Severity of BPAR

Severity of BPAR is reported by three studies at one year (Table 97; Table 98).[167 205 206]. Flechner et al.2002 also report results for five years. ORs fluctuate between greater than and less than 1, with no statistically significant difference seen for any of the Banff classifications.

Table 97. Severity of BPAR - SRL+MMF vs CSA+MMF (pooled results)

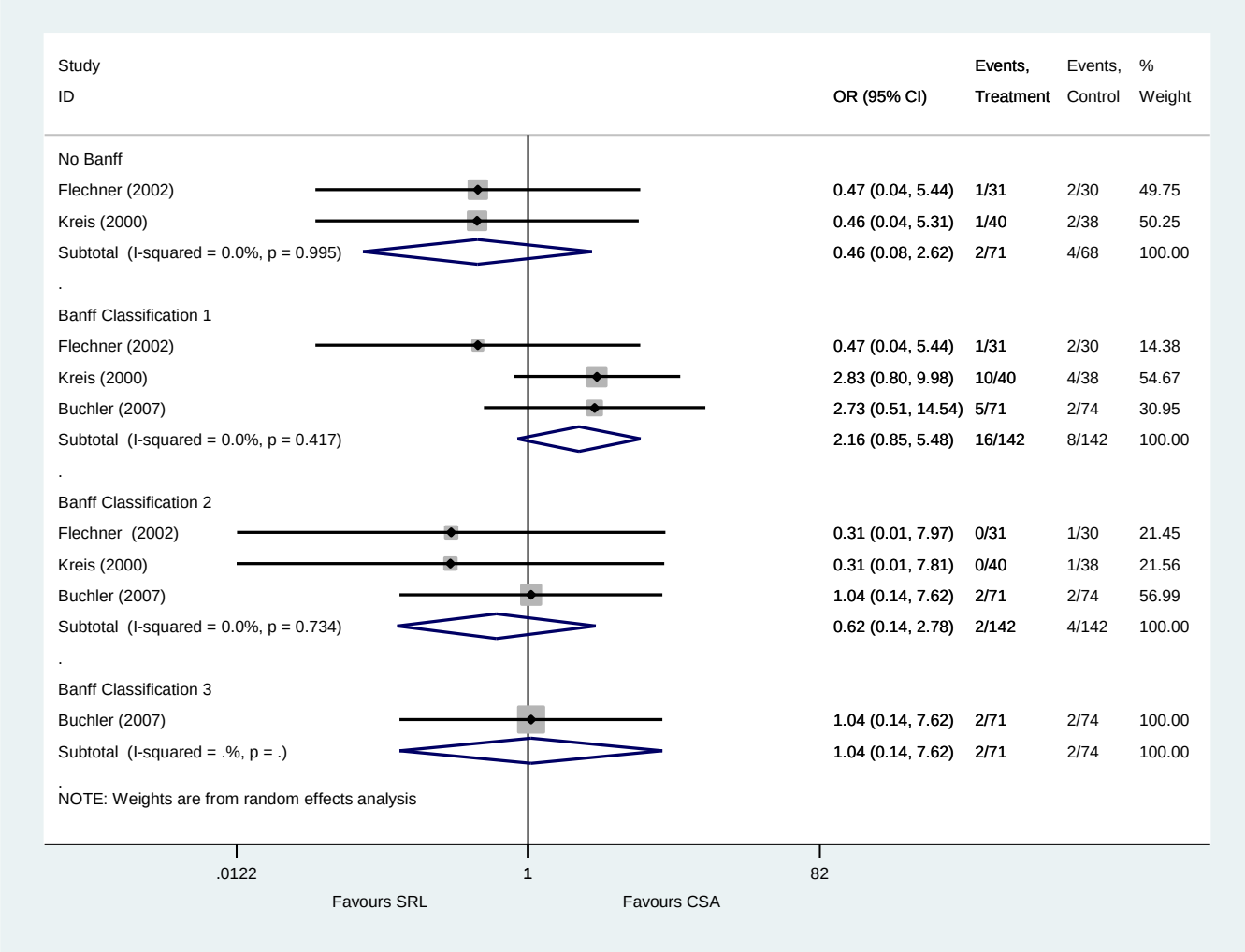
Study id	Time point	Banff classification	Trials	Odds ratio	95% CI	I^2	Tau^2
Flechner, 2002; Kreis, 2000	1 year	None	2	0.46	0.08 – 2.62	0.0%	0.0
Flechner, 2002; Kreis, 2000; Büchler 2007		1	3	2.16	0.85 – 5.48	0.0%	0.0
Flechner, 2002; Kreis, 2000; Büchler, 2007		2	3	0.62	0.14 – 2.78	0.0%	0.0
Büchler, 2007		3	1	1.04	0.14 – 7.62	NA	NA

Table 98. Severity of BPAR – SRL+MMF vs CSA+MMF (unpooled results)

Study	Time point	Banff classification	SRL+MMF, n/N (%)	CSA+MMF, n/N (%)	Odds ratio	95% CI
Flechner, 2002	5 years	1	4/31 (13)	2/30 (7)	2.07	0.35 – 12.27
		2	0/31 (0)	3/30 (10)	NA	NA
		3	0/31 (0)	2/30 (0.7)	NA	NA

Notes: All percentages calculated by PenTAG

Figure 63. Forest plot – severity of BPAR for SRL+MMF vs CSA+MMF



Summary of results for SRL+MMF vs CSA+MMF

- Eight studies report on mortality, with seven pooled at one year. [161 163 167 170 173 174 205 206] No statistically significant difference was evident at this time point (1 year, OR 0.98, 95%CI 0.28 to 3.42). At five years the OR is slightly in favour of CSA, however, the effect is also not statistically significant (5 years, OR 1.15, 95%CI 0.42 to 3.13).[161 207]

- Eight studies report on graft loss from 0.5 years to five years. [161 163 167 170 173 174 205 208]Seven studies are pooled at one year, however, there is no statistically significant difference between SRL+MMF and CSA+MMF (1 year, OR 1.06, 95%CI 0.44 to 2.56).[161 163 167 173 174 205 206]Flechner et al. 2002 and Buchler et al. 2007 report graft loss at five years, however, again, there is no statistically significant difference and

heterogeneity across studies is substantial (5 years, OR 0.57, 95%CI 0.05 to 7.25, I^2 76.6%).[167 205]

- Eight studies report on BPAR from 0.5 years to five years. [161 163 167 170 173 174 205 206] Seven studies are pooled at one year, however, there is no statistically significant difference between arms, although the OR falls in favour of CSA+MMF (1 year, OR 1.29, 95%CI 0.81 to 2.04).[161 163 167 173 174 205 206] Flechner et al. 2002 and Buchler et al. 2007 report BPAR at five years, however, again, there is no statistically significant difference and heterogeneity across studies is substantial (5 years, OR 0.77, 95%CI 0.37 to 1.63).[167 205]

- Six studies report graft function (note, this includes Lebranchu et al. 2009, with 68.9 ml/min for SRL and 64.4 ml/min for CSA, however a standard deviation is not provided). [163 167 170 174 175 205] Pooled analysis for 0.5 years and one year suggest that improved graft function is associated with TAC, although this effect is not statistically significant (0.5 year, WMD 6.99, 95%CI 0.45 to 13.53; 1 year, WMD 9.41, 95%CI -1.28 to 0.09). The individual studies for two, three, four and five years all have OR<1 and are statistically significant, therefore TAC appears beneficial in terms of graft function.

- Time to BPAR is reported by three studies (Table 96). [167 170 205]A statistically significant difference is seen by Durrbach et al. (2008) (SRL 56 days, sd 57; CSA 94 days, sd 47; p=0.0035). [170] The studies reported by Buchler et al. 2007 and Flechner et al. 2002 show no statistical difference between treatments (p=0.3858 and p=0.982, respectively).

- Severity of BPAR is reported by three studies at one year (Table 97; Table 98). [167 205 206]. Flechner et al. 2002 also report results for five years. ORs fluctuate between greater than and less than 1, with no statistically significant difference seen for any of the Banff classifications.

4.3.2.16. TAC+MMF vs SRL+MMF

Four studies report outcomes for this combination of treatments. [78 79 178 209] No time to BPAR or HRQoL is reported.

Mortality

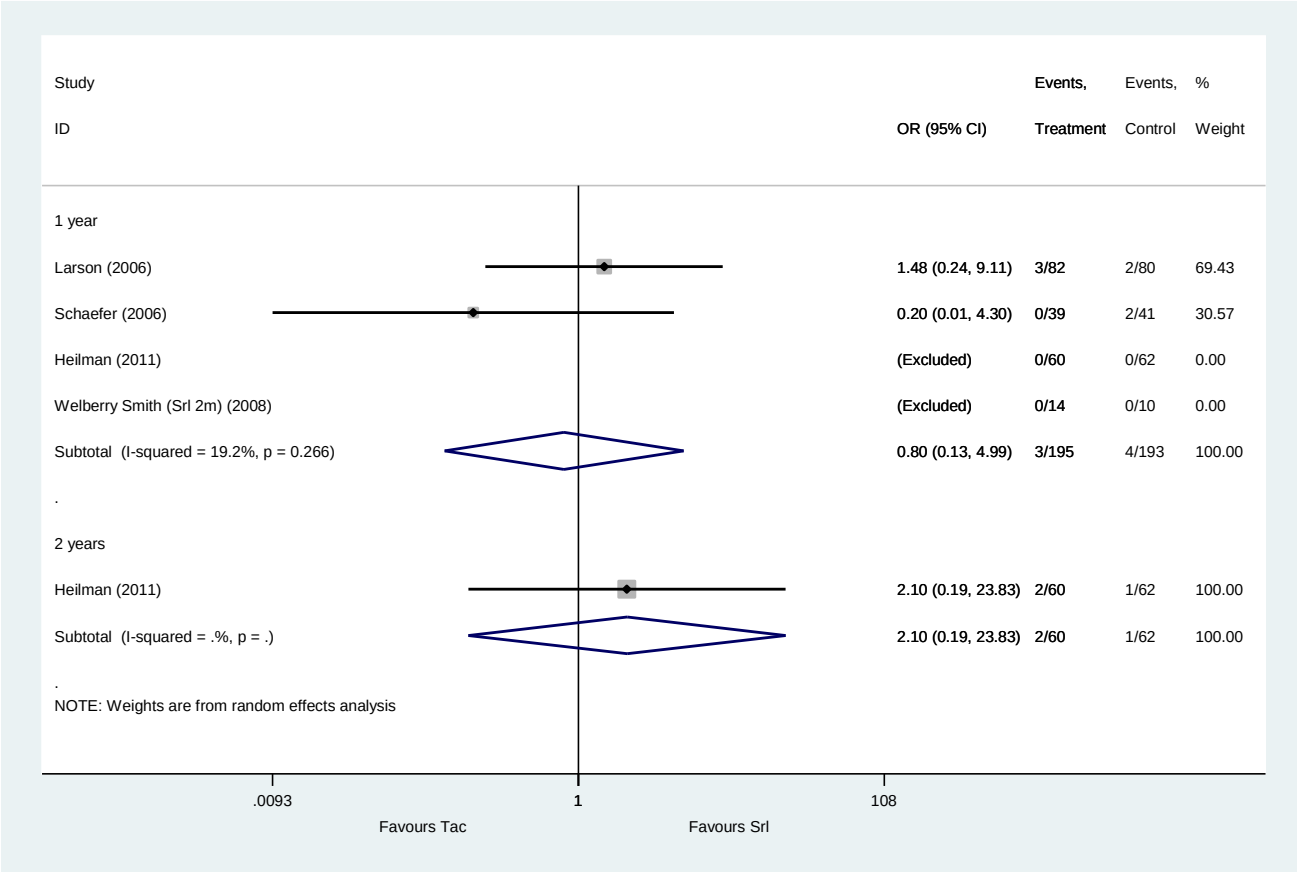
Four studies are pooled with one year results for mortality; however two of these studies had no deaths in either arm (Table 99;Figure 64). Analysis suggests no significant difference between TAC+MMF and SRL+MMF (OR 0.80, 95%CI 0.13 to 4.99)[78 79 178 209] Heilman et al. 2011 also present results at two years (Table 99). Again, results are not statistically significant (OR 2.10, 95% 0.19 to 23.83)

Table 99. Mortality for TAC+MMF vs SRL+MMF

Study id	Time point	Trials	Odds ratio	95%CI	I^2	Tau^2
Larson, 2006; Schaefer, 2006; Heilman, 2011; Welberry Smith, 2008	1 year	4[a,b]	0.80	0.13 – 4.99	19.2%	0.39
Heilman, 2011	2 years	1	2.10	0.19 – 23.83	NA	NA

Notes: (a) 3 arm trial with high dose excluded, (b) 2 trials excluded from pooled analysis due to no BPAR in both arms

Figure 64. Forest plot – mortality for TAC+MMF vs SRL+MMF



Graft loss

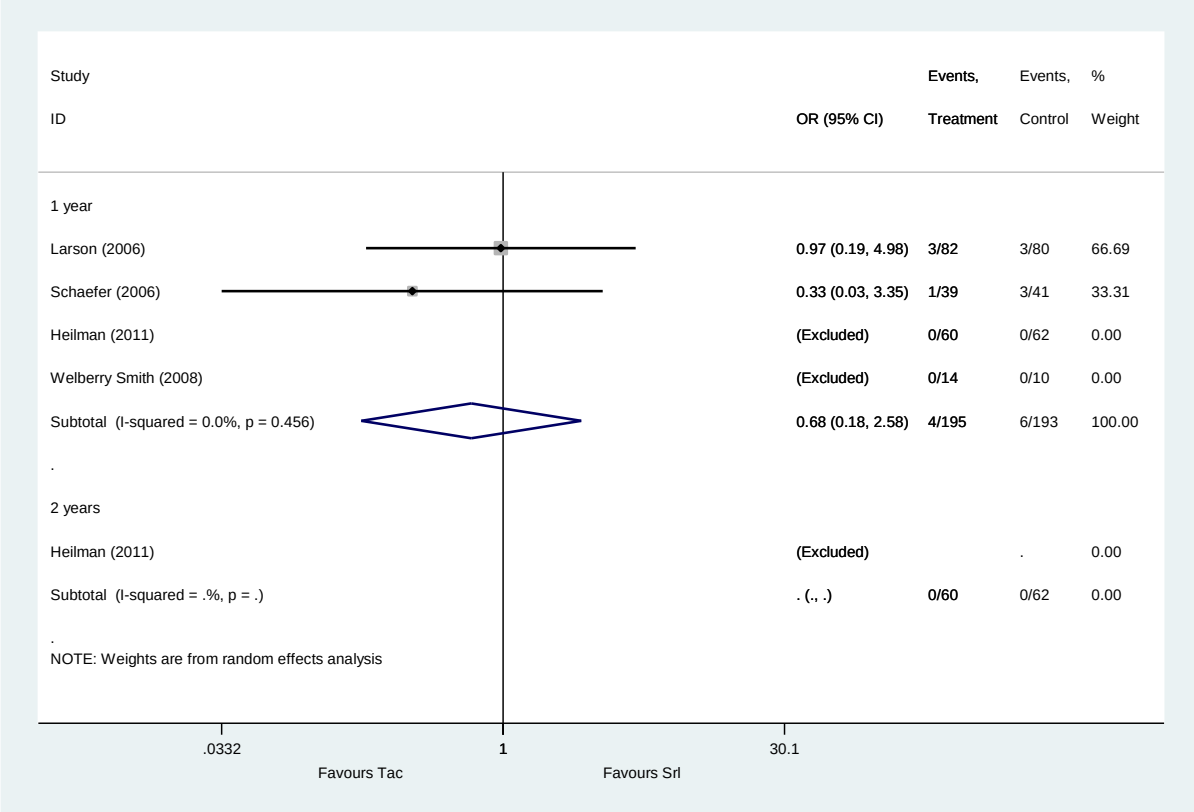
Four studies are pooled with one year results for graft loss (Table 100; Figure 65). [78 79 178 209] Again, two of these studies had no graft loss in either arm. [79 178] Although the OR implies reduced graft loss associated with TAC, this is not statistically significant (OR 0.68, 95%CI 0.18 to 2.58).

Table 100. Graft loss for TAC+MMF vs SRL+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Larson, 2006; Schaefer, 2006; Heilman, 2011; Welberry Smith, 2008	1 year	4[a]	0.68	0.18 – 2.58	0.0%	0.0
Heilman, 2011	2 years	1[b]	NA	NA	NA	NA

Notes: (a) 3 arm trial, (b) No graft loss in either arm

Figure 65. Forest plot – graft loss for TAC+MMF vs SRL+MMF



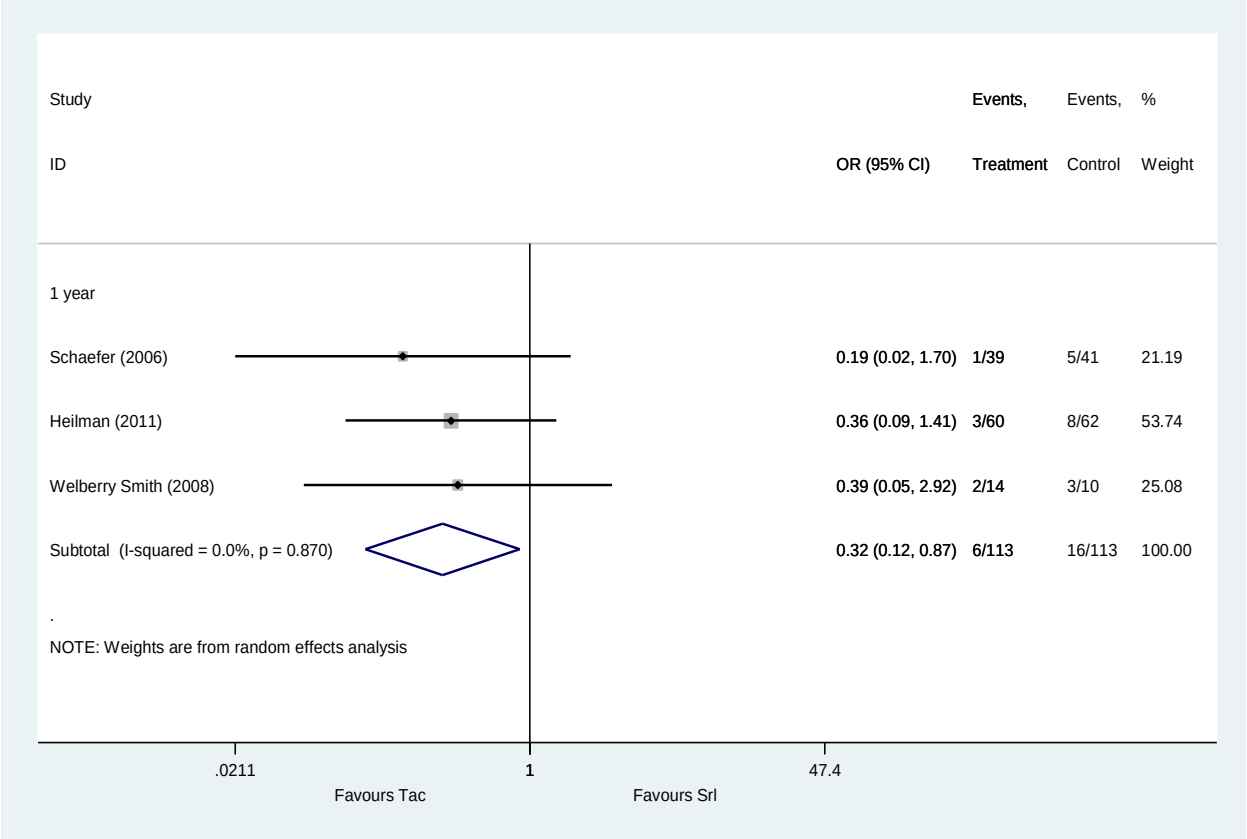
Biopsy proven acute rejection

BPAR is reported by three studies (Table 101; Figure 66). [78 79 178] Pooled results indicate that there are lower odds of BPAR associated with TAC at one year (OR 0.32, 95%CI 0.12 to 0.87). There does not appear to be any evidence of heterogeneity across studies (I^2 0.0%)

Table 101. Pooled results for BPAR - TAC+MMF vs SRL+MMF

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Schaefer, 2006; Heilman, 2011; Welberry Smith, 2008	1 year	3	0.32	0.12 – 0.87	0.0%	0.0

Figure 66. Forest plot – BPAR for TAC+MMF vs SRL+MMF



Graft function

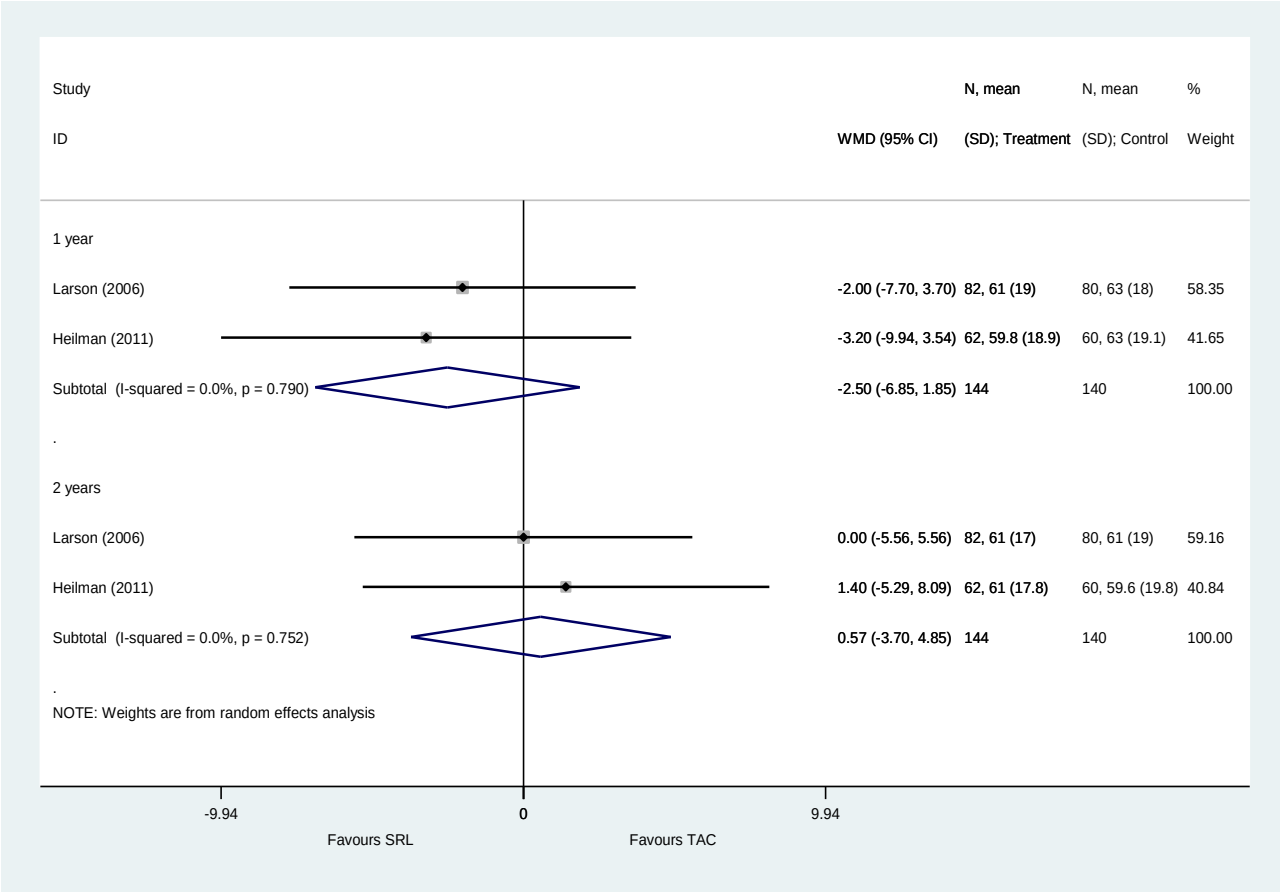
Two studies report graft function at one year and two years (Table 102; Figure 67). [178 209]

The pooled ORs for both time points indicate no statistically significant difference between TAC+MMF and SRL+MMF (1 year, WMD -2.500, 95%CI -6.853 to 1.853)

Table 102. Graft function for TAC+MMF vs SRL+MMF

Study id	Time point	Trials	Weighted mean difference (ml/min)	95% CI	I^2	Tau^2
Larson, 2006; Heilman, 2011	1 year	2'	-2.500	-6.85 – 1.85	0.0%	0.0
	2 years	2	0.57	-3.70 – 4.55	0.0%	0.0

Figure 67. Forest plot – graft function for TAC+MMF vs SRL+MMF



Severity of BPAR

Only one study reports on severity of BPAR (Table 103). [79] Banff classification 1 and 2 demonstrate no statistically significant difference at one year between TAC+MMF and SRL+MMF.

Table 103. Severity of BPAR for TAC+MMF vs SRL+MMF

Study	Time point	Banff classification	TAC+MMF, n/N (%)	SRL+MMF, n/N (%)	Odds ratio	95% CI
Welberry Smith 2008	1 year	1	2/10 (20)	1/13 (8)	3	0.23 – 38.87
		2	1/10 (10)	0/13 (0)	NA	NA

Notes: All percentages calculated by PenTAG

Summary of results for TAC+MMF vs SRL+MMF

- Four studies are pooled with one year results for mortality, however two of these studies had no deaths in either arm . Analysis suggests no significant difference between TAC+MMF and SRL+MMF (OR 0.80, 95%CI 0.13 to 4.99)[78 79 178 209] Heilman et al. (2011) also present results at two years Table 99. Mortality for TAC+MMF vs SRL+MMF. Again, results are not statistically significant (OR 2.10, 95% 0.19 to 23.83)

- Four studies are pooled with one year results for graft loss. [78 79 178 209] Again, two of these studies had no graft loss in either arm. [79 178] Although the OR implies reduced graft loss associated with TAC, this is not statistically significant (OR 0.68, 95%CI 0.18 to 2.58).

- BPAR is reported by three studies.[78 79 178] Pooled results indicate that there are lower odds of BPAR associated with TAC at one year (OR 0.32, 95%CI 0.12 to 0.87). There does not appear to be any evidence of heterogeneity across studies (I^2 0.0%)

- Two studies report graft function at one year and two years.[178 209] The pooled ORs for both time points indicate no statistically significant difference between TAC+MMF and SRL+MMF (1 year, WMD -2.500, 95%CI -6.853 to 1.853)

- Only one study reports on severity of BPAR (Table 103). [79] Banff classification 1 and 2 demonstrate no statistically significant difference at one year between TAC+MMF and SRL+MMF.

4.3.2.17. TAC+MPS vs SRL+MPS

Silva et al. (2013) is the only study to report on this combination, therefore a summary of outcomes at two years are presented in Table 104. The OR for BPAR appears to favour TAC (OR 0.63, 95%CI 0.3482 to 1.1397), however this is not statistically significant. All other outcomes also show no statistical difference between arms.

Table 104. Summary of outcomes for TAC+MPS vs SRL+MPS

Study id	Time point	Outcome	TAC+SRL	MMF+SRL	Odds ratio	95% CI
Silva (2013)	2 year	Patient survival, n/N (%)	104/107 (97)	94/97 (97)	0.9038	0.17 - 4.59
		Graft survival, n/N (%)	106/107 (99)	96/97 (99)	0.9057	0.06 - 14.68
		BPAR, n/N (%)	29/107 (27)	36/97 (37)	0.63	0.35 - 1.14
		Banff Classification none/borderline, n/N (%)	5/107 (5)	8/97 (8)	0.5576	0.18 - 1.77
		Banff Classification 1, n/N (%)	16/107 (15)	17/97(17)	0.8274	0.39 - 1.74
		Banff Classification 2, n/N (%)	NR	NR		
		Banff Classification 3, n/N (%)	NR	NR		

Key: (NR) Not reported, (a) sd not reported

4.3.2.18. TAC+SRL vs MMF+SRL

Hamdy et al. 2005 is the only study to report on this combination, therefore a summary of outcomes at one year to five years are presented in Table 105.[181] The OR for mortality appears to favour MMF (OR 4.39, 95%CI 0.48 to 40.39), however this is not statistically significant. All other outcomes also show no statistical difference between arms.

Table 105. Summary of outcomes for TAC+SRL vs MMF+SRL

Study id	Time point		TAC+SRL	MMF+SRL	Odds ratio	95% CI
Hamdy, 2005	1 year	Mortality, n/N (%)	2/65 (1.5)	0/67 (0)	NA	NA
		BPAR, n/N (%)	12/65 (18)	9/67 (13)	1.4591	0.57 - 3.74
		Graft function, mean (sd)	89 (30)	93 (25.2)		P=0.4078
	2 years	Mortality, n/N (%)	2/65 (1.5)	67/67 (0)	NA	NA
		Graft function, mean (sd)	79.6 (25.5)	94.9 (28.9)		P=0.0016
	3 years	Mortality, n/N (%)	4/65 (6.1)	1/67 (1.5)	4.3934	0.48 - 40.39
		BPAR, n/N (%)	12/65 (18)	9/67 (13)	1.4591	0.57 - 3.74
		Graft function, mean (sd)	76.1[a]	88[a]		NA
	5 years	Graft loss, n/N (%)	7/65 (11)	7/67 (11)	1.0345	0.34 - 3.13

Key: (NR) Not reported, (a) sd not reported
Notes: Percentages calculated by PenTAG

4.3.2.19. SRL+AZA vs CSA+AZA

One trial reported by Charpentier et al. 2003) investigating SRL+AZA vs CSA+AZA, therefore a summary of outcomes at 0.5 years and one year is presented (Table 106). [88] The outcome which stands out is graft function, where there is a significant difference between both arms at 0.5 years and one year in favour of SRL+AZA (p<0.0001).There is no statistically significant difference between arms for other outcomes.

Table 106. Summary of outcomes for SRL+AZA vs CSA+AZA

Study id	Time point	Outcome	SRL+AZA	CSA+AZA	Odds ratio	95% CI
Charpentier, 2003	0.5 years	BPAR, n/N (%)	17/41 (41)	16/42 (38)	1.151	0.4776 - 2.7742
		Graft function, mean (sd)	67 (4)	59 (3)		P<0.0001
		Banff Classification 1, n/N (%)	6/41 (15)	9/42 (21)	0.6286	0.2016 - 1.9599
		Banff Classification 2, n/N (%)	9/41 (22)	6/42 (14)	1.6875	0.5411 - 5.2631
		Banff Classification 3, n/N (%)	2/41 (5)	1/42 (2)	2.1026	0.1832 - 4.1267
	1 year	Patient survival, n/N (%)	41/41 (100)	41/42 (98)	NA	NA
		Graft survival, n/N (%)	40/41 (98)	39/42 (93)	0.325	0.0324 - 3.2603
		Graft function, mean (sd)	69.5 (4.1)	58.7 (3.6)		P<0.0001

Notes: Percentages calculated by PenTAG

4.3.2.20. TAC+SRL vs TAC+MMF

Three studies report on TAC+SRL vs TAC+MMF where all outcomes, other than time to BPAR and HRQoL are presented. [80 187 194]

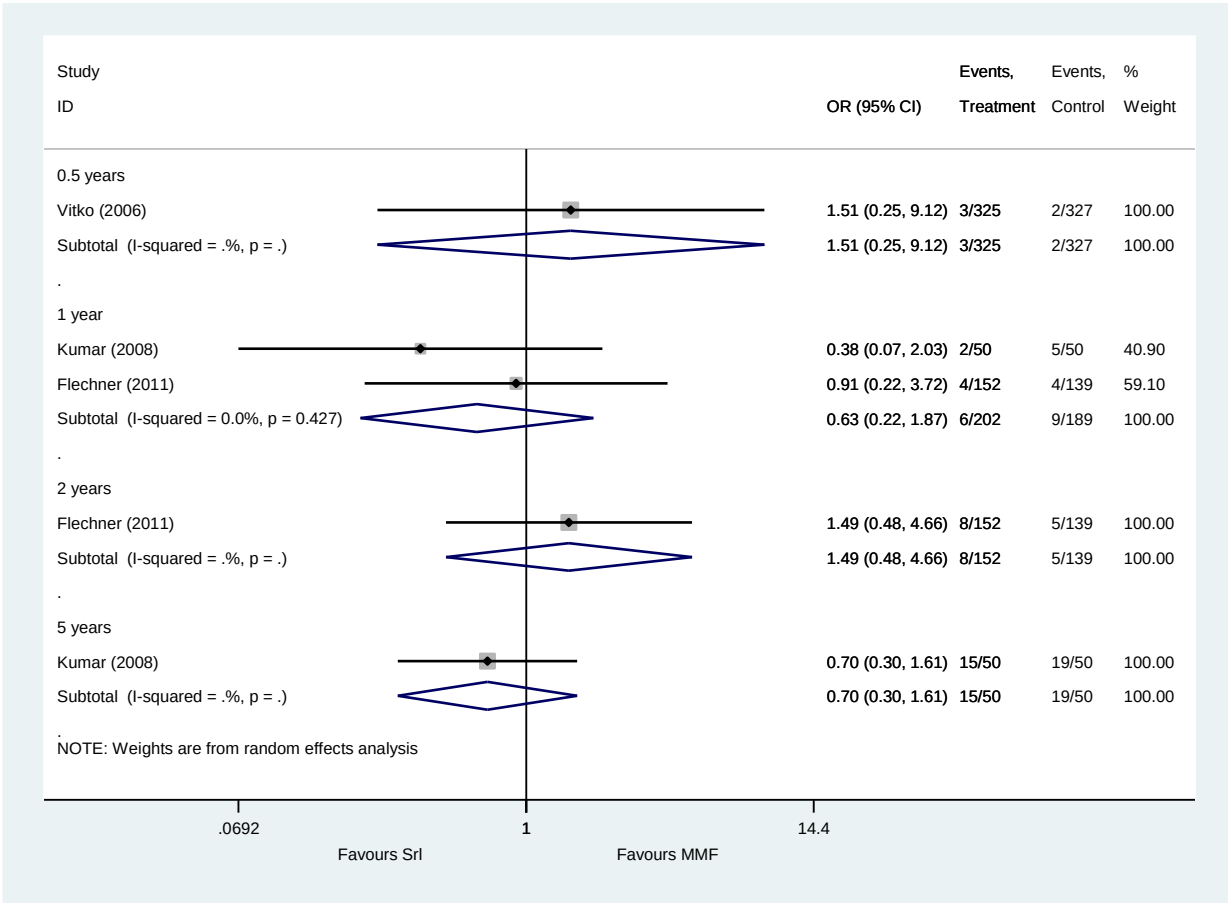
Mortality

Three studies report mortality for TAC+SRL vs TAC+MMF at 0.5 years to five years (Table 107; Figure 68). [80 187 194] Results of two studies are pooled for the one year time point.[187 194] The odds ratio suggests reduced mortality for TAC+SRL, however this effect is not statistically significant (OR 0.63, 95%CI 0.22 to 1.87). All other time points also suggest no effect.

Table 107. Mortality for TAC+SRL vs TAC+MMF

Study id	Time point	Trials	Odds ratio	95%CI	I^2	Tau^2
Vitko, 2006	0.5 years	1	1.51	0.25 – 9.12	NA	NA
Kumar, 2008; Flechner, 2011	1 year	2	0.63	0.22 – 1.87	0.0%	0.0
Flechner, 2011	2 years	1	1.49	0.48 – 4.66	NA	NA
Kumar, 2008	5 years	1	0.70	0.30 – 1.61	NA	NA

Figure 68. Forest plot – mortality TAC+SRL vs TAC+MMF



Graft loss

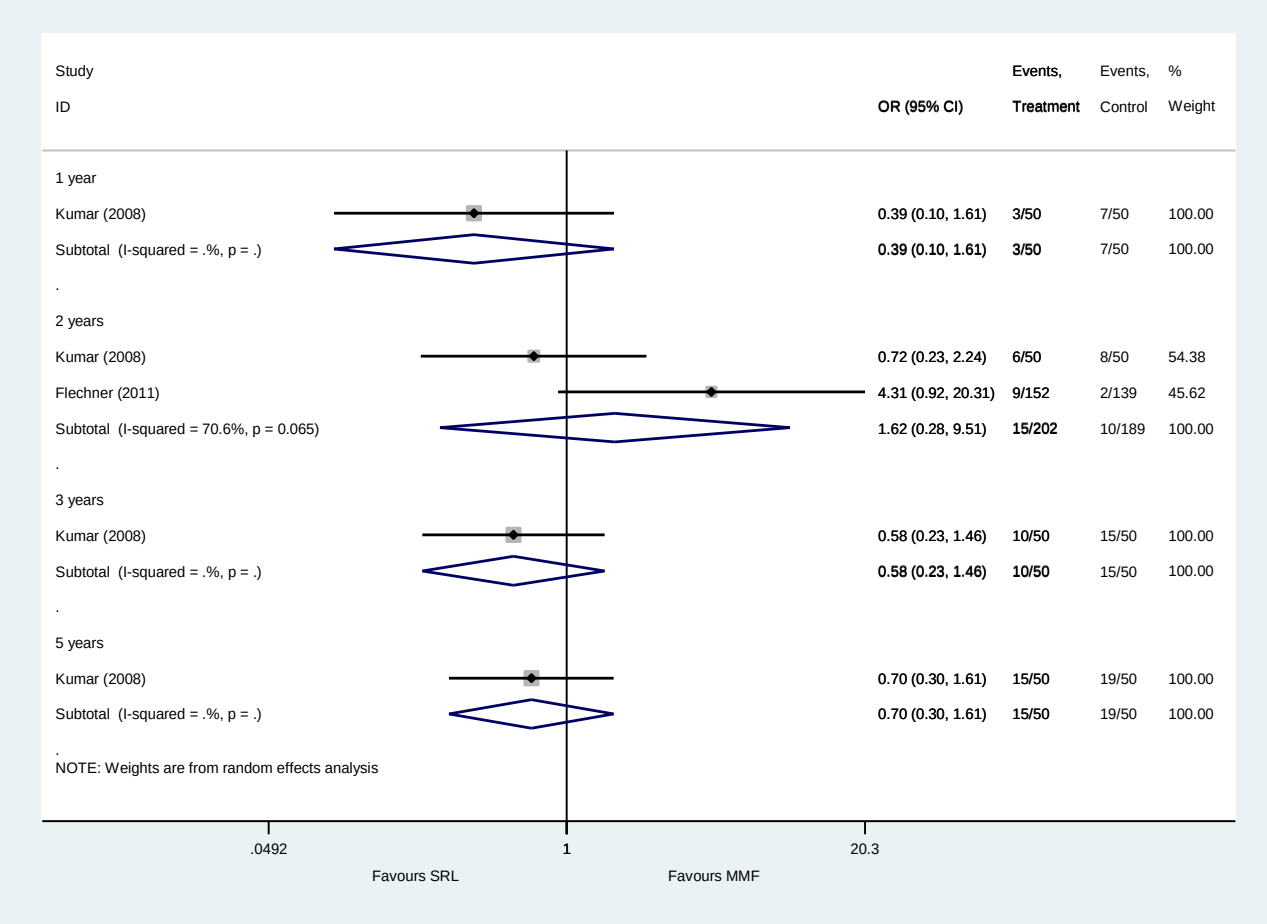
Graft loss is only reported by two studies (Table 108; Figure 69). [187] [194] Data is pooled at two years, however there is no statistically significant result and heterogeneity across studies is

substantial (OR 1.62, 95%CI 0.28 to 9.51, I^2 70.6%). No effect is seen at any other time point.

Table 108. Graft loss for TAC+SRL vs TAC+MMF

Study id	Time point	Trials	Odds ratio	95%CI	I^2	Tau^2
Kumar, 2008	1 year	1	0.39	0.10 – 1.61	NA	NA
Kumar, 2008; Flechner, 2011	2 years	2	1.62	0.28 – 9.51	70.6	1.16
Kumar, 2008	5 years	1	0.70	0.30 – 1.61	NA	NA

Figure 69. Forest plot – graft loss for TAC+SRL vs TAC+MMF



Biopsy proven acute rejection

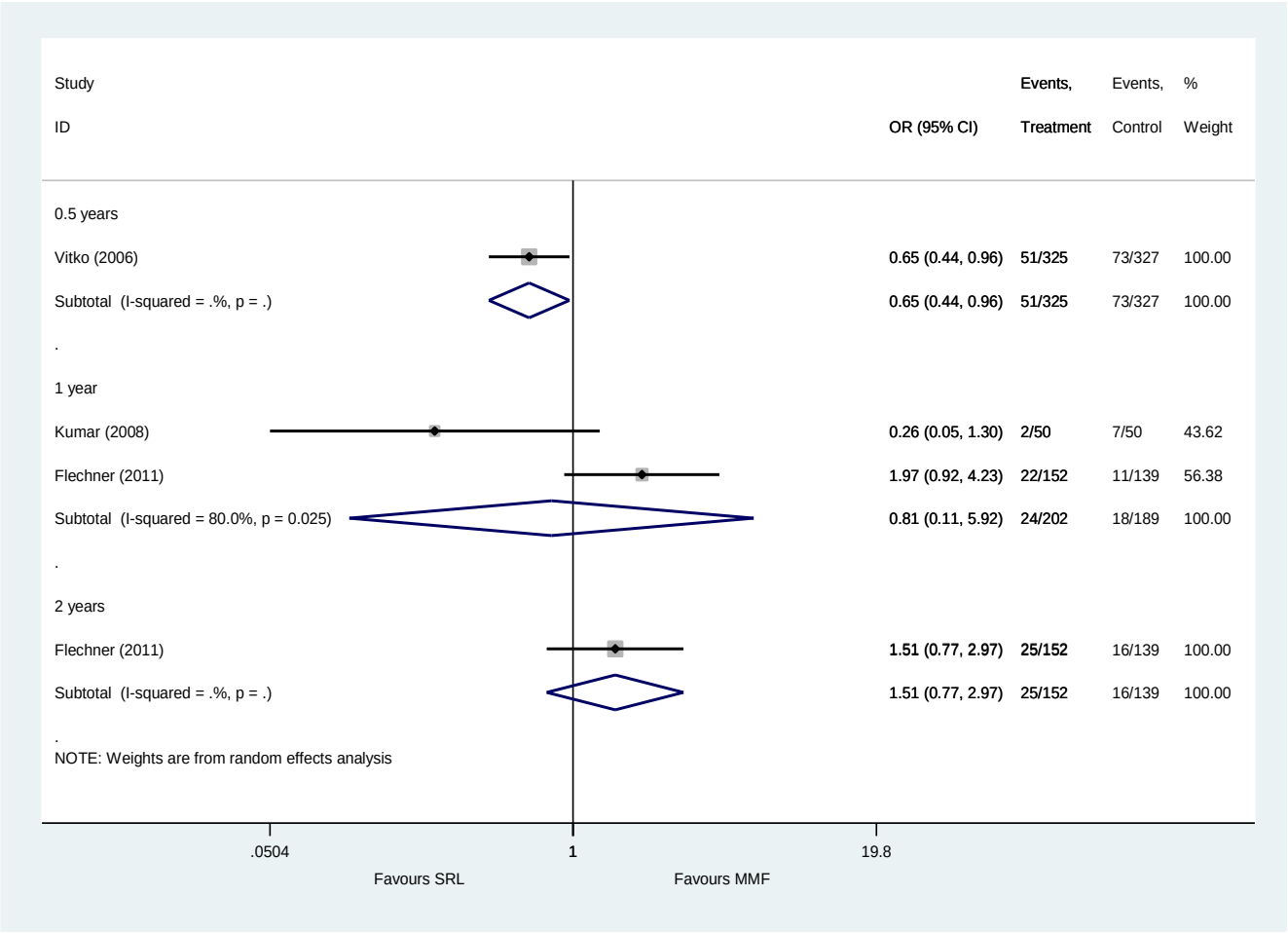
BPAR is reported by three studies from 0.5 years to two years (Table 109; Figure 70).[80 187 194].Vitko et al. 2006 present results for 0.5 years, where there is a statistically significant

result indicating reduced BPAR for TAC+SRL (OR 0.65, 95%CI 0.44 to 0.96). Although the OR<1 at one year for the two pooled studies, the confidence intervals are wide and cross OR=1. Furthermore, there is substantial heterogeneity across studies (I^2 80.0%). The 2 year result reported by Flechner et al. 2011 appears to favour TAC+MMF, however, this is not statistically significant.

Table 109. BPAR fot TAC+SRL vs TAC+MMF

Study id	Time point	Trials	Odds ratio	95%CI	I^2	Tau^2
Vitko, 2006	0.5 years	1	0.65	0.44 – 0.96	NA	NA
Kumar, 2008; Flechner, 2011	1 year	2	0.81	0.11 – 5.92	80.0%	1.68
Flechner, 2011	2 years	1	1.51	0.77 – 2.97	NA	NA

Figure 70. Forest plot – BPAR for TAC+SRL vs TAC+MMF



Graft function

Graft function is only reported by Vitko et al. 2006 at 0.5 years (mean reported creatinine clearance for TAC+SRL and TAC+MMF is 49.5 ml/min and 52.5 ml/min, respectively). Since no standard deviation is reported, no analysis can be performed.

Severity of Biopsy proven acute rejection

Two studies report severity of BPAR at 0.5 years, one year and two years (Table 110). [80] [187]The OR at one year for Banff classification 1 suggests higher odds of association for TAC+MMF (OR 3.37. 95%CI 1.2104 to 9.4094). All other results are not statistically significant.

Table 110. Severity of BPAR for TAC+SRL vs TAC+MMF

Study id	Time point	Banff classification	TAC+SRL, n/N (%)	TAC+MMF, n/N (%)	Odds ratio	95% CI
Vitko, 2006	0.5 years	3	3/325 (0.9)	2/327 (0.6)	1.514	0.2513 – 9.1208
Flechner, 2011	1 year	1	17/152 (11)	5/139 (4)	3.3748	1.2104 – 9.4094
		2	5/152 (3)	6/139 (4)	0.754	0.2249 – 2.5278
	2 years	1	20/152	10/139	1.9545	0.8809 – 4.3366
		2	5/152	6/139	0.754	0.2249 – 2.5278

Notes: Percentages calculated by PenTAG

Summary for TAC+SRL vs CSA+SRL

- Four studies report mortality for TAC+SRL vs TAC+MMF at 0.5 years to five years. [80] [187] [194] Results of two studies are pooled for the one year time point.[187] [194] The odds ratio suggests reduced mortality for TAC+SRL, however this effect is not statistically significant (OR 0.63, 95%CI 0.22 to 1.87). All other time points also suggest no effect.

- Graft loss is only reported by two studies. [187] [194] Data is pooled at two years, however there is no statistically significant result and heterogeneity across studies is substantial (OR 1.62, 95%CI 0.28 to 9.51, I^2 70.6%). No effect is seen at any other time point.

- BPAR is reported by three studies from 0.5 years to two years.[80] [187] [194].Vitko et al. (2006) present results for 0.5 years, where there is a statistically significant result indicating reduced BPAR for TAC+SRL (OR 0.65, 95%CI 0.44 to 0.96). Although the OR<1 at one year for the two pooled studies, the confidence intervals are wide and cross OR=1. Furthermore, there is substantial heterogeneity across studies (I^2 80.0%). The 2 year result reported by Flechner et al. 2011 appears to favour TAC+MMF, however, this is not statistically significant.

- Graft function is only reported by Vitko et al. 2006 at 0.5 years (mean CrCl for TAC+SRL and TAC+MMF is 49.5 ml/min and 52.5 ml/min, respectively). Sinceno standard deviation is reported, no analysis can be performed.

- Two studies report severity of BPAR at 0.5 years, one year and two years. [80] [187]The OR at one year for Banff classification 1 suggests higher odds of association for

TAC+MMF (OR 3.37. 95%CI 1.2104 to 9.4094). All other results are not statistically significant.

4.3.2.21. TAC+SRL vs CSA+SRL

Two studies reported this combination, presenting outcomes at one year and five years.[186 194]. No severity or time to acute rejection reported.

Mortality

Due to the same number events in either arm at both time points, there is no difference between TAC+SRL and CSA+SRL for mortality (Table 111).[186 194]

Table 111. Mortality for TAC+SRL vs CSA+SRL

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kumar, 2008; Chen, 2008	1 year	2[a]	1.00	0.14 – 7.39	NA	NA
Kumar, 2008	5 years	1	1.00	0.36 – 2.77	NA	NA

Notes: (a) One trial excluded due to no deaths in either arm

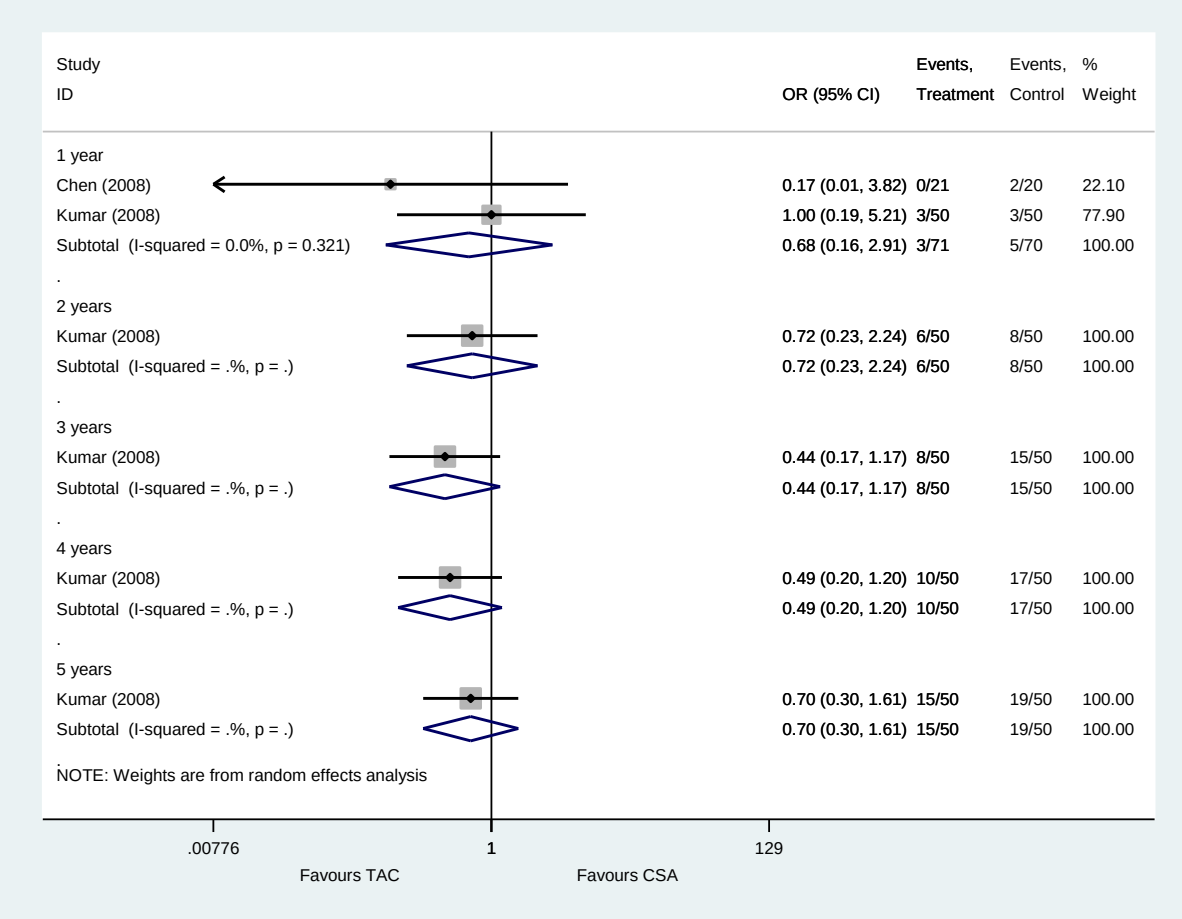
Graft loss

Two studies report graft loss, with pooled result at one year and individual results up to five years (Table 112; Figure 71). [186 194].Results are consistent across all time points that lower odds are associated with graft loss for TAC+SRL, however, the effect is not statistically significant (1 year, OR 0.68, 95%CI 0.16 to 2.90).

Table 112. Graft loss for TAC+SRL vs CSA+SRL

Study id	Time point	Trials	Odds ratio	95% CI	I^2	Tau^2
Kumar, 2008; Chen, 2008	1 year	2	0.68	0.16 – 2.90	0.0%	0.0
Kumar, 2008	2 years	1	0.72	0.23 – 2.24	NA	NA
	3 years	1	0.44	0.17 – 1.17	NA	NA
	4 years	1	0.49	0.20 – 1.20	NA	NA
	5 years	1	0.70	0.30 – 1.61	NA	NA

Figure 71. Forest plot – graft loss for TAC+SRL vs CSA+SRL



Biopsy proven acute rejection

This is only reported by Kumar et al. 2008 at one year (Table 113).[194] The odds ratio implies BPAR to be more likely for CSA+SRL, however, this is not statistically significant (OR 0.4792, 95%CI 0.0837 to 2.7434)

Table 113. BPAR for TAC+SRL vs CSA+SRL

Study id	Time point	TAC+SRL, n/N (%)	CSA+SRL, n/N (%)	Odds ratio	95% CI
Kumar, 2008	1 year	2/50 (4)	4/50 (8)	0.4792	0.08 - 2.74

Graft function

Chen et al. (2008) report graft function at 0.5 years and 1 year (Table 114), which appears to be statistically significantly greater greater for TAC+SRL at 0.5 years and one year (p<0.0001, p=0.0004).[186]

Table 114. Graft function for TAC+SRL vs CSA+SRL

Study id	Time point	TAC+SRL, n/N (%)	CSA+SRL, n/N (%)	Mean difference	95% CI
Chen, 2008	0.5 years	52.77 (3.86)	46.42 (3.95)	6.35	P<0.0001
	1 year	52.04 (4.38)	46.79 (4.38)	5.25	P=0.0004

Summary of results for TAC+SRL vs CSA+SRL

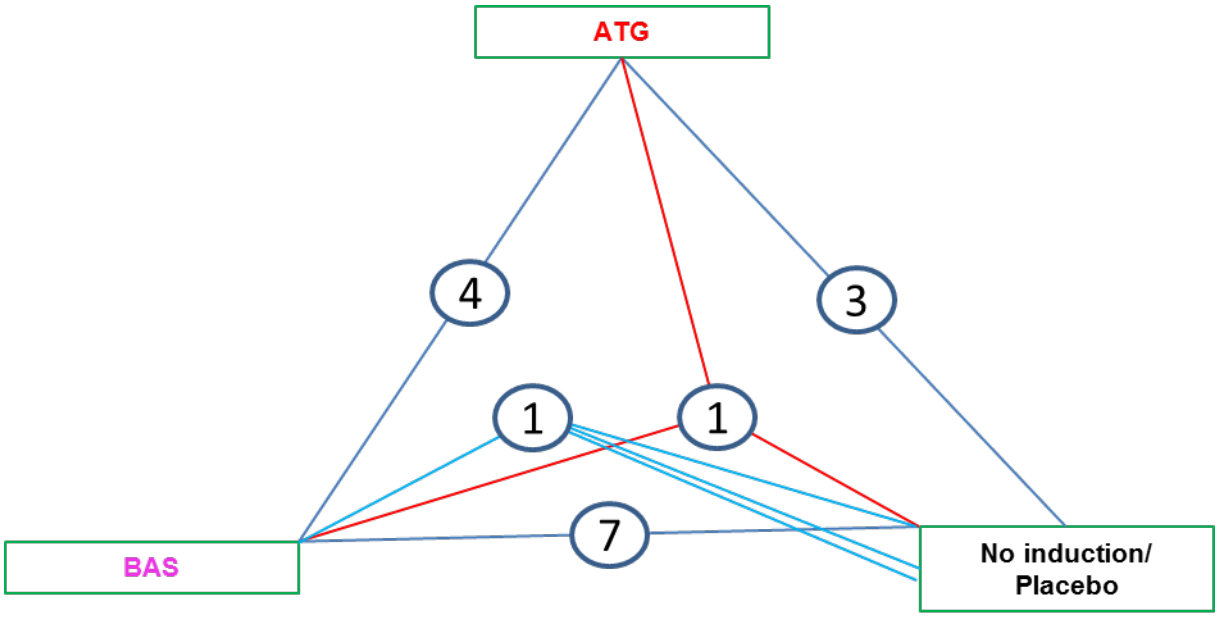
- Due to the same number events in either arm at both time points, there is no difference between TAC+SRL and CSA+SRL for mortality. [186 194].
- Two studies report graft loss, with pooled result at one year and individual results up to five years. [186 194].Results are consistent across all time points that lower odds are associated with graft loss for TAC+SRL, however, the effect is not statistically significant (1 year, OR 0.68, 95%CI 0.16 to 2.90).
- BPAR is only reported by Kumar et al. (2008) at one year.[194] The odds ratio implies BPAR to be more likely for CSA+SRL, however, this is not statistically significant (OR 0.4792, 95%CI 0.0837 to 2.7434)
- Chen et al. (2008) report graft function at 0.5 years and 1 year, which appears to be statistically significantly greater greater for TAC+SRL at 0.5 years and one year (p<0.0001, p=0.0004). [186]

4.3.3. Network meta-analyses

4.3.3.1. Induction therapy results

Network meta-analysis was performed for all induction studies reporting graft loss, mortality, BPAR and eGFR at one year follow-up. Figure 72 displays the network for included induction studies.

Figure 72. Network diagram for all included induction studies

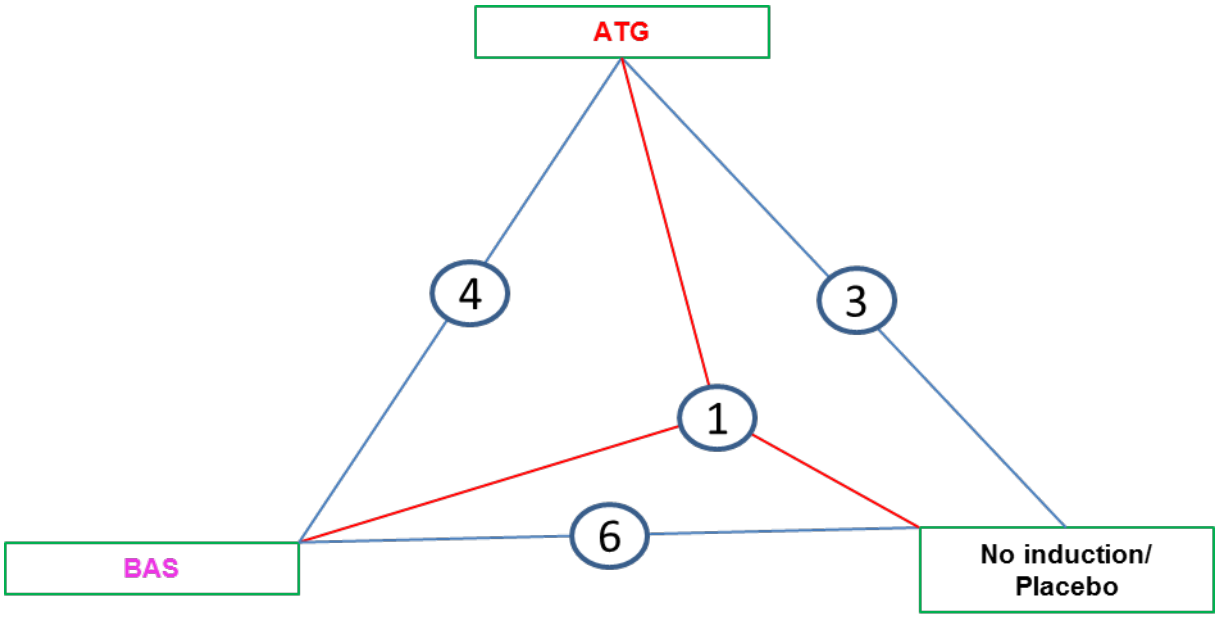


Key: ATG, Antithymocyte globulin; BAS, basiliximab.
Notes: Circles denote number of studies

Graft Loss

14 RCTs (including one 3-arm RCT) informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for graft loss (Figure 73).

Figure 73. Network diagram for induction studies reporting graft loss



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

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, thus only the results of the fixed effects model are shown in Table 115. Results from fitting a random effects model are presented in Appendix 6.

Table 115. ORs for induction therapy from a fixed effects model (Posterior mean (95%CI))

Treatment comparison	Graft loss	Mortality	BPAR
BAS vs placebo/no treatment	0.84 (0.59, 1.21)	0.89 (0.49, 1.62)	**0.50 (0.40, 0.62)**
ATG vs placebo/no treatment	0.78 (0.45, 1.34)	0.68 (0.28, 1.39)	**0.35 (0.25, 0.49)**
ATG vs BAS	0.92 (0.53, 1.59)	0.72 (0.34, 1.47)	**0.70 (0.51, 0.97)**

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

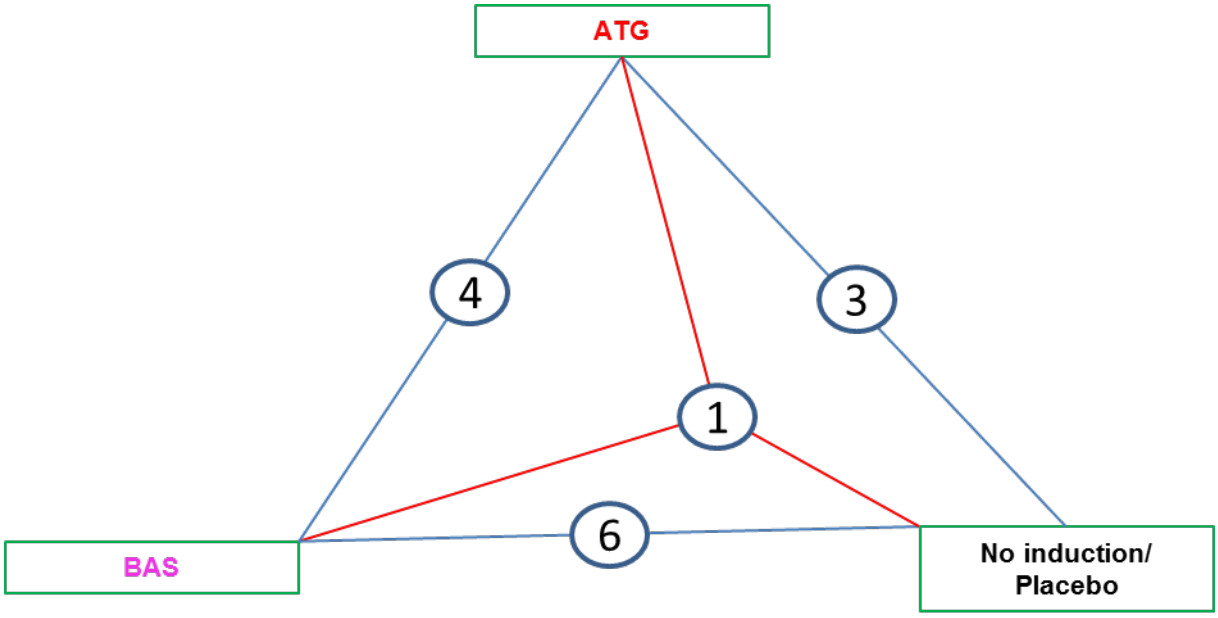
From these analyses there is little evidence to suggest that BAS and ATG are more effective than no induction/placebo in reducing graft loss as the 95% CIs include OR of one. Furthermore, there is little evidence to suggest that ATG is more effective than BAS. Of the three treatments analysed in this network, ATG was estimated as having a 59% probability of being the most effective treatment, with BAS having a 35% probability of being the most effective treatment.

Analyses suggested that there was little evidence of inconsistency within this network (Appendix 6).

Mortality

14 RCTs (including one 3-arm RCT) informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for mortality (Figure 74).

Figure 74. Network diagram for induction studies reporting mortality



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

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, thus only the results of the fixed effects model are shown in Table 115. Results from fitting a random effects model are presented in Appendix 6.

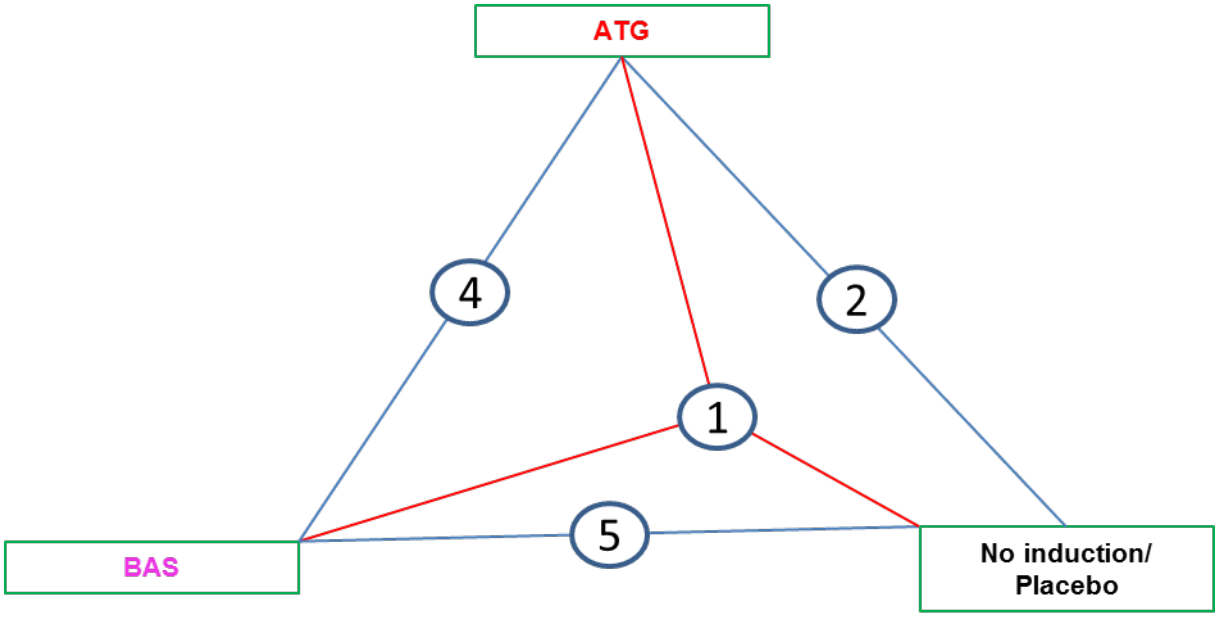
From these analyses there is little evidence to suggest that BAS and ATG are more effective than no induction/placebo in reducing mortality as the 95% CIs include OR of 1 (Table 115) and there is little evidence to suggest that ATG is more effective than BAS. Of the three treatments analysed in this network, ATG was estimated as having a 77% probability of being the most effective treatment, with BAS having a 14% probability of being the most effective treatment.

Analyses suggested that there was little evidence of inconsistency within this network (Appendix 6).

Biopsy proven acute rejection

12 RCTs (including one 3-arm RCT) informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for mortality (Figure 75).

Figure 75. Network diagram for induction studies reporting BPAR



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

The DIC suggested little difference between the fit of the fixed and random effects model, with the fixed effects being the slightly better fit, and so only the results of the fixed effects model are shown in Table 115. Results from fitting a random effects model are presented in Appendix 6.

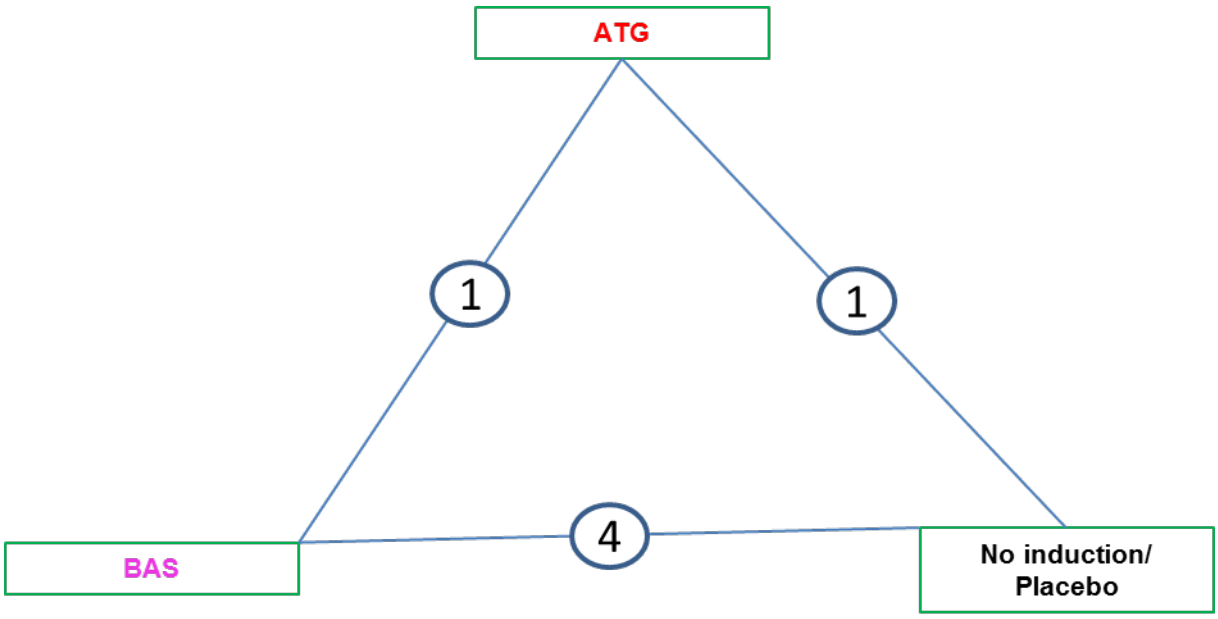
From these analyses evidence suggests that BAS and ATG are more effective than no induction/placebo in reducing BPAR and that ATG is more effective than BAS: 0.70 (0.51, 0.97). Of the three treatments analysed in this network, ATG was estimated as having a 98% probability of being the most effective treatment, with BAS having a 2% probability of being the most effective treatment.

Analyses suggested that there was little evidence of inconsistency within this network (see Appendix 6).

Graft function

Six RCTs informing the effectiveness of 3 treatments (no induction/placebo, BAS and ATG) were included in the network for mortality (Figure 76).

Figure 76. Network diagram for induction studies reporting graft function



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

The DIC suggested very little difference between the fit of the fixed and random effects model. For comparison with the above outcomes, the results of the fixed effects model are shown in Table 116. Results from fitting a random effects model are presented Appendix 6.

Table 116. Mean effects for induction therapy for the outcome graft function from a fixed effects model (Posterior mean (95%CI))

	Graft function
BAS vs placebo/no treatment	**2.62 (0.13, 5.08)**
ATG vs placebo/no treatment	0.75 (-3.99, 5.48)
ATG vs BAS	-1.86 (-6.72, 3.00)

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

There is evidence to suggest that BAS is more effective than placebo/no induction, but no evidence to suggest it is more effective than ATG. BAS has a 76% probability of being the

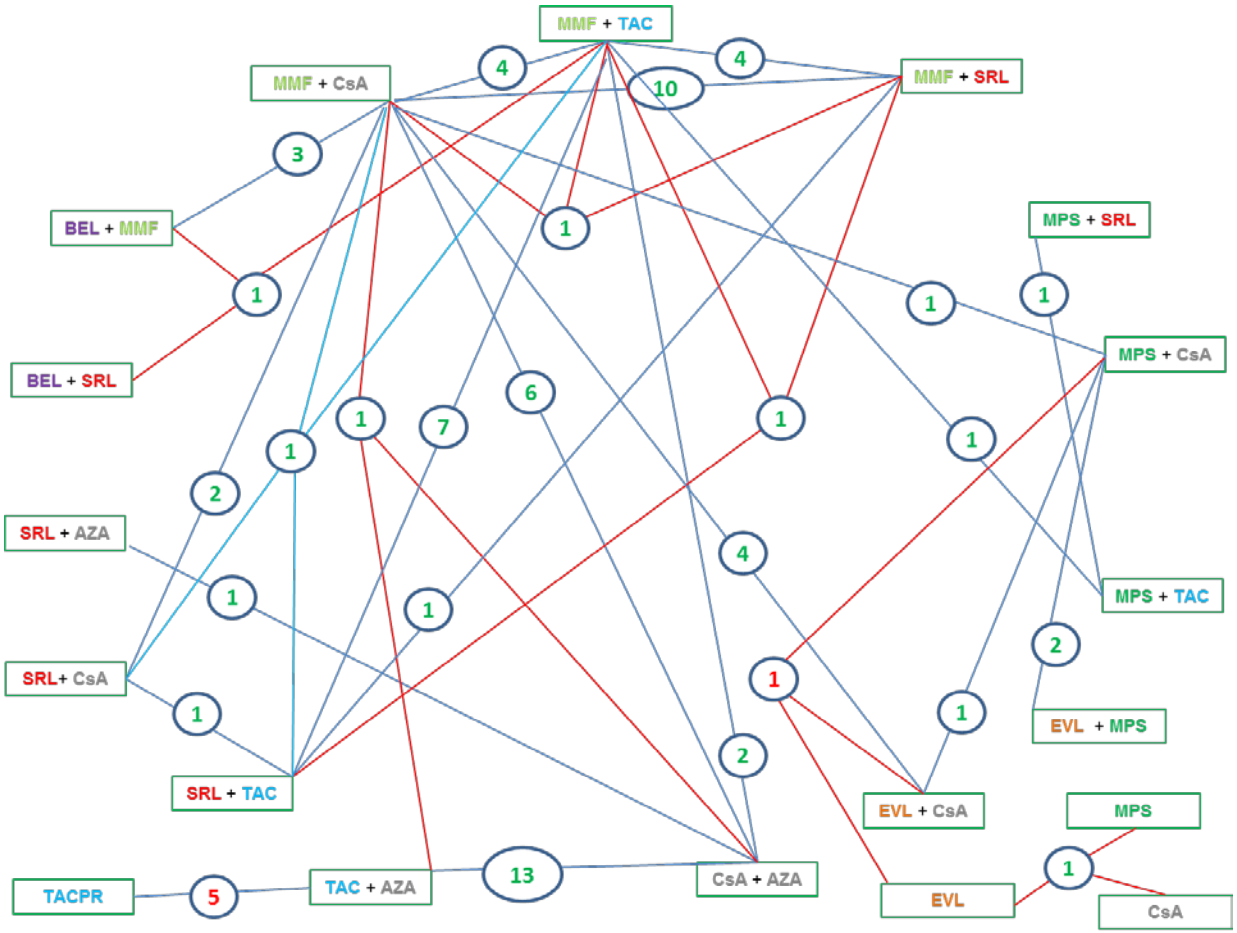
most effective treatment, while ATG has 22% probability and placebo/no treatment just 1% probability.

Analyses suggested that there was little evidence suggestion of inconsistency within this network (see Appendix 6).

4.3.3.2. Maintenance therapy results

Network meta-analysis was performed for all maintenance studies reporting graft loss, mortality, BPAR and eGFR at one year follow up. Figure 77 displays the network for included induction studies.

Figure 77. Network diagram for all included maintenance studies

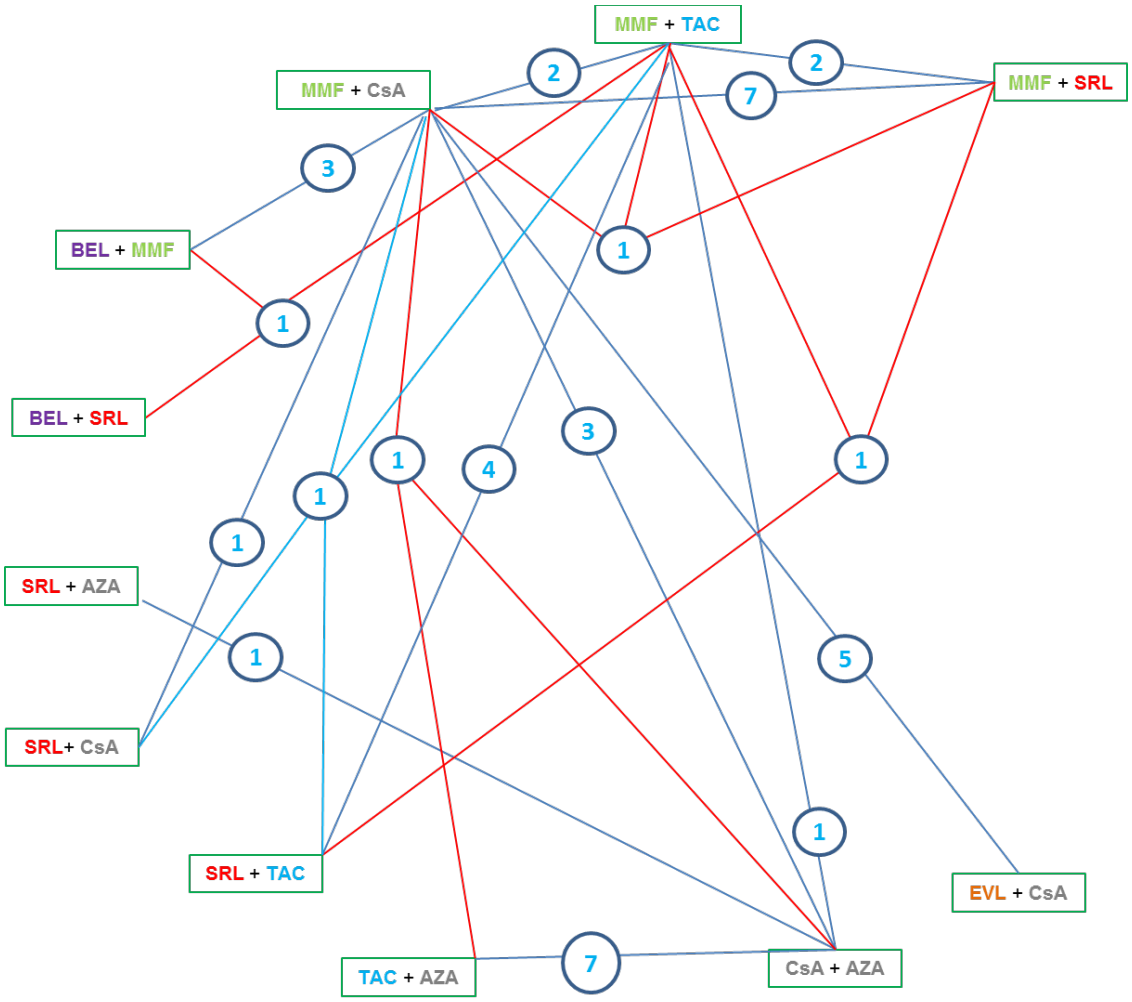


Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus. Notes: Circles denote number of studies.

Graft loss

Data on 13 treatments from 52 studies were potentially includable in the network meta-analysis (Figure 78). However, eleven studies had zero events in all treatment arms so would not contribute information to the network meta-analysis, therefore they were excluded from the network meta-analysis. Due to the exclusion of these studies, the treatment EVL + MPS could not be included in the network. Therefore data from 40 studies (including five 3-arm studies and one 4-arm study) on the effectiveness of 12 treatments to reduce graft loss informed the network meta-analysis. 13 of the 40 studies had at least one treatment arm with no graft loss events, therefore 0.5 was added to each cell.

Figure 78. Network diagram for maintenance studies reporting graft loss



Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Notes: Circles denote number of studies.

The DIC indicated that the random effects model was a slightly better fit to the data than the fixed effects model (154.4 vs 157.5), and so only results from the random effects models are

presented here. The results of the fixed effects models are given in the Appendix 6. The probabilities that each treatment was the most effective in reducing graft loss compared to all other treatments is shown in Table 117.

Table 117. Probability that each treatment is the most effective treatment for reducing graft loss

	Probability of being 'best' treatment
EVL	60%
SRL + AZA	29%
SRL + CSA	6%
BEL + SIR	2%
BEL + MMF	2%
EVL + CSA	1%
CSA + AZA	<1%
TAC + AZA	<1%
MMF + CSA	<1%
TAC + MMF	<1%
SRL + TAC	<1%
SRL + MMF	<1%

Although the results suggest that EVL has a 60% probability of being the most effective treatment for reducing graft loss compared to all other treatments (with SRL+AZA having a 29% probability), there is little evidence to suggest that treatment with EVL reduces graft loss compared to other treatments. The posterior median ORs for EVL compared to all other treatments are <1, indicating a reduction in the odds of having a graft loss, however the upper 95% CIs limits are >1 suggesting that EVL could increase the odds of a graft loss compared to all other treatments (see Table 118). In fact there is little evidence from the network meta-analysis to suggest that any treatment is more effective at reducing graft loss than any other treatment.

Table 118. ORs (for Intervention vs Comparator treatment) for the outcome graft loss from a random effects network meta-analysis (Posterior median (95%CI))

	Comparator treatment									
Intervention treatment	**CSA + AZA**	**TAC + AZA**	**MMF + CSA**	**TAC + MMF**	**BEL + SRL**	**BEL + MMF**	**EVL + CSA**	**SRL + TAC**	**SRL + CSA**	**SRL + MMF**	**SRL + AZA**
TAC + AZA	1.13 (0.67, 2.15)										
MMF + CSA	0.76 (0.35, 1.44)	0.67 (0.24, 1.50)									
TAC + MMF	0.69 (0.28, 1.55)	0.61 (0.19, 1.56)	0.92 (0.48, 1.77)								
BEL + SRL	1.41 (0.14, 13.14)	1.24 (0.11, 12.02)	1.89 (0.20, 16.49)	2.05 (0.22, 18.01)							
BEL + MMF	0.62 (0.20, 1.78)	0.55 (0.14, 1.72)	0.82 (0.35, 1.97)	0.89 (0.32, 2.53)	0.43 (0.05, 3.94)						
EVL + CSA	0.63 (0.20, 1.58)	0.56 (0.14, 1.58)	0.84 (0.39, 1.63)	0.91 (0.33, 2.27)	0.44 (0.04, 4.47)	1.02 (0.31, 2.95)					
SRL + TAC	1.19 (0.38, 3.35)	1.05 (0.28, 3.27)	1.57 (0.64, 3.93)	1.71 (0.80, 3.69)	0.83 (0.08, 8.57)	1.92 (0.56, 6.48)	1.88 (0.62, 6.32)				
SRL + CSA	0.54	0.48	0.73	0.79	0.38	0.88	0.87	0.46			

	(0.10, 2.56)	(0.07, 2.42)	(0.15, 3.10)	(0.16, 3.36)	(0.03, 5.31)	(0.15, 4.66)	(0.16, 4.54)	(0.09, 2.05)			
SRL + MMF	1.06 (0.38, 2.43)	0.94 (0.27, 2.45)	1.40 (0.72, 2.58)	1.52 (0.74, 2.92)	0.74 (0.08, 7.09)	1.71 (0.56, 4.70)	1.67 (0.66, 4.40)	0.89 (0.34, 2.15)	1.92 (0.41, 9.74)		
SRL + AZA	0.25 (0.01, 3.10)	0.22 (0.01, 2.86)	0.33 (0.01, 4.71)	0.36 (0.01, 5.39)	0.17 (0.01, 5.68)	0.40 (0.01, 6.53)	0.40 (0.01, 6.52)	0.21 (0.01, 3.45)	0.46 (0.01, 9.83)	0.24 (0.01, 3.68)	
EVL	0.09 (0.01, 2.15)	0.08 (0.01, 1.96)	0.13 (0.01, 2.67)	0.14 (0.01, 3.12)	0.06 (0.01, 3.00)	0.15 (0.01, 3.65)	0.15 (0.01, 3.34)	0.08 (0.01, 1.96)	0.17 (0.01, 5.60)	0.09 (0.01, 2.09)	0.36 (0.01, 41.00)

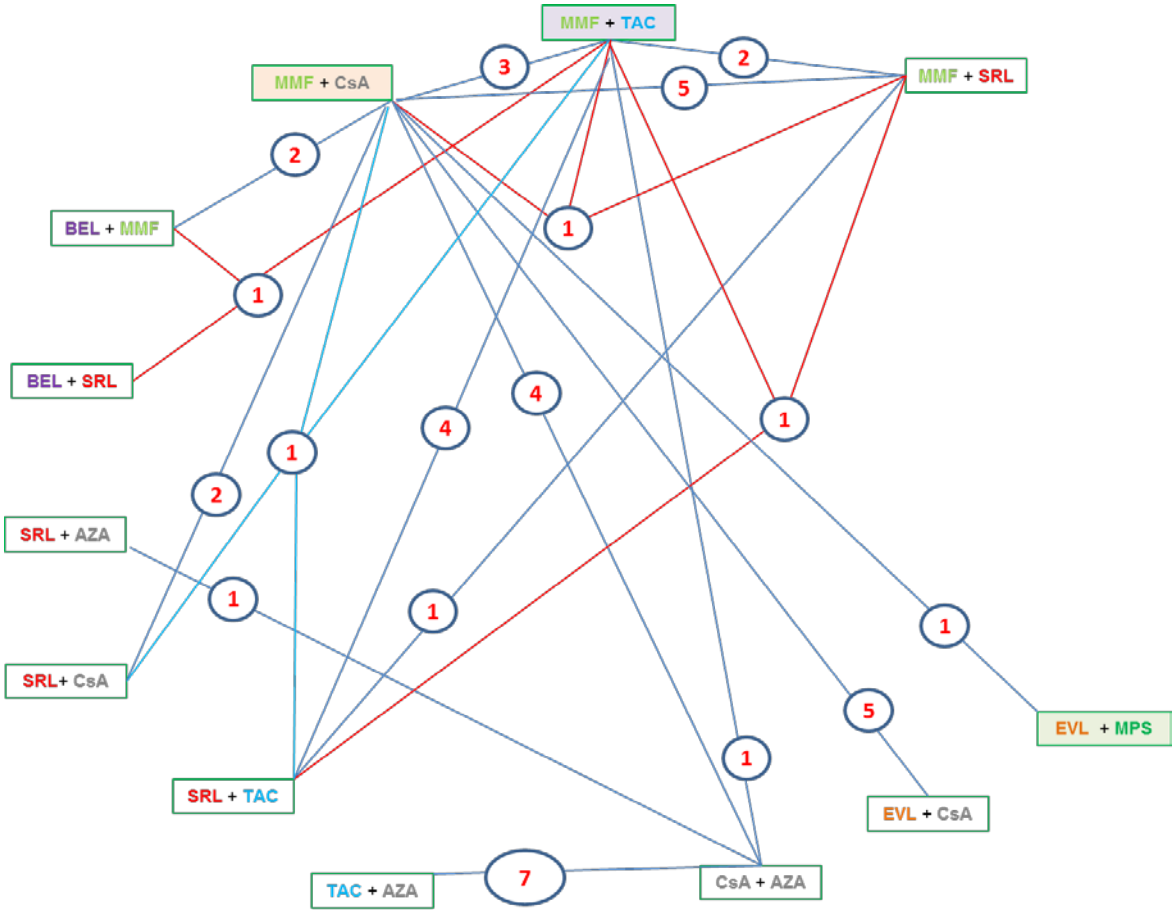
Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Note: OR < 1 favours intervention treatment, OR > 1 favours comparator treatment; If applicable, evidence suggesting a difference between treatments was highlighted in bold

There is no evidence to suggest that this network is affected by inconsistencies between the direct and indirect evidence (see Appendix 6). The DICs were very similar between the consistency and inconsistency models (154.4 vs 153.7) and the 95% CIs based on the direct evidence overlapped those based on the direct and indirect evidence.

Mortality

Thirteen treatments and 42 studies were considered for the network meta-analysis (Figure 79). Ten trials had zero events in all arms and were excluded from the network meta-analysis, resulting in 32 trials contributing to the network meta-analysis (including four 3-arm trials and one 4-arm trial). Twelve of the 42 included trials had zero events in at least one treatment arm and so 0.5 was added to all cells in those trials.

Figure 79. Network diagram for maintenance studies reporting mortality



Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Notes: Circles denote number of studies.

Although the DIC indicated that the fixed effects model was a slightly better fit to the data than the random effects model (137.7 vs 139.5), the random effects results are presented here and used in the economic model for consistency as the remaining maintenance treatment analyses indicated the random effects model to be the best fitting model. The results of the fixed effects models are given in Appendix 6. The probabilities that each treatment was the most effective in reducing graft loss compared to all other treatments are shown in Table 119.

Table 119. Probability that each treatment is the most effective treatment for reducing mortality

	Probability of being 'best' treatment
SRL + AZA	34%
EVL	30%
BEL + SRL	27%
EVL + MPS	4%
BEL + MMF	3%
SRL + CSA	3%
CSA + AZA	<1%
TAC + AZA	<1%
MMF + CSA	<1%
EVL + CSA	<1%
SRL + TAC	<1%
SRL + MMF	<1%
TAC + MMF	0%

Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.

SRL+AZA (34%), EVL (30%) and BEL+SRL (27%) were estimated with the greatest probabilities of being the most effective treatments to reduce mortality compared to all others, while the remaining treatments had a very low probability of being the best treatment. This reflects the findings presented in Table 120 where SRL+AZA, EVL and BEL+SRL are consistently estimated to have posterior median ORs <1 compared to all treatments, but as the upper 95% CrI limits are >1, there is the possibility that these treatments could increase mortality comparted to other treatments.

The network meta-analysis suggests that BEL+MMF is more effective than TAC+MMF and SRL+MMF at reducing mortality. However there is a great deal of uncertainty associated with many of the results presented Table 120 especially for BEL+SRL.

Table 120. ORs (for Intervention vs Comparator treatment) for the outcome mortality from a random effects network meta-analysis (Posterior median (95%CrI))

	Comparator treatment											
Intervention treatment	**CSA + AZA**	**TAC + AZA**	**MMF + CSA**	**TAC + MMF**	**BEL + SRL**	**BEL + MMF**	**EVL + MPS**	**EVL + CSA**	**SRL + TAC**	**SRL + CSA**	**SRL + MMF**	**SRL + AZA**
TAC + AZA	1.38 (0.74, 2.60)											
MMF + CSA	0.94 (0.45, 1.95)	0.68 (0.26, 1.78)										
TAC + MMF	1.53 (0.63, 3.71)	1.10 (0.37, 3.28)	1.61 (0.89, 3.00)									
BEL + SRL	0.31 (0.01, 8.78)	0.22 (0.46, 6.65)	0.34 (0.01, 8.57)	0.21 (0.01, 5.21)								
BEL + MMF	0.47 (0.15, 1.38)	0.34 (0.09, 1.18)	0.50 (0.21, 1.11)	**0.31 (0.11, 0.83**)	1.49 (0.05, 729.6)							
EVL + MPS	0.94 (0.08, 10.78)	0.68 (0.06, 8.29)	1.00 (0.09, 10.09)	0.62 (0.05, 6.73)	3.24 (0.05, 2374)	2.03 (0.16, 24.24)						
EVL + CSA	1.40 (0.52, 3.65)	1.01 (0.32, 3.20)	1.47 (0.77, 2.84)	0.91 (0.37, 2.21)	4.47 (0.16, 2219)	2.98 (1.04, 8.75)	1.48 (0.13, 17.37)					

SRL + TAC	1.38 (0.49, 3.88)	1.00 (0.30, 3.32)	1.46 (0.65, 3.23)	0.91 (0.48, 1.70)	4.40 (0.16, 2217)	2.95 (0.96, 9.45)	1.46 (0.13, 17.68)	0.99 (0.36, 2.76)				
SRL + CSA	0.62 (0.14, 2.70)	0.45 (0.09, 2.24)	0.66 (0.17, 2.37)	0.41 (0.10, 1.53)	2.03 (0.06, 1055)	1.33 (0.27, 6.22)	0.66 (0.04, 9.51)	0.44 (0.10, 1.88)	0.45 (0.10, 1.80)			
SRL + MMF	1.72 (0.68, 4.31)	1.24 (0.41, 3.78)	1.81 (0.98, 3.42)	1.13 (0.62, 2.01)	5.48 (0.21, 2627)	3.65 (1.35, 10.62)	1.81 (0.17, 20.70)	1.23 (0.50, 3.05)	1.24 (0.58, 2.67)	2.75 (0.70, 11.71)		
SRL + AZA	0.19 (0.01, 6.03)	0.14 (0.01, 4.51)	0.20 (0.01, 6.91)	0.13 (0.01, 4.39)	0.66 (0.01, 634.1)	0.41 (0.01, 15.87)	0.19 (0.01, 14.58)	0.14 (0.01, 4.89)	0.14 (0.01, 5.11)	0.30 (0.01, 13.73)	0.11 (0.01, 3.91)	
EVL	0.25 (0.01, 6.20)	0.18 (0.01, 4.84)	0.27 (0.01, 5.96)	0.17 (0.01, 3.92)	0.81 (0.01, 759.8)	0.54 (0.01, 13.82)	0.25 (0.01, 13.72)	0.18 (0.01, 4.11)	0.18 (0.01, 4.55)	0.40 (0.01, 12.89)	0.15 (0.01, 3.52)	1.27 (0.01, 1184)

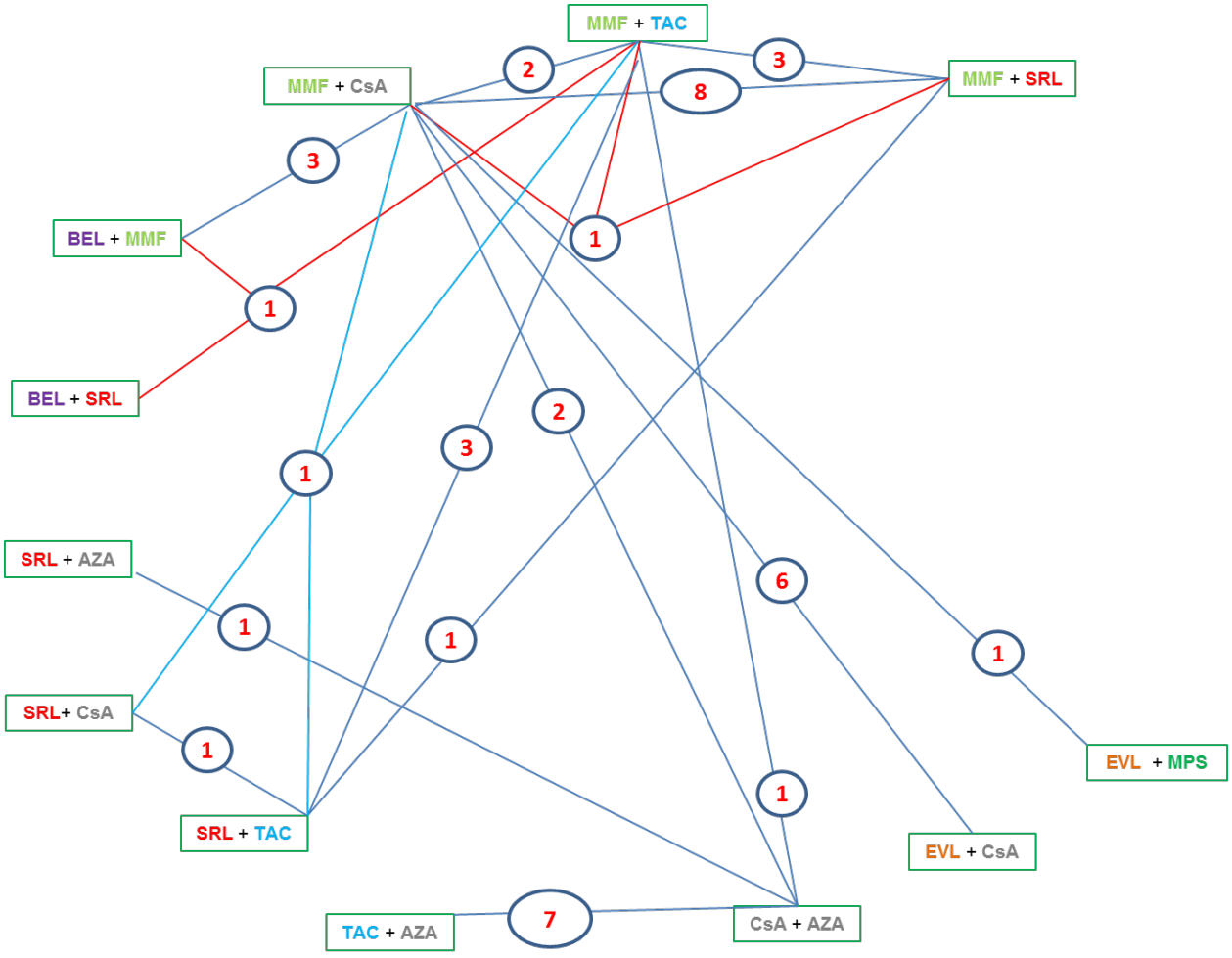
Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Note: OR < 1 favours intervention treatment, OR > 1 favours comparator treatment ; If applicable, evidence suggesting a difference between treatments was highlighted in bold

There is no evidence to suggest that this network is affected by inconsistencies between the direct and indirect evidence (Appendix 6). The DICs were slightly lower for the consistency model compared to the inconsistency model (139.5 vs 143.9) and the 95% CIs based on the direct evidence overlapped those based on the direct and indirect evidence.

Biopsy proven acute rejection

Thirteen treatments and 42 studies (including two 3-arm studies and two 4-arm studies) contribute to this network meta-analysis (Figure 80).

Figure 80. Network diagram for maintenance studies reporting BPAR



Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Notes: Circles denote number of studies.

The DIC for the random effects models was lower than that for the fixed effects model (156.3 vs 170.8) and so the random effects model results are reported here (see Appendix 6) for fixed effects results). The probabilities that each treatment was the most effective in reducing graft loss compared to all other treatments are shown in Table 121.

Table 121. Probability that each treatment is the most effective treatment for reducing BPAR

	Probability of being 'best' treatment
BEL + SRL	58%
SRL + CSA	27%
SRL + TAC	5%
TAC + MMF	2%
EVL + CSA	2%
SRL + MMF	2%
TAC + AZA	1%
MMF + CSA	<1%
BEL + MMF	<1%
EVL + MPS	<1%
SRL + AZA	<1%
EVL	<1%
CSA + AZA	0%

Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.

BEL+SRL has the highest probability (58%) of being the most effective treatment compared to all others for reducing BPAR, however there is no evidence that BEL+SRL is any more effective than the other treatments (Table 122). CSA+AZA has a 0% probability of being the best treatment and there is evidence to suggest that many treatments are more effective than CSA+AZA (Table 122). The results from the network meta-analysis also indicate that MMF+CSA, TAC+MMF and SRL+TAC are all more effective than EVL+MPS at reducing BPAR. However, as with the other network meta-analyses for maintenance therapy, there is a great deal of uncertainty associated with the estimated ORs. Therefore, apart from CSA+AZA and EVL+MPS performing poorly in some comparisons, it is difficult to say that any one treatment is more effective than another as the 95% CIs are so wide.

Table 122. ORs (for Intervention vs Comparator treatment) for the outcome BPAR from a random effects network meta-analysis (Posterior median (95%CI))

	Comparator treatment											
Intervention treatment	**CSA + AZA**	**TAC + AZA**	**MMF + CSA**	**TAC + MMF**	**BEL + SRL**	**BEL + MMF**	**EVL + MPS**	**EVL + CSA**	**SRL + TAC**	**SRL + CSA**	**SRL + MMF**	**SRL + AZA**
TAC + AZA	**0.58 (0.36, 0.93)**											
MMF + CSA	**0.47 (0.25, 0.88)**	0.81 (0.37, 1.80)										
TAC + MMF	**0.40 (0.19, 0.79)**	0.69 (0.29, 1.60)	0.85 (0.52, 1.35)									
BEL + SIR	0.17 (0.01, 1.74)	0.30 (0.01, 3.18)	0.37 (0.01, 3.40)	0.43 (0.01, 4.08)								
BEL + MMF	0.81 (0.34, 1.94)	1.39 (0.51, 3.80)	1.71 (0.91, 3.20)	2.02 (0.96, 4.38)	4.64 (0.52, 150.5)							
EVL + MPS	1.48 (0.40, 5.54)	2.56 (0.65, 10.40)	**3.14 (1.01, 10.10)**	**3.71 (1.10, 13.26)**	8.77 (0.69, 333.80)	1.84 (0.50, 6.96)						
EVL + CSA	**0.46 (0.21, 0.99)**	0.79 (0.32, 1.97)	0.97 (0.61, 1.54)	1.14 (0.60, 2.26)	2.64 (0.27, 89.39)	0.57 (0.26, 1.24)	0.31 (0.09, 1.05)					
SRL + TAC	**0.38**	0.67	0.82	0.96	2.24	0.48	**0.26**	0.84				

	(0.16, 0.93)	(0.24, 1.82)	(0.40, 1.64)	(0.51, 1.80)	(0.22, 76.12)	(0.19, 1.20)	**(0.07, 0.98**)	(0.36, 1.94)				
SRL + CSA	0.28 (0.06, 1.08)	0.48 (0.10, 2.04)	0.59 (0.15, 2.03)	0.70 (0.18, 2.38)	1.63 (0.12, 62.23)	0.34 (0.08, 1.37)	0.19 (0.03, 1.01)	0.61 (0.14, 2.28)	0.72 (0.18, 2.52)			
SRL + MMF	0.43 (0.22, 0.92)	0.75 (0.32, 1.85)	0.92 (0.61, 1.44)	1.09 (0.67, 1.89)	2.53 (0.26, 84.18)	0.54 (0.26, 1.17)	0.29 (0.09, 1.02)	0.95 (0.52, 1.84)	1.13 (0.57, 2.38)	1.57 (0.45, 6.39)		
SRL + AZA	1.16 (0.34, 3.96)	2.00 (0.53, 7.50)	2.45 (0.62, 9.71)	2.89 (0.71, 12.11)	6.88 (0.49, 272.60)	1.43 (0.32, 6.48)	0.78 (0.13, 4.66)	2.53 (0.59, 10.83)	3.00 (0.66, 13.93)	4.19 (0.67, 28.50)	2.66 (0.62, 10.91)	
EVL	1.26 (0.33, 4.81)	2.18 (0.53, 9.08)	2.67 (0.83, 8.77)	3.16 (0.90, 11.48)	7.47 (0.58, 289.90)	1.56 (0.41, 6.02)	0.85 (0.16, 4.43)	2.76 (0.84, 9.21)	3.28 (0.84, 13.15)	4.58 (0.83, 27.72)	2.91 (0.81, 10.03)	1.09 (0.18, 6.71)

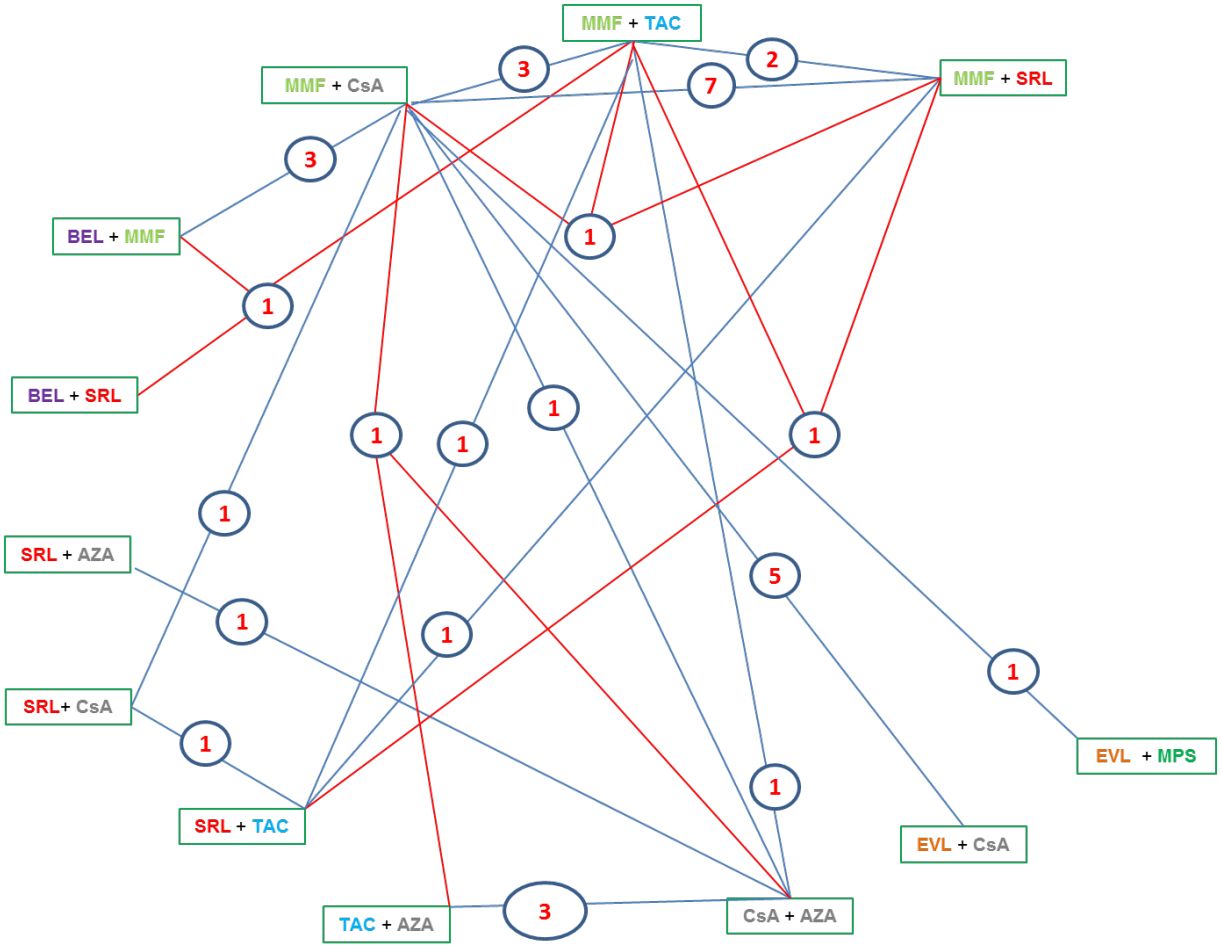
Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Note: OR < 1 favours intervention treatment, OR > 1 favours comparator treatment; If applicable, evidence suggesting a difference between treatments was highlighted in bold

There is no evidence to suggest that this network is affected by evidence inconsistencies (see Appendix 6). The DIC was slightly lower for the consistency model compared to the inconsistency model (156.3 vs 159.7) and the 95% CIs based on the direct evidence overlapped those based on the direct and indirect evidence.

Graft function

Twelve treatments and 35 studies (including four 3-arm studies) contribute to this network meta-analysis (Figure 81).

Figure 81. Network diagram for maintenance studies reporting BPAR



Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Notes: Circles denote number of studies.

The DIC was lower for the random effects model than fixed effects model (147.8 vs 323.7), suggesting a better fit to the data for the random effects model. Therefore the random effects model results are reported here (see Appendix 6 for fixed effects model results). The treatment with the highest probability of being the most effective (Table 123) is BEL+SRL

(44% probability), with SRL+AZA having a 28% probability. The results in Table 124 suggest that a number of treatments (TAC+AZA, TAC+MMF, BEL+MMF and SRL+AZA) are more effective than CSA+AZA, and also that TAC+AZA, TAC+MMF and BEL+MMF are more effective than SRL+TAC. However, due to the limited direct evidence informing many of the comparisons, the 95% CIs are very wide for a number of comparisons, limiting conclusions to be made on the effectiveness of one treatment over another.

For the random effects model, there was little evidence of inconsistency within the network (see Appendix 6).

Table 123. Probability that each treatment is the most effective treatment for graft function

	Probability of being ' best' treatment
BEL + SRL	44%
SRL + AZA	28%
BEL + MMF	17%
TAC + AZA	9%
EVL + MPS	1%
TAC + MMF	<1%
EVL + CSA	<1%
SRL + TAC	<1%
SRL + CSA	<1%
SRL + MMF	<1%
CSA + AZA	0%
MMF + CSA	0%

Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.

Table 124. Mean differences (for Intervention vs Comparator treatment) for the outcome Graft Function from a random effects network meta-analysis (Posterior median (95%CI))

	Comparator treatment										
Intervention treatment	**CSA + AZA**	**TAC + AZA**	**MMF + CSA**	**TAC + MMF**	**BEL + SRL**	**BEL + MMF**	**EVL + MPS**	**EVL + CSA**	**SRL + TAC**	**SRL + CSA**	**SRL + MMF**
TAC + AZA	**9.31 (4.32, 14.28)**										
MMF + CSA	1.61 (-4.16, 7.41)	**-7.70 (-14.53, -0.86)**									
TAC + MMF	**6.53 (0.38, 12.68)**	-2.78 (-10.08, 4.54)	**4.92 (0.87, 8.98)**								
BEL + SRL	12.33 (-3.97, 28.60)	3.01 (-13.75, 19.72)	10.71 (-4.81, 26.20)	5.79 (-9.53, 21.06)							
BEL + MMF	**10.54 (2.47, 18.66)**	1.24 (-7.65, 10.19)	**8.94 (3.13, 14.79)**	4.02 (-2.72, 10.73)	-1.76 (-17.52, 13.94)						
EVL + MPS	0.33 (-12.22, 12.96)	-8.98 (-22.07, 4.18)	-1.27 (-12.45, 9.93)	-6.19 (-18.06, 5.70)	-12.01 (-31.12, 7.20)	-10.21 (-22.81, 2.44)					
EVL + CSA	4.85 (-2.84, 12.58)	-4.44 (-12.97, 4.08)	3.26 (-1.82, 8.34)	-1.66 (-8.19, 4.84)	-7.47 (-23.76, 8.87)	-5.69 (-13.44, 2.08)	4.52 (-7.80, 16.81)				

PenTAG

SRL + TAC	-0.34 (-8.53, 7.85)	**-9.66 (-18.68, -0.59)**	-1.96 (-8.35, 4.43)	-6.88 (-13.01, -0.75)	-12.67 (-29.08, 3.69)	-10.90 (-19.40, -2.43)	-0.68 (-13.59, 12.15)	-5.22 (-13.35, 2.94)			
SRL + CSA	-1.63 (-11.13, 7.96)	**-10.93 (-21.14, -0.63)**	-3.23 (-11.07, 4.64)	-8.16 (-16.34, 0.09)	-13.95 (-31.08, 3.24)	-12.18 (-21.86, -2.43)	-1.95 (-15.66, 11.69)	-6.49 (-15.83, 2.85)	-1.26 (-8.97, 6.45)		
SRL + MMF	3.84 (-2.72, 10.43)	-5.47 (-13.02, 2.12)	2.24 (-1.55, 6.05)	-2.69 (-6.92, 1.57)	-8.47 (-24.16, 7.24)	-6.71 (-13.52, 0.12)	3.50 (-8.29, 15.31)	-1.02 (-7.35, 5.33)	4.20 (-2.02, 10.41)	5.47 (-2.72, 13.67)	
SRL + AZA	**10.78 (1.07, 20.44)**	1.47 (-9.41, 12.35)	9.17 (-2.13, 20.47)	4.24 (-7.23, 15.73)	-1.52 (-20.45, 17.46)	0.24 (-12.40, 12.84)	10.43 (-5.48, 26.36)	5.93 (-6.47, 18.29)	11.12 (-1.55, 23.81)	12.41 (-1.20, 25.99)	6.93 (-4.77, 18.61)

Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.
Note: Posterior mean >0 favours Intervention treatment, posterior mean <0 favours comparator treatment; If applicable, evidence suggesting a difference between treatments was highlighted in bold

Summary for network meta-analysis

Induction therapy

- There is no evidence to suggest BAS or ATG are more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality
- ATG and BAS are both estimated to be more effective than placebo/no induction, with ATG being more effective than BAS at reducing BPAR
- Evidence suggests that while no treatment effect is seen for ATG, BAS is estimated to be more effective than placebo/no induction for increasing CRC-GFR

Maintenance therapy

None of the maintenance regimens performed consistently well on all four outcomes. An overview of probability ranking on the four outcomes is presented in Table 125. However, because the analyses included between 12 and 13 treatment regimens for each of the four outcomes, the results should be treated with great caution.[210] In addition, differences between treatments in probability of being best of less than 90% cannot be given much credence.[210]

Table 125. Probability that each treatment is the most effective treatment for mortality, reducing graft loss, biopsy proven acute rejection and graft function

	Probability of being 'best' treatment			
	Mortality	Graft loss	BPAR	GRF
SRL + AZA	34%	29%	<1%	28%
EVL	30%	60%	<1%	<1%
BEL + SRL	27%	2%	58%	44%
EVL + MPS	4%	NA	<1%	NA
BEL + MMF	3%	2%	<1%	17%
SRL + CSA	3%	6%	27%	<1%
TAC + MMF	0%	<1%	2%	<1%
MMF + CSA	<1%	<1%	<1%	0%
SRL + TAC	<1%	<1%	5%	<1%
SRL + MMF	<1%	<1%	2%	<1%
EVL + CSA	<1%	1%	2%	1%
TAC + AZA	<1%	<1%	1%	9%
CSA + AZA	<1%	<1%	0%	0%

Key: AZA, azathioprine; BEL, belatacept;CSA, ciclosporine;EVL, everolimus; MMF, mycophenolate mofetil; NA, not applicable. SRL, sirolimus; TAC, tacrolimus. Note: The order of the treatments is based on the results for mortality.

In all network meta-analyses for maintenance therapy there is a great deal of heterogeneity:

- There is no evidence to suggest that one treatment is any more effective at reducing the odds of graft loss than any other treatment.
- There is evidence to suggest that BEL+MMF is more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF, but no other treatments are estimated to be any more effective at reducing mortality than any other treatment.
- MMF+CSA, TAC+MMF and SRL+TAC are estimated to be more effective than CSA+AZA and EVL+MPS at reducing the odds of BPAR. In addition,TAC+AZA and EVL+CSA are also estimated to be more effective than and CSA+AZAat reducing the odds of BPAR. However, apart from CSA+AZA and EVL+MPS performing poorly in some comparisons, it is difficult to say that any one treatment is more effective than another as the 95% CIs are very wide.
- Similarly, number of treatments TAC+AZA, TAC+MMF and BEL+MMF, are estimated to be more effective than CSA+AZA and MMF+CSA at increasing graft function. In addition, SRL+AZA is estimated to be more effective than CSA+AZA at increasing graft function. However, due to the limited direct evidence informing many of the

comparisons, the 95% CIs being very wide and limiting conclusions to say that CSA+AZA and MMF+CSA are performing poorly in some comparisons.

4.3.4. Adverse events

Adverse events for each study are presented below. We conducted numerous comparisons and meta-analyses of the adverse effects of treatment reported in included RCTs at one year, since other time points had insufficient data for pooling. All the meta-analyses (and associated forest plots) are in Appendix 7, rather than the main body of the report, however the results are summarised as follows:

- Some evidence suggested more CMV infections in rATG regimens compared with BAS regimens(Mourad at al.2004)[199], and in rATG regimens compared with no induction (Charpentier et al. 2001).[82] However this finding was contradicted by results of the three-arm comparing BAS, rATG and no induction (Kyllonen et al. 2007).[86]

- The meta-analysis comparing TAC and CSA regimens (including 8 studies) suggested more cases of NODAT in TAC regimens compared with CSA regimens.

- The meta-analyses comparing BEL with CSA regimens (including 3 studies). suggested more cases of NODAT in CSA regimens compared with BEL regimens (including 3 studies).

- The meta-analyses comparing SRL and CSA regimens (including 7 studies) suggested more cases of NODAT in CSA regimens compared with SRL.

- The meta-analysis comparing MMF and EVL (including 3 studies) suggested more cases of CMV infections in MMF regimens compared with EVL.

4.3.4.1. Induction therapy

All 16 induction studies reported some adverse events (AE) data. The time of follow –up varied from six months to 10 years in the individual studies (see Table 126 for an overview). Most studies reported a one year follow-up, although the AE reported varied across the studies. The following AE are summarised below: new onset diabetes (NODAT), post-transplant lymphoproliferative disorder (PTLD), malignancy (including PTLD), any infections, and cytomegalovirus (CMV).

Table 126. Adverse events overview; Induction therapies

N	Study (multiple publications)	n	Maintenance used	Adverse events
BAS vs placebo (5 studies)				
1	Bingyi 2003	12	**CsA +AZA + CCS**	1yr
2	Kahan 1999	346	**CsA + CCS**	1yr
3	Law en 2003	123	**CsA + MMF + CCS**	6m
4	Nashan 1997	380	**CsA + CCS**	1yr
5	Ponticelli 2001, (2001)	340	**CsA + Aza+ CCS.**	6m
BAS vs no induction (2 studies)				
6	Albano 2013 (OSAKA trial;NCT00717470)	1251	**CsA + MMF + CCS**	6m
7	Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	100	**CSA +AZA+ CCS**	3yr, 5yr, 7yr
ATG vs no induction (4 studies)				
8	Charpentier 2001	309	**TAC + AZA + CCS**	1yr
9	Samsel 2008	79	**CsA + MMF (converted to AZA) + CCS**	1yr, 5yr
10	Sheashaa 2008	80	**CNI + prolif + CCSen.**	5yr
11	Charpentier 2003	555	**TAC + AZA + CCS**	6m
BAS vs ATG (4 studies)				
12	Brennan 2006	278	**CsA + MMF + CCS**	1yr
13	Lebranchu 2002	100	**CsA + MMF + CCS**	6m, 1yr
14	Mourad 2004	105	**CsA + MMF + CCS**	1yr
15	Sollinger 2001	135	**CsA + MMF + CCS.**	1yr
BAS vs ATG vs no induction (1 studies)				
16	Kyllonen 2007	155	**CsA + AZA + CCS**	1yr

New onset diabetes

Eight studies reported NODAT events, their frequencies are shown in Table 127. The studies that reported NODAT events showed frequencies ranging from 0 to 5/58 (9%). None of the comparisons suggest a statistically significant difference.

Table 127. New onset diabetes; induction regimens

N	Study (multiple publications)	6 Months	1 Year	3 Years	5 Years	7 Years
BAS vs placebo (5 studies)						
1	Bingyi 2003	NR	0/6 vs 0/6	NR	NR	NR
2	Kahan 1999	NR	NR	NR	NR	NR
3	Lawen 2003	NR	NR	NR	NR	NR
4	Nashan 1997	NR	NR	NR	NR	NR
5	Ponticelli 2001, (2001)	NR	NR	NR	NR	NR
BAS vs no induction (2 studies)						
6	Albano 2013 (OSAKA trial;NCT00717470)	31/247 vs 35/265	NR	NR	NR	NR
7	Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	NR	NR	4/50 vs 7/50	4/50 vs 7/50	4/50 vs 7/50
ATG vs no induction (4 studies)						
8	Charpentier 2001	NR	5/145 vs 7/154	NR	NR	NR
9	Samsel 2008	NR	NR	NR	NR	NR
10	Sheashaa 2008	NR	NR	NR	4/40 vs 7/40	NR
11	Charpentier 2003	13/177 vs 7/173	NR	NR	NR	NR
BAS vs ATG (4 studies)						
12	Brennan 2006	NR	NR	NR	NR	NR
13	Lebranchu 2002	NR	1/51 vs 1/50	NR	NR	NR
14	Mourad 2004	NR	NR	NR	NR	NR
15	Sollinger 2001	NR	NR	NR	NR	NR
BAS vs ATG vs no induction (1 studies)						
16	Kyllonen 2007	NR	5/58 vs 2/53 vs 1/44	NR	NR	NR

Key: * p<0.05; NR, not reported

Malignancy and post-transplant lymphoproliferative disorder

Fourteen studies reported malignancy, including post-transplant lymphoproliferative disorder. The frequency of these events can be seen in Table 128. Frequencies ranged from 0 to 3/168 (2%). No statistically significant differences between treatments were noted.

Table 128. Malignancy and Post-transplant lymphoproliferative disorder; induction regimens

N	Study (multiple publications)	6 Months	1 Year	3 Years	5 Years	7 Years
BAS vs placebo (5 studies)						
1	Bingyi 2003	NR	0/6 vs 0/6	NR	NR	NR
2	Kahan 1999	NR	2/173 vs 6/173	NR	NR	NR
3	Lawen 2003	no malignancy data (0/59 vs 0/64)	NR	NR	NR	NR
4	Nashan 1997	NR	3/190 vs 2/186	NR	NR	NR
5	Ponticelli 2001, (2001)	NR	3/168 vs 6/172 (a)	NR	NR	NR
BAS vs no induction (2 studies)						
6	Albano 2013 (OSAKA trial;NCT00717470)	3/283 vs 2/302	NR	NR	NR	NR
7	Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	NR	NR	1/50 vs 1/50	1/50 vs 2/50	1/50 vs 3/50
ATG vs no induction (4 studies)						
8	Charpentier 2001	NR	NR	NR	NR	NR
9	Samsel 2008	NR	0/40 vs 0/39	NR	1/40 vs 0/39	NR
10	Sheashaa 2008	NR	NR	NR	1/40 vs 2/40	NR
11	Charpentier 2003	4/186 vs 1/185	NR	NR	NR	NR
BAS vs ATG (4 studies)						
12	Brennan 2006	NR	1/137 vs 5/141	NR	NR	NR
13	Lebranchu 2002	0/51 vs 0/50	0/51 vs 0/50	NR	NR	NR
14	Mourad 2004	NR	NR	NR	NR	NR
15	Sollinger 2001	NR	1/70 vs 3/65	NR	NR	NR
BAS vs ATG vs no induction (1 studies)						
16	Kyllonen 2007	NR	0/58 vs 2/53 vs 1/44	NR	NR	NR

KEY: a, assumed 1 year data reported ; NR, not reported

Infections

Twelve studies reported infections related to the induction therapies, Table 129. Frequencies ranged from 0 to 129/173 (75%). At 6 months and 1 year, a statistically significant difference in favour of BAS is indicated.

Table 129. Infections; induction therapies

N	Study (multiple publications)	6 Months	1 Year	3 Years	5 Years	7 Years
	BAS vs placebo (5 studies)					
1	Bingyi 2003	NR	0/6 vs 0/6	NR	NR	NR
2	Kahan 1999	NR	129/173 vs 127/173	NR	NR	NR
3	Lawen 2003	37/59 vs 45/64	NR	NR	NR	NR
4	Nashan 1997	NR	161/190 vs 161/186	NR	NR	NR
5	Ponticelli 2001, (2001)	110/168 vs 113/172	NR	NR	NR	NR
	BAS vs no induction (2 studies)					
6	Albano 2013 (OSAKA trial;NCT00717470)	74/287 vs 76/309	NR	NR	NR	NR
7	Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	NR	NR	NR (a)	NR (a)	NR (a)
	ATG vs no induction (4 studies)					
8	Charpentier 2001	NR	NR (a)	NR	NR	NR
9	Samsel 2008	NR	NR	NR	26/40 vs 26/39 (b)	NR
10	Sheashaa 2008	NR	NR	NR	NR (a)	NR
11	Charpentier 2003	126/186 vs 108/185	NR	NR	NR	NR
	BAS vs ATG (4 studies)					
12	Brennan 2006	NR	103/137 vs 121/141*	NR	NR	NR
13	Lebranchu 2002	33/51 vs 43/50*	NR	NR	NR	NR
14	Mourad 2004	NR	22/52 vs 28/53	NR	NR	NR
15	Sollinger 2001	NR	53/70 vs 50/65	NR	NR	NR
	BAS vs ATG vs no induction (1 studies)					
16	Kyllonen 2007	NR	NR	NR	NR	NR

key: * p<0.05; a, different infections reported individually available; b, based on patients with no infection; NR, not reported

Cytomegalovirus

Sixteen studies reported cytomegalovirus events in induction therapies, Table 130. Frequencies ranged from 0 to 49/151 (32%), with a statistically significant difference noted for BAS vs rATG (3 studies). For Lebranchu et al. 2002 and Mourad et al. 2004, a reduced occurrence of CMV is seen for the BAS arm, whereas for the study reported by Brennan et al. 2006, fewer occurences are seen for rATG.

Table 130. Cytomegalovirus; induction regimens

N	Study (multiple publications)	6 Months	1 Year	3 Years	5 Years	7 Years
BAS vs placebo (5 studies)						
1	Bingyi 2003	NR	0/6 vs 0/6	NR	NR	NR
2	Kahan 1999	NR	12/173 vs 16/173	NR	NR	NR
3	Lawen 2003	8/59 vs 12/64	NR	NR	NR	NR
4	Nashan 1997	NR	39/190 vs 50/ 186	NR	NR	NR
5	Ponticelli 2001, (2001)	29/168 vs 25/172	NR	NR	NR	NR
BAS vs no induction (2 studies)						
6	Albano 2013 (OSAKA trial;NCT00717470)	9/287 vs 12/309	NR	NR	NR	NR
7	Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	NR	NR	3/50 vs 3/50	3/50 vs 4/50	4/50 vs 4/50
ATG vs no induction (4 studies)						
8	Charpentier 2001	NR	49/151 vs 30/158*	NR	NR	NR
9	Samsel 2008	NR	NR	NR	4/40 vs 0/39	NR
10	Sheashaa 2008	NR	NR	NR	3/40 vs 4/40	NR
11	Charpentier 2003	45/186 vs 29/185*	NR	NR	NR	NR
BAS vs ATG (4 studies)						
12	Brennan 2006	NR	24/137 vs 11/141*	NR	NR	NR
13	Lebranchu 2002	6/51 vs 19/50 *	NR	NR	NR	NR
14	Mourad 2004	NR	11/52 vs 22/53*	NR	NR	NR
15	Sollinger 2001	NR	13/70 vs 11/65	NR	NR	NR
BAS vs ATG vs no induction (1 studies)						
16	Kyllonen 2007	NR	9/58 vs 9/53 vs 5/44	NR	NR	NR

Key: * p<0.05; NR, not reported

4.3.4.2. Maintenance therapy

Most of the 76 maintenance studies reported some adverse events (AE) data. The time of follow –up varied from 6 months to 10 years (see Table 131 for an overview). Most studies reported 1 year follow-up, although the AE reported varied across the studies. The following AE are summarised below: new onset diabetes (NODAT), post-transplant lymphoproliferative disorder (PTLD), malignancy (including PTLD), any infections, and cytomegalovirus (CMV). All AE are tabulated and narratively described in the sections below.

Table 131 Adverse events overview; Maintenance therapies

[redacted]	Study	Adverse events
Tac + Aza vs CsA + Aza (13 studies)		
1	Schleibner 1995	NR
2	Laskow 1996	1yr
3	Mayer 1997 (Mayer 2002,1999)	1yr, 4yr, 5yr
4	Radermacher 1998	1yr
5	Jarzembowski 2005	1yr
6	Baboolal 2002	1yr
7	Campos 2002	1yr
8	Margreiter (2002) (Kramer 2005 and Kramer 2008)	6m, 2yr, 3yr
9	Van Duijnhoven 2002	NR
10	Waller 2002 (Murphy 2003)	1yr
11	Charpentier 2003	6m
12	Toz 2004	NR
13	Hardinger 2005 (Brennan 2005)	1yr
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)		
14	Sollinger 1995	6m
15	Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	6m, 1yr, 3yr
CsA + MMF vs CsA + AZA (4 studies)		
16	Sadek 2002	1yr
17	Tuncer 2002	NR
18	Merville 2004	1yr
19	Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	6m, 5yr
TAC + MMF vs CsA + AZA (2 studies)		
20	Wlodarczyk 2005 (Wlodarczyk 2002)	6m
21	Vacher-Coponat 2012	1yr, 3yr
TAC + MMF vs CsA + MMF (4 studies)		
22	Zadrazil 2012	NR
23	Hernandez 2007	2yr
24	Rowshani 2006	NR
25	Ulsh 1999 (Yang 1999)	1yr
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)		
26	Weimer 2006 (Weimer 2005)	1yr
TAC + MMF vs TAC PR + MMF (4 studies)		
27	Wlodarczyk 2009	NR

28	Kramer 2010 (NCT00189839)	1yr
29	Tsuchiya 2013	1yr
30	Oh 2014	NR
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)		
31	Albano 2013: (NCT00717470) OSAKA Trial	6m
MMF + TAC vs MPS + TAC (1 study)		
32	Ciancio 2008 / (Ciancio 2011 (3016), Ciancio 2006 (218) R01DK25243-25)	1yr, 4yr
MMF + CsA vs MPS + CsA (1 study)		
33	Salvadori 2004	1yr
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)		
34	Vincenti 2005 (Vincenti 2010)	1yr, 2yr, 3yr, 4yr, 5yr
35	BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	1yr, 2yr, 3yr, 5yr
36	BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	1yr, 2yr, 3yr, 5yr
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)		
37	Ferguson 2011	1yr
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)		
38	Lorber 2005	3yr
39	ATLAS Vitko 2005 (Vitko 2004 & 2005b)	1yr, 3yr
40	Takahashi 2013	1yr
EVL vs CsA vs MPS (1 study)		
41	Bemelman 2009	NR
EVL vs EVL +CsA vs CsA + MPS (1 study)		
42	Chadban 2013 (SOCRATES)	1yr
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)		
43	Tedesco Silva 2010	1yr
EVL + CsA vs MPS + CsA (1 study)		
44	Bertoni 2011	1yr
EVL + MPS vs CsA + MPS (2 studies)		
45	Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	1yr, 2yr, 3yr
46	Mjornstedt 2012 (NCT00634920)	1yr
SRL + CsA vs MMF + CsA (2 studies)		
47	Barsoum 2007	2yr
48	Stallone 2003	NR
SRL + TAC vs MMF + TAC (6 studies)		
49	Anil Kumar 2005	1yr
50	Mendez 2005 / (Gonwa 2003)	6m, 1yr
51	Sampaio 2008	1yr
52	Gelens 2006	NR
53	Gallon 2006 (Chhabra 2012)	3yr, 8.5yr
54	Van Gurp 2010	6m
SRL + MMF vs CsA + MMF (10 studies)		
55	Flechner 2002 (Flechner 2004, 2007)	1yr, 5yr
56	Noris 2007/ (Ruggenenti 2007)	2yr
57	Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	1yr, 4yr
58	Büchler 2007 (Lebranchu 2012, Joannides 2010)	1yr, 5yr
59	Soleimani 2013	5yr
60	Durrbach 2008 : (0468E1 – 100969)	6m
61	Kreis (2000) - Identified from Campistol 2005	1yr
62	Guba 2010	1yr

63	Martinez-Mier 2006	1yr
64	Nafar 2012 : (IRCT138804333049N7)	NR
TAC + MMF vs SRL + MMF (4 studies)		
65	Larson 2006 (Stegall 2003)	NR
66	Schaefer 2006	1yr
67	Heilman 2011 (Heilman, 2012; NCT00170053)	1yr
68	Welberry Smith 2008	NR
TAC + MPS vs SRL + MPS (1 study)		
69	Silva 2013 (NCT01802268)	2yr
TAC + SRL vs MMF + SRL (1 study)		
70	Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	1yr, 2yr, 5yr
SRL + AZA vs CsA + AZA (1 study)		
71	Charpentier 2003 (Groth 1999)	1yr
TAC + SRL vs CsA + SRL (1 study)		
72	Chen 2008	1yr
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)		
73	Vitko 2006	6m
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)		
74	Flechner 2011 / (the ORION study, NCT00266123)	1yr, 2yr
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)		
75	Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	1yr, 3yr
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)		
76	Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	5yr

Key: a, 6-weeks pilot study; MMF, Mycophenolate mofetil; TAC, Tacrolimus; CsA, CSAlosporine; SRL, Sirolimus; EVL, Everolimus; MPA, Mycophenolic acid.

New onset diabetes

Only one of 13 studies found statistically significant difference for TAC+AZA vs CSA+AZA at the 6 month time point in favour of CSA (Charpentier et al. 2003) (Table 132). Vincenti et al. 2005 found CSA+MMF to have a statistically significant difference to BEL+MMF, but, again, only at 6 months. For SRL low+TAC vs SRL high+TAC vs MMF+TAC, at 6 months for SRL high+TAC a statistically significant increase in NODAT is apparent.[80] Two other studies show an increase in NODAT. Grinyo et al. 2009 for MMF + low TAC and Kumar et al. 2008 for TAC+MMF.

Table 132. New onset diabetes; maintenance therapies

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
Tac + Aza vs CsA + Aza (13 studies)								
1	Schleibner 1995	NR	NR	NR	NR	NR	NR	NR
2	Laskow 1996 (a)	NR	12/92 vs 1/28	NR	NR	NR	NR	NR
3	Mayer 1997 (Mayer 2002,1999)	NR	17/303 vs 3/145	NR	NR	17/303 vs 3/145 (b)	NR	NR
4	Radermacher 1998	NR	NR	NR	NR	NR	NR	NR
5	Jarzembowski 2005	NR	3/14 vs 4/21	NR	NR	NR	NR	NR
6	Baboolal 2002	NR	NR	NR	NR	NR	NR	NR
7	Campos 2002	NR	10/85 vs 3/81	NR	NR	NR	NR	NR
8	Margreiter (2002) (Kramer 2005 and Kramer 2008)	13/286 vs 5/271	NR	8/286 vs 4/271	NR	NR	NR	NR
9	Van Duijnhoven 2002	NR	NR	NR	NR	NR	NR	NR
10	Waller 2002 (Murphy 2003)	NR	NR	NR	NR	NR	NR	NR
11	Charpentier 2003	13/177 vs 2/177*	NR	NR	NR	NR	NR	NR
12	Toz 2004	NR	NR	NR	NR	NR	NR	NR
13	Hardinger 2005 (Brennan 2005)	NR	5/134 vs 1/66	NR	NR	NR	NR	NR
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)								
14	Sollinger 1995	NR	NR	NR	NR	NR	NR	NR
15	Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	NR	NR	NR	NR	NR	NR	NR
CsA + MMF vs CsA + AZA (4 studies)								
16	Sadek 2002	NR	NR	NR	NR	NR	NR	NR
17	Tuncer 2002	NR	NR	NR	NR	NR	NR	NR
18	Merville 2004	NR	NR	NR	NR	NR	NR	NR
19	Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs CsA + AZA (2 studies)								
20	Wlodarczyk 2005 (Wlodarczyk 2002)	27/243 vs 27/246	NR	NR	NR	NR	NR	NR
21	Vacher-Coponat 2012	NR	8/128 vs 11/137	NR	21/143 vs 17/146	NR	NR	NR
TAC + MMF vs CsA + MMF (4 studies)								
22	Zadrazil 2012	NR	NR	NR	NR	NR	NR	NR

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
23	Hernandez 2007	NR	NR	15/55 vs 9/58	NR	NR	NR	NR
24	Rowshani 2006	NR	NR	NR	NR	NR	NR	NR
25	Yang 1999 and Ulsh (1999)	NR	1/24 vs 1/21	NR	NR	NR	NR	NR
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)								
26	Weimer 2006 (Weimer 2005)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR + MMF (4 studies)								
27	Wlodarczyk 2009	NR	NR	NR	NR	NR	NR	NR
28	Kramer 2010 (NCT00189839)	NR	17/298 vs 18/284	NR	NR	NR	NR	NR
29	Tsuchiya 2013	NR	NR	NR	NR	NR	NR	NR
30	Oh 2014	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)								
31	Albano 2013: (NCT00717470) OSAKA Trial	44/274 vs 35/265 vs 49/268	NR	NR	NR	NR	NR	NR
MMF + TAC vs MPS + TAC (1 study)								
32	Ciancio 2008 / (Ciancio 2011 (3016), Ciancio 2006 (218) R01DK25243-25)	NR	7/61 vs 6/55	NR	NR	13/61 vs 8/55	NR	NR
MMF + CsA vs MPS + CsA (1 study)								
33	Salvadori 2004	NR	NR	NR	NR	NR	NR	NR
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)								
34	Vincenti 2005 (Vincenti 2010)	NR	1/71 vs 1/74 vs 6/73*	7/102 vs 2/26	8/102 vs 2/26	8/102 vs 2/26	9/102 vs 2/26	NR
35	BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	NR	7/226 vs 11/219 vs 16/221	NR	NR	NR	NR	NR
36	BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	NR	7/175 vs 3/184 vs 11/184	NR	18/175 vs 9/184 vs 17/184	NR	NR	NR
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)								
37	Ferguson 2011	NR	0/33 vs 2/26 vs 1/30	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)								
38	Lorber 2005	NR	NR	NR	NR	NR	NR	NR
39	ATLAS Vitko 2005 (Vitko 2004 & 2005b)	NR	NR	NR	13/194 vs 25/198 vs 11/196	NR	NR	NR
40	Takahashi 2013	NR	7/61 vs 3/61	NR	NR	NR	NR	NR
EVL vs EVL +CsA vs CsA + MPS (1 study)								

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
42	Chadban 2013 (SOCRATES)	NR	8/49 vs 12/30 vs 13/47	NR	NR	NR	NR	NR
	EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)							
43	Tedesco Silva 2010	NR	14/274 vs 22/278 vs 19/273	NR	NR	NR	NR	NR
	EVL + CsA vs MPS + CsA (1 study)							
44	Bertoni 2011	NR	NR	NR	NR	NR	NR	NR
	EVL + MPS vs CsA + MPS (2 studies)							
45	Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	NR	2/155 vs 3/145	NR	NR	NR	NR	NR
46	Mjornstedt 2012 (NCT00634920)	NR	NR	NR	NR	NR	NR	NR
	SRL + CsA vs MMF + CsA (2 studies)							
47	Barsoum 2007	NR	NR	3/76 vs 3/37	NR	NR	NR	NR
48	Stallone 2003	NR	NR	NR	NR	NR	NR	NR
	SRL + TAC vs MMF + TAC (6 studies)							
49	Anil Kumar 2005	NR	2/75 vs 2/75	NR	NR	NR	NR	NR
50	Mendez 2005 / (Gonwa 2003)	10/132 vs 9/117	10/132 vs 9/117 (c	NR	NR	NR	NR	NR
51	Sampaio 2008	NR	12/50 vs 6/50	NR	NR	NR	NR	NR
52	Gelens 2006	NR	NR	NR	NR	NR	NR	NR
53	Gallon 2006 (Chhabra 2012)	NR	NR	NR	2/37 vs 1/45	NR	NR	9/37 vs 6/45
54	Van Gurp 2010	25/318 vs 32/316	NR	NR	NR	NR	NR	NR
	SRL + MMF vs CsA + MMF (10 studies)							
55	Flechner 2002 (Flechner 2004, 2007)	NR	NR	NR	NR	NR	1/31 vs 2/30	NR
56	Noris 2007/ (Ruggenenti 2007)	NR	NR	1/11 vs 2/10	NR	NR	NR	NR
57	Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	NR	3/96 vs 2/97	NR	NR	7/96 vs 2/97	NR	NR
58	Büchler 2007 (Lebranchu 2012, Joannides 2010)	NR	9/71 vs 3/74	NR	NR	NR	2/63 vs 4/68 (d)	NR
59	Soleimani 2013	NR	NR	NR	NR	NR	NR	NR
60	Durrbach 2008 : (0468E1 – 100969)	NR	NR	NR	NR	NR	NR	NR
61	Kreis (2000) - Identified from Campistol 2005	NR	1/40 vs 1/38	NR	NR	NR	NR	NR
62	Guba 2010	NR	5/69 vs 4/71	NR	NR	NR	NR	NR
63	Martinez-Mier 2006	NR	1/20 vs 1/21	NR	NR	NR	NR	NR

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
64	Nafar 2012 : (IRCT138804333049N7)	NR	NR	NR	NR	NR	NR	NR
	TAC + MMF vs SRL + MMF (4 studies)							
65	Larson 2006 (Stegall 2003)						Mean followup 33 months (17-47 months)	
66	Schaefer 2006	NR	5/39 vs 6/41	NR	NR	NR	NR	NR
67	Heilman 2011 (Heilman, 2012; NCT00170053)	NR	NR	NR	NR	NR	NR	NR
68	Welberry Smith 2008	NR	NR	NR	NR	NR	NR	NR
	TAC + MPS vs SRL + MPS (1 study)							
69	Silva 2013 (NCT01802268)	NR	NR	NR	NR	NR	NR	NR
	TAC + SRL vs MMF + SRL (1 study)							
70	Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	NR	18/65 vs 13/65	NR	NR	19/65 vs 15/67	NR	NR
	SRL + AZA vs CsA + AZA (1 study)							
71	Charpentier 2003 (Groth 1999)	NR	1/41 vs 1/42	NR	NR	NR	NR	NR
	TAC + SRL vs CsA + SRL (1 study)							
72	Chen 2008	NR	1/21 vs 1/20	NR	NR	NR	NR	NR
	SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)							
73	Vitko 2006	20/296 vs 44/290 vs 28/295*	NR	NR	NR	NR	NR	NR
	SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)							
74	Flechner 2011 / (the ORION study, NCT00266123)	NR	27/120 vs 7/117 vs 12/110*	NR	NR	NR	NR	NR
	MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)							
75	Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	NR	23/384 vs 17/408 vs 34/403 vs 25/380	NR	19/233 vs 12/248 vs 30/249 vs 18/228*	NR	NR	NR
	TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)							
76	Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	NR	NR	NR	NR	NR	12/50 vs 8/50 vs 0/50 vs 8/50*	NR

Key: *p<0.05; a, - data for low, medium, high TAC regimens combined; b, no new cases of NODAT reported; c, text reporting same % as 6 monts results; d, 2/63 vs 4/68 new cases between year 1 and 5 were reported; NR, not reported

Malignancy and Post-transplant lymphoproliferative disorder

For all combinations reporting malignancy and PTLD, no statistically significant difference was seen between arms (Table 133).

Table 133 Malignancy and Post-transplant lymphoproliferative disorder; maintenance regimens

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
Tac + Aza vs CsA + Aza (13 studies)								
1	Schleibner 1995	NR	NR	NR	NR	NR	NR	NR
2	Laskow 1996	NR	NR	NR	NR	NR	NR	NR
3	Mayer 1997 (Mayer 2002,1999)	NR	6/303 vs 3/145	NR	NR	NR	21/303 vs 11/145	NR
4	Radermacher 1998	NR		NR	NR	NR		NR
5	Jarzembowski 2005	NR	(no cases reported)	NR	NR	NR	NR	NR
6	Baboolal 2002	NR	NR	NR	NR	NR	NR	NR
7	Campos 2002	NR	NR	NR	NR	NR	NR	NR
8	Margreiter (2002) (Kramer 2005 and Kramer 2008)	NR	NR	3/237 vs 1/222	7/231 vs 5/217	NR	NR	NR
9	Van Duijnhoven 2002	NR	NR	NR	NR	NR	NR	NR
10	Waller 2002 (Murphy 2003)	NR	NR	NR	NR	NR	NR	NR
11	Charpentier 2003	2/185 vs 4/184	NR	NR	NR	NR	NR	NR
12	Toz 2004	NR	NR	NR	NR	NR	NR	NR
13	Hardinger 2005 (Brennan 2005)	NR	2/134 vs 0/66	NR	NR	NR	NR	NR
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)								
14	Sollinger 1995	8/165 vs 2/164 vs 3/166	NR	NR	NR	NR	NR	NR
15	Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	NR	18/171 vs 12/162 vs 14/164	NR	25/171 vs 29/162 vs 19/164	NR	NR	NR
CsA + MMF vs CsA + AZA (4 studies)								
16	Sadek 2002	NR	NR	NR	NR	NR	NR	NR
17	Tuncer 2002	NR	NR	NR	NR	NR	NR	NR
18	Merville 2004	NR	NR	NR	NR	NR	NR	NR
19	Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	NR	NR	NR	NR	NR	8/124 vs 13/124	NR
TAC + MMF vs CsA + AZA (2 studies)								
20	Wlodarczyk 2005 (Wlodarczyk 2002)	NR	NR	NR	NR	NR	NR	NR
21	Vacher-Coponat 2012	NR	3/143 vs 5/146	NR	3/143 vs 6/146	NR	NR	NR
TAC + MMF vs CsA + MMF (4 studies)								
22	Zadrazil 2012	NR	NR	NR	NR	NR	NR	NR
23	Hernandez 2007	NR	NR	2/80 vs 2/80	NR	NR	NR	NR
24	Rowshani 2006	NR	NR	NR	NR	NR	NR	NR
25	Ulsh (1999) (Yang 1999)	NR	0/24 vs 1/21	NR	NR	NR	NR	NR
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)								

26	Weimer 2006 (Weimer 2005)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR + MMF (4 studies)								
27	Wlodarczyk 2009	NR	NR	NR	NR	NR	NR	NR
28	Kramer 2010 (NCT00189839)	NR	8/336 vs 6/331	NR	NR	NR	NR	NR
29	Tsuchiya 2013	NR	0/50 vs 1/50	NR	NR	NR	NR	NR
30	Oh 2014	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)								
31	Albano 2013: (NCT00717470) OSAKA Trial	1/309 vs 2/302 vs 3/304	NR	NR	NR	NR	NR	NR
MMF + TAC vs MPS + TAC (1 study)								
32	Ciancio 2008 / (Ciancio 2011 (3016), Ciancio 2006 (218) R01DK25243-25)	NR	0/61 vs 0/55	NR	NR	2/61 vs 1/55	NR	NR
MMF + CsA vs MPS + CsA (1 study)								
33	Salvadori 2004	NR	5/210 vs 5/213	NR	NR	NR	NR	NR
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)								
34	Vincenti 2005 (Vincenti 2010)	NR	0/71 vs 2/74 vs 2/73	NR	NR	NR	14/102 vs 3/26	NR
35	BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	NR	4/226 vs 5/219 vs 1/221	9/226 vs 18/219 vs 11/221	10/226 vs 18/219 vs 12/221	NR	10/165 vs 9/155 vs 12/136	NR
36	BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	NR	4/175 vs 4/184 vs 6/184	14/175 vs 17/184 vs 15/185	15/175 vs 16/184 vs 19/184	NR	8/113 vs 10/104 vs 9/87	NR
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)								
37	Ferguson 2011	NR	0/33 vs 1/26 vs 1/30	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)								
38	Lorber 2005	NR	NR	NR	9/193 vs 10/194 vs 12/196	NR	NR	NR
39	ATLAS Vitko 2005 (Vitko 2004 & 2005b)	NR	NR	NR	10/194 vs 9/198 vs 9/196	NR	NR	NR
40	Takahashi 2013	NR	2/61 vs 0/61	NR	NR	NR	NR	NR
EVL vs EVL +CsA vs CsA + MPS (1 study)								
42	Chadban 2013 (SOCRATES)	NR	2/49 vs 0/30 vs 1/47	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)								
43	Tedesco Silva 2010	NR	NR	NR	NR	NR	NR	NR
EVL + CsA vs MPS + CsA (1 study)								
44	Bertoni 2011	NR	0/56 vs 2/50	NR	NR	NR	NR	NR
EVL + MPS vs CsA + MPS (2 studies)								
45	Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	NR	NR	NR	5/155 vs 7/145	NR	NR	NR
46	Mjornstedt 2012 (NCT00634920)	NR	2/102 vs 2/100	NR	NR	NR	NR	NR
SRL + CsA vs MMF + CsA (2 studies)								
47	Barsoum 2007	NR	NR	4/76 vs 0/37	NR	NR	NR	NR
48	Stallone 2003	NR	NR	NR	NR	NR	NR	NR
SRL + TAC vs MMF + TAC (6 studies)								

49	Anil Kumar 2005	NR	NR	NR	NR	NR	NR	NR
50	Mendez 2005 / (Gonwa 2003)	0/185 vs 0/176	2/185 vs 1/176	NR	NR	NR	NR	NR
51	Sampaio 2008	NR	0/50 vs 0/50	NR	NR	NR	NR	NR
52	Gelens 2006	NR	NR	NR	NR	NR	NR	NR
53	Gallon 2006 (Chhabra 2012)	NR	NR	NR	NR	NR	NR	2/37 vs 0/45
54	Van Gurp 2010	2/318 vs 2/316	NR	NR	NR	NR	NR	NR
SRL + MMF vs CsA + MMF (10 studies)								
55	Flechner 2002 (Flechner 2004, 2007)	NR	NR	NR	NR	NR	3/31 vs 6/30	NR
56	Noris 2007/ (Ruggenenti 2007)	NR	NR	NR	NR	NR	NR	NR
57	Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	NR	2/96 vs 0/97	NR	NR	6/96 vs 9/97	NR	NR
58	Büchler 2007 (Lebranchu 2012, Joannides 2010)	NR	1/71 vs 3/74	NR	NR	NR	4/63 vs 9/68	NR
59	Soleimani 2013	NR	NR	NR	NR	NR	NR	NR
60	Durrbach 2008 : (0468E1 – 100969)	0/33 vs 4/36	NR	NR	NR	NR	NR	NR
61	Kreis (2000) - Identified from Campistol 2005	NR	0/40 vs 0/38	NR	NR	NR	NR	NR
62	Guba 2010	NR	0/69 vs 4/71	NR	NR	NR	NR	NR
63	Martinez-Mier 2006	NR	NR	NR	NR	NR	NR	NR
64	Nafar 2012 : (IRCT138804333049N7)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs SRL + MMF (4 studies)								
65	Larson 2006 (Stegall 2003)					Mean followup 33 months (17-47 months)		
66	Schaefer 2006	NR	NR	NR	NR	NR	NR	NR
67	Heilman 2011 (Heilman, 2012; NCT00170053)	NR	NR	NR	NR	NR	NR	NR
68	Welberry Smith 2008	NR	NR	NR	NR	NR	NR	NR
TAC + MPS vs SRL + MPS (1 study)								
69	Silva 2013 (NCT01802268)	NR	NR	2/142 vs 2/141	NR	NR	NR	NR
TAC + SRL vs MMF + SRL (1 study)								
70	Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	NR	NR	0/65 vs 0/65	NR	NR	0/65 vs 0/67	NR
SRL + AZA vs CsA + AZA (1 study)								
71	Charpentier 2003 (Groth 1999)	NR	0/41 vs 2/42	NR	NR	NR	NR	NR
TAC + SRL vs CsA + SRL (1 study)								
72	Chen 2008	NR	NR	NR	NR	NR	NR	NR
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)								
73	Vitko 2006	0/325 vs 2/325 vs 0/327	NR	NR	NR	NR	NR	NR
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)								
74	Flechner 2011 / (the ORION study, NCT00266123)	NR	NR	7/152 vs 5/152 vs 5/139	NR	NR	NR	NR
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)								
75	Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	NR	5/384 vs 4/408 vs 8/403 vs 9/380	NR	8/233 vs 7/248 vs 8/249 vs 7/228	NR	NR	NR
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)								

76	Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	NR	NR	NR	NR	NR	10/50 vs 2/50 vs 9/50 vs 2/50	NR

Key: NR, not reported

Infections

Maintenance therapy studies that reported infection rates gave frequencies of 9/237 (4%) to 85/85 (100%), (Table 134). Despite the relatively common occurrence of infections, only one study displayed a statistically significant difference between arms in favour of SRL low+TAC, as opposed to SRL high+TAC and MMF+TAC (Vitko et al. 2006).

Table 134. Infections; maintenance regimens

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
Tac + Aza vs CsA + Aza (13 studies)								
1	Schleibner 1995	NR	NR	NR	NR	NR	NR	NR
2	Laskow 1996	NR	NR (a)	NR	NR	NR	NR	NR
3	Mayer 1997 (Mayer 2002,1999)	NR	229/303 vs 109/145	NR	NR	NR	NR	NR
4	Radermacher 1998	NR	NR (a)	NR	NR	NR	NR	NR
5	Jarzembowski 2005	NR	NR	NR	NR	NR	NR	NR
6	Baboolal 2002	NR	NR	NR	NR	NR	NR	NR
7	Campos 2002	NR	85/85 vs 81/81	NR	NR	NR	NR	NR
8	Margreiter (2002) (Kramer 2005 and Kramer 2008)	NR	NR	9/237 vs 9/222 (b)	9/231 vs 10/217 (b)	NR	NR	NR
9	Van Duijnhoven 2002	NR	NR	NR	NR	NR	NR	NR
10	Waller 2002 (Murphy 2003)	NR	NR	NR	NR	NR	NR	NR
11	Charpentier 2003	126/186 vs 138/184	NR	NR	NR	NR	NR	NR
12	Toz 2004	NR	NR	NR	NR	NR	NR	NR
13	Hardinger 2005 (Brennan 2005)	NR	NR	NR	NR	NR	NR	NR
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)								
14	Sollinger 1995	74/165 vs 75/164 vs 78/166	NR	NR	NR	NR	NR	NR
15	Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	NR (a)	NR	NR	NR (a)	NR	NR	NR
CsA + MMF vs CsA + AZA (4 studies)								
16	Sadek 2002	NR	122/162 vs 103/157	NR	NR	NR	NR	NR
17	Tuncer 2002	NR	NR	NR	NR	NR	NR	NR
18	Merville 2004	NR	NR	NR	NR	NR	NR	NR
19	Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	NR	NR	NR	NR	NR	79/124 vs 89/124	NR
TAC + MMF vs CsA + AZA (2 studies)								
20	Wlodarczyk 2005 (Wlodarczyk 2002)	NR	NR	NR	NR	NR	NR	NR
21	Vacher-Coponat 2012	NR	NR (a)	NR	NR	NR	NR	NR
TAC + MMF vs CsA + MMF (4 studies)								
22	Zadrazil 2012	NR	NR	NR	NR	NR	NR	NR
23	Hernandez 2007	NR	NR	NR (a)	NR	NR	NR	NR

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
24	Rowshani 2006	NR	NR	NR	NR	NR	NR	NR
25	Ulsh 1999 (Yang 1999)	NR	11/30 vs 5/30	NR	NR	NR	NR	NR
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)								
26	Weimer 2006 (Weimer 2005)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR + MMF (4 studies)								
27	Wlodarczyk 2009	NR	NR	NR	NR	NR	NR	NR
28	Kramer 2010 (NCT00189839)	NR	NR (a)	NR	NR	NR	NR	NR
29	Tsuchiya 2013	NR	NR	NR	NR	NR	NR	NR
30	Oh 2014	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)								
31	Albano 2013: (NCT00717470) OSAKA Trial	79/311 vs 76/309 vs 72/307	NR	NR	NR	NR	NR	NR
MMF + TAC vs MPS + TAC (1 study)								
32	Ciancio 2008 / (Ciancio 2011 (3016), Ciancio 2006 (218) R01DK25243-25)	NR	10/75 vs 11/75	NR	NR	23/75 vs 29/75	NR	NR
MMF + CsA vs MPS + CsA (1 study)								
33	Salvadori 2004	NR	154/210 vs 148/213	NR	NR	NR	NR	NR
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)								
34	Vincenti 2005 (Vincenti 2010)	NR	52/71 vs 54/74 vs 55/73	NR	NR	NR	NR (a)	NR
35	BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	NR	158/226 vs 152/219 vs 157/221	181/226 vs 173/219 vs 175/221	185/226 vs 175/219 vs 176/221	NR	25/165 vs 26/155 vs 26/136 (month 36-60)	NR
36	BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	NR	NR	144/175 vs 147/184 vs 147/184	144/175 vs 145/184 vs 151/184	NR	NR (a)	NR
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)								
37	Ferguson 2011	NR	26/33 vs 20/26 vs 20/30	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)								
38	Lorber 2005	NR	NR	NR	NR (a)	NR	NR	NR
39	ATLAS Vitko 2005 (Vitko 2004 & 2005b)	NR	NR	NR	NR (a)	NR	NR	NR
40	Takahashi 2013	NR	50/61 vs 57/61	NR	NR	NR	NR	NR
EVL vs EVL +CsA vs CsA + MPS (1 study)								
42	Chadban 2013 (SOCRATES)	NR	33/49 vs 18/30 vs 34/47	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)								
43	Tedesco Silva 2010	NR	169/274 vs 178/278 vs185/273	NR	NR	NR	NR	NR
EVL + CsA vs MPS + CsA (1 study)								
44	Bertoni 2011	NR	NR	NR	NR	NR	NR	NR
EVL + MPS vs CsA + MPS (2 studies)								
45	Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	NR	96/155 vs 75/145	35/155 vs 30/145	31/155 vs 29/145	NR	NR	NR
46	Mjornstedt 2012 (NCT00634920)	NR	59/102 vs 52/100	NR	NR	NR	NR	NR

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
SRL + CsA vs MMF + CsA (2 studies)								
47	Barsoum 2007	NR	NR	NR	NR	NR	NR	NR
48	Stallone 2003	NR	NR	NR	NR	NR	NR	NR
SRL + TAC vs MMF + TAC (6 studies)								
49	Anil Kumar 2005	NR	NR	NR	NR	NR	NR	NR
50	Mendez 2005 / (Gonwa 2003)	NR	NR	NR	NR	NR	NR	NR
51	Sampaio 2008	NR	NR	NR	NR	NR	NR	NR
52	Gelens 2006	NR	NR	NR	NR	NR	NR	NR
53	Gallon 2006 (Chhabra 2012)	NR	NR	NR	NR	NR	NR	9/37 vs 11/45
54	Van Gurp 2010	149/318 vs 162/316	NR	NR	NR	NR	NR	NR
SRL + MMF vs CsA + MMF (10 studies)								
55	Flechner 2002 (Flechner 2004, 2007)	NR	NR	NR	NR	NR	14/31 vs 16/30	NR
56	Noris 2007/ (Ruggenenti 2007)	NR	NR	NR (a)	NR	NR	NR	NR
57	Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	NR	NR	NR	NR	4/96 vs 4/97	NR	NR
58	Büchler 2007 (Lebranchu 2012, Joannides 2010)	NR	NR	NR	NR	NR	NR	NR
59	Soleimani 2013	NR	NR	NR	NR	NR	NR	NR
60	Durrbach 2008 : (0468E1 – 100969)	NR	NR	NR	NR	NR	NR	NR
61	Kreis (2000) - Identified from Campistol 2005	NR	NR	NR	NR	NR	NR	NR
62	Guba 2010	NR	36/69 vs 43/71	NR	NR	NR	NR	NR
63	Martinez-Mier 2006	NR	NR (a)	NR	NR	NR	NR	NR
64	Nafar 2012 : (IRCT138804333049N7)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs SRL + MMF (4 studies)								
65	Larson 2006 (Stegall 2003)					Mean followup 33 months (17-47 months)		
66	Schaefer 2006	NR	NR	NR	NR	NR	NR	NR
67	Heilman 2011 (Heilman, 2012; NCT00170053)	NR	NR	NR	NR	NR	NR	NR
68	Welberry Smith 2008	NR	NR	NR	NR	NR	NR	NR
TAC + MPS vs SRL + MPS (1 study)								
69	Silva 2013 (NCT01802268)	NR	NR	NR	NR	NR	NR	NR
TAC + SRL vs MMF + SRL (1 study)								
70	Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	NR	NR (a)	NR	NR	NR	NR (a)	NR
SRL + AZA vs CsA + AZA (1 study)								
71	Charpentier 2003 (Groth 1999)	NR	NR (a)	NR	NR	NR	NR	NR
TAC + SRL vs CsA + SRL (1 study)								
72	Chen 2008	NR	4/21 vs 3/20	NR	NR	NR	NR	NR
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)								
73	Vitko 2006	124/325 vs 149/325 vs 160/327 *	NR	NR	NR	NR	NR	NR
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)								

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
74	Flechner 2011 / (the ORION study, NCT00266123)	NR	NR	93/152 vs 97/152 vs 93/139	NR	NR	NR	NR
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)								
75	Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	NR	Severe infection only: 58/384 vs 57/408 vs 60/403 vs 78/380	NR	184/233 vs 171/248 vs 177/249 vs 169/228	NR	NR	NR
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)								
76	Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	NR	NR	NR	NR	NR	NR	NR

Key: * p<0.05; a, different infections reported individually available; b, severe infections; NR, not reported

Cytomegalovirus

Studies that reported the frequencies of cytomegalovirus showed that this ranged from 0 to 7/27 (26%), Table 135.

The CSA+MMF arm of the following trials displayed a statistically significant difference, in terms of increased episodes of CMV; Sadek et al 2002, Vitko et al 2005, Takahashi et al. 2013, Buchler et al. 2007, Kreise et al. 2000, Tedesco Silva 2010 and Grinyo et al. 2009. Kramer et al. 2010 reported a statistically significant difference for TAC PR+MMF vs TAC+MMF and Van Gurp et al 2010 found increased events for TAC+MMF as opposed to SRL+TAC.

Table 135. Cytomegalovirus; maintenance regimens

N	Study	6 months	Year 1	Year 2	Year 3	Year 4	Year 5	Year 8.5
Tac + Aza vs CsA + Aza (13 studies)								
1	Schleibner 1995	NR	NR	NR	NR	NR	NR	NR
2	Laskow 1996	NR	NR	NR	NR	NR	NR	NR
3	Mayer 1997 (Mayer 2002,1999)	NR	41/303 vs 24/145	NR	NR	NR	NR	NR
4	Radermacher 1998	NR	NR	NR	NR	NR	NR	NR
5	Jarzembowski 2005	NR	0/14 vs 0/21	NR	NR	NR	NR	NR
6	Baboolal 2002	NR	7/27 vs 7/24	NR	NR	NR	NR	NR
7	Campos 2002	NR	NR	NR	NR	NR	NR	NR
8	Margreiter (2002) (Kramer 2005 and Kramer 2008)	NR	NR	NR	NR	NR	NR	NR
9	Van Duijnhoven 2002	NR	NR	NR	NR	NR	NR	NR
10	Waller 2002 (Murphy 2003)	NR	NR	NR	NR	NR	NR	NR
11	Charpentier 2003	45/186 vs 52/184	NR	NR	NR	NR	NR	NR
12	Toz 2004	NR	NR	NR	NR	NR	NR	NR
13	Hardinger 2005 (Brennan 2005)	NR	5/134 vs 4/66	NR	NR	NR	NR	NR
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)								
14	Sollinger 1995	15/165 vs 10/164 vs 18/166 (a)	NR	NR	NR	NR	NR	NR
15	Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	NR	12/171 vs 18/164 vs 10/162 (a)	NR	12/171 vs 11/164 vs 18/162 (a)	NR	NR	NR
CsA + MMF vs CsA + AZA (4 studies)								
16	Sadek 2002	NR	32/162 vs 17/157*	NR	NR	NR	NR	NR
17	Tuncer 2002	NR	NR	NR	NR	NR	NR	NR
18	Merville 2004	NR	11/37 vs 17/34	NR	NR	NR	NR	NR
19	Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	43/168 vs 42/168	NR	NR	NR	NR	39/124 vs 45/124	NR
TAC + MMF vs CsA + AZA (2 studies)								
20	Wlodarczyk 2005 (Wlodarczyk 2002)	12/243 vs 14/246	NR	NR	NR	NR	NR	NR
21	Vacher-Coponat 2012	NR	25/143 vs 28/146	NR	NR	NR	NR	NR

TAC + MMF vs CsA + MMF (4 studies)								
22	Zadrazil 2012	NR	NR	NR	NR	NR	NR	NR
23	Hernandez 2007	NR	NR	20/80 vs 16/80	NR	NR	NR	NR
24	Rowshani 2006	NR	NR	NR	NR	NR	NR	NR
25	Ulsh (1999) Yang 1999	NR	3/30 vs 0/30	NR	NR	NR	NR	NR
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)								
26	Weimer 2006 (Weimer 2005)	NR	7/28 vs 11/25 vs 13/31	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR + MMF (4 studies)								
27	Wlodarczyk 2009	NR	NR	NR	NR	NR	NR	NR
28	Kramer 2010 (NCT00189839)	NR	19/336 vs 33/331*	NR	NR	NR	NR	NR
29	Tsuchiya 2013	NR	7/52 vs 4/50	NR	NR	NR	NR	NR
30	Oh 2014	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)								
31	Albano 2013: (NCT00717470) OSAKA Trial	21/311 vs 12/309 vs 17/307	NR	NR	NR	NR	NR	NR
MMF + TAC vs MPS + TAC (1 study)								
32	Ciancio 2008 / (Ciancio 2011 (3016), Ciancio 2006 (218) R01DK25243-25)	NR	1/75 vs 0/75	NR	NR	0/75 vs 1/75	NR	NR
MMF + CsA vs MPS + CsA (1 study)								
33	Salvadori 2004	NR	43/210 vs 46/213	NR	NR	NR	NR	NR
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)								
34	Vincenti 2005 (Vincenti 2010)	NR	11/71 vs 10/74 vs 13/73	NR	NR	NR	1/102 vs 1/26	NR
35	BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	NR	10/226 vs 9/219 vs 6/221	12/226 vs 12/219 vs 7/221	26/226 vs 22/219 vs 25/221	NR	NR	NR
36	BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	NR	24/175 vs 21/184 vs 24/184	16/175 vs 17/184 vs 12/184	27/175 vs 32/184 vs 31/184	NR	4/113 vs 4/104 vs 3/87	NR
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)								
37	Ferguson 2011	NR	1/33 vs 1/26 vs 2/30	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)								
38	Lorber 2005	NR	NR	NR	10/196 vs 8/194 vs 12/196	NR	NR	NR
39	ATLAS Vitko 2005 (Vitko 2004 & 2005b)	NR	10/194 vs 15/198 vs 38/196*	NR	11/194 vs 16/198 vs 40/196*	NR	NR	NR
40	Takahashi 2013	NR	3/61 vs 21/61*	NR	NR	NR	NR	NR
EVL vs EVL +CsA vs CsA + MPS (1 study)								
42	Chadban 2013 (SOCRATES)	NR	2/49 vs 2/30 vs 4/47	NR	NR	NR	NR	NR
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)								
43	Tedesco Silva 2010	NR	2/274 vs 4/278 vs 16/273*	NR	NR	NR	NR	NR
EVL + CsA vs MPS + CsA (1 study)								
44	Bertoni 2011	NR	NR	NR	NR	NR	NR	NR
EVL + MPS vs CsA + MPS (2 studies)								
45	Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	NR	10/155 vs 14/145	NR	NR	NR	NR	NR
46	Mjornstedt 2012 (NCT00634920)	NR	9/102 vs 13/100	NR	NR	NR	NR	NR
SRL + CsA vs MMF + CsA (2 studies)								

47	Barsoum 2007	NR	NR	NR	NR	NR	NR	NR
48	Stallone 2003	NR	NR	NR	NR	NR	NR	NR
SRL + TAC vs MMF + TAC (6 studies)								
49	Anil Kumar 2005	NR	NR	NR	NR	NR	NR	NR
50	Mendez 2005 / (Gonwa 2003)	NR	NR	NR	NR	NR	NR	NR
51	Sampaio 2008	NR	6/50 vs 6/50	NR	NR	NR	NR	NR
52	Gelens 2006	NR	NR	NR	NR	NR	NR	NR
53	Gallon 2006 (Chhabra 2012)	NR	NR	NR	1/37 vs 1/45	NR	NR	NR
54	Van Gurp 2010	9/318 vs 38/316*	NR	NR	NR	NR	NR	NR
SRL + MMF vs CsA + MMF (10 studies)								
55	Flechner 2002 (Flechner 2004, 2007)	NR	3/31 vs 2/30	NR	NR	NR	2/31 vs 3/30	NR
56	Noris 2007/ (Ruggenenti 2007)	NR	NR	0/11 vs 4/10	NR	NR	NR	NR
57	Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	NR	4/96 vs 6/97	NR	NR	NR	NR	NR
58	Büchler 2007 (Lebranchu 2012, Joannides 2010)	NR	4/71 vs 17/74*	NR	NR	NR	NR	NR
59	Soleimani 2013	NR	NR	NR	NR	NR	14/29 vs 16/59	NR
60	Durrbach 2008 : (0468E1 – 100969)	1/33 vs 1/36	NR	NR	NR	NR	NR	NR
61	Kreis (2000) - Identified from Campistol 2005	NR	2/40 vs 8/38*	NR	NR	NR	NR	NR
62	Guba 2010	NR	5/69 vs 20/71	NR	NR	NR	NR	NR
63	Martinez-Mier 2006	NR	1/20 vs 0/21	NR	NR	NR	NR	NR
64	Nafar 2012 : (IRCT138804333049N7)	NR	NR	NR	NR	NR	NR	NR
TAC + MMF vs SRL + MMF (4 studies)								
65	Larson 2006 (Stegall 2003)				Mean followup 33 months (17-47 months)			
66	Schaefer 2006	NR	NR	NR	NR	NR	NR	NR
67	Heilman 2011 (Heilman, 2012; NCT00170053)	NR	8/62 vs 8/60	NR	NR	NR	NR	NR
68	Welberry Smith 2008	NR	NR	NR	NR	NR	NR	NR
TAC + MPS vs SRL + MPS (1 study)								
69	Silva 2013 (NCT01802268)	NR	NR	4/107 vs 5/97	NR	NR	NR	NR
TAC + SRL vs MMF + SRL (1 study)								
70	Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	NR	NR	NR	NR	NR	NR	NR
SRL + AZA vs CsA + AZA (1 study)								
71	Charpentier 2003 (Groth 1999)	NR	6/41 vs 5/42	NR	NR	NR	NR	NR
TAC + SRL vs CsA + SRL (1 study)								
72	Chen 2008	NR	NR	NR	NR	NR	NR	NR
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)								
73	Vitko 2006	16/325 vs 13/325 vs 26/327	NR	NR	NR	NR	NR	NR
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)								
74	Flechner 2011 / (the ORION study, NCT00266123)	NR	NR	NR	NR	NR	NR	NR
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)								
75	Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	NR	55/384 vs 45/408 vs 39/403 vs 23/380*	NR	Yes	NR	NR	NR
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)								

76	Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	NR	NR	NR	NR	NR	1/50 vs 0/50 vs 1/50 vs 0/50	NR

Key:* p<0.05; a, tissue invasive CMV; NR, not reported

4.3.5. Current assessment (TA85)

Relevant to this review, the current assessment (TA85) found that basiliximab, tacrolimus and MMF consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy. The independent use of basiliximab, tacrolimus and MMF was associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%).

The trials did not assess how the improvement in trials, the impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain.

The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical effectiveness challenging.

4.3.6. Ongoing studies

Searches of ClinicalTrials.gov and Controlled Trials were conducted (see Appendix 1 for the search strategy used). All searches were carried out in January 2015. Two hundred and fifty six trials were considered as relevant to this review and were investigated further. Sixty nine studies were identified as ongoing (active not recruiting, n=16 and not yet recruiting n=7) or recruiting (n=46). In 26 trials the current status was recorded as 'unknown'. Twenty three trials had terminated, two had been suspended and three withdrawn; of these, five had results available. Finally, 133 studies were completed. Summary of the trials is provided in Table 136. The search of ongoing studies did not identify any additional randomised control trials (RCT's) for inclusion in PenTAG systematic review; eighteen studies were already considered in PenTAG review. An overview of these trials is provided in Appendix 8.

Table 136. Summary of studies

Trial Status (N)	N; included in PenTAG	N; excluded (reason)
Active, not recruiting (16)	3	13 (7 – no publication, 1 – no data, 1 – mixed transplants, 4 – not relevant)

Not yet recruiting (7)	0	7 (no data)
Recruiting (46)	0	46 (no data)
Unknown (26)	2	24 (12 – no publication, 2 – mixed population, 2 – no data, 1 – dosing studies, 7 – not relevant)
Suspended (2)	0	2 (2 – no publication)
Withdrawn (3)	0	3 (1 – no publication, 2 – not relevant)
Terminated (23)	0	23 (2 – no publication, 1 – mixed population, 6 – treatment (dosing or conversion), 14– not relevant)
Completed (133)	13	120 (60 – no publication, 6 – mixed population, 6 – no data, 15 – treatment (dosing or conversion), 33– not relevant)

Key: N, number of studies; PenTAG, PenTAG systematic review.

4.4. Summary of clinical effectiveness

4.4.1. Summary of systematic review results

4.4.1.1. Induction

- We found no evidence to suggest BAS or rATG are more effective than placebo, no induction or each other in reducing the odds of mortality. Similarly, for graft loss, we found no evidence of a statistically significant difference for BAS or rATG vs placebo, no induction or each other.

- For the head-to-head comparisons, we found evidence to suggest that rATG and BAS are more effective than placebo or no induction at reducing BPAR (rATG at 1 yr, OR 0.34, 95%CI 0.22 to 0.52, I^2 8.9%; BAS at 1 yr, OR 0.53, 95% CI 0.40 to 0.70, I^2 0.0%). However, there is no statistically significant difference between BAS and rATG.

- Time to BPAR is only reported for rATG vs no induction and BAS vs rATG. Only one study of three for rATG vs no induction found a statistically significant difference in favour of rATG, where first mean time to BPAR was 20.78 days (sd 14.78) for rATG and 9.21 days (sd 3.91) for no induction ($p<0.0001$).

- A statistically significant difference was found for the severity of BPAR, comparing BAS vs rATG, where BAS was associated with lower odds of Banff 3 (1 year, OR 0.04, 95%CI 0.00 to 0.65)

4.4.1.2. Maintenance

- We found no evidence that any maintenance therapies were preferable to others in terms of mortality.

- For graft loss outcomes reported by maintenance studies, we found evidence that at five years that BEL+MMF may be superior to CSA+MMF (OR 0.40, 95%CI 0.19 to 0.87, I^2 0.0%). At 0.5 years, there are greater odds of reduced graft loss for CSA+MMF as compared to CSA+AZA (OR 0.58, 95%CI 0.04 to 0.59, I^2 72.2%).

- Several treatments showed a beneficial effect with regard to reducing BPAR, although this varied across time points. For all the following combinations, the arm containing TAC displayed lower odds associated with BPAR - TAC+AZA vs CSA+AZA (0.5 years OR 0.50 95%CI 0.32 to 0.79, I2 50.1%; 1 year OR 0.50, 95%CI 0.39 to 0.64, I2 8.1%; 4 years OR 0.38, 95%CI 0.25 to 0.57); TAC+MMF vs CSA+AZA (0.5 year OR 0.64, 95%CI 0.41 to 0.98; 1 year OR 0.35, 95% CI 0.15 to 0.82); TAC+MMF vs CSA+MMF (1 year OR 0.59, 95%CI 0.37 to 0.94, I^2 19.3%); TAC+MMF vs SRL+MMF (1 year OR 0.32, 95%CI 0.12 to 0.87, I^2 0.0%); TAC+SRL vs TAC+MMF (0.5 years OR 0.65 95%CI 0.44 to 0.96).

- For CSA+MMF vs CSA+AZA, at 0.5 years and one year, there is statistically significant evidence to suggest MMF is more effective (0.5 years OR 0.50, 95%CI 0.35 to 0.72, I^2 35.1%).

- TAC is also associated with lower odds of reduced graft function for TAC+MMF vs CSA+MMF (3 years, WMD 4.60 ml/min, 95%CI 1.35 to 7.85); TAC+MMF vs TAC PR+MMF (0.5 years, WMD 1.90 ml/min, 95%CI 1.70 to 2.10); TAC+SRL vs CSA+SRL (0.5 years, MD 6.35 ml/min, p<0.0001; 1 year MD 5.25, p=0.0004). For MMF+TAC vs MPS+TAC, MPS at 1 year and 3 years is more effective (1 year, MD 1.9 ml/min, p<0.0001; 3 years MD 0.5 ml/min, p=0.0016). BEL appears more effective at one year and three years for BEL+MMF vs CSA+MMF (1 year, WMD 7.83 ml/min, 95%CI 1.57 to 4.10, I^2 73.6%; 3 years WMD 16.08 ml/min, 95%CI 5.59 to 26.56, I^2 89.5%) however, heterogeneity across studies is substantial. Where there are two comparisons involving SRL and CSA, the regimen including MMF suggests CSA to

be more beneficial up to five years (5 years, WMD 9.10 ml/min, 95%CI 1.68 to 16.52), yet in contrast, the regimen including AZA suggests SRL to be more effective (1 year, MD 10.8 ml/min, p<0.0001).

- Time to BPAR is generally poorly reported and therefore challenging to form a conclusion. Again, TAC+AZA vs CSA+AZA shows conflicting results for two studies, however, the statistically significant result suggests that BPAR is achieved more quickly for participants receiving TAC rather than CSA (MD 24 days, p=0.0033). This is also true for TAC+MMF vs CSA+MMF (MD 46.7 days, p<0.0001). Where SRL+TAC and MMF+TAC are compared, a reduced time to BPAR is seen for MMF (MD 48.6 days, p=0.0017). For SRL+MMF vs CSA+MMF, one of three studies demonstrates a statistically significant difference in favour of CSA (MD 38 days, p=0.0035), however, the other two studies show no difference.

- For TAC+AZA vs CSA+AZA, there are lower odds of the more severe BPAR for the arm containing TAC, although there is substantial heterogeneity across studies (Banff 3 OR 0.28, 95%CI 0.12 to 0.66). Similarly, for TAC+MMF vs TAC PR+MMF, TAC has a lower proportion of people experiencing the more severe BPAR of Banff 3 (OR 0.11, 95%CI 0.01 to 0.87, I^2 0.0%).

4.4.2. Summary for network meta-analysis

4.4.2.1. Induction therapy

- There is no evidence to suggest BAS or ATG are more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality

- ATG and BAS are both estimated to be more effective than placebo/no induction, with ATG being more effective than BAS at reducing BPAR

- Evidence suggests that while no treatment effect is seen for ATG, BAS is estimated to be more effective than placebo/no induction for increasing CRC-GFR

4.4.2.2. Maintenance therapy

- For all network meta-analyses for maintenance therapy there is a great deal of heterogeneity

- There is no evidence to suggest that one treatment is any more effective at reducing the odds of graft loss than any other treatment

- There is evidence to suggest that BEL+MMF is more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF, but no other treatments are estimated to be any more effective at reducing mortality than any other treatment

- A number of treatments are estimated to be more effective than CSA+AZA and EVL+MPS at reducing the odds of BPAR, and CSA+AZA and SRL+TAC at increasing GFR, but no other treatments are estimated to be any more effective at reducing the odds of BPAR or increasing GFR than any other treatment

4.5. Critique of company submission's search strategies

Four company submissions were presented summarising evidence on the effectiveness of immunosuppressive therapies in renal transplantation; Sandoz, Astellas, Bristol Myers Squibb and Novartis.

4.5.1. Sandoz

The company's literature searching is primarily focused on finding studies which report on Adoport, Sandoz's licensed version of tacrolimus. The searches presented by Sandoz are transparent, replicable and consistent with the aims of the company's submission, which is a systematic review of Adoport with no economic model.

Their literature searches have been conducted in a range of bibliographic databases, including: MEDLINE, EMBASE, Cochrane CENTRAL and NHS EEDS. These searches have been supplemented with an unreported search of Sandoz's internal databases.

We believe these searches to be adequate but are unable to exclude the possibility of reporting bias. The search strategies are geared to locate studies which include the brand name (Adoport) or Drug Name (tacrolimus) AND Company Name (Sandoz). It is feasible that a title/abstract might merely mention the drug name without a brand or company stated and, if such a study existed, this would be missed by the company's literature searches. The nature of RCT reporting makes this unlikely for trial data but, for adverse event or economic literature, it is a possibility. However, as the manufacturer made an unreported search of their own databases it is unlikely they would have missed one of their own trials.

Sandoz submission summarised the evidence on Adoport and compared Adoport, Sandoz's licensed version of tacrolimus with Prograft, Astellas licensed version of tacrolimus. They identified 26 papers; one randomised control trial (reported in two papers; RCT) and 24 non-randomised studies (non-RCT). The RCT was a pharmacokinetics study and had no clinical effectiveness data. None of the included studies are considered in PenTAG systematic review (Table 137).

In summary, the results of Sandoz submission are not comparable with the results of the current HTA review.

Table 137. Sandoz submission; included studies

First author and year	Included in PenTAG review	Reason for exclusion
Alloway et al. 2012a[211]		Study design
Bloom et al. 2013[212]		Study design
Connor et al. 2012[213]		Study design
Connor et al. 2013[214]		Study design
Heavner et al. 2013[215]		Study design
Marfo et al. 2013[216]		Study design
McDevitt-Potter et al. 2011[217]		Study design
Richards et al. 2014[218]		Study design
Rosenborg et al. 2014[219]		Study design
Spence et al. 2012[220]		Study design
Babu et al. 2013[221]		Abstract
Betmouni et al. 2012b[222]		Abstract
Chiu et al. 2012[223]		Abstract
Crowther et al. 2012[224]		Abstract
Dick et al. 2011[225]		Abstract
Heldenbrand et al. 2012[226]		Abstract
Jogia et al. 2013[227]		Abstract
Kendrew et al. 2013[228]		Abstract
Qazi et al. 2012[229]		Abstract
Sharma et al. 2013[230]		Abstract
Shiu et al. 2013[231]		Abstract
Siddiqi et al. 2011[232]		Abstract
Storey et al. 2013[233]		Abstract
Venkataraman et al. 2012[234]		Abstract
Wilcock et al. 2013[235]		Abstract
Marsen et al. 2012[236]		Study design

4.5.2. Astellas

The literature searches have been conducted in the key bibliographic databases, MEDLINE, EMBASE, the Cochrane Library and Cochrane NHS EEDS.

The literature searches used minimal free-text search terms without the use of truncation or controlled indexing, and selective synonyms were used for the interventions/comparators. This reflects poor sensitivity and, combined with the fact that searching has been conducted on only the abstracts of potentially includable studies; it is possible that some studies may have been missed.

The submission set out to compare efficacy and safety of Tacrolimus (Prograf) therapy, with current alternative treatments (PR tacrolimus [Advagraf], ciclosporin, sirolimus and belatacept) in addition to everolimus, as primary immunosuppressive therapies in people undergoing renal transplantation.

Thirty eight RCT's were identified; 19 studies comparing TAC and CSA regimens, ten studies comparing sirolimus and TAC regimens: CNI avoidance (6 studies), CNI avoidance and steroids withdrawal (1 study), CNI minimisation (3 studies), three trials comparing TAC-PR and TAC regimens, two studies reporting on belatacept and six studies reporting on everolimus. Two studies included information for two comparisons: Silva et al. 2007[237] and Ekberg et al. 2007. [238] No head-to-head studies comparing tacrolimus with belatacept, and tacrolimus with everolimus were identified (Table 138). Two separate NMA were performed; NMA comparing TAC with EVL, and NMA comparing TAC with BEL.

In summary, Astellas results suggest no significant differences between TAC and EVL regimens, and less BPAR in BEL compared with TAC. In the head-to-head comparisons, no differences between TAC and TAC-PR were identified. In addition, more AR episodes were identified in CSA compared with TAC and in SRL compared with TAC.

In comparision, the PenTAG NMA found evidence to suggest that BEL+MMF is more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF, but no other treatments were estimated to be any more effective at reducing mortality than any other treatment. In addition, BEL+MMF are estimated to be more effective than CSA+AZA and MMF+CSA at increasing graft function. The head to head comparisons suggested that the clinical effectiveness of TAC-PR and TAC are similar with TAC having a lower proportion of people experiencing the more severe BPAR of Banff 3 (OR 0.11, 95%CI 0.01 to 0.87, I^2 0.0%). We also found some benefits to using TAC regimes compared with CSA regimens, for full summary of head-to-head comparisions refer to section 4.4.1.

Table 138. Astellas submission; included studies

First author and year	Included in PenTAG review	Reason for exclusion
Ekberg, et al. 2007[238]	✓	
Abou-Jaoude, et al. 2003[239]		Study design
Abou-Jaoude et al. 2005[240]		Study design
Busque et al. 2001[241]		Study design
Campos 2002[102]	✓	
Hardinger et al. 2005[108]	✓	
Johnson et al. 2000[242]		Population
Margreiter R. 2002[103]	✓	
Martin Garcia et al. 2003[243]		Study design
Morris-Stiff et al. 1998[244]		Population
Murphy et al 2003[106]	✓	
Raofi et al. 1999[245]	✓	
Silva et al. 2007[237]		Population
Toz et al. 2004[107]	✓	
Vincenti et al. 2007[246]		Study design
Wang et al. 2000[247]		Abstract
White et al. 2000[248]		Abstract
Williams et al. 1999[249]		Abstract
Yang et al. 1999[123]	✓	
Flechner et al. 2011[187]	✓	
Glotz et al. 2010[250]		Study design
Larson et al. 2006[209]	✓	
Chhabra et al. 2013[251]		Study design
Lo et al. 2004[252]		Study design
Hamdy et al. 2005[181]	✓	
Ciancio et al. 2004; 2004[253 254]		Population
Gonwa et al. 2003[155]	✓	
Mendez et al. 2005[154]	✓	
Vincenti et al. 2010[54]	✓	
Durrbach et al. 2010[135]	✓	
Bertoni 2011[146]	✓	
Tedesco Silva, et al. 2010[145]	✓	
Albano et al. 2013[87]	✓	
Kramer et al. 2010[72]	✓	

Langer et al. 2012[255]	**Study design**
Chan et al. 2008[256]	**Study design**
Favi et al. 2012[257]	**Abstract**
Ruiz et al. 2011[258]	**Abstract**

4.5.3. Bristol Myers Squibb

The literature searching used for this submission is not sufficient to provide a systematic and transparent review of belatacept. The literature searching takes the following structure: (terms for tacrolimus) AND (a methodological search filter to limit to RCTs). The literature search does not include any search terms for belatacept, the intervention under submission by the company, or ciclosporine.

In practice, this means that the searches will only pick up studies of belatacept, if belatacept is in comparison with tacrolimus. The company state (p52) that belatacept has not been compared with Tacrolimus in head-to-head RCTs, noting that, in the case of BENEFIT and BENEFIT-EXT, ciclosporine was main licensed treatment used in clinical practice. This statement further confuses the rationale for using tacrolimous as the named intervention in the literature searching for this submission. It is therefore likely that includable trials have been missed (Table 139).

In summary, because of the issues with the literature searches in Bristol Myers Squibb submission, Bristol Myers Squibb conclusions are not comparable with the results of the current HTA review. (Table 139).

Table 139. Bristol Myers Squibb submission; included studies (RCTs)

First author and year	Included in PenTAG review	Reason for exclusion
Abou-Jaoude et al. 2005[259]		Study design
Busque et al. 2001[241]		Study design
Campos et al. 2002[102]	✓	
Charpentier et al. 2003[88]	✓	
Chen et al. 2008[186]	✓	
Cheung et al. 2006[260]		Study design
Egfjord et al. 2002[261]		Abstract
Ekberg et al. 2007[238]	✓	
El Haggan et al. 2002[262]		Abstract
Hardinger et al. 2005[108]	✓	
Hernandez et al. 2007[121]	✓	
Liu et al. 2003[263]		Population
Margreiter et al. 2002[103]	✓	
Mayer et al. 1997[96]	✓	
Murphy et al. 2003[106]	✓	
Radermacher et al. 1998[99]	✓	
Rowshani et al. 2006[122]	✓	
Toz et al. 2004[107]	✓	
Tsinalis et al. 2000[264]		Abstract
Van Duijnhoven et al. 2002[73]	✓	
Vincenti et al. 1996[95]	✓	
Vincenti et al. 2007[246]		Study design
Wang et al. 2000[247]		Abstract
Yang et al. 1999[123]	✓	Included
Yu et al. 2000[265]		Abstract
Nichelle et al. 2002[266]		Study design
Heering et al. 1998[267]		Data
Ichimaru et al. 2001[268]		Study design
Anil Kumar et al. 2008[194]	✓	
BENEFIT[54]	✓	
BENEFIT EX[135]	✓	
Vincenti et al. 2005[71]	✓	

4.5.4. Novartis

The company's literature searching for this submission is systematic, robust and transparent. The company has searched all of the required databases and made an exhaustive attempt to locate published and unpublished studies. The submission compared the efficacy and safety of MPS and everolimus, as primary immunosuppressive therapies in people undergoing renal transplantation. A total of seven RCTs, three open-label extension studies of RCTs, as well as three non-RCTs with MPS regimen were identified in the systematic review. A total of 14 studies (25 publications and two unpublished clinical study reports) with everolimus regimen were identified in the systematic review; eight RCT's, five prospective studies, and one observational study (Table 140).

In summary, Novartis results suggest that MMF and MPS are comparable. Similar conclusions were made in the current HTA review in head to head studies. In addition, the submission suggested the use of EVL in early CNI minimization. The NMA results of the current HTA review did not suggest that EVL regimens were better in reducing mortality, graft loss, and improving graft function, when compared to all other treatments. However, EVL+MPS regimen was estimated to be less effective than MMF+CSA regimen at reducing the odds of BPAR. In addition, EVL+CSA regimen was estimated to be more effective than and CSA+AZA at reducing the odds of BPAR. However, apart from CSA+AZA and EVL+MPS performing poorly in some comparisons, it is difficult to say that any one treatment is more effective than another as the 95% CIs are very wide.

Table 140. Novartis submission; included studies

First author and year	Included in PenTAG review	Reason for exclusion
Salvadori et al. 2001[269]; Salvadori et al. 2004[132]; Salvadori et al. 2006[270]	✓	
Budde et al. 2004[271]; Budde et al. 2005[272]; Budde et al. 2006[273]		Intervention
Shehata et al. 2009[274]		Study design
Ortega et al. 2011[275]		Study design
Langone et al. 2013[276]; Chan et al. 2013[277]		Study design
Shah et al. 2013[278]		Study design
Ciancio et al. 2008[130]; Ciancio et al. 2011[131]	✓	
Langone et al. 2011[279]		Study design
Chan et al. 2006[280]		Study design
Hwang et al. 2010[281]		Study design
Novartis CSR, Tedesco Silva et al. 2010[282]; Cibrik et al. 2013[283]	✓	
Takahashi et al. 2013[143]; Takahara et al. 2012[284]; Saito et al. 2013[285]	✓	
Paoletti et al. 2012a[286]; Paoletti et al. 2012b[287]		Study design
Favi et al. 2009a[288]; Favi et al. 2009b[289]; Favi et al. 2010[290]; Favi et al. 2013a[291]		Study design
Gonzalez et al. 2010[292]		Study design
Miserlis et al. 2008[293]		Study design
Watarai et al. 2013[294]		Study design
Loriga et al. 2010[295]		Study design
Vitko et al 2004[141]; Dantal et al 2002[296]; Vitko et al 2005[142]; Oppenheimer et al 2003[297]	✓	
Lorber et al. 2005[139]	✓	
Novartis CSR (NCT01025817; CRAD001AUS92)[298]		Data

Tedesco et al. 2012[299] ; Tedesco-Silva et al. 2013[300]	Abstract
Favi et al. 2012[257]; Favi et al. 2013b[301]	Abstract
Kamar et al. 2005[302]; Rostaing et al. 2001[303]	Design

5. Assessment of Cost-Effectiveness

5.1. Review of 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 TA85]), in renal transplantation in adults.

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 November 18th 2014. 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). 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).[304] Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips et al. (2004; 2006).[305 306]

5.1.1.4. Synthesis

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

5.1.2. Results

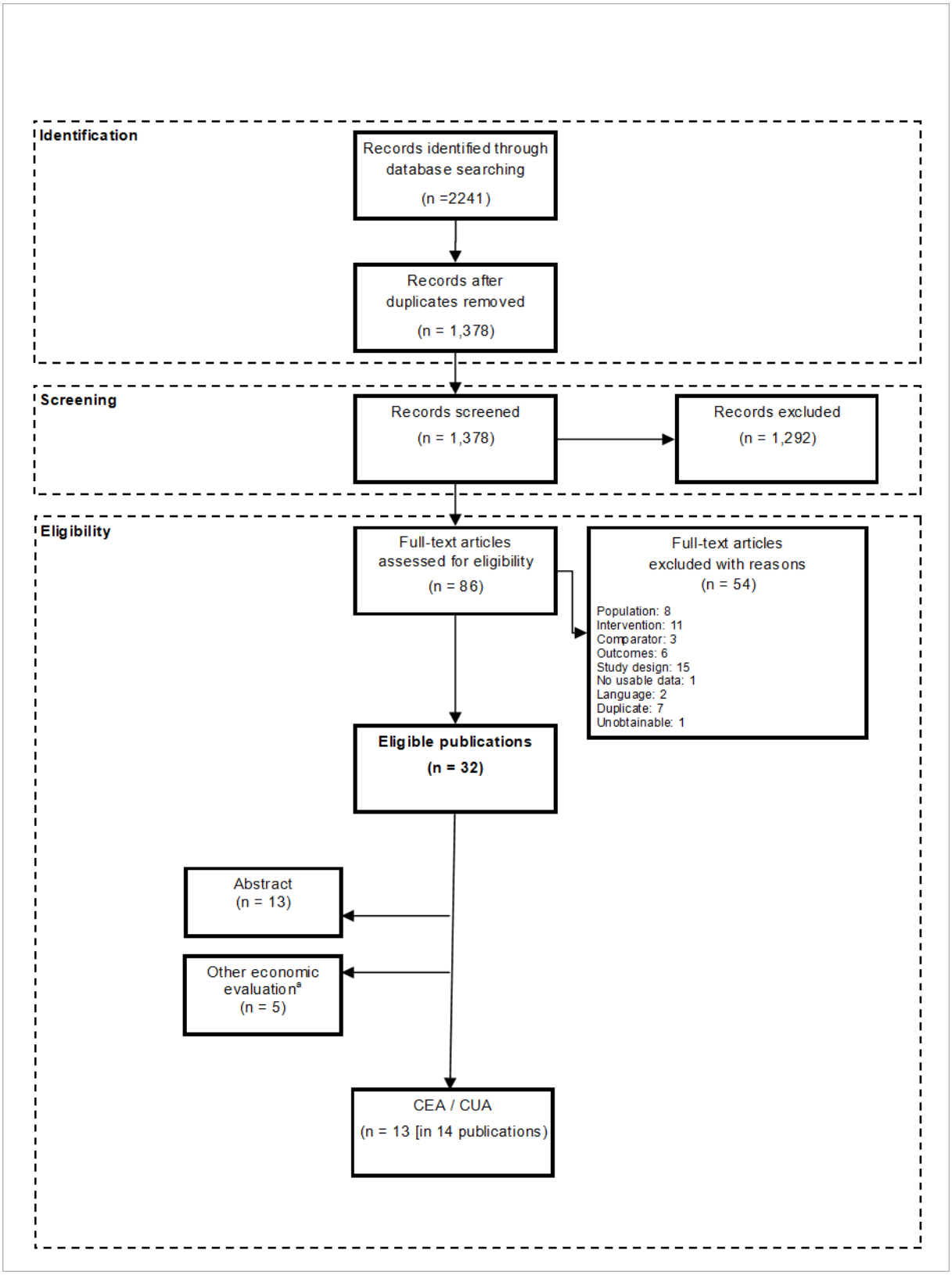
5.1.2.1. Identified studies

The electronic database search for cost-effectiveness evidence identified 2241 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. Nineteen full texts were deemed to meet the eligibility criteria for the review. The study selection process is detailed in Figure 82.

Twelve economic evaluations were included in the review (published in 14 publications) (Chilcott et al., 2002; Craig et al., 2002; Lazzaro et al., 2002; Crompton et al., 2003; Emparan et al., 2003; Orme et al., 2003; Walters et al., 2003; McEwan et al., 2005; Woodroffe et al., 2005; Emparan et al., 2006; McEwan et al., 2006; Abecassis et al., 2008; Earnshaw et al., 2008; Juergensen et al., 2010.[60 307-319] Update searches, conducted on 18 November 2014, yielded an additional six reports on economic evaluations eligible for inclusion in the review (Chamberlain et al., 2014; Jurgensen et al., 2014; Muduma et al., 2014a; Muduma et al., 2014b; Muduma et al., 2014c; Popat et al., 2014).[41 320-323]. Of these, one report was an update on a study identified by the original search (Jurgensen et al. 2014), and another three constituted multiple reports on a newly identified study (Muduma et al., 2014a; Muduma et al., 2014b; Muduma et al., 2014c).

Fifteen studies were included in this review. Five were studies of induction regimens, three of which were studies of UK adults, and 10 were studies of initial and maintenance immunosuppression, five of which were of UK adults. In what follows, studies of induction regimens are reviewed before reviewing studies of initial and maintenance immunosuppressive regimens, by country setting (UK vs other). Table 141 describes the characteristics of included studies of induction regimens. Table 142 describes the characteristics of included studies of initial and maintenance regimens. All but one study were sponsored by the industry or co-authored by an individual person affiliated with a company manufacturing or commercialising one of the evaluated treatments.

Figure 82. PRISMA Flow Chart



Key: CEA = cost-effectiveness analyses; CUA = cost utility analyses
Notes: a Includes studies reporting UK costs and effects without economic evaluation, and standalone cost analyses based in the UK NHS

Table 141. Characteristics of included studies of induction regimens

Author	Country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Chilcott et al (Chilcott et al. 2002)	Seven countries (EU); including UK and presents results by country	BAS+CsA+ST vs PBO+CsA+ST	Adult renal transplant recipients (mean 47.4 and 47.0years)	Cost (along-side trial) analysis	Hospital	Aggregate mean total cost of resources per patient Cost per suspected rejection episode	1 year	No	Funded by Novartis
Crompton et al (Crompton et al. 2003)	USA	BAS vs no BAS (given with CsA+AZA+ST)	Adult renal transplant recipients	CEA	Not stated	acute rejection; graft and patient survival; graft function; incidence of infection, malignancy	1 year	No	Not reported
Emparan et al. (Emparan et al. 2003, Emparan et al. 2005)	Spain	Bas+CsA Bas+CsA+MMF TAC + MMF (ST tapering for all)	Old to old renal transplant recipients (mean 69.3 years and 68.2 years)	CEA	Not stated	Graft function; rejection at 1 year; survival at 1 year; dialysis required; creatinine clearance; cost difference	1 year	unclear	Not reported
Popat et al. (Popat et al. 2014)	UK	IL2Mab (basiliximab or daclizumab) vs. ATG (given with CsA+MMF+ST; a minority given	Adult renal transplant recipients from donors after cardiac death (mean 48 and 54	CEA	Hospital	Patient survival Death censored graft survival	1 year	No	Supported by Genzyme

		TAC+MMF+ST)	years)						
Walters et al (Walters et al. 2003)	UK	BAS+CsA+ST vs PBO+CsA+ST	Adult renal transplant recipients - adults aged 18-70 years	Cost (alongside trial)	UK NHS	Aggregate mean total cost of resources per patient Cost per treatment failure avoided	6 months	No	Funded by Novartis

ATG: Antithymocyte globulin; CsA: ciclosporin; TAC: tacrolimus; MMF: mycophenolate mofetil; AZA: azathioprine; ST: steroids; PBO: placebo; CEA: cost-effectiveness analysis

Table 142. Characteristics of included studies of initial and maintenance regimens

Author	Country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Abecassis et al. (Abecassis et al. 2008)	USA	TAC BID + MMF vs TAC OD + MMF	Renal transplant recipients - no age reported but Vincenti et al. 2002 paper on which this is based is adults	CEA	Not stated	Incidence of acute rejection; graft survival; costs (drug cost; graft loss; transplantation; mortality); total costs	5 yrs	Yes	Not reported - of note, one author Astellas Pharma
Juergensen et al. (Jurgensen et al. 2008, 2014)	Germany	Sir + ST (CsA withdrawal) Sir (CsA minimisation) Eve (CsA minimisation) TAC (low-dose) MMF + ST	Renal transplant recipients - age not stated	CEA	SHI perspective	Cost per life year gained Cost per year with functioning graft gained	24 mths 120 mths	Yes	Funding source not reported (COI are reported)
Lazarro et al Lazarro et al. 2002; Craig et al. 2002	Austria, Belgium, Germany, Italy, Luxembourg, Spain and Switzerland	TAC+AZA+St CsA+AZA+ST	Adult renal transplant recipients	CEA	Italian Hospital Perspective	cost per patient with a functioning graft, cost per surviving patient	12 mths	No	Supported by an unrestricted grant from Fujisawa GmbH Munich Germany
McEwan et al McEwan et al. 2005, McEwan et al. 2006	UK	Sir vs TAC Sir vs CsA	Renal transplant recipients - mean age 45.9 yrs	CUA CEA	NHS & PSS	Mean time to graft failure and mean life expectancy converted to health utility Cost/QALY	10 yrs 20 yrs	Yes	Not reported - of note, one author employee Wyeth Laboratories

Moduma et al. Moduma et al. 2014	UK	Tac (Advagraf), Tac (Prograf) Belatacept, CsA Sir CNI minimization Sir CNI avoidance (all given with MMF + ST)	Renal transplant recipients – age 45 years.	CUA	NHS & PSS	Biopsy confirmed acute rejection Re-transplants Life years Cost/QALY	25 yrs	Yes	Funded by Astellas
Orme et al. Orme et al. 2003	UK	CsA+AZA+ST vs TAC+AZA+ST Given with induction TAC or CsA pre transplant and methylprenisolone+ AZA periop	Adult renal transplant recipients - based on Jurewicz et al 2003	CEA	UK Transplant Unit	Cumulative cost Cost per survivor Cost per patient with functioning graft Cost per patient rejection free	10 yrs	Yes	Funded by Fujisawa
Earnshaw et al. Earnshaw et al. 2008	USA	SRL+ST; MMF+CsA+ST; MMF+TAC+ST	Adult renal transplant recipients - mean age 45.89 yrs	CUA CEA	Not stated	Serum creatinine; Immunosuppressive drug and other medical costs; life-years gained; QALYs	Lifetime	Yes	Wyeth Pharmaceuticals
Woodroffe et al. Woodroffe et al. 2005	UK	- Tacrolimus vs. ciclosporin with a) AZA +ST b) MMF +ST - MMF vs azathioprine with a) TAC+ST b) CS+ST	Adult renal transplant recipients	CUA	NHS & PSS	Costs QALYs	10 yrs	Yes	NIHR HTA Programme - NICE

ATG: Antithymocyte globulin; CsA: ciclosporin; TAC: tacrolimus; Sir: sirolimus; Eve: Everolimus; MMF: mycophenolate mofetil; AZA: azathioprine; ST: steroids; PBO: placebo; CEA: cost-effectiveness analysis; CUA: cost-utility analysis.

Induction therapy

UK studies

Walters et al. 2003 [317]

In a multi-European country RCT basiliximab induction was compared with placebo in people given triple therapy with ciclosporin, azathioprine and steroids (Walters et al. 2003). Information on costs of immunosuppressant drugs, hospitalisations, procedures, outpatient visits, laboratory tests, renal biopsies, concomitant medications, dialysis and nephrectomy was prospectively collected for the trial follow-up period of 6 months. Re-transplantation costs were not included. A cost-effectiveness analysis conducted alongside the trial included all costs up to 6 months and the costs of dialysis up to 12 months. This analysis adopted a NHS hospital perspective; it pooled the data on clinical outcomes and resource utilisation from all countries and people involved in the trial (n=340) but evaluated resource use using UK national and local unit costs (1997-1999 prices).

Basiliximab was found to reduce the incidence of first confirmed acute rejection episodes by 6 months (absolute risk reduction 0.14). The rate of graft failure with Basiliximab was 11% and 18% in the placebo arm (p=0.24). The mortality rate was 2% and 3%, respectively (p=1.00). In terms of the number of people with adverse events or infections reported as serious the comparisons had p≥0.65.

In terms of costs, hospitalisations were the largest element of the total, followed by dialysis and acute rejection. Comparisons by resource use category between arms had all p≥0.05. Over the six-month period post-transplantation basiliximab had an incremental cost of £231 (95% CI: -1983 to 2446). (Including the 6-12 months costs of dialysis the basiliximab had an incremental total costs of -30 (-2326, 2686)). In the six month period post transplantation, the incremental costs per case of treatment failure (i.e. no acute rejection, graft failure or death) avoided with basiliximab was £1,650.

The authors found that, despite the fears of increased adverse events from over immunosuppression, basiliximab given with triple therapy resulted in fewer acute rejections and no difference in costs relative to placebo in the first six months.

The study provides valuable evidence of data on resource use and short term outcomes of induction therapy with basiliximab. For our present purposes, the main limitation of this study is the lack of relevant comparators such as induction with rATG. Further, as the authors point out, the use of these regimens in combination with triple therapy immunosuppressive regimens commonly used in recent years, in particular a CNI with MMF and steroids, would have added relevance to the study.

The authors do not include the costs of re-transplantation in their one year analysis, despite including the costs of dialysis. Nor does it provide any evidence of the impact of induction on health related quality of life. In addition, an attempt to investigate the potential long-term implications of acute rejection rate prevention with basiliximab is warranted, using the framework linking biomarkers to longer terms patient and graft survival outcomes using a predictive model.

A major limitation of the study is the fact that the quantities of resource utilisation were derived from a sample of people being treated in the UK and 11 other countries (Walters et al. 2003). The authors acknowledge that important differences may exist between these countries, as evidenced by the length of hospital stay such that “whereas prevention of early episodes of acute rejection may save a readmission in the US, this would not necessarily lead to an earlier hospital discharge following transplantation in some of the countries involved in this study (e.g. Israel, Poland, Turkey)” (Walters et al. 2003, p. 136). This limits the validity of the results of this study, which was designed from an English NHS perspective.

Chilcott et al. 2002[308]

In a separate study of a similar design to that used in the study by Walters, Chilcott and colleagues compared the costs of renal immunosuppression in centres in Canada and six European countries, including the UK. The study followed people for 12 months and unlike the study by Walters, which calculated costs for the UK using pooled resource utilisation data from all countries, only resource utilisation data from each country were used to estimate the respective costs. Country-specific unit costs were adjusted for purchasing power parity (PPP) to reflect the actual opportunity costs of healthcare resources in each country (Chilcott et al. 2002).

The study involved 376 people (Basiliximab, n=190; Placebo, n=186) and, as Walters et al. had found for 6-month post-transplantation outcomes, observed that basiliximab reduced the rate of (suspected) acute rejections (basiliximab 37%, placebo 54.8%; absolute risk difference (ARD) -16.9, 95% CI: -29 to -4), without affecting graft loss (ARD: -1.3; 95% CI: -8.1 to 5.4) and patient survival (ARD: 2.0, 95% CI: -1.8 to 5.9), at 12 months. The authors

report that no re-transplantations were recorded in any group over the 12 month post transplantation period studied.

Tests of differences in resource quantities used between the trial arms were all associated with p>0.05. The costs estimates were reported in terms of PPP US$ (1996 prices). After converting them back to PPP £ using the £0.4=US$1 conversion rate provided by the (Chilcott et al. 2002, Table 141), the mean total per patient cost in the Basiliximab arm was £19,174 and 18,510 in the placebo (difference 664; 95% CI: -1660 to 2944). The incremental cost per suspected case of acute rejection avoided at 12 months post transplantation was £3929. In addition, and unlike the similar study by Walters et al. 2003,[317] the study by Chilcott presents total cost estimates for the subgroup of UK adults (n= 37) in the trial. (The report only presents these figures in chart form; Chilcott et al. 2002, Figure 4). The total incremental cost of basiliximab over 12 months is approximately £3,500. This implies an incremental cost per suspected case of acute rejection avoided of £8,284. Despite the sampling uncertainty in the subgroup analysis by country, results presented in Figure 4 of the report by Chilcott et al. 2002 suggest heterogeneous findings across countries.[308]

A similar critique applies to this report as that formulated above for the report by Walters et al., with a couple of qualifications. First, Chilcott et al. present results for the subgroup of UK adults. Although these results are based on small numbers they suggest possible heterogeneity of findings across countries since the point estimate of incremental costs of Basiliximab range from almost US$0 in Germany and France to US$3,500 in the UK, to US$10,000 in Belgium and Switzerland (Chilcott et al. 2002, Figure 4). A second strength of the Chilcott study relative to the that by Walters lies in its longer period of follow-up during which information on all costs was collected, 12 month post transplantation vs. the 6 month period of Walters et al.' study (the latter also included costs for a 6-month extension period, but only for dialysis).

Popat et al. 2004[324]

A recent study (Popat et al. 2014) reports evidence of costs and health outcomes associated with two immunosuppressive induction therapies given to recipients of renal transplants from donors after cardiac death (DCD) in a single centre in London. This was a before-and-after comparison of one year outcomes after transplantation, between a IL2Mab induction regimen (basiliximab or daclizumab) given to people receiving a renal transplant from January 2007 to July 2008 and induction with ATG given to renal transplantation people starting from the time of its adoption at the centre in August 2008 to August 2009.

The study included 24 adults in the old induction arm (IL2Mab 2mg/kg) who had a mean age 54.3 vs. 48.0 in the new (ATG 3.75 mg/kg) induction group of 21 adults. There was some imbalance in terms of gender and race, as 71% in the IL2Mab group were male vs. 38% in those given ATG, and 62% in the former group were white vs. 33% in the latter. Forty-two of 45 people were given standard immunosuppression with ciclosporin, mycophenolate mofetil and prednisolone, and 3 out of 45 were given tacrolimus, mycophenolate mofetil and prednisolone. At 1 year post-transplantation, 91.7% of people in the IL2Mab group were alive, while at 3 years 83.4% survived. In the ATG group all people were alive at both time points. In terms of graft survival (censored by death), all people in both groups had a functioning graft at 1 year, whereas 95.8% had a functioning graft at 3 years in the IL2Mab group versus 95.2% with ATG. The authors interpreted these results as evidence of no significant differences in patient and graft survival.

The study also looked at delayed graft function, the duration of delayed graft function measured by the number of haemodialysis sessions, the rate of BPAR, and incidence of infections requiring hospital admission. ATG resulted in 42.8% of people having delayed graft function and 62.5% of people treated with IL2Mab experienced such outcome (p=0.08). More people required HD sessions, experienced BPAR, had infections requiring admission, were readmitted, and had had CMV infections in the latter group than in the former ($p \leq 0.03$ for all of these comparisons).

The study reported a cost analysis associated with observed outcomes up to 12 months post-transplantation using local NHS unit costs for hospital bed day and haemodialysis sessions and BNF drug prices for induction and maintenance immunosuppression applicable at the time people received the transplant. Their results are converted to per patient costs and presented in the Table 143.

Table 143. Per patient cost analysis by induction regimen arm in Popat et al. 2014 trial

Cost category	IL2Mab arm (£)	ATG arm (£)
Immunosuppression (acquisition costs)	1,729	2,250
Inpatient bed days post-transplantation	6,967	4,552
Inpatient bed days for readmission	2,867	933
HD sessions	836	494
CMV prophylaxis and treatment	1,954	2,229
Clinic visits	6,967	4,465
Total cost per patient at 1 year post-transplant*	18,929	14,904

*p=0.002. Apart from the results in the bottom row, the study reported the results only as total costs for all patients in each arm, and presented statistical tests of differences in those totals, without any evidence that the study accounted for the different in size between the two arms (IL2MAb n=24; ATG arm n=21).

ATG was found to result in savings in inpatient bed-days post-transplantation and those due to readmissions, as well as haemodialysis costs and clinic visits, while the additional costs of ATG induction (£479 per patient, calculated by PenTAG) were not found to be statistically significant. The drivers of the cost savings by ATG were found in the inpatient bed-days after transplantation and clinic visits.

The main contribution of this study is to provide evidence on health and economic outcomes in a comparison of two active induction regimens. Due to its small size, the results may be influenced by outliers, thus limiting the validity of the reported findings. In addition lack of power is of concern for statistical inference of differences in health outcomes and more so for inference on costs which tends to require larger samples than those required by studies of clinical effects (Drummond et al., 1987).[325] Moreover, results may be confounded by the fact that the IL2Mab arm was treated in an earlier date than the ATG arm; some of the difference in costs may be due to different discharge practice across the two periods as opposed to an effect of the induction regimen.

The importance of clinic visits as a driver of total costs found in this study is consistent with evidence submitted to NICE by the company sponsoring one of the drugs being evaluated for this appraisal (BMS), on post-transplantation costs in standard practice from the renal

transplant database in Cardiff Wales. The same finding is analysed in an international context in a published report of the same evidence (Chamberlain et al. 2014).[41] Nevertheless, evidence from a larger study is required to confirm the findings reported by Popat and colleagues, where induction regimens are given in combination with current triple therapy, i.e. low dose tacrolimus with MMF and steroids, and relevant outcomes not measured in their study, especially HRQoL outcomes, are measured.

Non-UK studies

In a US study Crompton et al. 2003, 54 living donor transplant recipients were randomised in a 1:1 ratio to receive basiliximab induction or no induction, and all were given triple immunosuppressive therapy with ciclosporin ME, azathioprine and corticosteroids.[326] At 12 months post transplantation, the rate of acute rejection episodes in the induction intervention arm was 22% vs. 15% in the control ($p>0.05$). Differences between arms in serum creatinine measured at 1, 2, 3, 6 and 12 months had all $p>0.05$, and no adverse events were associated with basiliximab. Four graft losses occurred during follow-up, all in the intervention arm; it was stated that only one was immunologic but no additional information was reported. The study evaluated differences in resource use using charges as opposed to economic costs of the resources consumed. Basiliximab provided no clear clinical benefit or evidence of being cost-effective in this low risk patient population. However, insufficient numbers of people were included in the study to allow one to derive conclusive findings. Another limitation is its use of basiliximab in people receiving triple therapy of ciclosporin with azathioprine and steroids, instead of current standard regimens combining CNI, MMF and steroids.

A study from Spain (Emparan et al. 2005, Emparan et al. 2003) investigated two regimens of Basiliximab induction, a) a CNI-avoidance regimen (ciclosporin 8 mg/kg daily was introduced when the creatinine level reached a value below 3 mg/dL) and b) a CNI minimisation regimen (ciclosporin 4 mg/kg daily with MMF 500 mg/12 h from day 1), and compared them against a tacrolimus (Prograf 0.3 mg/kg daily with a through level 8 to 12) with MMF (500 mg/12 hours) and steroids regimen in elderly people. [327] [328] The reports identified for this study provided Markov-model simulated costs and health outcomes for eight people in each of options A and B and 15 people the tacrolimus comparator up to one year post-transplantation, but were only in summary form, and lacked information on methodology, related to model structure, cost definition, sources and values of unit costs and effectiveness parameters to allow critical appraisal of the reported cost difference relative to tacrolimus arm (-€8355 for option a, and -€5695 for option b).

Initial and maintenance immunosuppression studies

UK studies

Orme et al. [318]

Orme and colleagues compared the costs and clinical outcomes of tacrolimus (Prograf) vs. ciclosporin ME given in triple therapy regimens including azathioprine and corticosteroids. Their study was based on data from the direct comparison of these regimens in a randomised controlled trial conducted at a single centre in Wales, in which clinical and resource use data were collected prospectively for each patient over a median follow-up of 2.7 (maximum 4) years. People in the trial had undergone renal transplantation between 1996 and 2000 (n=89 ciclosporin, n=90 tacrolimus arm). The resource items for which data were recorded in the study included number of days in specialised wards (transplant/ nephrology and ICU during the initial admissions and subsequent readmissions), number of dialysis sessions required in cases of a delayed graft function, number of diagnostic tests (e.g. transplant biopsy, ultrasound scan, and other radiological investigations), and minor surgical procedures and operations for complications. The economic evaluation adopted a 10-year analytical horizon and extrapolated the trial outcomes from 5 to 10-years using patient and graft survival data from the UK Transplant Support Service Authority (UKTSSA) Audit. During the extrapolated period, the rates of change in patient and graft survival rates were assumed to be the same between the tacrolimus and ciclosporin immunosuppressant regimens. The analysis also assumed that acute rejection rates changed by the same rates as graft survival rates for the extrapolation phase of the analysis. The per patient costs for year four to 10 were extrapolated using an average of annual costs with functioning graft and costs with graft failure (dialysis) in the trial, weighted by the proportion of people surviving with a function graft at the end of the year.

According to intention-to-treat analysis at four years, 89% of people survived on tacrolimus and 80% did on the ciclosporin arm. In terms of graft survival the figures were 81% and 71%. The proportion of people rejection free was observed to decline annually for the first four years of ciclosporin by 48, 5, 2, 1 percentage points, and by 37, 4, 1, 4 with tacrolimus. In terms of costs, the observed per patient costs in the first year post transplant were £9,990 under tacrolimus vs. £9,783 under ciclosporin. In the observed years 2-4, the tacrolimus arm had lower per patient costs, from £133 to £350 less, than ciclosporin arm due to the higher proportion of people with a failed graft and receiving dialysis in the latter. The study presented results in terms of incremental cost per additional survivor, per extra patient with a functioning graft, and per rejection free patient. Although the number of years of life achieved

after transplantation under each treatment was not presented, PenTAG approximated them by numerical integration using Newton-Cotes methods (Simpson's rule Atkinson 1989) from the percentages of people alive at the end of each of the 10 years of analysis reported by the study. This yielded an estimated 8.28 life years under tacrolimus and 7.61 under ciclosporin. The information provided in the paper also allowed us to adjust the cost discounting to convert results from the 6% annual rate used by the study to the current NICE recommended rate of 3.5%. Similarly methods were used to approximate discounted life years at that rate. The resulting discounted incremental cost per life year gained by tacrolimus over ciclosporin was £1457.

This study had detailed unit cost information reported, although quantities of resource utilisation were not provided, which limits the ability to assess the generalizability of results to England. This is regrettable since this is one of the studies with the longest prospective follow-up of healthcare use and health outcomes in kidney transplant recipients, and thus a potential source of longitudinal data on quantities of resource use and their inter-patient variability. Further, the study did not account for HRQoL effects of immunosuppression and did not consider the importance of outcomes in terms of renal function for costs and benefits. In particular there is emerging evidence that not only does CKD stage matters for current costs and health related quality of life experienced by the patient but has an important role as a prognostic factor and determinant of graft survival.[329] It is also noted that the time horizon of the analysis may now be too short to estimate cost adequately. Despite the inadequate measure used to synthesise cost-effectiveness in the study report, our calculations suggest that in the sample studied by Orme and collegues, tacrolimus is well within the NICE threshold of cost-effectiveness. Although we did not adjust prices to current levels, these are unlikely to raise the ICER per QALY gained in this sample of tacrolimus vs. ciclosporin beyond £5,000.

Woodroffe et al. 2005 (Assessment Group for NICE Technology Appraisal Guidance 85) [60]

Based on their review of models submitted by four sponsoring companies for the NICE technology appraisal guidance 85, the assessment group at Birmingham University performed an analysis based on the model submitted by Novartis, based on the information in the industry submissions and their own systematic review of the published evidence on effectiveness and cost-effectiveness.[60] The Novartis model simulated the experience of individual people after renal transplantation, represented by transitions between health states defined by acute rejection, no acute rejection, hospital dialysis, peritoneal dialysis and death. It included a model component that captured the effects on clinical outcomes of NODAT, which allowed accounting for the clinical implications of the high incidence of NODAT with

tacrolimus that the company found in their systematic review. The model also accounted for cause-specific mortality risks from five co-morbidities associated with diabetes or other causes. Costs and utilities were specific to each health state. A summary of the findings reported by the Birmingham group (Assessment Group for NICE technology appraisal guidance 85) is presented in Table 143. Tacrolimus was found to have incremental costs per QALY ratios in the range of £59,548 to 166,112 relative to ciclosporin when evaluated as candidate components of triple therapy containing azathioprine and corticosteroids. Larger ICERs were found for the comparison in the context of triple therapy constituted by MMF and corticosteroids. For the comparison of MMF vs Azathioprine, the ICER ranged from £39,297 to dominated, when evaluated alongside Tacrolimus and corticosteroids, and 52,166 to 109,549 as part of triple therapy containing ciclosporin and steroids. The authors refer to these ranges as 95% confidence intervals but since these did not account for the variation in costs, they are likely to misrepresent uncertainty.

Difficulties encountered by the Birmingham Assessment Group in implementing their analysis (Woodroffe et al. 2005), prevented them from satisfactorily accounting for uncertainty. [60] They could obtain 95% CI for incremental QALYs but not for costs, and thus the degree of uncertainty in their results was left unaddressed. A more fundamental problem arises however with the use of a model such as that of Novartis, which assumes that the main clinical outcomes, i.e. years of patient life and with a functioning graft gained, are adequately predicted by short term acute rejection rates and post-transplant diabetes mellitus. In recent years, evidence has emerged suggesting that renal function is a predictor of clinically and economically significant outcomes, and that acute rejection may be less relevant once CKD stage is accounted for (Schnitzler et al. 2011, Levy et al. 2014, Barnieh et al. 2014). Cost-effectiveness analyses published since the Birmingham Assessment Group's review was conducted, and reviewed in the rest of this chapter, reflect these methodological developments, as summarised in Table 142. At the time of the Birmingham review, the evidence was ambiguous about the prognostic predictive power of renal function relative to AR and, as they acknowledge, their analysis reflects this (Woodroffe et al. 2005, p. 52).[60 329-331].

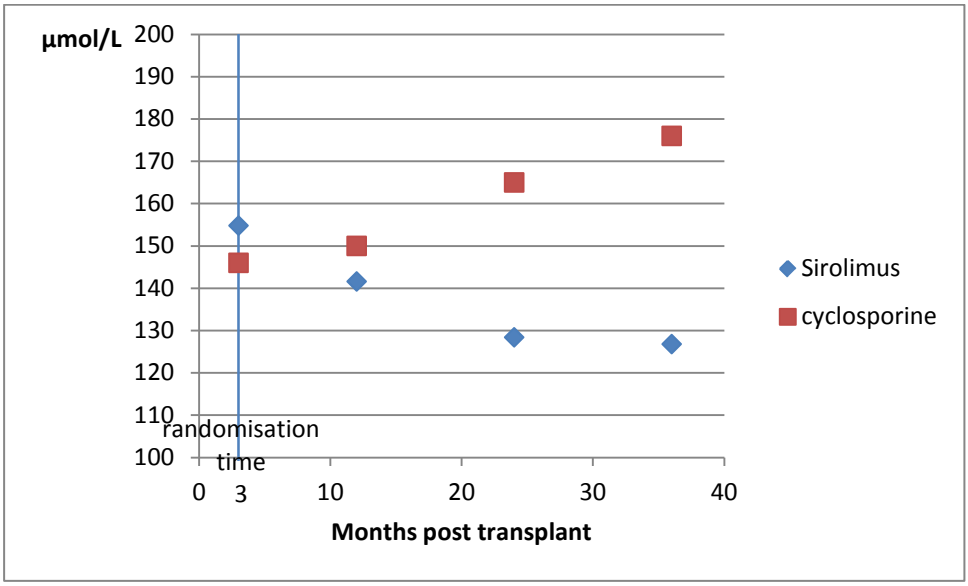
McEwan et al. 2005 and 2006[332 333]

In a couple of papers, McEwan et al. (McEwan et al. 2005, McEwan et al. 2006) evaluate the cost-utility of sirolimus against ciclosporin and sirolimus against tacrolimus for maintenance immunosuppression from the NHS perspective using a discrete event simulation model of individual patient evolution from the time of kidney transplantation until 20 years post-transplant.[314] The study was one of the first to account for renal function as a predictor of

transplant outcomes. It simulated the monthly evolution of a patient's health status by transitions between three mutually exclusive health states: 1) patient with a functioning graft, 2) patient with failed graft (dialysis), 3) death. In addition, acute rejection events were accounted for. The model allowed for re-transplants and different probabilities of experiencing an acute rejection, patient death, graft failure, and transplant after graft failure, depending on the number of transplants that the patient had received at each point in time. Movements between health states were associated with changes in costs and health related quality of life, while the occurrence of transplant, graft failure, and acute rejections and graft failure were only associated with costs.

The effects of sirolimus and ciclosporin on clinical outcomes were assumed to occur through their effects on renal function, which determined long term clinical outcomes independently of treatment. The relative efficacy of sirolimus versus ciclosporin was derived from a single trial involving 430 people from 57 centres in Europe, Canada and Australia (the Rapamume Maintenance Regimen Study, Oberbauer et al. 2003).[334] People included in this trial were given the same immunosuppression regimen (ciclosporin + sirolimus + steroids) for the first three months after transplantation and then randomised to continue on the regimen or switch to a regimen of once-daily sirolimus and steroids. Serum creatininine values in each trial arm at the time of randomisation, i.e. 3-month post-transplantation, and at 1, 2, and 3 years were used as inputs (surrogate measures) in estimated equations for predicting the risk of long term clinical events; see Figure 2. The authors also assumed that in 50% of subjects treated with sirolimus, graft survival "would prevail for the entire time horizon".[332]

Figure 83. Serum creatinine levels (Oberbauer et al. 2003) used by McEwan model



The surrogate relationship between renal function and clinical events defining transitions between health states in the model was estimated from analysis of longitudinal data on outcomes experienced by 937 transplant patients up to 20 years post-transplantation in routine practice, recorded at the University Hospital of Wales, Cardiff. People were treated over the period 1982-2001, during most of which ciclosporin was the standard immunosuppressant therapy.[332]

The authors found that sirolimus regimen would cost the NHS £62,120 per patient over 20 years, while ciclosporin would cost £69,525 (at 2003 prices and 6.5% annual discount rate). Sirolimus was found to result in more discounted years with a functioning graft and in 0.16 additional discounted life years per patient; it also resulted in more QALYs than those achieved with ciclosporin. These results were based on the assumption that 50% of sirolimus patients would maintain their graft survival over the entire modelled period; when this value was set to 0% the incremental cost per QALY gained by sirolimus was 51,778 under the 10-year horizon and £11,161 under the 20-year horizon. The same analysis was performed for the comparison of sirolimus vs. tacrolimus [333] using the creatinine levels observed in people receiving ciclosporin in the Rapamune trial as proxies for creatinine levels in people receiving tacrolimus in the model, and replacing the price of ciclosporin with that for tacrolimus. The results were qualitatively similar with sirolimus both saving costs and producing health benefits relative to tacrolimus.

The main strength of the study is its account for the effect of renal function on long term outcomes and use of probabilities of clinical events from observational data of people treated

in routine practice. Further it is the only study to have accounted for the temporal variation in risk factors for those events over a 20 year period. However, the internal validity of the results are questionable due to the differences between the trial population on which the efficacy data were based and the patient population of the model. In addition, the study did not account for the incidence of clinical conditions such as malignancy, cardiovascular events and NODAT. This is an important limitation in the light of the expected benefits of sirolimus on malignancy. Most important, however, are the safety concerns (increased death risk) associated with the drug that suggest sirolimus may not be justified in people who have kidney transplants other than those at high risk of cancer.[335]. It must also be noted that, while the study accounts for the role of renal function as a predictor of long term outcomes, it does not allow for its impact on costs (Chamberlain et al. 2014) and health related quality of life (Neri et al. 2012).[41 336]

Muduma et al. (Muduma et al. 2014)

In a recent study the current UK standard treatment for adults, twice-daily immediate release tracolimus, Prograf, was compared with current options, namely, ciclosporin microemulsion (ME), sirolimus with CNI minimization, sirolimus without CNI, belatacept and one-day prolonged released tacrolimus, Advagraf, in terms of cost-effectiveness from the perspective of the NHS.[322]. The analysis considered each of these treatment options as part of a regimen that also included MMF and corticosteroids, and basiliximab induction (consisting, in the base case, of 20 mg 2 hours before surgery and 20 mg 4 days after surgery; an alternative scenario considered additional doses during the first few days after transplantation). The study found that while Prograf resulted in more efficient use of healthcare resources relative to ciclosporin ME and belatacept it was not cost-effective relative to sirolimus. Although Advagraf produced lower costs and higher benefits than Prograf, its cost effectiveness ratio against sirolimus (CNI minimisation regimen) was £58,350. These results were found to be sensitive to the time horizon and the effect of adherence.

Costs and health benefits were accumulated according to a Markov model of annual cycles that represented the evolution of the patient heath status following a successful transplant for up to 25 years. The model included four health states: 1) functioning graft without a history of BPAR, 2) functioning graft with a history of BPAR, 3) non-functioning graft, and 4) death. The occurrence of repeat transplantation was modelled using a tunnel state. The model assigned an excess risk of graft loss for the state of functioning graft with prior BPAR relative to the functioning graft without prior BPAR state, using estimates derived from the literature. The model was specified so that BPAR could only occur in the first year after transplantation,

which the authors justified on pragmatic grounds given the limited data available from the literature on BPAR outcomes beyond 1 year.

The study did not report adequate information on the methods and results of that review, the primary study sources for the probabilities of acute rejection used, or the actual values used for these parameters. The treatment-specific outcome data reported related to the advantage of Advagraf over Prograf in terms of adherence to treatment schedule. The differences in 1-year AR rates were used to predict patient and graft survival for the first 5 years post-transplantation using data from UK renal transplant summary statistics[337] and patient survival for the first 10 years after the start of the spell on dialysis were populated using UK data (UK Renal Registry 2012); the probabilities of re-transplantation while in dialysis were obtained from data reported by McEwan et al., reviewed in this chapter. [338] Exponential curves were used to extrapolate patient and graft survival curves and survival on time on dialysis to 25 years.

Despite its stated aim to comply with the NICE reference case specifications, this study faced limitations in terms of the availability of data to do so, the adopted model structure, issues of model implementation, and the quality of reporting. The model assumed that the cost-effectiveness was driven by the differences in the rate of acute rejection between treatment regimens, and that these fundamental differences only occurred during the first year post-transplant. The validity of this assumption and the results of this study hinges on the quality of the evidence on the relationship between AR and graft and patient survival.[339] In any case it results difficult to defend extrapolating results from 1 year surrogate measures to clinical outcomes 25 years into the future, as this study has done with the statistical model of AR and graft survival. Another problem with this report is its lack of any information on the values of the parameters driving the results, i.e. the relative differences in the risk of acute rejection between regimens. This fact makes impossible to replicate the results reported by the paper. Thirdly, based on the information provided, it appears that the amount of immunosuppressant use in the model might not have reflected the actual total use of the medications that brought about the acute rejection outcomes that were used to populate the effectiveness model parameters. The authors do not report any attempt to derive mean daily drug use or dose intensity from the RCT data from which the AR estimates were derived for populating the model. Another issue arises with the way transition probabilities were derived from the registry data on transplant and patient survival. Since this issue is discussed for one of the industry submissions, which used the same data and model, the reader is referred to that section (see Astellas model submission below).

Non-UK studies

Three identified reports investigated the cost-effectiveness of Sirolimus regimens, one in the US (Earnshaw et al. 2008)[319], and two in Germany (Jurgensen et al. 2014, Jurgensen et al. 2010).[319 323 340]. Two studies evaluated tacrolimus versus ciclosporin ME in European countries (Craig et al. 2002, Lazzaro et al. 2002).[309 316] One study investigated once vs twice daily tacrolimus in the US (Abecassis et al. 2008).[307]

In common with the UK study by McEwan (McEwan et al. 2005 and McEwan 2006) discussed before, the US study by Earnshaw and colleagues (Earnshaw et al. 2008) evaluated Sirolimus + ST after CNI withdrawal, but in this case it compared it against triple therapy of tacrolimus or ciclosporin combined with MMF and steroids.[319 332 333] Applying a decision analysis model extending over the lifetime of a 46 year old first-transplant patient, it found that the regimen was the dominant treatment for the adult renal transplantation population in general. Its use resulted in 0.30 extra years of life relative to tacrolimus containing-triple therapy and 0.06 extra years of life relative to triple therapy containing ciclosporin. In terms of discounted (at 3% per annum) QALYs the results were 0.30 and 0.12, respectively. Sirolimus CNI withdrawal produced a cost savings of US$33,000 relative to tacrolimus, and US$11,000 when compared against ciclosporin. The same qualitative results were found for the subgroup analysis by donor type (living, deceased non-extended criteria donor (ECD) and, deceased ECD).

The study by Earnshaw is different from other reports on the same topic in its attempt to provide evidence on cost-effectiveness across different donor types. In common with other studies evaluating sirolimus, it found the regimen to be cost-effective, in this case relative to current standard triple therapy containing a CNI. Similar criticisms as those made above to the UK reports by McEwan (McEwan et al. 2003, 2002), in relation to the current perception of sirolimus as having a restricted use due to issues about safety, may be applied to this study.[332 333] In terms of its methodology, this study used a model to predict long term graft survival from 1 year renal function outcomes specific to the three regimens, accounting for graft survival differences between donor types. Although the use of renal function as driving clinical outcomes is supported by recent statistical evidence in samples of people treated in routine practice (Scnitzler et al. 2011), the model structure adopted by Earnshaw et al. relies on a simplistic assumption of constant (instantaneous) probability (hazard rates) of graft failure over time, which more recent studies find to be inconsistent with the data.[329 330] In addition the study does not account for the direct effects of renal function on costs and HRQoL. Thus, important differences between therapies might not have been captured with this model as patient's accumulated time in the functioning graft state. [41 336]

One study presents the results of a Markov model of 10-year outcomes representing the transition across health states experienced by people after renal transplantation in Germany [323 340]. The model compares sirolimus ciclosporin avoidance with sirolimus ciclosporin minimisation and low-dose tacrolimus triple therapy with MMF and steroids. The latter was included in acknowledgement of the changes in immunosuppressant treatment practice following the publication of results from the SYMPHONY trials (Ekberg 2009, Ekberg[191 193] 2010, Claes 2012).[189] The analysis was conducted from the perspective of the German statutory health insurance. The study found that low-dose tacrolimus in triple therapy with MMF and steroids has a cost per life year gained in excess of €100,000, relative to the sirolimus ciclosporin minimisation regimen. All other comparators were found irrelevant for identifying the cost-effective treatment option as they were dominated by these two regimens.

The study provides new evidence about the cost-effectiveness of low dose tacrolimus regimens currently in favoured by current practice, which has emerged following the publication of the SYMPHONY trial results. One of the strengths of this analysis is the attempt to derive comparative evidence for the effects of the different regimens from evidence synthesis based on indirect comparisons, through network meta-analysis. Another is its account for adverse events including graft failure, malignancies, CMV infections, PTDM, wound healing disorders, and post-transplant anaemia, HMGCoA and hypertension treatments. However, the value of this study from an English NHS decision-making point of view is diminished by their choice of comparators, which excludes ciclosporin-based triple therapy and other new treatments such as belatacept. The study also has limited information use for informing NICE recommendations since it did not account for HRQoL outcomes. The model itself is not amenable to account for available evidence on HRQoL and costs associated with the effects of immunosuppressive regimens on renal function, since the renal function plays no role in the health status of people in the model or indeed has no prognostic effect on long-term graft or patient survival outcomes, which were assumed to be driven by 2-year differences in the rate of acute rejection between model arms.

A study, co-authored by an affiliate of Astellas' pharma US, modelled the expected costs and clinical outcomes of once-daily extended release tacrolimus and twice daily immediate release tacrolimus, each given in combination with MMF, for transplant recipients in the US (Abecassis et al. 2008). [307] The study used a stochastic state-transition Markov model extending 5 years post-transplantation to predict the amount of time people were alive with a functioning graft, receiving dialysis due to graft failure or dead. The total discounted (5% annually) costs per patient with once-daily tacrolimus were US$228,734 and US$238,144

with twice-daily tacrolimus. The low quality of reporting by this article prevents to assess its validity. The sources of values for some model parameters or the methods used to identify them were not reported. Moreover, the values of some parameters were not provided, preventing the replication of results by the reader.

The remaining study compared the resource use, costs and health outcomes over 6 months post transplantation of people randomised to receive tacrolimus (n=286) and ciclosporin ME (n=287), as part of triple immunosuppressive therapy with azathioprine and steroids (Lazarro et al. 2002, Craig et al. 2002). [309 316] This was a multi-country trial where tacrolimus was given at an initial daily dose of 0.3 mg/kg, while the starting dose of ciclosporin ME was 8 to 10 mg/kg per day. The study retrospectively measured resource use quantities and costs of immunosuppressant drugs, concomitant medications, hospitalisation, dialysis and rejection episodes from the 50 centres in seven Western European countries that participated in the trial. ITT analysis revealed per patient cost savings achieved by tacrolimus, ranging from €1776 in Italy to €524 in Spain (figures in year 2000 prices). The authors attribute part of the variation to the higher cost of hospitalisation in Italy than in the other countries. Most of the savings with tacrolimus were due to fewer days in hospital for the initial stay and readmissions (Italian case: 50%), lower costs of immunosuppressive medication for graft rejection (37%) and incidence of dialysis (13%).[316]

The length of follow-up in this study may was insufficient to capture important clinical events such as graft and patient survival or adverse events such as PTDM, with which tacrolimus-immunosuppression has been associated. In addition the study did not report any results in terms of changes in renal function, which has been observed to be associated with costs and health-related quality of life as well as a prognostic factor of graft and patient survival. Moreover, the detailed report on the Italian case found that differences in costs were statistically insignificant (i.e. $p>0.05$), suggesting that the overall reduction in costs may have been due to chance alone. In any case, the study may have had insufficient power to perform statistical inference on cost effects.[325] Therefore the conclusion that “the overall costs of treating a patient with tacrolimus during the 6-month post-transplantation period are substantially lower [than that for ciclosporin ME]” may not be supported by the results of the study.

Table 144. Characteristics of models in economic evaluations of immunosuppressive therapy in adults with renal transplants

Study	Population	Comparators	Horizon	Model structure	Surrogates to model long term	Health states/events modelled	Risk factors	Adverse events	Key factors (sensitivity analysis)	Comments
Abecassis et al., 2008	Adult US	TAC BID + MMF vs TAC OD + MMF	5 years	Markov - stochastic state-transition model	Graft loss	-Functioning transplant -On dialysis following graft loss -Death	Re-transplant – reduction in 5 year graft survival relative to original graft	None	Rate of relative non-adherence between once and twice daily tacrolimus	Renal transplant recipients - no age reported but trial[5] on which clinical parameters are based was conducted in adults
Woodroffe et al., 2005	Adult UK	DAC, BAS, TAC, MMF, MPS, SIR	10 years	Meta-model of Simulation model outputs	AR impact on graft loss PTDM impact on survival	-AR -no AR -hospital dialysis -peritoneal dialysis -death	DM on graft loss Comorbidities on Death: Diabetic nephron-pathy, retino-phathy, neuro-pathy, CHD, CVD	PTDM	ARR	Assumes tracrolimus twice the DMPT rate of other drugs
McEwan et al., 2005, 2006	Adult UK	Sirolimus vs TAC vs ciclosporin -all with AZA + ST	10 and 20 years	DES model; monthly cycles	Serum creatinine levels at 3 mo, 1, 2 and 3 years	-AR -Graft failure -Retransplant -Haemodialysis -Peritoneal dialysis -Death	Number of transplants DM Age (for patient survival)	Switch from Sirolimus to TAC/Cs (in-tolerance)	% with graft function for entire 10 yrs % switching from SIR % low dose cycliosporine	Includes costs of: Antihypertensives, Prophylaxis CMV -/+, CV, bone loss, Anemia, Bone loss, OKT3
Earnshaw et al., 2008	Adult, de novo, 45.89 yrs US	SIR + steroids MMF,+CsA+ST MMF+TAC+ST	Life-time	DA of first year +Markov (may return to DA for a sub-sequent transplant)	Serum creatinine 12 months (based on Hariharan et al. 2002)	-Functioning graft -Functioning graft with AR -Graft loss (dialysis) -Dialysis (waiting on retransplant) -Death	Donor type (baseline) Transplant number	Increased triglyceride and/or cholesterol levels [1] Diabetes incidence (at 3, 12, 36 mo.)	Discount rate DM-related parameters: incidence, excess death, and costs Serum creatinine (by design)	-People were allowed one additional transplant graft -No induction use -Subgroups: Donor type -Time to graft loss was assumed to follow an exponential distribution -% with DM was remained constant after 3 years [2]

Study	Population	Comparators	Horizon	Model structure	Surrogates to model long term	Health states/events modelled	Risk factors	Adverse events	Key factors (sensitivity analysis)	Comments
Orme et al., 2003	Adults UK	Induction: TAC or CsA pre transplant & ST +AZA periop Maintenance: CsA+AZA+ST vs TAC+AZA+ST	10 years	Extrapolation from 4- year patient and graft survival outcomes	None	-Functioning graft -Functioning graft with rejection -Graft loss -Death	None	Not reported	-Costs of immuno-suppressive regimen -LOS	The rates of change of rejection rates were assumed equal to those for graft loss, which were based on data from the UL Renal Audit data and may bias results against tacrolimus.
Jurgensen et al., 2010; 2015	Adults Germany (age not stated[2])	1) SIR+CNI Min+ST 2)SIR CNI+ST 3)EVE+CNI Min+ST 4) Cs+MMF+ST 5)TAC+MMF+ST	2 and 10 years	Markov to extrapolate 2 year outcomes, Monthly cycles	-Acute rejection -Graft Failure (differences across arms only lasted for two years in terms of these & survival outcome)	-Functioning graft -Acute rejection -Graft failure -Dialysis (waiting on re-transplant) -Death	None	Malignancies; CMV infections; PT Diabetes; Anemia; Dyslipidaemia; Hypertension; Wound healing disorders	-Costs of immuno-suppression -Cost of dialysis	Allowed unrestricted number of re-transplants. Data for the first 2 years from systematic review of RCTs[3]. Extrapolation from year 2 to 10 using registry data[4]. Malignancy data for CsA & TAC up to 6 years.
Emparan et al., 2003; 2005	Old to old transplant recipient (68-69 yrs) Spain	BAS+CsA BAS+CsA+MMF TAC+MMF ST TAPERING FOR ALL	1 year	Markov simulation Monte Carlo; cycle duration was not stated	Not applicable	Creatinine clearance (day 7), Dialysis requirements (first month); rejection, infections; Graft function; patient survival.	None	Infections (30 days)	Not reported	Inadequate reporting of methods prevents assessment of study quality

Study	Population	Comparators	Horizon	Model structure	Surrogates to model long term	Health states/events modelled	Risk factors	Adverse events	Key factors (sensitivity analysis)	Comments
Moduma et al., 2014	Adults age≥18 years UK	TAC [a) Advagraf, b) Prograf]+MMF +ST Sirolimus [a) without CNI, b) CNI minimisation]+MMF ME+ ST Cs+MMF ME+ST Belatacept+MMF ME+ST	5 and 25 years	Markov; annual cycles with tunnel states for functioning graft with previous BPAR and for re-transplantations	Biopsy Proven Acute Rejection (effects lasted only for the first year)	Functioning Graft without previous BPAR; Functioning Graft with previous BPAR; Graft failure; Death	None	Adverse events were referred to as accounted for in the model but no further information was provided.	Time horizon Effect of Increased adherence (TAC a vs b) Costs and utilities of dialysis (haemodialysis & CAPD) Inclusion of adverse events (for the comparison TAC vs Cs	Did not provide any information on sources & values for the relative efficacy parameter (in terms of BPAR).The drug resource use estimates were not derived from the samples of relative efficacy parameter estimates. The authors implemented the mortality risks so that only the maximum of the background and risk with a functioning/failed graft, applied at any one time.

CAS: Ciclosporin, Azathioprine, Steroid; TAS: Tacrolimus, Azathioprine, Steroid; CMS: Ciclosporin, Micophenolate Mofetil (MMF), Steroid; BCAS: Basiliximab, Ciclosporin, Azathioprine, Steroid; DCAS: Daclizumab, Ciclosporin, Azathioprine, Steroid; BTAS:Basiliximab, Tacrolimus, Azathioprine, Steroid; CMS: Ciclosporin, MMF, Steroids; MMF ME: Micophenolate Mofetil microemulsion; ST: steroids. Notes on other acronyms: PTDM: post-transplant diabetes mellitus; ARR: acute rejection rate.

[1]Proxied by lipid-lowering agent use in RCTs; assumed people on statins at 12 months remained on it until graft loss/patient death. [2]'throughout the life of the graft'; those without DM by 3 years would not develop it [3]But would correspond to the age of people in studies included in the Cochrane systematic review that provided the source of estimated effects at two years after start of immunosuppressive therapy (Webster et al., 2006). [4] reported in McEwan et al., 2005. The distribution of AR incidence in first 2 years and CMV incidence after 2 years were based on expert opinion. [5] Vincenti et al., 2002.

Table 145. Results of model-based studies of intial and maintenance immunosuppression in the UK

Study	Regiments compared	Patient characteristics	Time horizon	Years with a functioning graft	Life years (un-discounted)	Discounted Incremental costs (£)	ICER Incremental cost per QALY	Notes on ICER
Orme et al. 2003	Tacrolimus Ciclosporin ME	Mean age 44-48 yrs DM 7-9% BMI 24-26	10 yrs		7.09 6.54	£795	1,457*	Costs & ICER are adjusted to 3.5% discounting of costs and life years gained, and are in 1999 prices
McEwan et al. 2005, 2006	Sirolimus Ciclosporin Tacrolimus	Mean age 43 Weight 77 kg DM 7%	10 years 20 years	14.27 12.35 12.09	15.37 15.18 NR.	£62,120 £69,525 £75,265	Sirolimus dominant	Cost discounting 6%, QALYS 3.5%. Source of difference in effectiveness between tac and cs unclear: identical parameter values & methods were used for them
Woodroffe et al. 2005	- Tacrolimus vs. ciclosporin with a) AZA +ST b) MMF +ST - MMF vs azathioprine with a) TAC+ST b) CS+ST	NR	10-years	NR	NR	Tac vs. Csa a) 13,557 b) 20,849 MMF vs. Aza a) 11,581 b) 10,021	Tac vs Csa a)110,626 [59,548,166112] b)421,382 [405,453,dominated] MMF vs Aza a)78,593 [39,297 to dominated] b)78,249 [52166 to 109549]	Cost discounting 6%, QALYS 3.5%.Results of a meta-regression of outputs from patient simulation model submitted to NICE by Novartis, as a function of ARR and PTDM (tacrolimus was given 14% vs 7% rate for other regimens). Figures in brackets reflect ranges of incremental QALY associated with 95% CI of AR rates in systematic review by Woodroffe et al.
Moduma et al. 2014	TAC [a) Advagraf, b) Prograf]+MMF +ST Sirolimus [a) without CNI, b) CNI minimisation]+MMF ME+ ST Cs+MMF ME+ST Belatacept+MMF ME+ST	45 (range 18-65) Weight 70.3 kg	25 years	NR	NR	Relative to Prograf: Ciclosporin - 10,928 Sirolimus a: - 8,777 Sirolimus b:- 23,765 Belatacept: 33,521 Relative to Advagraf: Prograf:10,928	Relative to Prograf: Ciclosporin: 21,244 Sirolimus a:143,697 Sirolimus b:1542,449 Belatacept: dominated Relative to Advagraf: Prograf dominated	Discounting at 3.5% of costs and QALYs. In year 2013 prices.

* Derived by PenTAG from information in the study report. NR: Not reported

Table 146. Results of model-based studies of intial and maintenance immunosuppression in other countries

Study and country	Regiments compared	Patient characteristics	Time horizon	Years with a functioning graft	Life years (un-discounted)	Discounted Incremental costs (£)	ICER Incremental cost per QALY or per life year (if QALYs not available)	Notes on ICER
Earnshaw et al. 2008 US	Sirolimus + steroids (CNI withdrawal) Ciclosporin + MMF + steroids Tacrolimus + MMF + steroids	Mean age 46 yrs.	Life-time	NR	11.43 11.37 11.13	US$472,799 US$484,020 US$505,420	Sirolimus dominant	Cost and QALYs discounted at 3%, QALYS 3.5%. Model based on 1-year post transplantation serum creatinine values and graft survival by donor type. Third-party payer perspective.
Jurgensen et al. 2014, 2010) Germany	Sirolimus + steroids (ciclosporin withdrawal) Sirolimus (ciclosporin minimisation) Everolims (ciclosporin minimisation) Tacrolimus (low-dose) MMF + steroids	Not stated.	10 yrs.	4.99 5.83 5.19 5.90	5.64 6.47 5.98 6.49	€145,788 €107,246 €154,822 €114,612	Tacrolimus regimen vs. Sirolimus (ciclosporin minimisation): €387,684 (other regimens are dominated)	Incremental cost per life year gained -QALYs were not calculated. Statutory Health Insurance perspective Study evaluates low dose tacrolimus in accordance with ELiTE SYMPHONY trial. Use of MTC in Network meta-analysis. Detailed account of adverse event probabilities and costs.
Abecassis et al. 2008 US	Tacrolimus OD + MMF Tacrolimus BD + MMF	Not stated	5 years	4.30 4.19	4.53 4.52	US$228,734 US$ 238,144	Tacrolimus OD is dominant	Year 2006 prices. Discounted costs at 5%.

Figure 84. Evers checklist (Evers 2005) –Review of published economic evaluation studies

	Jurgensen et al. 2010, 2014	Earnshaw et al. 2008	Orme et al. 2003	McEwan et al. 2005, 2006	Woodroffe et al. 2005	Crompton et al. 2003	Emparan et al. 2003, 2005	Chilcott et al. 2002	Walters et al. 2003	Popat et al. 2014	Moduma et al. 2014	Craig et al. 2002, Lazarro et al. 2003	Abecassis et al. 2008
Item	I & M	I & M	I & M	I & M	I & M	Ind	Ind	Ind	Ind	I & M	I & M	I & M	I & M
1. Is the study population clearly described?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
2. Are competing alternatives clearly described?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Is a well-defined research question posed in answerable form?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
4. Is the economic study design appropriate to the stated objective?	N	Y	N	Y	Y	N	N	N	N	N	Y	N	N
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	N	N	N	Y	N	N	N	N	N	N	Y	N	N
6. Is the actual perspective chosen appropriate?	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	?
7. Are all important and relevant costs for each alternative identified?	N	N	Y	N	Y	N	N	Y	Y	N	?	N	N
8. Are all costs measured appropriately in physical units?	Y	N	N	Y	?	?	?	N	Y	N	?	?	N
9. Are costs valued appropriately?	Y	?	Y	Y	?	N	?	?	Y	?	?	?	N
10. Are all important and relevant outcomes for each alternative identified?	N	N	N	N	N	N	N	N	N	N	?	N	N
11. Are all outcomes measured appropriately?	N	N	N	N	?	N	N	Y	Y	N	?	N	N
12. Are outcomes valued appropriately?	N	X	N	N	?	N	N	N	N	N	?	N	N
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y/N	Y	Y
14. Are all future costs and	Y	Y	N	Y	?	N/A	N/A	N/A	N/A	N/A	Y	N/A	Y

outcomes discounted appropriately?													
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Y	Y	Y	Y	N	N	N	Y	Y	N	?	N	?
16. Do the conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y	N	Y	N	Y	?	N	Y
17. Does the study discuss the generalizability of the results to other settings and patient/ client groups?	N	N	N	N	N	N	N	Y	Y	N	N	N	N
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	N	N	N	N	Y	N	N	N	N	Y	N	N	N
19. Are ethical and distributional issues discussed appropriately?	N	N	N	N	N	N	N	N	N	N	N	N	N

6. Critical Appraisal of Company Submissions

Three companies submitted economic models to NICE, Astellas, Novartis and Bristol Myers Squibb.

6.1. Astellas submission

6.1.1. Overview

The submission compared twice-daily immediate release (IR) tacrolimus (Prograf) with once-daily prolonged release (PR) tacrolimus (Advagraf), and against belatacept, everolimus and sirolimus. IR-tacrolimus 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 PR-tacrolimus relative to the current standard regimen, IR-tacrolimus, since the former became available in 2009. In addition, everolimus was included in the evaluation despite its lack of market authorisation in the UK, as requested by the NICE scope.

The analysis found that IR-tacrolimus resulted in reduced total costs and health benefits relative to the comparators, everolimus and belatacept, while PR-tacrolimus was concluded to be cost effective and should be the new standard of care.Although the health benefits of IR-tacrolimus were found insufficient to compensate for its increased cost relative to sirolimus, the latter regimen was consider to apply only to a selected subgroup of adults receiving a kidney transplant.

The submission pointed to evidence on the relationship between treatment adherence and acute and long-term graft rejection, and graft failure as surrogate markers of outcomes. In particular, it 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.[341] This is then used to translate the observed improvement in adherence with PR tacrolimus relative to IR tacrolimus (Kuypers et al. 2013) into graft and patient survival benefits.[342] In addition, the company claims that PR-tacrolimus has a better pharmacokinetic profile than BID tacrolimus (lower intra-patient variability (Wu et al. 2011), which results in a lower risk of long-term graft failure (Borra et al. 2010).[343 344] The company also cites analyses from the Collaborative Transplant

Study (CTS) for Europe presented at the 2014 World Transplant Congress, which shows that people treated with PR-tacrolimus had higher patient and graft survival rates than people treated with IR-tacrolimus 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). [345] The company argues that these estimates may have been the result of people 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 PR-tacrolimus with IR-tacrolimus (Kramer 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. [72] It is noted, however, that the latter evidence had no bearing on the meta-analysis finding of a higher relative risk of PTDM with tacrolimus than ciclosporin.

6.1.1.1. Efficacy and effectiveness evidence

The submission reports a systematic review of the RCT evidence of effectiveness of immunosuppression after first kidney-only transplant. The review involved an electronic search of bibliographic databases covering studies published during the period 2002 to June 2014, and was complemented by relevant studies from two published reviews (Woodroffe et al., 2005, and Webster et al., 2005). [60 346]

Based on 6 month and 1 year pooled data from 19 RCTs including 3796 people, IR tacrolimus had a lower rate of BPAR than ciclosporin ME (RR 0.69, 95% CI: 0.57-0.82). However, based on data from 10 studies which reported the outcome in 1859 people, IR tacrolimus resulted in higher incidence of PTDM (1.57, 95% CI: 1.16-2.12). In terms of other outcomes (graft survival, patient survival, and death censored graft survival) differences were found not to be statistically significant at the 5% level.

Pooled effect estimates for IR tacrolimus vs. sirolimus given as a CNI avoidance regimen, were obtained from 4 RCTs of 6-12 months follow-up involving 1,397 people. Neither patient survival nor PTDM differed in statistically significant manner between the arms, whereas sirolimus produced a higher risk of developing acute rejection (RR 2.28, 95% CI: 1.37-3.79) and lower survival probability (RR 0.95, 95% CI: 0.92-0.98). In the sirolimus CNI minimisation

regimen, 2 studies were found, involving 461 people in the comparison of IR tacrolimus/Sirolimus/steroids vs IR tacrolimus/MMF and steroids. No differences were found in patient and graft survival, acute rejections, and PTDM at 6-12 months post-transplant, whereas more discontinuations were found in the former arm.

For the comparison between PR tacrolimus and cyclosporin ME, the submission cites one multicentre study that compared these two options and an IR tacrolimus option, all in combination with MMF and steroids. The study found similar efficacy across the three treatment arms in terms of patient and graft survival and acute rejection but there is no measure of uncertainty reported alongside the respective event rates presented.

Astellas present results from their own meta-analysis of two studies comparing IR-tacrolimus vs PR- tacrolimus for *de novo* kidney transplantation in terms of BPAR stratified for people with (RR 1.16, 0.82, 1.63) and without induction (RR 1.28, 95% CI: 0.98-1.68). They cite results of a published meta-analysis that included observational data (Ho et al. 2013), as consistent with the claim that PR- tacrolimus is as effective as IR-tacrolimus in preventing BPAR and graft failure at 12 months post kidney transplantation.

For the tacrolimus minimisation versuss everolimus comparison, no difference in patient and graft survival at 6-12 months was found in three studies involving 358 people (RR, 1.01). The submission also cites results from the ASSET trial (Lenger et al., 2012) regarding a higher 12 month rate of BPAR (RR 2.19, 95% CI: 0.20-23.77) with a low dose tacrolimus with everolimus regimen vs. standard dose tacrolimus with everolimus (both regimens were given from 3 month post-transplantation after an initial three month regimen of standard TAC). [255] For the comparison of Tacrolimus withdrawal with everolimus introduction versus the continuation of an initial three month regimen of tacrolimus, MPS and steroids, one study was cited (Ruiz et al., 2011) as reporting no graft failure or patient death in either group at 12 months; renal function by eGFR of 53.38 ml/min in the tacrolimus continuation group and 57.27 ml/min in the everolimus group (p=0.25); no BPAR case in the tacrolimus group and 17.5% incidence in the everolimus group (RR 0.05, 95% CI: 0.00-0.79). [258] Given the absence of RCTs of tacrolimus vs. everolimus, Astellas estimated their relative effects indirectly from head-to-head studies of everolimus plus low-dose ciclosporin vs standard ciclosporin (two studies, reporting RRRs between 0.98 and 1.01 for AR, graft and patient survival outcomes at 3-12 months) and studies of tacrolimus vs. ciclosporin.

Likewise for tacrolimus versus belatacept, estimates were obtained from indirect comparisons, through studies of each of these regimens against ciclosporin. The tacrolimus studies have been described in this section. As for belatacept, data from two phase III trials

with three year follow-up data were used for the indirect comparison, one included adults receiving a living donor or standard criteria deceased donor kidney (BENEFIT study), and the other was a study of similar design but included extended criteria donors (BENEFIT-EXT study). The company presented separate and combined results of analyses of 1-year data from both trials stratified by a more and a less intensive belatacept regimen. In general, belatacept was found to have higher BPAR rates, less chronic allograft nephropathy (for the more intensive belatacept regimen) and improved renal function over ciclosporin. Belatacept also reduced the incidence of NODAT.

Combining up to 1-year results from BENEFIT and BENEFIT-EXT, the meta-analysis of IR tacrolimus vs. ciclosporin (n of studies: AR, 19; Graft survival, 11 ; Patient survival, 10, Weighted mean difference in GFR, 2), and outcomes of PR tacrolimus vs ciclosporin from the phase III trial reported by Silva et al. (Silva et al. 2007), PR-tacrolimus was found to result in a lower ARR (RR, 0.24 95% CI: 0.12-0.51), and lower weighted mean differences in GFR (mean difference -10.50, 95% CI: -16.57,-4.43) than both the more intensive and less intensive belatacept regimens. [347], The company also cites the results of an indirect comparative analysis conducted by Bristol-Myers Squibb that showed 'no significant difference' between belatacept and tacrolimus for mortality, graft loss or GFR at 12 and 36 months (AWMSG 2012), and higher ARR and lower incidence of NODAT for belatacept than tacrolimus.[348]

Another indirect comparison by Astellas produced estimates of acute rejection, graft survival and patient survival for IR-tacrolimus relative to everolimus. The RRR (95% CI) were respectively 0.70 (0.48, 1.03), 0.97 (0.93, 1.03) and 0.98 (0.95,1.02).

6.1.1.2. 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 EED, The Cochrane Collaboration, Medline and other database not specified) it identified and included in its review 12 "representative studies because they met the inclusion criteria" (Astellas' submission p.28 Chapter 8 Review of economic studies – it states that 11 studies were included in the review but 12 are actually cited). No details were provided about the inclusion criteria for the review of economic studies; such criteria, therefore, presumably refers to criteria employed for the effectiveness review in the submission. One of the included studies compared IR tacroliums vs. PR tacrolimus (Abecassis et al., 2008; this study is reviewed in section 1.2) [307] four studies

compared Tacrolimus vs. ciclosporin (three of which met the criteria for inclusion in the review of section 1.2 Craig et al. 2002, Lazzaro et al. 2002, Orme et al. 2003, the remaining study was excluded from the review of section 1.2 because it only measured costs for medication Hardinger et al., 2005),[108 309 316 318] and seven studied sirolimus in CNI avoidance or minimisation strategies versus tacrolimus (four included in the review of section 1.2: Earnshaw et al. 2008, McEwan et al. 2006, Jurgensen et al. 2010, Jurgensen et al. 2014,[319 323 333 340] and three that were excluded from it due to the country to which they apply: Gamboa et al. 2001, Rely et al. 2012, and Niemczyk et al. 2006, from Colombia, Mexico and Poland, respectively [349-351]

The submission briefly described the main results of these studies without critically assessing their validity and applicability to a UK setting, although a warning is issued about 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. 2008, Rely et al. 2012 and Gamboa et al. 2011) share the characteristics of models described and discussed in section 4.2 (one of them Earnshaw et al. 2008 is reviewed in that section). [349 350 352]

6.1.1.3. Economic Evaluation by the company

The cost-effectiveness analysis submitted by Astellas is an update of a published Markov model-based assessment of the cost-effectiveness of tacrolimus, in either its prolonged release formulation, PR-tacrolimus, or the current standard therapy of immediate release (IR-tacrolimus) by Moduma et al. (2014), reviewed in section 5.2.[322] 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. The submission extends the effectiveness review for the model from June 2013, the cut-off date of the published study (Moduma et al., 2014), to June 2014. In addition, the analysis in the submission to NICE adds Everolimus in a CNI minimisation regimen to the list of treatments evaluated in the published paper.

Efficacy data used in the model

The model represents differences in outcomes between regimens as caused by their impact on biopsy confirmed acute rejection (BCAR). The model was based on the assumption that

the effects of treatment on this surrogate outcome lasted only for the first year post-transplantation. This assumption, was combined with a) the estimated relative risk of graft failure for a functioning graft with previous BCAR versus no previous BCAR and b) the 1-year post-transplant BCAR frequency, both from estimates reported by Opelz et al. [339], to derive the graft survival curves for grafts without prior AR and grafts with history of AR from the 5-year graft survival profile in UK registry data (NHSBT 2013). The model extrapolation was complemented by using exponential survival curves to extend survival from 5 years up to 25 years post transplantation.

With regard to patient survival, the model used the 1, 2 and 5-year post-transplantation survival rates from the NHSBT Report 2012-2013[353] 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 people on dialysis followed for 10 years from the UK Renal Registry.[3] The graft and patient survival rates were extrapolated to 25 years by estimating an exponential curve on the available data (including graft survival rates for years 3 and 4 derived by linear interpolation) and projecting survival rates from the last observed rate with the estimated curve. There is no mention in the submission about adjusting for increases in background mortality as the cohort in the model ages.

In addition to the difference in efficacy, measured in terms of AR rates, the model allowed for differences in effectiveness between the tacrolimus arms through the differences in adherence induced by the once daily, prolonged release (Adagraf) vs. the two daily immediate release formulations of the drug (IR-tacrolimus). The model employed comparative estimates of adherence with PR-tacrolimus vs IR-tacrolimus of 88.2% vs 78.8% from a published study (Kuypers et al. 2013) and combined them with an estimated relative risk of graft failure in non-adherent vs adherent people 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 5 and, by exponential curve extrapolation, thereafter) that were common to all other immunosuppressive treatment strategies in the model. [342 354]

There are two logical inconsistencies with this modelling procedure. First, accounting for the advantages in adherence with PR-tacrolimus over IR-tacrolimus makes comparison of PR-tacrolimus with 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).[355] Thus regardless of the validity of the comparative analysis of PR-tacrolimus and IR-

tacrolimus, the indirect comparisons of model results between PR-tacrolimus and Sirolimus, Everolimus and Belatacept are then invalid.

Second, while the model was adjusted to include the effect of adherence on graft survival in the PR-tacrolimus vs IR-tacrolimus 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 questionable assumption that improvements in graft survival, such as those obtained with PR-tacrolimus relative to IR-tacrolimus (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 PR-tacrolimus and overestimating its costs.

Inspection of the Excel model spreadsheets revealed that the tacrolimus drug regimen options (PR-tacrolimus and IR-tacrolimus) and everolimus were the only treatment arms populated by data on actual immunosuppressive drug use (from the RCT sample on which the efficacy for the regimen was estimated); drug consumption values for belatacept and sirolimus regimens were based on treatment guidelines (BNF or summary of product characteristics).

Table 147. One-year acute graft rejection rates used in the model

Product	Rate, %	Comment
IR-tacrolimus (base comparator)	12.6	[72] [87] [237]
PR-tacrolimus	14.6	[72] [87] [237] and meta-analysis (Section 2 of company submission)
Belatacept	30.7	[72] [87] [237] and meta-analysis (Sections 2, 3)
Everolimus (CNI minimization)	18.0	[72] [87] [237] and meta-analysis (Sections 2, 3)
Sirolimus (CNI minimization)	16.5	[72] [87] [237] and meta-analysis (Section 2)
Sirolimus (CNI avoidance)	28.7	[72] [87] [237] 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) but no disutility. The adverse event incidence rates in the model, reproduced in Table 148, 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), the values adopted by the published economic model for Germany by Jurgensen et al. reviewed in section 1.2 of the company's submission (Jurgensen, et al. 2010), and trial outcomes from the BENEFIT and BENEFIT-EXT trials (Vincenti 2010, Durrbach 2010).[134 203 340 356].

Table 148. Adverse events in the Astellas model (%)

Product	Adverse event	Year 1	Year 2	Year 3 and
PR-tacrolimus/IR-tacrolimus	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	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}[258], Jürgensen et al. 2010, Vincenti et al.2010, and Durrbach et al. 2010.

The rates of adverse events were assumed to be the same with PR-tacrolimus and IR-tacrolimus and for the two sirolimus regimens (CNI avoidance and CNI minimisation). According to the incidence rates 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.

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 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 people on dialysis, and peritoneal dialysis (0.53), received by the rest.[357]

The model allows for the occurrence and effects of re-transplantation, using the time to re-transplantation data reported by McEwan et al. (McEwan et al. 2005, 2006) that was reviewed in section 4.2 of this review. 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.[332 333] This is likely to bias 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.

In addition, one incorrect calculations was identified in the excel spreadsheets of the model submitted by Astellas. The problem was that 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 25, p. 35 in the submission by Astellas) to populate the patient survival parameters of people with a functioning graft, ignoring the fact that such data on survival rates were likely to include deaths from both people 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 people with a failed graft. In other words, the Astellas model is likely to overestimate mortality in the functioning graft states, which in turn underestimates the benefits of any gains in efficacy (i.e. reductions in AR in the model) that any regimen may have over another (e.g. tacrolimus over the comparators).

Unit costs

The cost per milligram of PR-tacrolimus used was 23% lower than that of IR-tacrolimus. (The authors present sensitivity analyses of discounts on tacrolimus list prices limited to the first

90 days post-transplantation). Prices for other immunosuppressant regimens were based on BNF prices.

Treatment of acute rejections was assigned costs of IV steroids plus, for the 20% of steroid resistant BPAR cases, the treatment costs of a regimen of rATG and an inpatient hospital stay for acute kidney injury without complications (£1737 overall mean cost). This assumed zero medical management costs for the 80% of people with steroid-sensitive AR, ignores any costs of follow-up to monitor treatment efficacy. The cost per year of dialysis was £38,387 and the cost of re-transplant was £25,953. The costs of adverse events adopted are presented in Table 149 (which reproduces Table 35 in the Astellas submission).

Table 149. Costs of adverse events (per year)

Variable	Value	Comment
Malignancies	£8,801	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.
Cytomegalovirus (CMV) infections	£1,863	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	£1,186.61	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.

Results

The Astellas submission produces life expectancies (censored after 25 years) of 16.60 for tacrolimus (IR-tacrolimus), 16.57 for sirolimus CNI minimisation, 16.56 for everolimus, 16.48 for sirolimus CNI avoidance, and 16.47 for belatacept in a cohort of people of mean age 45, 37% of whom are women. The expected discounted (at 3.5%) QALYs were 8.01, 7.99, 7.99, 7.94 and 7.94, respectively. For tacrolimus once-daily prolonged release formulation (PR-tacrolimus), total life expectancy was 16.96 and discounted QALYs 8.21.

In the base case results, IR-tacrolimus produced more QALYs than any of the comparators and lower costs than Belatacept and Everolimus, whereas it had higher cost against the Sirolimus regimens. The ICER against Sirolimus CNI minimisation strategy was in excess of £1 million and the ICER against Sirolimus CNI avoidance strategy was £174,842. In the

comparison of tacrolimus regimenss, PR-tacrolimus dominated IR-tacrolimus, given its lower costs and higher QALYs (both discounted and indiscounted).

The results were found to be similar after changing assumptions, including the time horizon, from the base case of 25 years to 10, 15 and 20 years, the exclusion of discounting, 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: prolonged release tacrolimus was found to dominate Sirolimus as CNI avoidance regimen when both were given with daclizumab induction, 2 g MMF and steroids. In discussing these findings the authors note that 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 1 year than the sirolimus regimen.

On the basis of these results, the company concludes that tacrolimus is cost-effective and that PR-tacrolimus should become the standard of care as it produces lower costs and better health outcomes than IR-tacrolimus. 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 PR-tacrolimus relative to IR-tacrolimus. In addition, the authors argue that the results of the SYMPHONY trial have discouraged 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.

Critical appraisal

The analysis presented 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. However, it omits one relevant comparator: ciclosporin. There is no justification in the submission as to why this drug regimen option was not considered in the analysis. Moduma et al. 2014 presents the results of the same analysis based on data from the literature recorded in electronic databases up to one year earlier than the review in the Astellas submission (i.e. June 2013 vs June 2014, respectively). [322] The results reported by Moduma et al., who acknowledge employment by Astellas in the publication, are very similar to those presented by the Astellas submission for those drug regimens that were common to both reports (i.e. PR-tacrolimus, IR-tacrolimus, belatacept, sirolimus CNI minimisation and

sirolimus CNI avoidance). Unlike the Astellas submission Moduma et al. report results for ciclosporin. The ICER of IR-tacrolimus against Ciclosporin was £21,244 (Moduma et al. 2014, Table 1, base case results) and the cost-effectiveness acceptability curve for the comparison showed that the tacrolimus option had a 59.5% probability of being cost-effective at the £30,000 willingness to pay for a QALY threshold. The sensitivity analysis showed that the result of this comparison was sensitive to the inclusion of the adverse event costs; i.e.when omitting them altogether the ICER for tacrolimus increased to £35,446.

This evidence cast doubt on the robustness of the cost-effectiveness results and conclusions in the Astellas submission, and suggests that the results presented may be misleading due to the exclusion of a relevant comparator. It is unfortunate that the submission did not include cyclosporin, given the previous published degree of uncertainty in the cost-effectiveness of tacrolimus.

There is use of inadequate data within the model. As discussed above the estimates of patient survival in the functioning graft state may have been underestimated. This works against the more efficacious treatments such as tacrolimus, which had the lowest AR rates of all the regimens compared. 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 PR-tacrolimus, this may suffer from the previous criticism about the incomplete set of comparators, and the fact that the PR-tacrolimus vs IR-tacrolimus comparison is based on what is in effect a different model of the outcomes of renal transplantation from that used to compare IR-tacrolimus against all the other regimens. In fact, the model used for comapring PR-tacrolimus vs. IR-tacrolimus contradicts the fundamental premise of the model used to compare IR-tacrolimus with all regimens other than PR-tacrolimus: 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 people 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.

Another concern relates to how the timing of transplantation was implemented in the model. Markov models 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 of calculation of expected costs and benefits that arise from having a long cycle length given the frequency of state transitions. The model, however, assumed that the proportion of people who undergo re-transplantation in the very first cycle 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 people with de novo kidney transplants, 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, that is a minimum of two cycles, one for each event, is required.

In summary, the main limitations of the Astellas economic analyses are:

- Omission of ciclosporin as a relevant comparator (without justification)
- Patient survival estimates in the functioning graft state may have been underestimated, which works against treatments with low rates of AR like tacrolimus. The underestimation is in part due to an error in using UK registry data on survival rates from people with both functioning and failed grafts to inform the survival rates for those in the model with a functioning graft.
- The analyses comparing the extended-release tacrolimus regimes with other non-tacrolimus regimes are invalid, because whereas the two tacrolimus regimes incorporate differences in treatment adherence this is not accounted for in the other regimes.
- Drug dosage levels for belatacept and sirolimus were based on treatment guidelines whereas for other regimes they were based on actual trial data.
- The cost and HRQoL of dialysis was not included for recipients of second or subsequent transplantations.
- The analysis does not account for the role of graft function in a) long-term graft survival outcomes and b) current costs and utilities.

6.2. Novartis submission

Novartis, the company that produces everolimus submitted a simulation model of an individual patient's health experience for the lifetime remaining after renal transplantation in the English NHS. The following treatments were evaluated for a group of simulated people of mean age 45.7 years (SD 12.7), mean weight 70 kg (SD 10), 68.5% of whom were male, and mean DMRD eGFR 9.03 mL/min/1.73m^2 (SD 7.9):

- Everolimus + reduced dose ciclosporin + steroids vs.
    - Tacrolimus + MMF + steroids
    - Standard dose ciclosporin + MMF + steroids.
- Micophenolate acid (enteric coated) + standard dose ciclosporin + steroids vs.
    - Standard dose ciclosporin +MMF+ steroids

The model was specified as monthly transitions between six health states:

- stable post-transplant state (functioning graft),
- acute rejection,
- graft failure,
- dialysis,
- retransplantation and
- death (from CKD or other causes).

Moving between these states is associated with changes in direct healthcare costs, while HRQoL (utility) changes are accounted for transitions between the states of having a functioning graft to a failed graft, and from any of these to the absorbing state of death. In addition, the model accounts for the changes in mortality risks, utilities and monitoring costs (outpatient specialist visit) with renal function. While the costs associated with adverse events emerging following transplantation were measured for six type of events (proteinuria, BKV infection, CMV infection, hyperlipidaemia, wound, and hypertension), only for two of these was the loss of utility measured in the analysis (proteinuria and hypertension).

The model assumes that acute rejection may happen up to 3 years after a transplant, and applies the same probabilities of this type of event to first and subsequent transplantations. The probability of chronic rejection (i.e. graft failure) is independent of renal function in the model. Once a patient's graft fails dialysis is started and given until the time a new transplant is received, which is determined by a random normal distribution process with mean 36 and SD 12 months. This feature of the model is what gives it its discrete event simulation nature.

The model allows different rates of change in renal function (eGFR) between the first year (during which they are specific to the immunosuppressive treatments), the second, and the third and subsequent years, when the rate of eGFR change is common to all treatment arms in the model.

The model parameters for the everolimus and Micophenolate acid regimens were populated with efficacy and safety outcomes at 12 months from the study by Tedesco-Silva et al. 2010,[358] a multi-country trial that compared everolimus 1.5 mg/day against micophenolate acid 1.44 g/day in people receiving a primary kidney-only transplant in the period October 2005-October 2008. The values for the tacrolimus regimen were obtained from a trial reported by Larson et al. [209] that compared tacrolimus with sirolimus in people receiving a kidney-only transplant (79% of whom were primary transplants in the tacrolimus arm) in the period April 2001-January 2004 in the US. The source of the efficacy and safety data for the MMF regimen was the multinational trial report by Vitko et al. 2004, which compared Everolimus with MMF in primary transplant patients who were recruited between August 1998 and August 1999.[142]

The indirect nature of the relative efficacy data used as inputs to the cost effectiveness model of the three comparisons submitted by Novartis presents some problems for valid estimation. In addition to the different dates when the respective trials were conducted and the type of transplant (primary-only or mixed) for the everolimus vs. tacrolimus comparison, there were differences between the two studies in terms of the use of induction. Tedesco-Silva et al. reported that participants in their trial of everolimus were administered two basiliximab 20mg doses, one within two hours before transplantation and the other at four days post-transplantation, "or according to local practice" [359], whereas Larson and others reported that all people received thymoglobulin 1.5 mg/kg/day on days 0, 1, 2, 4, and 6 post-transplant.[209] The sample of tacrolimus participants was also slightly older but more balanced in terms of gender and had a higher proportion of living donor transplants. The major issue, however, is the fact that the actual amount of tacrolimus use in the efficacy trial was different from the dose used to cost the same regimen in the model. Larson et al. report that the tacrolimus was started at a 3mg twice daily.[209] The estimated mean daily dosing at one year,

separately reported for the first 59 people randomised to tacrolimus, was 6.3 (SD 0.9) mg per day (Dean et al. 2004). The model however, applied costs to the tacrolimus arm at a quoted BNF recommended dose of 0.25 mg/kg/day for a group of individuals of 70 kg mean weight, thus resulting in a mean daily dose of 17.5 mg which is considerably higher than the actual drug use that corresponds to the efficacy outcomes used by the model. The dose behind the tacrolimus drug acquisition costs used in the Novartis submission is also larger than the mean daily doses for IR-tacrolimus reported by Silva et al. [347], which Astellas adopted in their submission and that are consistent with the report of Dean et al. [360].

In relation to the data sources for the comparison of everolimus with the MMF and cyclosporin regimen, the respective trial samples differ in terms of the period covered by the study and the country mix. The proportion of cadaveric donors transplant recipients was 46.6% in the everolimus group vs. >90% in the MMF with ciclosporin one.[141]. Moreover, the MMF regimen was given without induction therapy, in contrast with the trial which provided the outcome data for the everolimus model arm (Tedesco-Silva et al. 2010). [358] The same issues applied to the comparison of micophenolate acid vs. MMF and ciclosporin since the data source for micophenolate acid was the same trial as that for everolimus (Tedesco-Silva et al. 2010).

Costs

Immunosuppressive costs of the micophenolate sodium and everolimus treatment regimens were based on the dosing protocols of the individual trial that was the respective source of efficacy data, whilst the costs of drug acquisition for the comparators, i.e. the tacrolimus regimen and MMF with ciclosporin regimen, were based on BNF recommended starting dosages. Other healthcare costs included the costs of monitoring GP visits, which increased with higher CKD state. The cost of an acute rejection event was taken from that reported by McEwan et al. [332]. The annual costs of dialysis, £22,877 were obtained from a 2011 NICE costing report on organ donation for transplantation.[361] Re-transplantation involved an estimated cost of £17,736, a weighted average of NHS Reference costs 2012/2013 for transplant procedures for varying ages and donor types.

Utilities

Estimates of utilities were derived from the study by Neri et al. [362], who reported EQ-5D health states measured in a cross-sectional study of people with kidney-only transplants in the UK, valued using UK tariffs, as a function of CKD states. As renal function deteriorated so did the HRQoL (utility) values experienced by the simulated patient in the model. The

model accounted for negative impacts on HRQoL (disutilities) of two adverse effects, proteinuria (reduced utility by 0.043) and hypertension (reduced utility by 0.010).

Results

- Everolimus + reduced ciclosporin vs. tacrolimus + MMF

Novartis reports a life expectancy at transplantation in a patient group of mean age 45.7 years (SD 12.7) of 25.71 life years under the everolimus immunosuppression vs. 23.39 life years under tacrolimus, and discounted QALYs of 8.86 and 7.37, respectively (Novartis submission Table 5.18 Base case analysis – deterministic ICERs). Given the respective discounted costs per patient that result under these options, £135,358 for everolimus and £140,972 for tacrolimus, everolimus was found the preferred, option since it is less costly and more effective than tacrolimus.

Further results accounting for uncertainty in model inputs relating to uncertain parameters (acute rejection rates, chronic rejection rates, rate of change in eGFR after 12 months post-transplant, health state utilities, and event costs) confirmed that the probability of everolimus being cost-effective was 100% at thresholds ranging from 0 to £200,000 per QALY.

- Everolimus + reduced ciclosporin vs. MMF + standard dose ciclosporin

The everolimus regimen was found to produce 1.76 extra years of life over the MMF with ciclosporin regimen in the base case of a cohort of mean age 45.7. This corresponded to 0.99 extra discounted QALY (Novartis submission Table 5.18 Base case analysis – deterministic ICERs). The everolimus containing triple therapy was also associated with £59,354 extra discounted costs over the MMF with ciclosporin regimen, and a practically identical ICER figure, given the 0.99 discounted QALY benefit with everolimus.

In probabilistic sensitivity analysis accounting for the uncertain parameters (as listed for the results of the everolimus vs. tacrolimus comparison), the everolimus had a 0% probability of being cost-effective relative to MMF for cost-effectiveness thresholds ranging from 0 to approximately £86,000 willingness to pay per QALY, and was still below 15% at £200,000 per QALY.

The fact that the probabilistic sensitivity analysis yielded a willingness-to-pay per QALY threshold at which everolimus had a 50% chance of being cost-effective (> £200,000 per QALY) that was more than 3 times its deterministic ICER of £59,354 indicates that the model has important nonlinearities and that using the deterministic values for decision making is

incorrect. Although neither in this comparison nor the previous one discussed (i.e. everolimus vs. tacrolimus) would this warning have made any difference to a decision based on a £30,000 per QALY threshold (i.e. both determinist and probabilistic results led to the same conclusion), the distinction does matter for interpreting the results of the third comparison presented by Novartis, of EC-MPS vs. MMF, discussed next.

- Enteric coated micophenolate acid vs. MMF + standard dose ciclosporin

In the deterministic, base case analysis the micophenolate regimen was found to result in 25.48 life years, and 8.69 discounted QALYs per patient (Table 5.18 Base case analysis – deterministic ICERs). Micophenolate acid had an extra 1.31 life years and 0.80 discounted QALYs per treated patient relative to MMF. Given its additional discounted costs of £10,588, everolimus had an ICER of £13,209 per QALY relative to MMF with ciclosporin.

In the probabilistic sensitivity analysis that accounted for the effect of uncertain parameter estimates (as listed in the results of everolimus relative to tacrolimus) micophenolate acid had a 50% chance of being cost-effective at a threshold value of around £28,000 willingness to pay per QALY.

Although the determinstc ICER for micophenolate acid is below the lower cost-effectiveness threshold adopted by NICE (£20,000), the willingness to pay threshold corresponding to the 50% probability of micophenolate acid being cost-effective in the probabilistic sensitivity analysis is ~£28,000) suggesting that everolimus may be borderline cost-effective, in relation to the £30,000 maximum acceptable amount NICE is willing to pay for a QALY. This comparison shows that the deterministic results are potentially midleading for informing decisions or deriving model predictions about treatment outcomes in this model.

Critique

The Novartis model uses a patient simulation model of monthly cycles to calculate the costs and health outcomes of immunosuppressant regimens over the remaining lifetime (i.e. 50 years post-transplantation). The main strength of the model is its account of the occurrence of clinical events that determine health status, i.e. acute rejection, graft and patient survival, as well as the effect of renal function on costs and health related quality of life.

The study failed to conduct adequate evidence synthesis, since their methods of identification of relevant evidence on efficacy was not systematic, as acknowledged by the authors. The model analyses were based on data from single trials, and their analyses were restricted to undertake pairwise indirect comparisons of the treatments investigated in each

of those individual trials. This led to results that were at odds with findings from the systematic review of the clinical evidence undertaken by PenTAG (section 4.4.1) which found no statistically significant improvement in efficacy outcomes (acute rejection, graft failure, death) of EC-MPS vs MMF, whereas the Novartis model-based analysis produced an extra 1.31 life years for EC-MPS. Therefore, the results by Novartis are likely to be biased, and consideration of additional efficacy evidence from direct and indirect comparisons would have allowed the company to provide a more reliable technology assessment.

Some errors were identified in the calculation of unit costs of immunosuppression for the ciclosporin component of the everolimus regimen, which was common to two other comparators, but was is not part of the current standard clinical practice in England. This had the effect of underestimating costs for the ciclosporin containing regimens.

The model accounted for some important adverse events, but omitted one of the most important determinants of patient and graft survival: post-transplant diabetes mellitus (PTDM).

A major flaw in the model is the assumption that graft failure occurs independently of the graftt function or the occurrence of acute rejection. The probability of graft failure (labelled chronic rejection in the submission) is based on 12-month post transplantation trial data for each regimen, which, given that this probability is constant over the 50 year time horizon of the model, casts serious doubt about the validity of the findings.

In summary, the main strength of the Novartis analysis is its account for the effect of differences in graft function between treatment arms on current costs and utilities. Its main limitations are:

- The use of treatment effectiveness data from single selected RCTs, not systematic reviews or meta-analysis, and based on pairwise indirect comparisons of those trials. The estimated effectiveness of EC-MPS versus MMF is therefore substantially greater than that estimated from the assessment group's systematic review and meta-analysis.

- The model structure contains the assumption that graft failure occurs independently of graft function or the occurrence of acute rejection. Instead, the probability of graft failure is based on the trial-derived rates at 1 year post-transplant, which are then assumed to remain constant throughout the modelled period.

- Regimens involving ciclosporin (including the everolimus regimen) had incorrect unit costs for ciclosporin; this would underestimate the cost of those regimens
- The estimate of the annual cost of dialysis is from an unusual source, and substantially lower than current costs as in the NHS reference costs.
- The adverse event PTDM is not included in the model (despite others being included)

6.3. BMS submission

The following regimens, all following basiliximab induction, were compared in the Bristol Myers Squibb (BMS) submission:

- Belatacept (less intensive dosing (LI))+ MMF + steroids *vs* Ciclosporin +MMF + steroids
- Belatacept LI + MMF + steroids vs. Tacrolimus (immediate release) + MMF + steroids

Two patient populations were studied, namely standard criteria donor recipients, and the extended criteria donor recipients of de novo renal transplants. In addition the submission presented subgroup analyses for people of weight >90 kg.

In their review of the effectiveness evidence the company justifies its exclusion of sirolimus from the analysis arguing that in practice, its use "is generally restricted to treating renal transplant patients whose renal function is steadily declining on tacrolimus or ciclosporin, and in whom other measures (such as dose adjustment) have not been successful" (BMS submission Chapter 3, Efficacy section). As for tacrolimus extended release, the company argued that there was insufficient direct or indirect evidence to include it as a comparator. Everolimus was excluded from the analysis due to its lacking UK marketing authorisation. As for MMF and micophenolate sodium, the company states that they were not included as comparators because they are required to be given with corticosteroids as part of triple therapy containing belatacept, tacrolimus or ciclosporin.

The evidence used to populate the efficacy and safety parameters in the model used in the BMS analysis were derived from the BENEFIT (Vincenti et al., 2010[54]) and BENEFIT-EXT (Durrbach et al., 2010[135]) trials, which compared belatacept with ciclosporin. The efficacy and safety parameter values for belatacept relative to tacrolimus immediate release were obtained from indirect comparisons in a network meta-analysis of 32 studies, 29 of which

compared tacrolimus with ciclosporin and three (including BENEFIT and BENEFIT-EXT) studies of belatacept vs. ciclosporin.

In making the case for belatacept the submission argues that the intravenous mode of administration is likely to result in increased adherence with treatment relative to tacrolimus and ciclosporin, which are administered orally and require routine monitoring to drug exposure and dose adjustment. The company claims that this would be expected to result in improved outcomes with belatacept over the CNI comparators. Further, in setting the context of the economic evaluation (BMS submission Chapter 6, Cost-effectiveness of belatacept) the company states that the drivers of the evaluation were:

- The acquisition cost of belatacept
- The number of years of functioning graft
- The costs and utility (health related quality of life) of dialysis following graft failure

which led them to perform subgroup analyses in those whose expected graft survival is short. Therefore, because "post-transplant renal function is a well-established predictor of graft survival this analysis focused on people with a post-transplant eGFR <30ml/min/1.73m^2 as these people represent those for whom improved post-transplant renal function is most likely to have significant health and cost benefits."

The analysis is based on the 3 year outcomes from the pooled data from BENEFIT and BENEFIT-EXT, including renal function (eGFR), the cumulative incidence of NODAT, Acute Rejection, PTLD, graft failure and death, where eGFR <15/ml/min/1.73m^2 was assumed to identify people with graft failure. The Markov model developed by Levy et al.[330] was then used to extrapolate these outcomes to the long term. To avoid repeating the description in section 5.1.2.1, the main features of this model are summarised here.

The model represents annual transitions among the following health states:

1. Functioning graft (including distinguishing four categories of renal function according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative [NKF-KDOQI])
    - GFR stage 2 = GFR ≥ 60 mL/min/1.73m^2.
    - GFR stage 3a = 45 mL/min/1.73m^2 ≤ GFR < 60 mL/min/1.73m^2.
    - GFR stage 3b = 30 mL/min/1.73m^2 ≤ GFR < 45 mL/min/1.73m^2.

- GFR stage 4 = 15 mL/min/1.73m^2 ≤ GFR < 30 mL/min/1.73m^2.

2. Graft failure/Dialysis defined as:

   - GFR stage 5 = GFR < 15 mL/min/1.73m^2.

3. Functioning re-graft/Re-transplantation.

4. Death.

The probabilities of transitions between these states were populated by time to event models estimated by Levy et al. using US registry data.[330] The survival models were the following:

- Weibull time to event models for graft survival (two models, a) graft failure 1-4 years after transplant, and b) graft failure >4 years)

- Weibull time to event model for patient survival (two models, a) death with a functioning graft 1-4 years after transplant, and b) death with functioning graft >4 years)

- Exponential survival model of time from graft failure to re-transplant

- Exponential survival model of time from re-transplant to graft failure

- Exponential patient survival on dialysis (after graft failure)

- Exponential patient survival after re-transplant

The Weibull survival model adjusted for covariates including patient age, sex, baseline eGFR, weight, NODAT, acute rejection events, PTLD, donor type and other, calendar year, and patient and donor characteristics.[330] The conditioning of these models' predictions on baseline eGFR allowed the derivation of separate survival curves for the different starting (i.e. at three years post-transplant) renal functioning health states in the model. In order to assign costs and utilities for each starting eGFR group, the total time spent with a functioning graft predicted from the survival models (adjusted for death risks) was allocated to different eGFR categories by assuming that eGFR declined linearly over time from its starting level (the midpoint of the starting eGFR stage) until reaching graft failure, which was associated with an eGFR level of 15 mL/min/1.73m^2. Thus, for example, the group of people who entered the Markov model in the GFR stage 2 (at three years post-transplant), at the midpoint GFR level of 67.5 mL/min/1.73m^2 ; among those in these group who experienced graft failure, say, on the fifth annual cycle (that is 8 years post-transplant), would be assumed

to have traversed from eGFR stage 2 to eGFR 5, at an annual rate of 10.5 mL/min/1.73m^2 (=[67.5 – 15]/5). Thus, the members of this illustrative group of modelled people would have made a transition from GFR 2 to GFR 3a stage in the first year (at the end of which they would reach a GFR level of 57), remain in eGFR during the second year (to finish it at a GFR of 46.5), then make a transition to and end the third year in stage 3b (at a GFR level of 36), make a transition to GFR stage 4 in year four (to end the year at GFR 25.5), and experience graft failure at the end of the fifth year (GFR level 15). In the model some people die without graft failure, and they were assumed to have remained in the same eGFR stage as that in which they entered the model (on the basis of regression analysis of USRDS data on which the survival models were estimated).

After calculating expected costs and outcomes in the Markov model for each starting eGFR stage over 37 years (which, added to the initial 3 year period amounts to the modelled horizon of 40 years adopted in the base case), the expected costs and outcomes for the whole population were calculated by a weighted average of the expected costs and QALYs across starting model stages. The proportions were the frequency distributions of people at 3 year post-transplant across functioning graft stages (approximated by a normal distribution using mean and standard deviation of eGFR values), dialysis stage, and death. Finally the expected costs and QALYs over the extrapolated Markov phase were added to costs and QALYs associated with the observed trial outcomes in the trial to calculate total QALYs and costs over 40 years for each trial arm in BENEFIT and BENEFIT-EXT.

Efficacy parameter estimates

The main inputs for the model were those estimated from the network meta-analysis at 36 months. These are presented in Table 150, which reproduces table in the industry submission (BMS submission Section 6.1, Model inputs - Table 28). In the model the effect of NODAT on graft and patient survival curves is accounted for by applying hazard ratios from the literature (Kasiske et al. 2013).[363] PTLD and cardiovascular disease were accounted for in the model by assigning a 50% chance of death to each of them. The sources of these estimates were not given.

Table 150. Relative effect of tacrolimus and belatacept versus ciclosporin at 36 months

	Odds Ratio (95% Confidence interval)	
Outcome	Tac vs. CsA	Bela vs. CsA
Graft loss*	0.86 (0.63, 1.17)	0.92 (0.44, 1.93)
Patient death*	1.27 (0.88, 1.89)	0.77 (0.37, 1.55)
ARE*	0.63 (0.50, 0.81)	1.57 (0.80, 3.03)
NODAT†	[redacted]	[redacted]
PTLD†	[redacted]	[redacted]
	Difference in True Mean Value (95% Confidence Interval)	
eGFR*	6.20 (0.64, 12.47)	16.04 (6.19, 25.53)

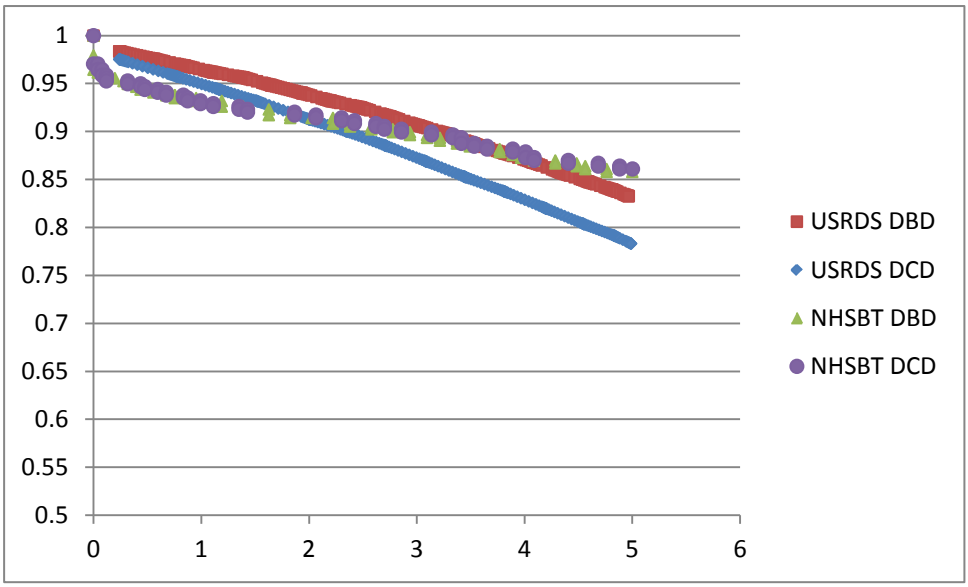
AR, acute rejection; ARE, acute rejection event; Bela, belatacept; CsA, ciclosporin; eGFR, estimated glomerular filtration rate; NODAT, new- onset diabetes after transplantation; PTLD, post-transplant lymphoproliferative disorder; Tac, tacrolimus
Note: Figures in bold are statistically significant using a 5% significance level.
*Odds ratios for Graft loss, AR, patient death and difference in eGFR are reported in Goring *et al*.[364]
†Odds ratios for NODAT and ARE are taken from the original 2009 NMA, Appendix 2.

According to the BMS submission, the distribution of the patient cohort at the start of the Markov model for each of the three regimens evaluated, belatacept, tacrolimus and ciclosporin, was calculated from the pooled BENEFIT and BENEFIT-EXT trial data on GFR outcomes at 36 months post-transplant. They assumed that GFR level followed a normal distribution to derive the distribution across functioning graft states, and used the observed means of 38.6, and standard deviation of 22.93, for ciclosporin, 54.64 for belatacept (from the BENEFIT trials) and 44.8 for tacrolimus (from network meta-analysis relative to ciclosporin). But the assumption of normally distributed GFR is problematic since it implies that in the ciclosporin arm, 4.6% of people at the end of the trial phase (and therefore at the start the Markov model phase) have a negative GFR value. However, inspection of the model's excel spreadsheets revealed that these values were not used in the model, but rather a mean of 50.80 and SD of 21.80 for ciclosporin, which implies 0.9% of people having a negative GFR value at 3 years post-transplant. The means for tacrolimus and belatacept were in turn 58.47 and 66.96, and they also applied the SD of ciclosporin, 21.80 (these imply negative GFR values for <0.4% of people).

To validate the survival curves underpinning their Markov model, which were estimated from US data, the company compared the predictions from their Weibull survival models to UK data from the NHSBT 2013 report (these have been discussed in relation to the model submitted by Astellas, submission section 6.1). The comparison covers the predicted survival

curves from the BMS model by type of donor, (donor after brain death (DBD) and donor after circulatory death (CBD)) with the corresponding UK data points at year 1, 2 and 5 post-transplant. Due to the difficulty of visualising the chart presented by BMS (BMS submission – Figure 22) the 5-year survival curves reported by the NHSBT 2013 report are reproduced in Figure 85 alongside the corresponding predictions in the survival model informing the Markov model in the company's submission. It shows that the model predictions for the donor after brain death graft survival (DBD predictions based on USRDS) converge towards actual UK data for the corresponding donor type. The model predictions based on the donor after circulatory death (DCD) patient population, however, appear to diverge from the trend observed in UK data for the respective donor type. This is of concern since predictions from this model were used to extrapolate three year trial outcomes for 37 years.

Figure 85. Validation of graft survival predictions of the BMS model (based on US data from the USRDS) with NHS data (NHSBT) by donor type.



DBD: Donor after brain death; DCD: Donor after circulatory death

Changes in eGFR stages were associated with changes in utilities and costs. Utilities were derived from a cross-sectional study of UK renal transplant patients.[336] Adverse events including acute rejection, NODAT and PTLD were given estimated annual utility losses of 0.50, 0.06 and 0.44 reported from the literature.

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Costs

The submission provides actual data on estimated costs of clinical events following transplantation in standard practice at a single centre in Wales. The analysis has been published as part of a multinational study report described in the section 5.1.2 cost-effectiveness literature review [41], which shows some common and divergent practice between this site and other European centres. Briefly, costs were estimated in a retrospective analysis of computerised records from the Cardiff Renal Transplant Database, related to all individuals aged 18 or older who received a kidney-only transplant recorded between January 1998 and December 2005. They were followed up to 3 years and the analysis included those who had at least 12 months of data recording after transplant and the data included their most recent transplant in the studied period.

The study provided evidence previously unavailable for the UK on actual costs of post-transplantation care and events stratified by GFR at 1 year post-transplant. The sample for analysis included 370 people, and for whom a variety of treatment regimens were used. The most frequent of the twenty different treatmets used in this period was tacrolimus given as part of triple therapy including steroids and either MMF (18%) or Azathioprine (19%). Tacrolimus in double therapy with azathioprine or MMF were the third most frequently used regimens (9% each). By the second year the proportion of people on these tracolimus triple regimens had declined (to 14% and 12% of the sample) while the proportion of people on the double therapy tacrolimus had increased (to 14% and 13%). The same observation was made from 24 months to the 24+ follow-up point.

Another aspect of this data source is the observed amount of tacrolimus immunosuppressant doses used over the follow up period in this sample. While for tacrolimus given as part of triple therapy alongside MMF and steroids the dose of tacrolimus was continually reduced over the first year from the mean of 10.31mg at month 1 to 6.36mg at month 12, and was 5.73mg and 5.71mg at month 24 and month 24+, the dose was kept at 11.23 mg throughtout the observation period in the triple regimen that included azathioprine (BMS submission – Appendix 5 Preliminary report PORTRAIT database study Cardiff).

On the basis of the resource use estimates from the PORTRAIT study report the tacrolimus drug regimen and the ciclosporin regimen costs were estimated. Drug use was valued at BNF 67 prices (for tacrolimus the average price of IR-tacrolimus 1 mg of 50 and 100-cap packs was used; the average price of Capimune, Capsorin, Deximune and Befloral, 30 cap packs was used for ciclosporin). Administration costs included one lab test per outpatient appointment to determine CNI level, and accounted for the observed number of outpatient

appointments in years 1, 2 and 2+. The costs of belatacept administration included the costs of IV infusion which were obtained from a previous HTA report on abatacept (from which belatacept was derived, and that has the same method and frequency of administration). Thus, the annual drug acquisition and administration costs of the regimens in the first year of the model for a 75kg patient were £13,472 for belatacept, £3,937 tacrolimus (IR-tacrolimus), and £1972 for ciclosporin. These costs were smaller in the second and subsequent years by about 30%, 25% and 15% in the belatacept, tacrolimus and ciclosporin arms, respectively.

Results of BMS analyses

In the base case results for a cohort of people with starting average age 43 years, at 40 years post initial transplant, 11% of people would be alive under belatacept, whereas that would be 8.8% under tacrolimus and 7.4% under ciclosporin. By that point, in 75.6% of people the graft would have failed under belatacept, while that would have happened in 73.8% of people under tacrolimus and 76.9% under ciclosporin. Correspondingly, 19.3% of people received re-transplantation under belatacept, 19.2% under tacrolimus and 20.6% under ciclosporin.

When comparing total discounted costs, belatacept resulted in incremental costs of £91,001 over tacrolimus and £92,216 over ciclosporin. In turn the incremental discounted QALYs were 0.62 relative to tacrolimus and 0.97 relative to ciclosporin. The incremental cost per additional QALY of belatacept relative to tacrolimus was £147,334, while that for tacrolimus relative to ciclosporin was £3,375.

These results were driven by the higher costs of belatacept immunosuppression, which, despite its associated savings in dialysis costs relative to the other regimens (£15,469 relative to ciclosporin and £2,248 relative to tacrolimus), incurred 7 and 3 times the cost of immunosuppression of the cylsoporine (additional costs £109,402) and tacrolimus (£95,159 difference) regimens, respectively. These results were confirmed by probabilistic sensitivity analyses and deterministic sensitivity analyses which showed the ICER to be insensitive to variation in uncertain parameters.

The submission presented additional analyses for a special group of people with a shorter expected graft survival that that for the overall patient population. This is referred to as ‘subgroup analysis’ by the company and implemented by defining the group as those people with GFR<30ml/min/1.73m^2 at one year post-transplant. They implement a post hoc adjustment to the model so that the effect of eGFR improvements within that range may be accounted for in the model, which originally was specified in discrete eGFR categories and

thus restricted all people entering the model in the same category to have the same benefits. The company found that in these people, belatacept results in higher benefits (0.46 extra QALYs in both comparisons) and lower costs (-£1,478 relative to ciclosporin and -£4,166 relative to tacrolimus).

However, this analysis suffers from a logical flaw. It assumes that those people who the company claims to have identified as able to benefit from their drug regimen may be identified with precision. In fact they may not. The meaningful definition of subgroup analyses in a setting where risk and uncertainty influence the outcomes of treatment such as this, so that the outputs of a decision model are mathematic expectations of cost and benefits, identifies a selected group of people for special management on the basis of observable characteristics defined at the outset. The defining characteristic of the selected group of people in the subgroup analysis by BMS is an outcome of treatment, and thus not known at the time of transplant (which would be required for sound decision making analysis about choice of maintenance treatment).

A subgroup analysis presented by BMS finds that belatacept may be cost-effective in people with body weight of approximately 90kg and more. At this body weight, belatacept use incurrs minimimal vial wastage, thus maximising effectiveness for the given cost.

Table 151. Costs and utilities by GFR in the BMS model

Functioning graft			Costs [1]	Utilities[2]
	Belatacept	Tac	Cs	
GFR 2 Year 1	5580	5,677	5,600	0.64
GFR 3a Year 1	5,637	5,735	5,657	0.58
GFR 3b Year 1	7,800	7,897	7,820	0.58
GFR 4 Year 1	8,132	8,230	8,152	0.49
GFR 2 Year 2	1,562	1,659	1,582	0.64
GFR 3a Year 2	1,850	1,947	1,870	0.58
GFR 3b Year 2	3,073	3,170	3,093	0.58
GFR 4 Year 2	4,102	4,200	4,122	0.49
GFR 2 Year 3+	1,570	1,668	1,590	0.64
GFR 3a Year 3+	1,922	2,019	1,942	0.58
GFR 3b Year 3+	3,366	3,433	3,355	0.58
GFR 4 Year 3+	4,258	4,356	4,278	0.49
Dialysis	43,650	43,748	43,670	0.28
Functioning re-graft	7,190	7,288	7210	Tacrolimus: 0.59[3] Belatacept or ciclosporin: 0.60[3]
One-time cost of graft failure				
Year 1			1,384	
Year 2			431	
Year 3+			191	
One time costs/disutility of PTLD			4,890	0.44
One time costs/disutility of acute rejection			3,483.28	0.50

1Costs by GFR function differ slightly (at the third decimal point) between arms due to their different incidence rates of NODAT between them, which had an annual cost of 1174 (Currie et al. 2005). For years 1-3 (trial data phase) differences in terms of costs of these health states between regimens were also affected by the risk of PTLD incidence, which was an independent death risk factor and was associated with a cost of 4890(based on off-license therapy with rituximab nonotherapy based on BNF), and by Acure rejection, which incurred a cost of 0.50 (Currie et al., 2005) 2. Utilities by GFR function differ slightly (at the third decimal point) between arms due to their different incidence rates of NODAT between them, which had a disutility of 0.04 (Currie et al. 2005). For years 1-3 (trial data phase) differences in terms of utilities of these health states between regimens were also affected by the risk of PTLD incidence, which was an independent death risk factor and was associated with a distuility of 0.44 (Beckwith et al. 2010) , and by Acure rejection, which incurred disutility of 0.50 (Morton et al. 2009) 3. Average of GFR 2, 3a, and 3c (after re-transplantation no differentiation by renal function is made in the model.

Critique

The model captures all the most important clinical outcomes and adverse events arising post transplantation, and accounts for the role of renal function as a prognostic factor for long term graft survival and its contemporaneous effects on HRQoL and costs. It also accounts for the effect of short term acute rejection on longer term graft and patient survival.

A major strength of the evidence presented by BMS is the cost study used to populate the costs of immunosuppressant drug use and administration in the model and the costs associated with renal function. This evidence has been reported as part of a wider study in a peer-reviewed publication (Chamberlain et al. 2014).[41]

The major limitation of this study is the questionable generalisability of the values used to populate the transition probabilities of the model used to extrapolate short term trial outcomes to 40 years. The survival models that inform the transition probabilities to the key events, i.e. graft failure after transplant, time to re-transplantation after graft failure, and possibly patient survival with a functioning graft, may reflect the experience of a patient population that does not correspond to that of the UK.

Another issue is the use of efficacy differences between regimens at 3 years post transplant to populate the entire initial three years, as if these differences had occurred from day 1 and remained constant until the end of the third year post- transplantation, which we knbow it was not the case and bias the analysis in favour of belatacept, the company's drug. In fact, inspection of the model spreadsheet reveals that discounted was not applied to the first three year costs and benefits.

A methodological limitation is the assumed linear, constant decline in eGFR, which was the driver of the Markov model used to extrapolated outcomes beyond 3 years, in order to estimate quality of life over the graft survival period conditional on intial eGFR value. This in turn reflected the limited information available on renal function from registry data; studies using multicentre cohorts could potential address this issue by measuring rather than imputing renal function periods longer than two-three years that are typically found in the experimental literature.

In summary, the BMS model has numerous strengths, but has the following main limitations:

- The use of US data to extrapolate the survival data for key transition probabilities to 40 years (graft failure, time-to-retransplantation after failure)

- The use of efficacy differences between regiments at three years post-transplant to invalidly calculate benefit differences throughout the first three years in the cost-effectiveness model, which favours the company's drug, belatacept.

- Lack of accounting for the costs of concomitant regimens used in the the triple therapy regimens investigated by the RCTs that served as the source of efficacy values in the model (discussed in the next subsection).

- Lack of discounting of costs and QALYs the first three years of the analysis, which invalidly raises the benefits of belatacept proportionally more than it increases its incremental costs.

- The assumed linear decline in eGFR after 3 years post-transplant at a rate, without validation or sensitivity analysis of this assumption.

- A 'subgroup analysis' based on people with poor graft function at one-year, but who would not be identifiable at the time of starting maintenance immunosuppression (and therefore also outside the scope of this technology assessment)

- Another sub-group analysis, of those with a bodyweight of 90kg, should be disregarded as this subgroup is only based on the cost differences that would be affected by the patient's weight.

Comparison between the model submissions

Besides the treatments compared by them, the industry submissions differ in terms of the models used to evaluate those treatments (see Table 152). Given the necessity to extrapolate short term outcomes reported in trials with typical follow-ups of 1-3 years, the main differences between extrapolating models employed by the three companies are reflected in the choice of surrogate outcome used to drive the disease course in people with renal transplantation and the duration of any relative effects of treatments.

Table 152. Summary of the economic analyses in company submissions

Study	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
Astellas	Age 45 years 70.3 kg England and Wales	-IR Tacrolimus -ER Tacrolimus -Belatacept -Ciclosporin -Everolimus (CNI minimization [60% CsA reduction]) -Sirolimus (CNI minimisation [80% CsA reduction] & CNI avoidance) All given with basiliximab induction & MMF +corticosteroids	Twenty five years	Markov model of annual cycles with tunnel states extrapolation of one year trial outcomes	Acute rejection Adherence (for analysis of IR Tac vs ER Tac only)	Functioning graft –no previous BCAR Functioning graft –previous BCAR Failed graft (dialysis), Functioning regraft –no previous BCAR Functioning regraft – previous BCAR Death	BCAR	Malignancies CMV infections PTDM Wound healing disorders Anaemia HMGCoA Hypertension	Improved adherence with ER medication IR Tacrolimus vs. Sirolimus: Graft survival (scenario with graft survival in Symphony trial [CNI minimisation] with daclizumab induction)	Assumes that BCAR only occur in the first 12 months. Graft and patient survival were estimated from UK transplant 5-year survival statistics (UK NHSBT Report 2012–13) extrapolated to 25 years by exponential function of time. Survival in dialysis was estimated from 10-year UK survival statistics, extrapolated by exponential function. Utility values of adverse events not accounted for. Model has flaws of implementation, especially in relation to re-transplants.
BMS	Age 43 years 69% male 75 kg BENEFIT trial (low risk) Reduced kidney function (GFR) BENEFIT-EXT trial (extended criteria donor)	Belatacept Ciclosporin Tacrolimus	Forty years	Markov model of annual cycles extrapolation (Levy et al., 2014 model) of 3 years trial outcomes	Acute rejection Glomerular filtration rates	Functioning graft stratified by level of renal function (eGFR≥60, 45≤eGFR<60, 30≤eGFR<45, 15≤eGFR<30) failed graft (eGFR<15), functioning regraft, death	Renal function Acute rejection, NODAT (separate from main model), donor and recipient characteristics	NODAT ARE PTLD	Price of IS (acquisition costs of belatacept) Number of years with functioning graft Cost and utility of dialysis	Based on observational study of resource utilisation of 3-year follow-up. Based on surrogate-clinical outcome model estimated from US patient population. Belatacept not cost-effective for renal transplant population. Conclusion that it is "likely cost-effective in ECD recipients, or in those anticipated to have low kidney function (GFR) post-transplantation and short graft survival" is flawed. Case made for use in higher weight categories/ those requiring higher doses of IS. Includes costs of IS admin.

Study	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
Novartis	Age 45.7 years eGFR 9.03 weight 70 kg 68% male England & Wales	Everolimus + ciclosporin (low dose) vs. Tacrolimus + MMF MMF + ciclosporin Enteric coated MPS + ciclosporin vs. MMF + ciclosporin All given with corticosteroids	50 years	Individual patient, discrete event simulation model	Glomerular filtration rates (annual rate of change)	CKD stage 1-2 (eGFR≥60) CKD stage 3a (45≤eGFR<60) CKD stage 3b (30≤eGFR<45) CKD stage 4 (15≤eGFR<30) CKD stage 5 (eGFR<15) death	None	Proteinuria BKV CMV Hyper-lipidaemia Delayed wound healing Hypertension	Everolimus vs. Tacrolimus & everolimus vs. MMF: drug discontinuation rate (this variation was linked to costs but not outcomes) EC-MPS vs. MMF: utility of CKD stage 3	eGFR (CKD stage) drives patient mortality; graft survival is an independent event based on treatment specific 1st yr post-transplant probabilities. All costs of adverse events measured; only disutilities of proteinuria and hypertension were measured. CKD monitoring costs were included. Interpretation of results of EC-MPS vs. MMF comparison is flawed: model is nonlinear in uncertain parameters and PSA results provide correct base case results: i.e. EC-MPS ICER falls between £20,000 to £30,000. Mistake found in calculation of ciclosporin costs.

Notes: IS immunosuppression. eGFR Estimated glomerular filtration rate. ECD extended criteria donor

The submission by Astellas uses a Markov structure to model the disease evolution and the effects of treatment in the relevant cohort of people. In this model the occurrence of biopsy confirmed acute rejection in the first year post-transplant (for the first transplant and any second transplant occurring in the first year of the model) affects the probability of graft failure in subsequent years. Renal function plays no role in this model. In contrast, differences in eGFR changes between the triple therapy regimens in the first year drive the modelled outcomes of subsequent years in the model by Novartis. While the risk, costs and health related quality of life consequences associated with acute rejections are accounted for in this model, these events do not affect graft survival. Graft failure is thus as likely to occur while individuals are at CKD stage 1-2, as when they are at CKD 5, and any state in between those two extremes for that matter. The model by BMS, unlike that by Novartis, assumes that eGFR at the end of year 1 determines graft survival. However, unlike Astellas and similarly to Novartis, the BMS model allows for the costs and consequences of changes in eGFR over time in the functioning graft state and for the effect of eGRF on the probability of patient death. An additional advantage of the BMS analysis over that of Novartis is its allowance for the effects of AR in the first year post transplant to affect patient and graft survival thereafter, as the analysis by Astellas does for the graft survival only.

The figures adopted by the Novartis submission seem to underestimate the costs of tacrolimus immediate release two-daily doses. Their cost per mg for tacrolimus is £0.82 whereas Astellas' own weighted average figure for the market share of the different presentations is 1.618. On the other hand the mean daily dose at a 70 kg bodyweight for tacrolimus in the Novartis submission is 17.5 mg, whereas the average daily dose for the first year used by Astellas is 7.17 mg. This results in an average maintenance monthly cost of tacrolimus that is 24% higher in the model by Novartis than in the model by Astellas (i.e. £438 vs. £353 per month).

Other differences were found in terms of the unit costs of the MMF therapy. Novartis used a £9.65 price per pack of 50 tablets of 500 mg each obtained from market data (Commercial Medicines Unit E-MIT 2014), whereas Astellas used a price almost 10 times as large, £82.26 per pack of 50 capsules of 500mg, citing the BNF 2014. The effect of the chosen MMF price is also different across the submitted analyses, since in the evaluation by Astellas, MMF is a concomitant medication across all immunosuppressive regimens analysed, whereas in the Novartis analysis MMF is not part of the regimens involving the company's own therapies (i.e. everolimus and enteric coated-micophenolate sodium). Thus while across submissions treatment regimens that include the companies' drugs may be associated with increased effectiveness, a higher MMF price has different implications across the submissios: it makes

it less attractive for the NHS to adopt such regimen (since people live longer and incur higher drug costs) in the Astellas analysis, while the opposite occurs in the Novartis case (since only the cost of comparator regimens increases).

Although the three models submitted to NICE for this assessment varied in terms of the way the health course of an individual evolved and the use of immunosuppression affected such path, accounting of costs was similar in some aspects once the cycle length of models was taken account of. Table 153 presents the most important costs for those elements that were common across the models.

Table 153. Major cost elements in the model submissions

Company	Astellas[1]	BMS[2,3]	Novartis[1,3]
Tacrolimus therapy (per year)	4,255 [4]	3,937 (1st year) 2,821 (2nd year+)[9]	£5,283
Tacrolimus administration	0	386 (1st year) 89 (2nd year)[9]	0
MMF therapy (per year)	2,402 [5]	0 [8]	282 [11]
Ciclosporin therapy	N/A[6]	1,971 (1st year) 1,562 (2nd year+)[9]	839 (1st year) 694 (2nd year+)
Ciclosporin administration	0	386 (1st year) 90 (2nd year)[9]	0
Belatacept (per year)	10,966 (1st year) 6,480 (2nd year+)	13,472 (1st year) 9,217 (2nd year+)	N/A
Belatacept administration	0	2,457 (1st year) 1,996 (2nd year+)	N/A
Corticosteroids	178	0 [8]	285
Acute rejection (event)	1,738	3,483	1,725
Dialysis (per year)	38,387[7]	43,586[10]	22,877
Re-transplantation	25,953	25,908	17,736
Re-transplantation: Organ procurement	0	12,954	0

[1] Adopted a 70 kg weight for representative patient in the model. The cost of Basilliximab induction (20 mg within 2 hour before transplantation and at 4 days post-transplant, BNF 2014 prices, £1,685) was included in all arms. [2] Adopted a 75 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] IR-tacrolimus. [5] 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. [6] Astellas does not evaluate ciclosporin in their submission. However, the model speadsheets include information where the annual costs of ciclosporin are calculated based on market shares to be £3,731 for the first and £3,514 for subsequent years.[7] From Beaudet et al. Beaudet et al. 2011 [8] BMS model did not include costs of concomitant medications in the triple therapy regimen for any treatment arm. [9] The BMS submission reports a cost (of drug acquisition or drug administration) for the second year that is different from the cost for the third and subsequent years but the model spreadsheet adopts the price given for the third year in the submission as the price of the second and subsequent years. The figure presented here is the one adopted by the model. [10] From Baboolal et al. Baboolal et al. 2008. [11] Based on 1 g daily starting within 72 h of transplantation, valued at £9.65 price for 500mg, 50 tab pack from Commercial Medicines Unit (CMU) Electronic Market Information Tool (E-MIT), 2014. [12] From supporting evidence of NICE guidance cg135 (NICE 2011).

While the acquisition costs of tacrolimus is comparable across the three industry submissions, only the one by BMS reports any estimates of drug administration, which have the merit of being based on observed data as opposed to assumptions about compliance with dosing guidelines or protocols. With respect to immunosuppression costs, it may be noted that BMS did not account for costs of other concomitant drugs that are part of triple therapy immunosuppression (e.g. MMF + corticosteroids, which were given in BENEFIT and BENEFIT-EXT).

More importantly for the results is the observation that BMS used an estimate of dialysis costs (Baboolal et al. 2008)[365] twice the size of the estimate adopted by Novartis (NICE

costing guideline 2011), and almost 13% higher than that of Astellas (Beaudet et al. 2011).[366]. Given the driving influence of dialysis costs for cost-effectiveness and an issue to be discussed next in relation to the time spent on dialysis in the models, the quality of evidence gained by the BMS model in estimating immunosuppression-related costs and event costs may have been partly offset by an overestimation of the cost savings to be obtained from reducing the time people experienced dialysis.

Table 154. Key features of effectiveness analysis in industry models

Company	Astellas[1]	BMS[2]	Novartis[2]
Time to graft failure (median)	Without BCAR at 12 months: 23 years With BCAR at 12 months: >25 years[3]	initial GFR 2 15.0 years initial GFR3a 11.5 years initial GFR3b 7.0 years initial GFR 4 2.5 years	Everolimus: 15.8 years EC-MPS: 21.3 years MMF + CSA: 7.2 years TAC + CSA: 8.3 years
Time to transplantation from graft failure (mean unless otherwise stated)	3.5 years (median)	16.5 years[4]	3 years (SD 1)
Annual change in GFR	N/A	-3 (4th year+)	-1.66 (2nd year) -2.68 (3rd year+)
Utility of functioning state –first transplant	0.71	0.49-0.64 (depending on GFR stage)	0.49-0.64 (depending on GFR stage)
Utility of functioning state -2nd+ transplants	0.71	0.59	0.49-0.64 (depending on GFR stage)
Utility of dialysis state	0.459	0.28	0.28

[1]Model was driven by surrogate marker of acute rejection [2]Models driven by GFR change over time. [3] Modelled time horizon was 25 years, by which point 53.9% of those with BCAR in the first twelve months still had their initial graft functioning. [4] This value was derived by the company from an exponential survival model (Levy et al. 2014) with predicted hazard rate for a person of average age 40.3 (BMS submission model excel file). The model had been estimated on USRDS data for a sample of Medicare-covered kidney transplant recipients (no information on sample characteristics were provided), which means that the model predictions are likely to be out of the age range of the sample on which the model was estimated.

In Table 155, the key feature of the effectiveness elements of the analyses performed by the companies are presented. A salient aspect of the comparison model specifications is the longer expected time to re-transplantation at the time dialysis starts for those people whose graft fails in the BMS model. It is noted that this estimate was derived from an exponential survival model from an older patient sample in the US (Medicare-covered transplant only people). This model has a hazard (instantaneous probability) of receiving a transplant that is constant over time and that is predicted according to donor and patient characteristics (Levy et al. 2014). [330] In the BMS model these characteristics are fixed over time and result in the

constant annual probability of 4% of receiving a transplant while on dialysis. This means that the expected waiting time for a re-transplant in a US sample with the BMS model characteristics (which match the BENEFIT and BENEFIT-EXT sample characteristics, as detailed in the BMS submission, is 16 and a half years at the start of dialysis. This waiting time is clearly longer than the waiting time currently expected in the UK, which may be closer to the values of adopted by Astellas and Novartis in their models.

In any case the median time to re-transplant may also be unrealistic for the US, even after considering issues about socio-economic barriers to access and related features of that system. After inspection of the estimated coefficients of the exponential model, reported by Levy et al. (Levy et al. 2014, Supplementary material file 1) and reproduced by the BMS submission as Appendix 4, Table 1), the age covariate (which remains fixed at 40.3 years throughout the 40 annual cycles of the Markov model, so that those proportions of the cohort who experience graft failure early in the model have the same probability of receiving a retransplant in any given cycle as that people who experience graft failure in the latter part of the modelled time horizon) is positively associated with the probability of re-transplant, which means that those who start dialysis at older ages have shorter expected waits for a re-transplant and suggests that the model was estimated in a cohort of much older people than the BMS modelled age of 40 years (e.g. for graft failure at age 70 years the model yields an expected wait of approximately 10 years to receive a re-transplant).

The overestimation of time to re-transplant in the BMS model just described has the implication of overestimating the time on dialysis with its associated costs and loss in quality of life. This in turn means that the model is likely to overestimate the benefits of any advantages in terms of graft survival that Belatacept has over its comparators, tacrolimus and ciclosporin. Likewise this likely exaggerates the costs savings and quality of life gains of tacrolimus over ciclosporin, which suggests its ICER (£3,375; this was not stated in the BMS submission but implicit in their numbers and calculated from them by PenTAG) is an underestimate. See Table 155 for a summary of model outputs for the three industry model submissions.

Table 155. Results of model-based analyses submitted by the companies

Submission	Regiment compared	Patient characteristics	Life years	QALYs (disc.)	Discounted costs (£)	ICER Incremental cost per QALY
Astellas	Tacrolimus TD		17.88	8.01	130,118	TAC vs. SIRI:
	Sirolimus I		17.82	7.99	104,905	£1,651,801
	Everolimus	Mean age 45 yrs	17.80	7.99	142,995	TAC vs. SIRII:
	Sirolimus II	Weight 70.3	17.73	7.94	119,371	£170,681
	Belatacept		11.72	7.94	163,740	
	Tacrolimus OD		18.19	8.21	118,907	TAC OD dominates
	Tacrolimus TD		17.88	8.01	130,118	
BMS	Belatacept	Mean age 43	19.53	7.14	296,503	Belatacept vs. Tac:
	Tacrolimus	Weight 75	18.02	6.53	205,502	£149,182
	Ciclosporin		17.38	6.17	204,287	Tac vs Cs £3,375
Novartis	Everolimus + ciclosporin (low dose)	Mean age 45.7 (SD 12.7)	25.71	8.86	135,358	Everolimus dominant
	Tacrolimus+ MMF	Weight 70 SD (10)	23.39	7.37	140,972	
	Everolimus + ciclosporin (low dose)	Mean eGFR 9.03 SD (7.9)	25.80	8.89	136,180	MM+Cs vs EVE+Cs:
	MMF + ciclosporin		24.04	7.89	76,826	>200,000
	EC-MPS + MMF		25.48	8.69	87,359	EC-MPS vs. MMF+
	MMF + ciclosporin		24.17	7.89	76,771	Cs: £29,000

Figure 86. Evers checklist (Evers 2005) – quality of published economic evaluation studies

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

7. PenTAG Economic Assessment

7.1. Summary

7.1.1. Methods

A de novo 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). The utility decrements were based on a published systematic review and meta-analysis of preference-based quality of life studies in patients undergoing renal replacement therapy (RRT), with EQ-5D (EQ-5D-3L) used for measurement and most likely valued using the UK valuation tariff based on a representative sample of the general population (see Section 7.3.5, page 439).[367] Costs and QALYs were discounted at 3.5% per annum and costs were inflated as necessary to 2014/15 prices.

7.1.1.1. 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.

Sixteen regimens were modelled in total:

- CSA+MMF
- TAC+MMF
- CSA+AZA
- TAC+AZA
- CSA+EVL
- TAC+SRL
- TAC-PR+MMF
- BAS+CSA+MMF
- BAS+TAC+MMF
- BAS+CSA+AZA
- BAS+SRL+MMF
- BAS+BEL+MMF
- BAS+CSA+MPS
- rATG+CSA+MMF

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

7.1.1.2. Model structure

Kidney transplant recipients (KTRs) were assumed to be in one of three health states at any time: FUNCTIONING GRAFT, GRAFT LOSS or DEATH (see Section 7.3.2.2, page 399 and Figure 87, page 400). In the FUNCTIONING GRAFT state, KTRs were not dependent on dialysis whereas in the GRAFT LOSS state, KTRs 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) was estimated, with corresponding costs (during the first year for acute rejection and CMV infection; ongoing for dyslipidaemia and NODAT). NODAT was also associated with a utility decrement based on EQ-5D measurements from kidney transplant patients in a US clinic, valued according to a US valuation tariff (see Section 7.3.5.4, page 441).[368] The incidence of acute rejection and NODAT were also used as surrogate determinants of graft survival and death with functioning graft (NODAT only).

Up to two retransplantations were modelled, which could take place from the graft loss state or from the functioning graft state (for the initial graft only) corresponding to pre-emptive retransplantation. KTRs would transition to the next FUNCTIONING GRAFT state if the retransplantation was successful or to the next GRAFT LOSS state if it was unsuccessful (i.e., in the event of primary non-function). The rate of retransplantations was assumed to reduce with age past 65 years, reaching zero by age 80 years (see Section 7.3.3.5, page 434).

Transitions out of the FUNCTIONING GRAFT state correspond to the clinical outcome of graft loss/survival 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 functioning graft were calculated from data from the UK Transplant Registry standard dataset. The rate of mortality following graft loss was based on UK data published in the UK Renal Registry 16th Annual Report[338] (section 7.3.3, page 402).

Baseline death-censored graft survival was taken directly for the first year from Kaplan–Meier analysis and from the first year onwards a Weibull curve was fitted which was demonstrated to fit the data well.

Death-censored graft survival at one year was estimated for each regimen based on the odds ratios of graft loss within 12 months. This was incorporated into the model by applying a proportional-odds assumption to death-censored graft survival in the first year.

A surrogate relationship between acute rejection, NODAT and graft function (eGFR) at 12 months and graft survival was modelled, based on applying a hazard ratio to the Weibull curve after the first year (see Section 7.3.3.2). The hazard ratio for acute rejection was 1.6,[369] for NODAT was 1.12,[369] and for eGFR was 1–5.80 depending on the eGFR interval.[330]

Patient survival at one year was estimated for each regimen based on the odds ratio of mortality within 12 months. This was incorporated into the model by applying a regimen-specific hazard ratio of death with functioning graft within the first year.

A surrogate relationship between NODAT and death with functioning graft after the first year was also modelled, with a hazard ratio of 1.41.[369]

7.1.1.3. Source of effectiveness estimates

The odds ratios for the incidence of biopsy-proven acute rejection (BPAR), graft loss and patient mortality, and the absolute difference in eGFR, were primarily estimated from the network meta-analyses of clinical effectiveness evidence. The results for induction agents and maintenance regimens were chained assuming independence. The results for TAC-PR+MMF and BAS+CSA+MPS were based on results for TAC+MMF and BAS+CSA+MMF with additional adjustment based on head-to-head comparisons. Section 7.3.4 (page 436) gives further details.

The incidences of NODAT, CMV and dyslipidaemia were also estimated using network meta-analyses of RCTs from the systematic review of clinical effectiveness, although some simplifying assumptions were made to overcome the limited amount of evidence.

7.1.1.4. Costs

See Section 7.3.6 (page 442) for further details.

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

The costs of acute rejection and CMV infection were taken from a microcosting study commissioned by Bristol Myers Squibb.

The significant costs of NODAT were estimated from a recent publication based on the UK Prospective Diabetes Study (UKPDS), which was conducted in the general population with type 2 diabetes.

The costs of KTR follow-up and monitoring were estimated based on a database study commissioned by Bristol Myers Squibb.

Infection prophylaxis costs were estimated based on the kidney transplant protocol of a UK hospital. Additional CMV prophylaxis costs for regimens containing rabbit ATG induction.

7.1.1.5. Uncertainty analyses

A probabilistic sensitivity analysis (PSA) was conducted to estimate the joint effect of parameter estimation uncertainty on cost-effectiveness. Structural sensitivity analyses relating to graft survival were conducted. A scenario analysis in which list prices were adopted for all drug acquisition costs was performed and a two-way threshold analysis was conducted relating to the costs of belatacept.

7.1.2. Results

7.1.2.1. Base case analyses

See Section 7.4.17.4 (page 470) for further details.

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

- Basiliximab (BAS)
- Immediate-release tacrolimus (TAC)
- Mycophenolate mofetil (MMF)

Relevant ICERs do not exist 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+MMF was predicted to be cost-effective at £20,000 and £30,000 per QALY.

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

- No induction (three comparisons): Dominated in deterministic and probabilistic analyses
- Rabbit ATG (three comparisons): Deterministic ICERs £133,000–£369,000 per QALY; Probabilistic ICERs £200,000–£1,185,000 per QALY
- Ciclosporin (four comparisons): Deterministic ICERs £161,000–£256,000 per QALY (three comparisons) or dominated (one comparison); Probabilistic ICERs £204,000–£384,000 per QALY (three comparisons) or dominated (one comparison)
- Prolonged-release tacrolimus (one comparison): Dominated in deterministic and probabilistic analyses
- Azathioprine (four comparisons): Dominated in deterministic and probabilistic analyses
- Mycophenolate sodium (one comparison): Deterministic ICER £145,000 per QALY; Dominated in probabilistic analysis
- Sirolimus (two comparisons): Dominated in deterministic and probabilistic analyses
- Everolimus (one comparison): Deterministic ICER £1,744,000 per QALY; Probabilistic ICER £5,425,000 per QALY

- Belatacept (one comparison): Deterministic ICER £519,000 per QALY; Probabilistic ICER £546,000 per QALY

7.1.2.2. Scenario analyses

See Section 7.4.2 (page 501) for further details.

In a scenario analysis investigating the impact of structural uncertainty in the surrogate effect of acute rejection, NODAT and graft function at 12 months on graft survival it was found that if the surrogate effect was weakened (by limiting its duration), no induction and ciclosporin became cost-effective at £20,000 and £30,000 per QALY versus basiliximab induction and immediate-release tacrolimus. The duration of surrogate effect had to be limited to one year for no induction to be cost-effective versus basiliximab at £20,000 per QALY and eliminated entirely to be cost-effective at £30,000 per QALY. The duration of surrogate effect had to be limited to 3–8 years or less (depending on the comparison) for ciclosporin to be cost-effective versus immediate-relase tacrolimus at £20,000 or £30,000 per QALY.

A second structural uncertainty analysis considered the possibility that calcineurin inhibitor-free regimens could result in prolonged graft survival by avoiding the nephrotoxic effects of calcineurin inhibitors. The graft survival for the sirolimus-containing regimen BAS+SRL+MMF had to be markedly different to the base case for sirolimus to become cost-effective at £20,000 or £30,000 per QALY and the belatacept-containing regimen BAS+BEL+MMF was not cost-effective at £20,000 or £30,000 per QALY at any point in the analysis.

When list prices were adopted instead of average NHS acquisition costs for drug acquisition costs, ciclosporin and azathioprine became cost-effective at £20,000 to £30,000 per QALY in some combinations (when ciclosporin was used in combination with mycophenolate mofetil and when azathioprine was used in combination with tacrolimus) with immediate-release tacrolimus and mycophenolate mofetil remaining cost-effective at £20,000 to £30,000 per QALY in other comparisons.

Belatacept was not found to be cost-effective at £20,000 to £30,000 per QALY even at zero price, or at list price with zero administration cost.

7.2. Introduction

The objective of this independent economic assessment was to answer the following study question in line with the NICE reference case[370]:

> What is the cost-effectiveness of immunosuppressive regimens in renal transplantation in adults, 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?

Although there have been a number of economic evaluations which partially address the study question (see Chapter 5, page 315), none has independently addressed the full study question in line with the NICE reference case[370] and therefore a new economic assessment was required.

A decision analytic model was developed in Excel 2010 (Microsoft Corporation, Redmond, WA, USA) to address the study question in a cost–utility analysis.

7.3. Methods

7.3.1. Modelling approach

7.3.1.1. Target population and subgroups

The target population was adults undergoing kidney-only transplantation (i.e., people receiving multi-organ transplants are not included). The donor may be living-related, living-unrelated or deceased (following brain death or cardiac death).

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

In the base case analysis KTRs were assumed to be aged 50 years (the median age of incident KTRs in 2012 was 50.5 years[371]) and 62% were men (UK Transplant Registry standard dataset, 2007–2012).

The mean weight of KTRs was estimated by identifying RCTs included in the systematic review of clinical effectiveness (Section 4) which reported weight as a baseline characteristic. A random-effects model was used, which resulted in estimated mean (SE) weight of 70.2 (1.2) kg.

7.3.1.2. Setting and location

The NHS in England and Wales.

7.3.1.3. Study perspective

In line with the NICE reference case,[370] the perspective adopted on outcomes was all direct health effects for patients and other people, and the perspective adopted on costs was that of the NHS and personal social services (PSS).

7.3.1.4. Comparators

As the immunosuppressive agents are used in combination and in sequence we used treatment regimens as 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 comparators if they were in current use in the NHS or if they would plausibly be used in the NHS (as advised by a number of clinical experts) and there was sufficient clinical evidence to estimate the costs and outcomes for KTRs receiving those regimens.

Table 156 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 (although no warranty or representation is given as to the correctness of the information presented in this regard).

Table 156. 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	Y
TAC+SRL	None	Immediate-release tacrolimus and sirolimus	N
TAC-PR+MMF	None	Prolonged-release tacrolimus and mycophenolate mofetil	U
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+SRL+MMF	Basiliximab	Sirolimus and mycophenolate mofetil	U
BAS+BEL+MMF	Basiliximab	Belatacept and mycophenolate mofetil	U[b]
BAS+CSA+MPS	Basiliximab	Ciclosporin and mycophenolate sodium	U
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

Key: Y, yes; N, no; U, unclear
a All maintenance regimens also included corticosteroids
b According to its summary of product characteristics, basiliximab is to be used concomitantly with ciclosporin-based therapy, although belatacept is recommended to be used with an IL-2RA (of which basiliximab is the only one currently

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

- BAS+CSA+SRL (although we have modelled TAC+SRL)
- BAS+CSA+EVL (although we have modelled CSA+EVL)

Bristol Myers Squibb and Novartis did not present any regimens which we have not modelled.

7.3.1.5. Time horizon

The time horizon was 50 years or age 100 years, whichever is earlier. The median age of incident KTRs in 2012 was 50.5 years.[371]

7.3.1.6. Discount rate

In line with the NICE reference case[370] the discount rate for costs and health effects was 3.5% per annum.

7.3.1.7. 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.[370] 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 or 3rd transplant

7.3.2. Model structure

7.3.2.1. Conceptualisation

We followed the approach to model conceptualisation described by Kalthenthaler et al. in NICE DSU Technical Support Document 13.[372]

Several meetings were held with Dr Jason Moore (Consultant Nephrologist; the Kidney Unit, Royal Devon & Exeter NHS Foundation Trust), during which problem-oriented conceptual models for various disease processes and service pathways were discussed and refined. The problem-oriented conceptual models were then circulated to the expert advisory group recruited for the assessment who made comments and suggestions. A design-oriented conceptual model was then developed, based heavily on the kidney logic conceptual model, and this formed the basis for the final model structure.

7.3.2.2. Finalised structure

In the final model structure KTRs were assumed at all times to be in one of three principal health states:

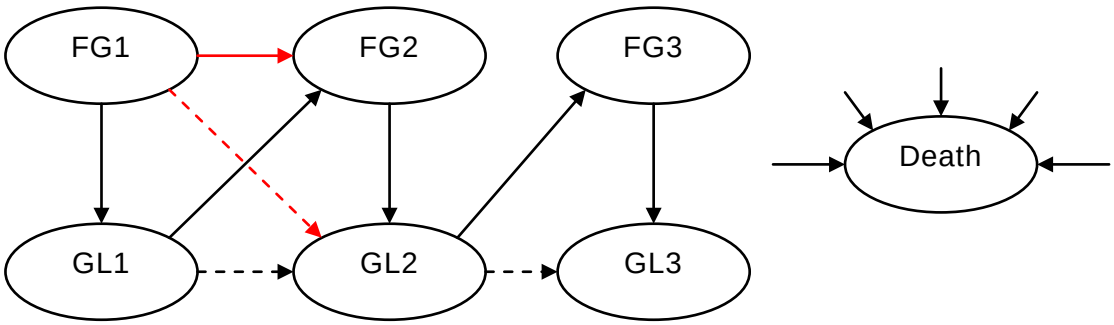
- FUNCTIONING GRAFT (not dialysis-dependent)
- GRAFT LOSS (dependent on dialysis)
- DEATH

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 two retransplantations are possible and therefore there are three substates for FUNCTIONING GRAFT and GRAFT LOSS reflecting the graft number (1–3). 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 or third graft. Pre-emptive retransplantation can occur from the original FUNCTIONING GRAFT state. 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 416) 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). See Section 7.3.3.5 (page 434) for our justification of this approach.

Figure 87 gives the model diagram showing the seven states in the model. Self-links are omitted from all states in both figures for clarity (there are no tunnel states).

Figure 87. Model diagram



Key: FG, FUNCTIONING GRAFT; GL, GRAFT LOSS; dashed arrows indicated primary non-function; red arrows indicate pre-emptive retransplantation

A Markov cohort model was used, such that individual KTRs were not simulated. The model was constructed in Microsoft Excel 2010.

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).

In some cases the transition rate was engineered to achieve a desired change in state membership, but in all cases a transition rate was calculated.

Table 157 gives a summary of how the transition rates were dependent on factors such as age, acute rejection and NODAT. BAS+TAC+MMF was assumed to be the baseline regimen most close to current UK practice and outcomes.

Table 157. Summary of determining factors for transition rates within the PenTAG 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	Age

	dialysis

7.3.3. Factors included in the model

7.3.3.1. Overall survival

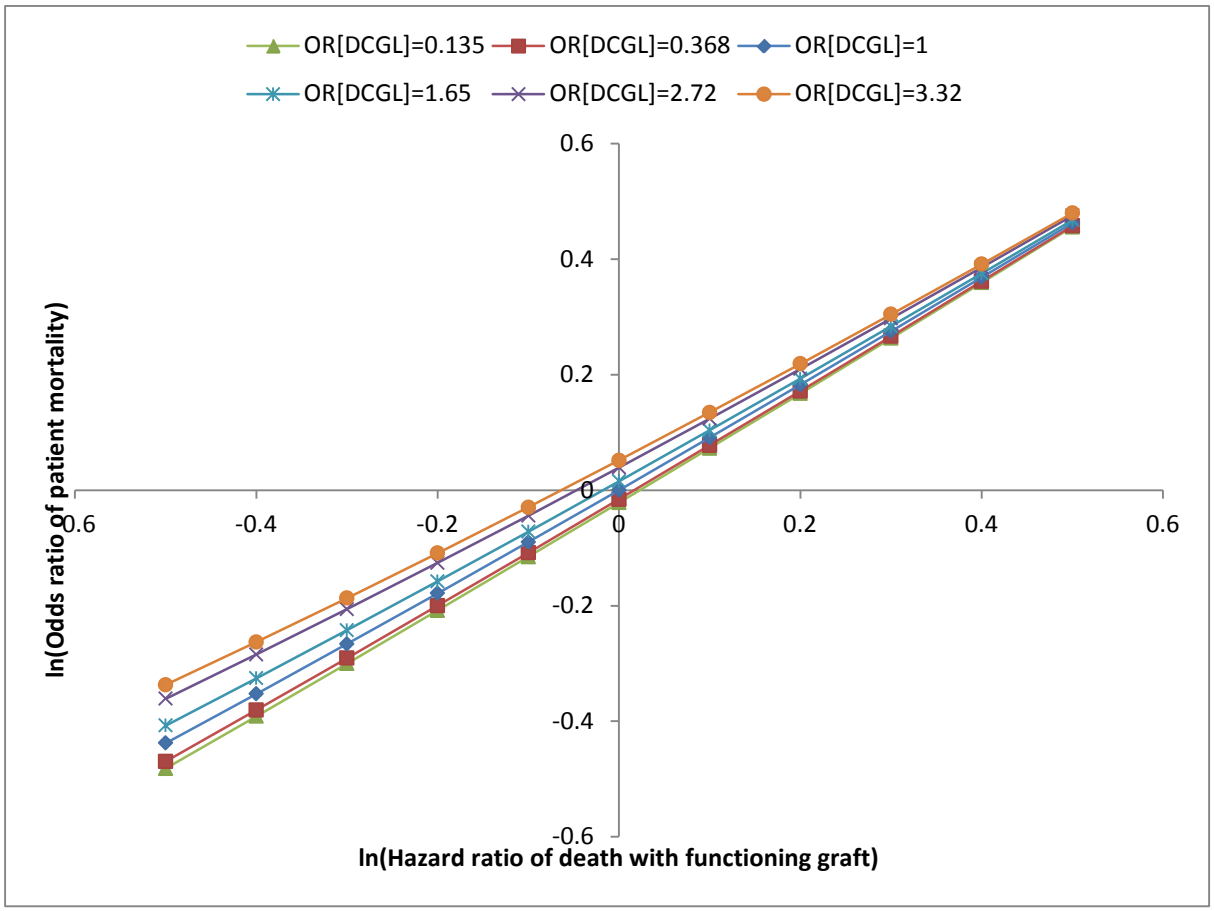
Overall survival was not explicitly included as an input to the model and therefore emerges from the two modelled rates of mortality, Death with functioning graft (page 432) and Mortality after graft loss (page 435).

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.

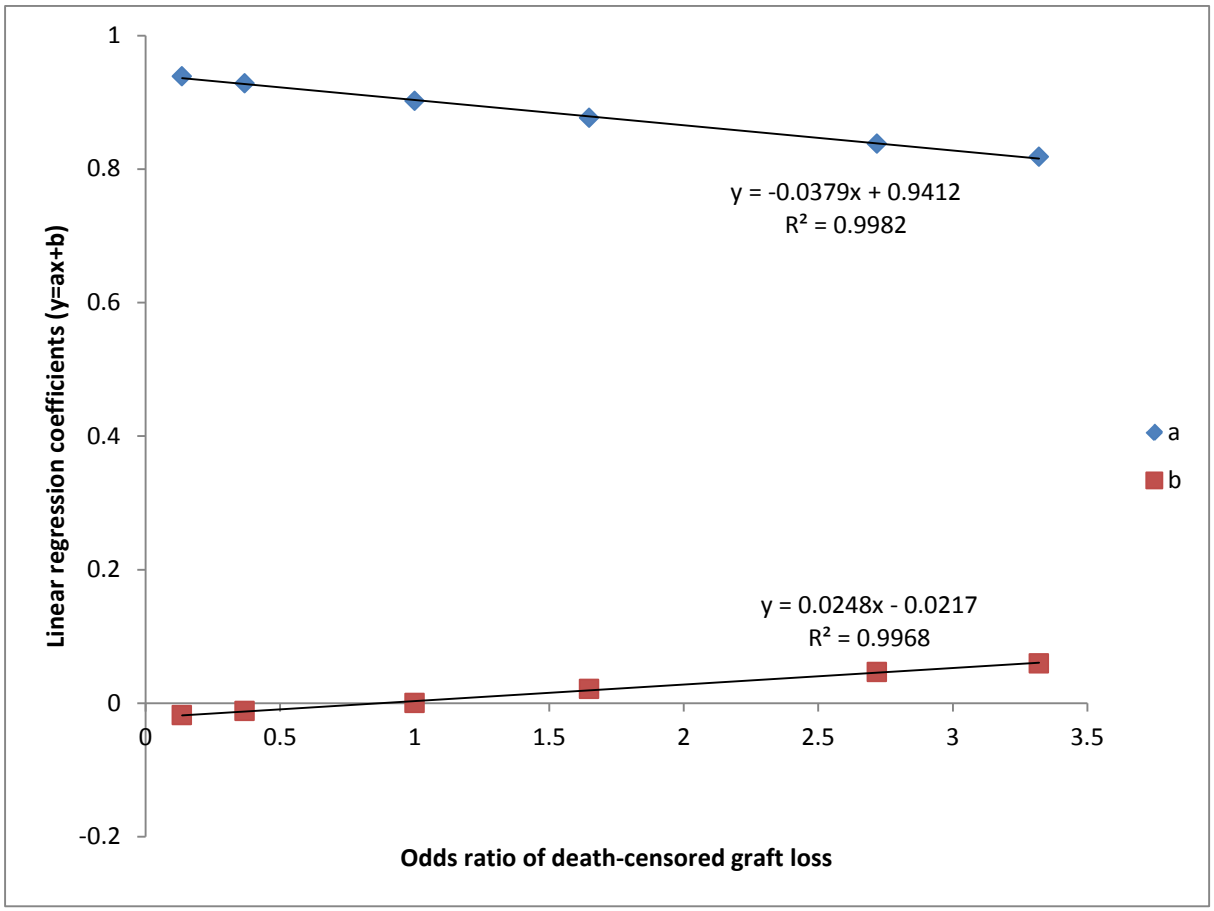
Therefore a regression approach was used instead. The two factors driving patient survival at 12 months which could vary between regimens were identified as the odds ratio of graft loss (after returning to dialysis the mortality rate increases) and the hazard ratio of death with functioning graft. The 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 88).

Figure 88. 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 89).

Figure 89. 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 is the odds ratio of graft loss, is the hazard ratio of death with functioning graft and is the odds ratio of patient death):

As can be seen in Table 158, the regression formulae perform well in most instances.

Table 158. Comparison of hazard ratios for death with functioning graft from regression and calculated using Solver

Regimen	Hazard ratio for death with functioning graft	
	From regression	Using Solver
CSA+MMF	0.659	0.654
TAC+MMF	1.129	1.133
CSA+AZA	0.689	0.685
TAC+AZA	0.990	0.995
CSA+EVL	1.026	1.030
TAC+SRL	0.990	0.995
TAC-PR+MMF	1.480	1.473
BAS+CSA+MMF	0.584	0.575
BAS+TAC+MMF	0.997	1.000
BAS+CSA+AZA	0.611	0.602
BAS+SRL+MMF	1.125	1.129
BAS+BEL+MMF	0.271	0.233
BAS+CSA+MPS	0.364	0.337
rATG+CSA+MMF	0.401	0.377
rATG+TAC+MMF	0.684	0.680
rATG+CSA+AZA	0.418	0.392

7.3.3.2. 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 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, page 435).

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 are given later in this section and in the section Death with functioning graft (page 416), but briefly:

- Graft survival censored for death with functioning graft is estimated by adjusting survival estimated 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 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). The split between these transitions is age-dependent (since the likelihood of pre-emptive retransplantation decreases with advancing age; see Table 159). The probability that a KTR in each age range is suitable for

retransplantation was taken from Table 32 of Bond et al. (2009)[373] which was in turn estimated from a figure in Chapter 5 of the UK Renal Registry Eighth Annual Report.[374] It was then assumed that 20% of these KTRs would receive a pre-emptive retransplantation.[375]

Table 159. Estimated split of transitions following loss of first graft

Age group	FG1 → GL1	FG1 → FG2	FG1 → GL2
18–34	89.2%	10.5%	0.3%
35–44	90.2%	9.6%	0.2%
45–54	92.4%	7.4%	0.2%
55–64	94.6%	5.3%	0.1%
65+	98.0%	2.0%	0.0%

Key: FG1, first FUNCTIONING GRAFT; GL1, GRAFT LOSS following first graft; FG2, second FUNCTIONING GRAFT; GL2, GRAFT LOSS following second graft

Estimation of graft survival

Graft survival for most people is now so long that most clinical trials do not follow-up or maintain randomisation sufficiently long to obtain mature estimates for graft survival. Acute rejection became the primary endpoint in most clinical trials and was treated as a surrogate marker by three of four economic analyses submitted by companies for the current guidance, TA85.[60]

Subsequently there have been analyses confirming that acute rejection and NODAT are predictors of graft loss,[369] as well as seemingly contradictory findings that immunosuppressive agents achieving lower acute rejection rates do not deliver improvements in graft survival.[376] Also several analyses have suggested that renal function at one year post-transplant is a good predictor of long-term graft survival.[330 377-380]

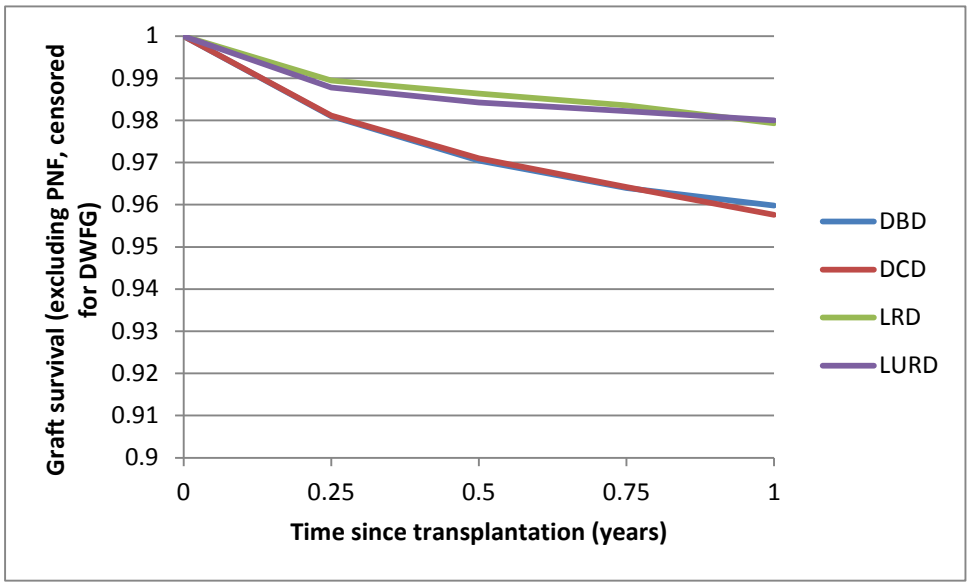
Throughout this section it should be noted that graft survival and failure does not include death with functioning graft, i.e., only considering people who are alive and who become dependent on dialysis or require retransplantation.

Baseline

Baseline graft survival for the first year was estimated from the UK Transplant Registry standard dataset using the Kaplan–Meier method, restricting to first graft for each patient and

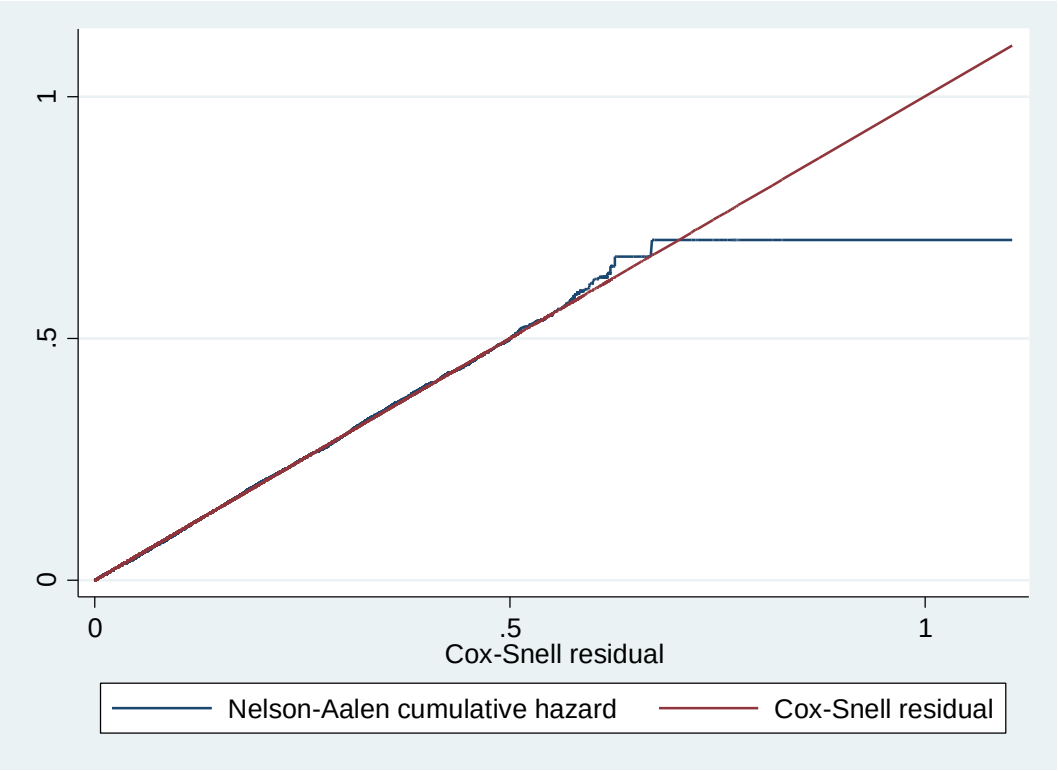
only transplants since 2007; survival was calculated separately for four different donor types (DBD, DCD, living-related, living-unrelated). Graft survival was then calculated as the weighted average according to the donor type distribution. KTRs with graft failure on the day of transplantation were assumed to have primary non-function (PNF) and were also excluded. Any KTRs dying with a functioning graft were censored at the time of death.

Figure 90. Graft survival in first year according to graft type



Baseline graft survival was extrapolated by fitting a Weibull curve to conditional survival from one year (i.e., fitted to KTRs whose grafts survived at least one year), with proportional hazards covariates for graft number, donor type and transplant period (1995–2000, 2001–2006, 2007–2012). The fit of this Weibull curve was verified with a graphical test of the Cox-Snell residuals (Figure 91), 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).

Figure 91. Graphical verification of the fit to graft survival



The baseline model for conditional graft survival from one year is then:

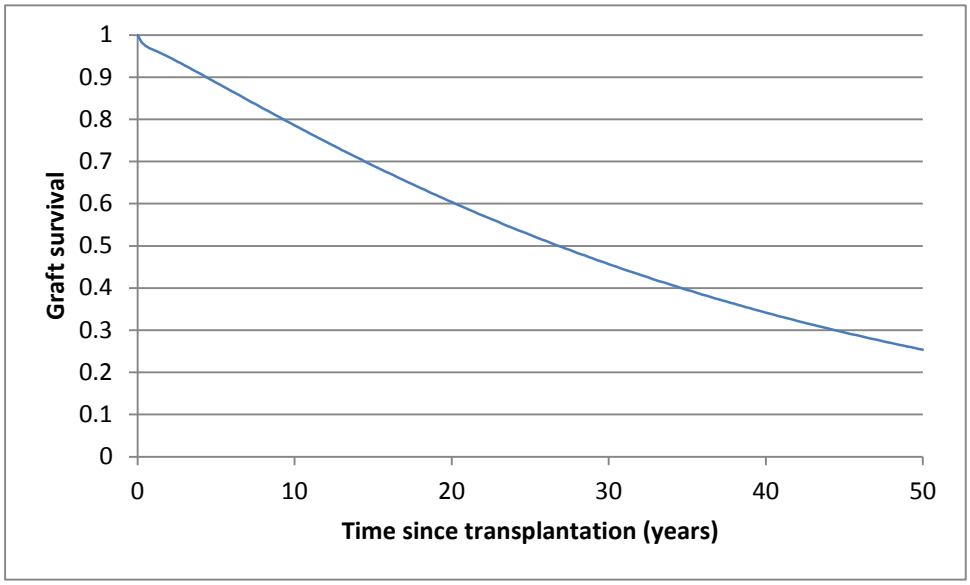
$S(t) = \exp\{-\lambda t^{\gamma}\}$

Where t is time after one year, λ is the rate parameter and γ is the shape parameter (with a value of 1.105 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: graft number = 1; donor type = {(DBD, 0.659), (DCD, 0.078), (Living-related, 0.195), (Living-unrelated, 0.068)}; transplant period = 2007–2012. These led to a baseline rate parameter value of 0.01809.

Baseline graft survival in the PenTAG model is shown in Figure 92.

Figure 92. Baseline graft survival 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 7.3.4 (page 436).

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, which are all predictors of graft loss.[330 369]

The surrogate relationship was implemented using proportional hazards and summarised in Table 160 and expanded in sections below. The rate parameters for all regimens (after adjusting according to the surrogate relationship) are given in Table 161. The resulting graft survival (excluding death with functioning graft) at one, three, five and ten years for each regimen are given in Table 162.

Table 160. Surrogate relationship hazard ratios for graft survival

Relationship	Hazard ratio	Source
Acute rejection within 12 months	1.60	Cole et al. 2008[369]
Renal function (eGFR) at 12 months	eGFR ≥ 60: 1 45 ≤ eGFR < 60: 1.409 30 ≤ eGFR < 45: 2.406 15 ≤ eGFR < 30: 5.801	Levy et al. 2014[330]
NODAT within 12 months	1.12	Cole et al. 2008[369]

Table 161. Rate parameters for graft survival after one year

Regimen	Rate parameter (λ)
CSA+MMF	0.0237
TAC+MMF	0.0205
CSA+AZA	0.0269
TAC+AZA	0.0197
CSA+EVL	0.0216
TAC+SRL	0.0248
TAC-PR+MMF	0.0247
BAS+CSA+MMF	0.0208
BAS+TAC+MMF	0.0181
BAS+CSA+AZA	0.0232
BAS+SRL+MMF	0.0196
BAS+BEL+MMF	0.0169
BAS+CSA+MPS	0.0192
rATG+CSA+MMF	0.0215
rATG+TAC+MMF	0.0187
rATG+CSA+AZA	0.0236

Table 162. 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	95.51%	90.76%	85.58%	72.99%
TAC+MMF	95.84%	91.71%	87.18%	75.97%
CSA+AZA	94.04%	88.76%	83.05%	69.34%
TAC+AZA	93.24%	89.38%	85.13%	74.60%
CSA+EVL	96.25%	91.88%	87.09%	75.34%
TAC+SRL	93.09%	88.25%	82.98%	70.23%
TAC-PR+MMF	95.05%	90.14%	84.79%	71.85%
BAS+CSA+MMF	96.19%	91.97%	87.34%	75.94%
BAS+TAC+MMF	96.48%	92.79%	88.73%	78.58%
BAS+CSA+AZA	94.93%	90.31%	85.27%	72.97%
BAS+SRL+MMF	94.78%	90.87%	86.57%	75.92%
BAS+BEL+MMF	96.84%	93.38%	89.54%	79.92%
BAS+CSA+MPS	96.69%	92.77%	88.45%	77.73%
rATG+CSA+MMF	96.48%	92.12%	87.35%	75.61%
rATG+TAC+MMF	96.74%	92.93%	88.72%	78.25%
rATG+CSA+AZA	95.32%	90.59%	85.44%	72.91%

Graft function at 12 months

The average graft function (eGFR) at 12 months for each regimen was estimated by first estimating the baseline average eGFR at 12 months in the UK. Pruthi et al. report (in text and in Figures 3.5a-c) the median and interquartile range (IQR) of eGFR at 12 months between 2005–2011 by donor type (DBD, DCD, living).[371] For each donor type a Normal distribution was fitted by setting the Normal distribution mean (μ) to the median and setting the standard deviation (σ) to IQR/1.349, as shown in Table 163.

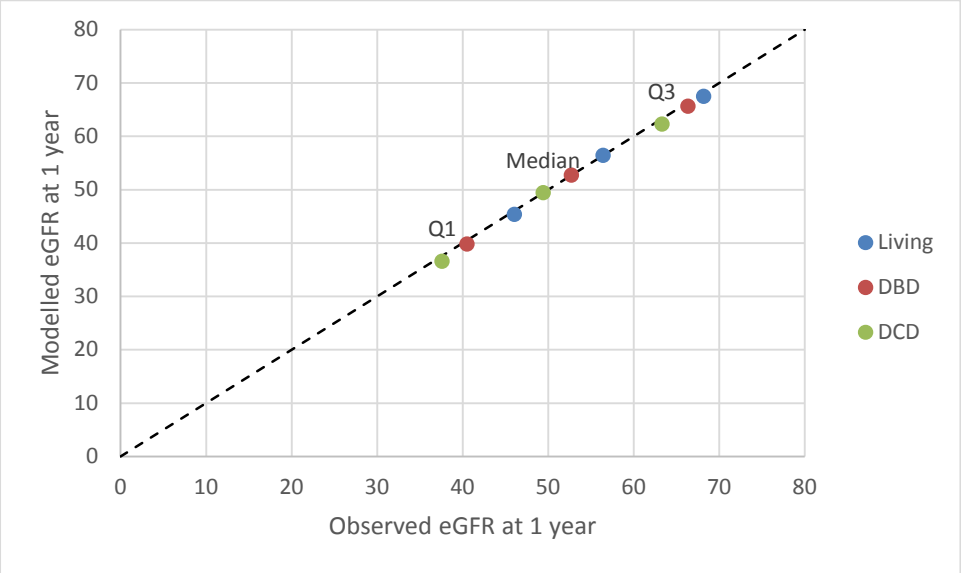
Table 163. Estimating the baseline eGFR distribution after 12 months

Donor type	Reported		Fitted distribution	Normal
	Median	IQR	μ	σ
Living	56.4	22.1	56.4	16.40
DBD	52.7	25.8	52.7	19.11
DCD	49.4	25.7	49.4	19.06

IQR, interquartile range

To validate the fit the predicted quartiles were plotted versus the reported quartiles (Figure 93). The scatter points are very close to the dashed line indicating equality.

Figure 93. Comparison of reported eGFR quartiles and modelled eGFR quartiles



To estimate the overall average eGFR (weighted according to the frequency of different donor types) a mixture distribution was created from the three Normal distributions and the following formulae were used to calculate the mean and variance of the resulting mixture distribution:

Acute rejection within 12 months

Acute rejection rates within 12 months were estimated using effectiveness estimates as described in Section 7.3.4 (page 436) and a baseline acute rejection rate for BAS+TAC+MMF.

The baseline acute rejection rate was estimated from Rowshani et al. 2006[122] and Tsuchiya et al. 2013[128] as these were the only studies with the exact regimen of BAS+TAC+MMF. Simple pooling was used for the deterministic estimate of the acute rejection rate, resulting in an estimate of 12.17%.

The effect of acute rejection on graft survival after the first year was then estimated using the hazard ratio of 1.60 from Cole et al. 2008.[369] As for graft function a raw hazard ratio was then calculated according to the weighted average of the hazard ratios for acute rejection 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+MMF).

Table 164 summarises the calculations and results for the effect of acute rejection on graft survival.

Table 164. 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	24.61%	1.148	1.070
TAC+MMF	21.61%	1.130	1.053
CSA+AZA	40.91%	1.245	1.161
TAC+AZA	28.57%	1.171	1.092
CSA+EVL	24.03%	1.144	1.066
TAC+SRL	21.00%	1.126	1.049
TAC-PR+MMF	21.20%	1.127	1.050
BAS+CSA+MMF	14.10%	1.085	1.011
BAS+TAC+MMF (baseline)	12.17%	1.073	1.000
BAS+CSA+AZA	25.82%	1.155	1.076
BAS+SRL+MMF	13.19%	1.079	1.006
BAS+BEL+MMF	21.90%	1.131	1.054
BAS+CSA+MPS	19.61%	1.118	1.042
rATG+CSA+MMF	10.34%	1.062	0.990
rATG+TAC+MMF	8.87%	1.053	0.982
rATG+CSA+AZA	19.64%	1.118	1.042

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 421).

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[369] and incorporated using the same methodology as for graft function and acute rejection. Table 165 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 165. Incidence of NODAT and effect on graft survival for each regimen

Regimen	Incidence of NODAT	Raw hazard ratio	Hazard ratio vs. baseline
CSA+MMF	4.98%	1.006	0.993
TAC+MMF	10.60%	1.013	1.000
CSA+AZA	4.98%	1.006	0.993
TAC+AZA	10.60%	1.013	1.000
CSA+EVL	4.74%	1.006	0.993
TAC+SRL	16.00%	1.019	1.006
TAC-PR+MMF	12.32%	1.015	1.002
BAS+CSA+MMF	4.98%	1.006	0.993
BAS+TAC+MMF	10.60%	1.013	1.000
BAS+CSA+AZA	4.98%	1.006	0.993
BAS+SRL+MMF	8.57%	1.010	0.998
BAS+BEL+MMF	2.18%	1.003	0.990
BAS+CSA+MPS	4.66%	1.006	0.993
rATG+CSA+MMF	4.98%	1.006	0.993
rATG+TAC+MMF	10.60%	1.013	1.000
rATG+CSA+AZA	4.98%	1.006	0.993

7.3.3.3. Mortality

Death with functioning graft

In adult KTRs death with functioning graft (DWFG) is a significant cause of graft loss. Compared to dialysis recipients, more KTRs die from infection and malignancy, the risk of both being increased by greater immunosuppression.[371] 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.[381]

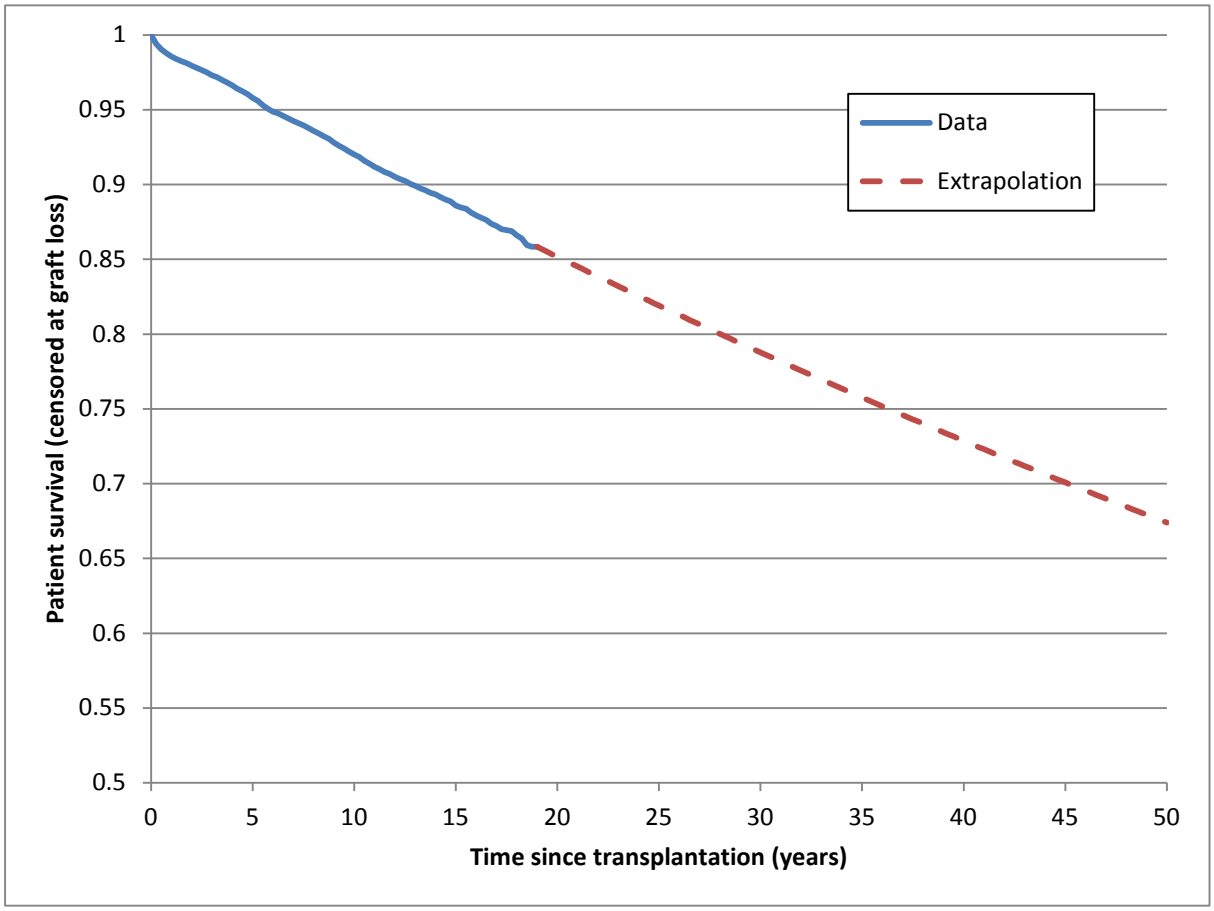
Crude estimates of DWFG will vary according to immunological risk and donor kidney type (i.e., living donor, DCD, DBD) because of differences in baseline demographics (living donor KTRs tend to be younger) and in immunosuppression (KTRs at greater immunological risk tend to receive greater immunosuppression which increases the risk of infection and malignancy).[382] The use of steroids is also linked to increased risk of death from cardiovascular disease and infection.[383]

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.[383]

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 94.

Figure 94. 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 166). 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 7.3.3.1, page 402), and thereafter a hazard ratio for NODAT was applied according to Cole et al. 2008.[369]

Table 166. 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.[338] An analysis by Webb et al. (2012) demonstrated that people waiting for re-transplantation following graft loss experience a greater mortality rate than incident dialysis recipients waitlisted for transplantation for at least three years when adjusted for age.[384] It is not clear,

however, that mortality across all dialysis recipients will differ according to whether the recipient has previously lost a graft.

Since it was not possible to incorporate any temporary increase in mortality rate immediately following graft loss and there was not sufficient evidence to suggest it should be included, 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 167).

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 167. Mortality rate for dialysis recipients

Age group	Hazard rate of mortality (SE)
20–24	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[338]

7.3.3.4. 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. For this model 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. For example, the current NICE guidance TA85[42] recommends that "The initial choice between [immediate-release] tacrolimus and ciclosporin should be based on the relative importance of their side-effect profiles for individual people."

Given the heterogeneity of reporting of adverse events it was felt to be unlikely to be useful to model many adverse events, but instead to focus where there was established clinical opinion that was also supported by RCTs in our systematic review (Section 4.2.1). Diabetes (NODAT) was considered very important to include (and has been included in previous economic evaluations, see Section 6), and cytomegalovirus infection and dyslipidaemia were judged suitable for inclusion as they had been identified by a recent Cochrane review[8 356] as linked to mTOR-I use (decreasing CMV infection incidence and increasing dyslipidaemia).

Anaemia was also included as an adverse event as it has been included in previous economic evaluations and is seen as an important cost relating to RRT, but it was assumed not to vary between regimens.

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 7.3.5.4, page 441).

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.[385] 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[385]). Tacrolimus has been repeatedly associated with the development of NODAT[2 369] and the same incidence pattern is observed of significantly elevated incidence in the first year post-transplant.[385]

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[385] 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.

Two competing factors will affect the proportion of people with diabetes after the first year. Firstly, additional incidence of diabetes will occur at a greater rate than that in the general population. Secondly, individuals with diabetes will face a greater mortality rate than those without diabetes. For simplicity we assume these factors approximately cancel each other out and we maintain the same prevalence of NODAT from one year onwards.

Baseline 12-month incidence of NODAT for BAS+TAC+MMF was estimated to be 10.6% based on the results of the Symphony study.[191]

We did not find significant evidence to suggest that induction therapies affected the incidence of NODAT, so the incidence of NODAT was modelled independently of induction agent.

Since all modelled maintenance regimens are triple-therapy regimens and to maximise statistical power it was assumed that the incidence of NODAT in each regimen could be estimated by combining independent estimates for replacing immediate-release tacrolimus and/or mycophenolate mofetil in the baseline regimen.

Table 168 and Table 169 list the studies (RCTs from the systematic review of clinical effectiveness) informing the impact of replacing immediate-release tacrolimus and mycophenolate mofetil respectively on 12-month NODAT incidence.

Table 168. Studies included to estimate the impact on NODAT incidence of replacing immediate-release tacrolimus

Study	Compares	NODAT in 12 months
Laskow 1996[94]	TAC vs. CSA	12/67 vs. 1/20
Mayer 1997[96]	TAC vs. CSA	17/303 vs. 3/145
Campos 2002[102]	TAC vs. CSA	10/85 vs. 3/81
Hardinger 2005[108]	TAC vs. CSA	5/134 vs. 1/66
Raofi 1999[245]	TAC vs. CSA	3/14 vs. 4/21
Yang 1999[123]	TAC vs. CSA	1/24 vs. 1/21
Kramer 2010[72]	TAC vs. TAC-PR	20/336 vs. 22/331
Tsuchiya 2013[128]	TAC vs. TAC-PR	0/52 vs. 1/50
Vincenti 2005[71](a)	CSA vs. BEL	6/73 vs. 1/71
BENEFIT[54](a)	CSA vs. BEL	16/221 vs. 7/226
BENEFIT-EXT[135](a)	CSA vs. BEL	11/184 vs. 7/175
Ferguson 2011[138](b)	TAC vs. BEL	1/30 vs. 0/33
Lebranchu 2009[163]	CSA vs. SRL	2/97 vs. 3/96
Buchler 2007[167]	CSA vs. SRL	3/74 vs. 9/71
Kreis 2000[206]	CSA vs. SRL	1/38 vs. 1/40
Guba 2010[173]	CSA vs. SRL	4/71 vs. 5/69
Martinez-Mier 2006[174]	CSA vs. SRL	1/21 vs. 1/20
Schaefer 2006[78]	TAC vs. SRL	5/39 vs. 6/41
Groth 1999[185]	CSA vs. SRL	1/42 vs. 1/41
Chen 2008[186]	TAC vs. CSA	1/21 vs. 1/20
SYMPHONY[238]	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

Table 169. Studies included to estimate the impact on NODAT incidence of replacing mycophenolate mofetil

Study	Compares	NODAT in 12 months
Ciancio 2008[130]	MMF vs. MPS	7/61 vs. 6/55
Ferguson 2011[138(a)]	MMF vs. SRL	0/33 vs. 2/26
Takahashi 2013[143]	MMF vs. EVL	3/61 vs. 7/61
Tedesco Silva 2010[145]	MMF vs. EVL	19/273 vs. 14/274
Anil Kumar 2005[153]	MMF vs. SRL	2/75 vs. 2/75
Gonwa 2003[155]	MMF vs. SRL	9/176 vs. 10/185
Sampaio 2008[156]	MMF vs. SRL	6/50 vs. 12/50

a TAC+MMF arm excluded

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 170 and Table 171.

Table 170. 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)				
	Mean	SD	Median	95% CrI	
TAC	(Baseline)				
TAC-PR	0.1694	0.3199	0.1687	−0.4546	0.8003
CSA	−0.8162	0.2086	−0.8136	−1.231	−0.4129
BEL	−1.671	0.381	−1.665	−2.431	−0.9394
SRL	−0.2345	0.2239	−0.2339	−0.6734	0.2016

Table 171. 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)				
	Mean	SD	Median	95% CrI	
MMF	(Baseline)				
MPS	−0.07041	0.6122	−0.0656	−1.291	1.126
SRL	0.4739	0.3318	0.4719	−0.1688	1.131
EVL	−0.05221	0.3194	−0.05309	−0.6831	0.5742

The mean log odds ratios were combined from the MTCs to estimate an overall odds ratio for each regimen, as shown in Table 172, 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 173.

Table 172. 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+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

Table 173. Estimated 12-month incidence of NODAT for each regimen

Regimen	NODAT incidence
CSA+MMF	4.98%
TAC+MMF	10.60%
CSA+AZA	4.98%
TAC+AZA	10.60%
CSA+EVL	4.74%
TAC+SRL	16.00%
TAC-PR+MMF	12.32%
BAS+CSA+MMF	4.98%
BAS+TAC+MMF	10.60%
BAS+CSA+AZA	4.98%
BAS+SRL+MMF	8.57%
BAS+BEL+MMF	2.18%
BAS+CSA+MPS	4.66%
rATG+CSA+MMF	4.98%
rATG+TAC+MMF	10.60%
rATG+CSA+AZA	4.98%

Cytomegalovirus infection

It was judged on the basis of examining the incidence of cytomegalovirus infection in RCTs included in the systematic review, and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster et al.,[8 356] 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 174 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.

Table 174. 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[141]	No mTOR-I vs. mTOR-I replacing antimetabolite	38/196 vs. 10/194
Takahashi 2013[143]	No mTOR-I vs. mTOR-I replacing antimetabolite	21/61 vs. 3/61
Tedesco Silva 2010[145]	No mTOR-I vs. mTOR-I replacing antimetabolite	16/273 vs. 2/274
Chadban 2013[144]	No mTOR-I vs. mTOR-I replacing antimetabolite	2/47 vs. 4/30
Sampaio 2008[156]	No mTOR-I vs. mTOR-I replacing antimetabolite	6/50 vs. 6/50
Mjörnstedt 2012[150]	No mTOR-I vs. mTOR-I replacing CNI	13/100 vs. 9/102
Flechner 2002[205]	No mTOR-I vs. mTOR-I replacing CNI	2/30 vs. 3/31
Lebranchu 2009[163]	No mTOR-I vs. mTOR-I replacing CNI	6/97 vs. 4/96
Büchler 2007[167]	No mTOR-I vs. mTOR-I replacing CNI	17/74 vs. 4/71
Kreis 2000[206]	No mTOR-I vs. mTOR-I replacing CNI	8/38 vs. 2/40
Guba 2010[173]	No mTOR-I vs. mTOR-I replacing CNI	20/71 vs. 5/69
Martinez-Mier 2006[174]	No mTOR-I vs. mTOR-I replacing CNI	0/21 vs. 1/20
SYMPHONY[238]	No mTOR-I vs. No mTOR-I vs. mTOR-I replacing CNI	39/403 vs. 45/408 vs. 23/380

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 175.

Table 175. 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)				
	Mean	SD	Median	95% CrI	
No mTOR-I	(Baseline)				
mTOR-I replacing CNI	−0.7981	0.3889	−0.806	−1.558	0.01047
mTOR-I replacing antimetabolite	−1.153	0.4916	−1.175	−2.091	−0.1184
σ (random effects parameter)	0.7915	0.4085	0.7538	0.08925	1.705

The baseline incidence of CMV infection (i.e., for no mTOR-I use) was estimated by fitting a logistic model to the absolute incidence of CMV infection in all RCT arms not using mTOR-I and reporting CMV infection incidence within 12 months (Table 176) with study-level random intercepts. The estimated average baseline CMV incidence is 10.72% (95% CI, 1.87–43.09%).

Table 176. Studies used to estimate the baseline incidence of CMV infection

Study	CMV infection within 12 months
Mayer 1997[96]	TAC+AZA: 41/303; CSA+AZA: 24/145
Hardinger 2005[108]	TAC+AZA: 5/134; CSA+AZA: 4/66
Raofi 1999[245]	TAC+AZA: 0/14; CSA+AZA: 0/24
Baboolal 2002[101]	TAC+AZA: 7/27; CSA+AZA: 7/24
Merville 2004[114]	CSA+MMF: 11/37; CSA+AZA: 17/34
Vacher-Coponat 2012[119]	TAC+MMF: 25/143; CSA+AZA: 28/146
Yang 1999[123]	TAC+MMF: 3/30; CSA+MMF: 0/30
Weimer 2006[125]	TAC+AZA: 7/28; CSA+AZA: 11/25; CSA+MMF: 13/31
Krämer 2010[72]	TAC+MMF: 19/336; TAC-PR+MMF: 33/331
Tsuchiya 2013[128]	TAC+MMF: 7/52; TAC-PR+MMF: 4/50
Ciancio 2008[130]	TAC+MMF: 1/75; TAC+MPS: 0/75
Salvadori 2004[132]	CSA+MMF: 43/210; CSA+MPS: 46/213
Vincenti 2005[71]	BEL+MMF: 11/71; CSA+MMF: 13/73
BENEFIT[54]	BEL+MMF: 10/226; CSA+MMF: 6/221
BENEFIT-EXT[135]	BEL+MMF: 24/175; CSA+MMF: 24/184
Ferguson 2011[138]	BEL+MMF: 1/33; TAC+MMF: 2/30
Vitko 2004[141]	CSA+MMF: 38/196
Takahashi 2013[143]	CSA+MMF: 21/61
Tedesco Silva 2010[145]	CSA+MPS: 16/273
Chadban 2013[144]	CSA+MPS: 2/47
Mjörnstedt 2012[150]	CSA+MPS: 13/100
Sampaio 2008[156]	TAC+MMF: 6/50
Flechner 2002[205]	CSA+MMF: 2/30
Lebranchu 2009[163]	CSA+MMF: 6/97
Buchler 2007[167]	CSA+MMF: 17/74
Kreis 2000[206]	CSA+MMF: 8/38
Guba 2010[173]	CSA+MMF: 20/71

Martinez-Mier 2006[174]	CSA+MMF: 0/21
SYMPHONY[238]	CSA+MMF: 45/408; TAC+MMF: 39/403

Combining the baseline incidence with the treatment effects results in the incidence rates for each regimen as shown in Table 177.

Table 177. CMV infection incidence rates used in the model

Regimen	CMV incidence within 12 months
CSA+EVL	3.65%
TAC+SRL	3.65%
BAS+SRL+MMF	5.13%
No mTOR-I	10.72%

Dyslipidaemia

It was judged on the basis of examining the incidence of cytomegalovirus infection in RCTs included in the systematic review, and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster et al.,[8 356] 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 178 details the RCTs from our systematic review (Section 4.2.1) which compared regimens with and without mTOR-I and which reported dyslipidaemia. The direction of effect is consistent across the studies.

Table 178. Studies included to estimate the impact on dyslipidaemia incidence of mTOR-I use

Study	Incidence of dyslipidaemia within 12 months	
	No mTOR-I	mTOR-I
Vitko 2004[141]	24/196	51/194
Takahashi 2013[143]	19/61	28/61
Tedesco Silva 2010[145]	43/273	57/274
Mjörnstedt 2012[150]	9/100	13/102
Sampaio 2008[156]	8/50	11/50
Flechner 2002[205]	16/30	20/31
Lebranchu 2009[163]	4/97	8/96
Büchler 2007[167]	38/74	50/71
Guba 2010[173]	5/71	14/69
SYMPHONY[238]	91/811	60/380

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 179.

Table 179. Fixed effects meta-analysis of the impact on dyslipidaemia incidence of mTOR-I use

mTOR-I use	Odds ratio vs. baseline (natural logarithmic scale)				
	Mean	SD	Median	95% CrI	
No mTOR-I	(Baseline)				
mTOR-I	0.5566	0.1005	0.5555	0.3604	0.7533

To estimate the baseline incidence of dyslipidaemia (without mTOR-I use) we identified all RCTs in our systematic review which reported dyslipidaemia and considered at least one regimen without mTOR-I use (Table 180). A logistic model was fitted as for CMV incidence and the average dyslipidaemia incidence for no mTOR-I use was estimated to be 20.17%

(95% CI, 3.56–63.37%). On this basis the incidence of dyslipidaemia for regimens including mTOR-I was estimated to be 30.59%.

Table 180. Studies included to estimate the incidence of dyslipidaemia without mTOR-I use

Study	Dyslipidaemia incidence within 12 months
Hardinger 2005[108]	TAC+AZA: 40/134; CSA+AZA: 26/66
Vacher-Coponat 2012[119]	TAC+MMF: 54/128; CSA+AZA: 78/137
Vincenti 2005[71]	BEL+MMF: 9/71; CSA+MMF: 6/73
Ferguson 2011[138]	BEL+MMF: 12/33; TAC+MMF: 12/30
Vitko 2004[141]	CSA+MMF: 24/196
Takahashi 2013[143]	CSA+MMF: 19/61
Tedesco Silva 2010[145]	CSA+MPS: 43/273
Mjörnstedt 2012[150]	CSA+MPS: 9/100
Sampaio 2008[156]	TAC+MMF: 8/50
Flechner 2002[205]	CSA+MMF: 16/30
Lebranchu 2009[163]	CSA+MMF: 4/97
Büchler 2007[167]	CSA+MMF: 38/74
Guba 2010[173]	CSA+MMF: 5/71
SYMPHONY[238]	CSA+MMF: 51/408; TAC+MMF: 40/403

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.[386] This prevalence was assumed to be the same regardless of time since transplantation, age, or other factors.

7.3.3.5. Retransplantation

The baseline rate of retransplantation following graft loss was estimated from the UK Transplant Registry standard dataset in the following way:

1. Data cleaning was performed:

2. Living (relationship unspecified), domino, altruistic and unrelated pooled donors were all reclassified as living unrelated donors;

    i. Transplant recipients missing codes for sex or age group were removed;

    ii. Transplant recipients whose earliest transplant in the dataset was not kidney-only were removed;

3. Transplant recipients whose first graft was still functioning, or who were lost to follow-up, or who died with a functioning graft, were removed;

4. The total number of recipients whose first transplant was recorded as failed and who had no subsequent transplant recorded was calculated as $N_1 = 5085$;

5. Recipients whose first transplant failed and had no subsequent transplant were removed if patient survival was not recorded or if patient survival (actual or censored at follow-up) was not greater than graft survival, leaving $N_{1*} = 1567$ recipients with only one transplant recorded and failed;

6. The total time for which those not receiving a subsequent transplant were followed was estimated as ([sum(patient survival in days) – sum(graft survival in days)] / 365.2425 × [N_1 / N_{1*}]) = 13,627.61 years;

7. The total time between graft failure and retransplantation for those with a subsequent transplant was estimated as (sum(year of second transplant) – [sum(year of first transplant) + sum(first graft survival in days) / 365.2425]) = 5955.05 years;

8. The total follow-up time was therefore estimated as 13,627.61 + 5681.06 = 19,582.66 years;

9. The number of retransplants was calculated by counting the number of recipients with two or more transplants recorded, $N_{>1} = 2031$;

10. The rate of retransplantation was estimated as 0.1037 with standard error 0.0023.

It was then assumed that the rate of retransplantation would reduce after age 65 and be zero by age 80, and that the rate would decline linearly between these ages. This assumption was corroborated with our EAG.

Pre-emptive retransplantations were also modelled from the first FUNCTIONING GRAFT state in the event of graft loss, as described in Section 7.3.3.2 (page 405).

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[387 388]; 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 181 summarises the parameters affecting subsequent grafts.

Table 181. 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

7.3.4. 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

Graft loss, patient death, acute rejection and graft function were primarily estimated from the network meta-analyses for induction and maintenance regimens (Sections 4.3.3.1 and 4.3.3.2, starting page 251), 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 182.

Table 182. Summary of mean treatment effects from network meta-analyses

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
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.

The effectiveness estimates were combined with the following estimated baseline values (for BAS+TAC+MMF): mortality within 12 months (odds) = 0.0153; graft loss within 12 months (odds) = 0.0365; eGFR at 12 months (ml/min/1.73 m^2) = 53.4; acute rejection within 12 months (odds) = 0.139. The resulting absolute effectiveness estimates are given in Table 183.

Table 183. Summary of absolute effectiveness estimates for each regimen

Regimen	Mortality within 12 months (odds)	Graft loss within 12 months (odds)	Mean eGFR (ml/min/1.73 m^2)	Biopsy proven acute rejection within 12 months (odds)
CSA+MMF	**0.0107**	**0.0470**	**45.9**	**0.326**
TAC+MMF	**0.0172**	**0.0434**	**50.8**	**0.276**
CSA+AZA	**0.0113**	**0.0633**	**44.3**	**0.692**
TAC+AZA	**0.0156**	**0.0725**	**53.6**	**0.400**
CSA+EVL	**0.0158**	**0.0390**	**49.1**	**0.316**
TAC+SRL	**0.0156**	**0.0742**	**43.9**	**0.266**
TAC-PR+MMF	**0.0220**	**0.0521**	**44.1**	**0.269**
BAS+CSA+MMF	**0.0095**	**0.0396**	**48.5**	**0.164**
BAS+TAC+MMF	**0.0153**	**0.0365**	**53.4**	**0.139**
BAS+CSA+AZA	**0.0101**	**0.0534**	**46.9**	**0.348**
BAS+SRL+MMF	**0.0173**	**0.0551**	**50.7**	**0.152**
BAS+BEL+MMF	**0.0047**	**0.0326**	**57.4**	**0.280**
BAS+CSA+MPS	**0.0062**	**0.0342**	**52.4**	**0.244**
rATG+CSA+MMF	**0.0067**	**0.0365**	**46.6**	**0.115**

rATG+TAC+MMF	**0.0109**	**0.0337**	**51.6**	**0.097**
rATG+CSA+AZA	**0.0071**	**0.0491**	**45.0**	**0.244**

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 421), Cytomegalovirus infection (page 427) and Dyslipidaemia (page 431).

7.3.5. Measurement and valuation of preference-based outcomes

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 (see syntax for full search strategy in Appendix 1. 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.

7.3.5.1. Baseline utility

Baseline utility was modelled using the following equation:

$Utility = 0.967981 - 0.001807 \times Age - 0.000010 \times Age^2 + 0.023289 \times Male$

This equation was derived from the Health Survey for England (2012)[389] using the well-established methodology of Ara and Brazier.[390]

7.3.5.2. Utility with dialysis

A systematic review and meta-analysis by Liem et al. (2008)[391] 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 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 184 below.

Table 184. 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 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).

7.3.5.3. Disutility due to established renal failure treated with transplantation (i.e. functioning graft)

The same systematic review and meta-analysis by Liem et al. (2008) [391] reported pooled estimates of utility for people living with a functioning renal graft [Liem meta-analysis]. It reported a random effects meta-analysis of five studies which had produced EQ-5D index

scores for people living with a functioning renal graft (range of means, some medians, 0.71 to 0.86; see Table 185).

Table 185. 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, so this absolute estimate was converted into a utility decrement from baseline of 0.053 (SE 0.049).

7.3.5.4. 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[368]). This is a recent study in the relevant patient 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[392]), 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 [393]. 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.

BMS incorporated disutility of 0.041 for NODAT citing Currie et al. (2005)[394] as their source, which is a study looking at costs. We believe they intended to cite the other Currie et al. (2005) paper,[395] 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 report the findings of Wyld et al. (2012),[396] 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.

7.3.6. 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

7.3.6.1. 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.[397]

Table 186. 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.

7.3.6.2. 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.[89] 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.[89]

Table 187. Resource use for induction therapy

Parameter	Value	Source
Basiliximab induction		
Basiliximab 20 mg doses	1.964	Brennan 2006[89]
Administration (IV infusion)	1.964	Brennan 2006[89]
Rabbit ATG induction		
Rabbit ATG mg/kg	6.5	Brennan 2006[89]
Administration (IV infusion)	4.525	Assumption based on Brennan 2006[89]

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

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.

The target whole blood concentrations are usually higher initially to ensure adequate immunosuppression and are then lowered to reduce the likelihood and impact of adverse events (including nephrotoxicity for CNIs).

There is a substantial body of evidence that the dosage required to achieve target whole blood concentrations is affected by concomitant treatments, and as such the model includes different dosage schedules for each agent according to concomitant treatment.

It was not possible to estimate the impact of different induction therapies on the required dosage in early days and weeks but this is unlikely to have a significant impact on overall costs.

Belatacept is administered intravenously according to a prescribed schedule. It was assumed that the “less intensive” regimen from the BENEFIT[54] and BENEFIT-EXT[135] 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.

Mean weight of KTRs was estimated by identifying RCTs included in the systematic review of clinical effectiveness which reported weight as a baseline characteristic. A random-effects model was used, which resulted in estimated mean (SE) weight of 70.2 (1.2) kg. The standard deviation of weight of KTRs was estimated by pooling the standard deviations reported, resulting in a standard deviation of 14.8 kg. A normal distribution was then assumed to calculate the expected number of vials required for 10 mg/kg and 5 mg/kg doses. It was estimated that 3.31 vials would be required for a 10 mg/kg dose and 1.91 vials for a 5 mg/kg dose (Table 188).

Table 188. Expected number of vials of belatacept required for patient weighing 70.2 ± 14.8 kg

Number of vials	10 mg/kg dose	5 mg/kg dose
1	0.1%	24.7%
2	8.5%	59.6%
3	54.2%	15.3%
4	35.0%	0.3%
5	2.2%	0.0%
Expected	3.31	1.91

Table 189. Resource use for maintenance therapy

Parameter	Value		Source
Immediate-release tacrolimus			
With azathioprine	Time	Dosage (mg/kg/day)	Margreiter 2002[103]
	0–1 month	0.225	
	1–3 months	0.175	
	3–6 months	0.135	
	6–12 months	0.110	
	12–36 months	0.090	
	36+ months	0.080	
With mycophenolate mofetil	Time	Dosage (mg/kg/day)	Rowshani 2006[122] for 0–12 months; assumed no higher than with azathioprine for 12+ months
	0–2 weeks	0.168	
	2–6 weeks	0.176	
	6–12 weeks	0.110	
	3–6 months	0.104	
	6–12 months	0.086	
	12+ months	0.080	
With sirolimus	Time	Dosage (mg/kg/day)	Starting dose from Gonwa 2003[155] (0–1 month); assumed no higher than with mycophenolate mofetil (1–6 months); Gonwa 2003,[155] Anil Kumar 2008[194] (6+ months)
	0–1 month	0.175	
	1–3 months	0.110	
	3–6 months	0.104	
	6–12 months	0.080	
	12+ months	0.070	
Prolonged-release tacrolimus			
With mycophenolate mofetil	As for immediate-release tacrolimus plus 0.015 mg/kg/day for 12 months		Wlodarczyk 2009,[127] Kramer 2010,[72] Tsuchiya 2013,[128] Oh 2014[129]
Ciclosporin			
With azathioprine	Time	Dosage (mg/kg/day)	Margreiter 2002[103]
	0–1 month	6.38	
	1–3 months	4.53	
	3–6 months	3.77	
	6–12 months	3.38	
	12–36 months	2.93	

	36+ months	2.84	
With mycophenolate mofetil or mycophenolate sodium	Time	Dosage (mg/kg/day)	Rowshani 2006[122]
	0–2 weeks	7.62	
	2–6 weeks	5.72	
	6–12 weeks	3.06	
	3–6 months	2.86	
	6–12 months	2.82	
	12+ months	2.82	
With everolimus	Time	Dosage (mg/kg/day)	Vitko 2004[141]
	0–12 months	3.9	
	12+ months	2.1	
Azathioprine			
With tacrolimus	Time	Dosage (mg/kg/day)	Starting dose 1–2 mg/kg/day; Laskow 1997[94]
	0–6 months	1.50	
	6+ months	1.20	
With ciclosporin	Time	Dosage (mg/kg/day)	Starting dose 1–2 mg/kg/day; Sadek 2002,[113] Vacher-Coponat 2012[119]; Vacher-Coponat 2012[119]; assumed
	0–6 months	1.50	
	6–12 months	1.40	
	12–36 months	1.22	
	36+ months	1.22	
Mycophenolate mofetil			
With tacrolimus	Time	Dosage (g/day)	Starting dose 2 g/day; SYMPHONY[238]
	0–3 months	2.00	
	3–12 months	1.74	
	12+ months	1.47	
With ciclosporin	Time	Dosage (g/day)	Starting dose 2 g/day; SYMPHONY[238]
	0–3 months	2.00	
	3–12 months	1.84	
	12+ months	1.67	
With sirolimus	Time	Dosage (g/day)	Starting dose 2 g/day; SYMPHONY[238]
	0–3 months	2.00	
	3–12 months	1.73	
	12+ months	1.47	
With belatacept	Time	Dosage (g/day)	Starting dose 2 g/day; BENEFIT[54]
	Throughout	2.00	
Mycophenolate sodium			
With ciclosporin	Time	Dosage (mg/day)	Starting dose; Mjornstedt 2012[150]
	0–3 months	1440	
	3–9 months	1211	
	9+ months	1107	
Sirolimus			
With tacrolimus	Time	Dosage (mg/day)	Anil Kumar 2008[194]
	0–12 months	3.70	
	12–60 months	2.75	
	60+ months	1.80	
With mycophenolate mofetil	Time	Dosage (mg/day)	Lebranchu 2009[163]
	0–3 months	5.20	
	3–6 months	4.45	
	6–9 months	3.50	
	9–12 months	3.25	
	12–48 months	2.90	
	48+ months	2.60	

Everolimus

With ciclosporin

Time	Dosage (mg/day)
0–3 months	2.94
3–6 months	2.75
6–9 months	2.53
9–12 months	2.60
12–24 months	2.60
24+ months	2.00

Tedesco Silva 2010[145]; Lorber 2005[139]

Belatacept (with mycophenolate mofetil)

Drug acquisition

Time	Dosage (vials/quarter)
0–3 months	16.53
3–6 months	7.13
6+ months	6.24

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
6+ months	3.26

Prednisolone

(All maintenance regimens)

Time	Dosage (mg/day)
Throughout	16.3

SYMPHONY[238]

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 190). The haemodialysis mix was reflected in incident and prevalent people on dialysis, but conversion costs (between dialysis modes) were not included.

Table 190. Proportion of dialysis patients receiving haemodialysis by age group

Age group	Proportion receiving haemodialysis
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%

Acute rejection

The number of KTRs suffering at least one acute rejection episode was derived as detailed in sections Acute rejection within 12 months (page 414) and Effectiveness estimates (page 436).

To account for the fact that some KTRs may experience more than one acute rejection episode a study (Charpentier et al. 2003[88]) 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.

Infection prophylaxis

Infection prophylaxis was based on the Royal Devon & Exeter transplant protocol.[398]

Cytomegalovirus prophylaxis is 200 days valganciclovir for high risk KTRs (donor seropositive and recipient seronegative). Intermediate and low-risk KTRs do not receive prophylaxis for CMV. The dosage of valganciclovir is adjusted based on Cockcroft–Gault creatinine clearance, being 900 mg daily for KTRs with CrCl > 60 ml/min, 450 mg daily for KTRs with CrCl 40–59 ml/min, 450 mg alternate days for KTRs with CrCl 25–39 ml/min and 450 mg twice weekly for CrCl 10–24 ml/min. It was assumed that KTRs in the Functioning

graft state were split equally in the 25–39, 40–59 and > 60 ml/min bands, and that KTRs in the Chronic allograft injury state were all in the 10–24 ml/min band. In the model, 23.2% of KTRs were assumed to be at high risk of CMV infection, based on Harvala et al. 2013.[399]

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 graft function receive more intensive monitoring to maximise graft survival.

A retrospective observational study was conducted by Ling and Chamberlain[400] and submitted by Bristol Myers Squibb which detailed the post-transplant outpatient tests conducted according to the Cardiff Renal Transplant Database.

It was assumed that every monitoring visit would involve full blood count, renal profile, liver function test and therapeutic drug monitoring (if appropriate) and therefore the test performed the most number of times in each time period was assumed to be representative of monitoring visits.

The data from the observational study clearly show that when patients are stratified by their eGFR at 12 months their monitoring is more intensive for lower eGFR ranges, but also that

even for the lowest eGFR groups there is a decrease in monitoring over time. The maximum follow-up in the study is to 36 months and therefore extrapolation methods should be considered carefully. Increased monitoring for KTRs with lower eGFR at 12 months is due in part to the absolute level of graft function but also to the trajectory of graft function. KTRs with rapidly declining graft function will receive more monitoring and clinics in an attempt to slow the rate of decline. It is therefore quite unlikely that costs associated with low eGFR in the first 36 months will be representative of costs in much later years for patients who eventually reach the same eGFR on a slower trajectory.

This, plus the paucity of data on the evolving eGFR distribution of KTRs over time, is a compelling reason to avoid having absolute eGFR levels driving costs to the extent that is observed in short-term follow-up.

We decided to use the data from the observational study for the first 36 months but thereafter to assume four clinics and blood tests a year, based on the Royal Devon & Exeter transplant protocol[398] which suggests that KTRs with stable graft function should have monitoring tapered to every 3–6 months.

Table 191 details the monitoring visits assumed in the model.

Table 191. Monitoring visits assumed in the model

Time	Number of monitoring visits	Rate of monitoring visits (number per year)
0–1 month	13.07	157
1–2 months	6.75	81
2–3 months	4.95	59
3–6 months	8.99	36
6–12 months	7.93	16
12–24 months	10.77	11
24–36 months	14.00	14
36+ months	4 per year (based on 3–6 monthly clinic+bloods in Royal Devon & Exeter protocol)	

Source: Ling and Chamberlain 2011[400] except where specified

Clinics were assumed to be as frequent as monitoring visits, except for the first three months where they were assumed to be once weekly on the basis of the Royal Devon & Exeter protocol.

Viral quantitative PCR was modelled based on the Royal Devon & Exeter protocol, in which KTRs at intermediate risk of CMV infection (i.e., seropositive recipients) receive CMV quantitative PCR once weekly for three months. In the model, 41.5% of KTRs were assumed to be at intermediate risk of CMV infection, based on Harvala et al. 2013.[399]

All KTRs receive BKV quantitative PCR at 3, 6 and 12 months.

KTRs at high risk of EBV disease (i.e., seronegative recipients from seropositive donors) receive monthly quantitative PCR to 6 months followed by tests at 9 and 12 months. The proportion of KTRs at high risk of EBV disease was estimated from Cavallo et al. 2010,[401] in which 289/290 recipients were EBV seropositive and 51/55 donors were EBV seropositive. Assuming that donor–recipient matching is independent of EBV risk, the chance of a KTR being EBV high risk is (1/290) × (51/55) = 0.32%.

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,[373] which we have reproduced in Table 192 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 192. 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.[402]

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.[402]

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.[402]

Medical management for dyslipidaemia was assumed to be one dietetics outpatient attendance per year and one GP appointment per year.

Anaemia

According to Vanrenterghem et al. 2003,[386] 207/3969 = 5.2% of KTRs required erythropoiesis stimulating agent (ESA) treatment for anaemia, with a mean weekly dose of 5,832 IU. It was therefore assumed that 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[403] 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.

7.3.6.3. Unit costs

The following sources were used to identify unit costs for drug acquisition:

- Commercial Medicines Unit electronic market information tool (eMit)[404]
- British National Formulary Volume 68 (January 2015 online update)[405]

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[406] (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 193.

Table 193. Drug acquisition costs for induction therapy

Agent	Pack details	Units	Unit cost	Source
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

Historically the prescribing of maintenance immunosuppression has in some cases (when people have stable dosing requirements) been transferred to primary care physicians with dispensing in the community. The NICE reference case states that for medicines predominantly prescribed in primary care, prices should be based on the Drug Tariff. Recently, however, NHS England and the Welsh Health Specialised Services Committee have directed that prescribing of immunosuppressants be repatriated to secondary care on the grounds of patient safety.[407 408] As a result, in this analysis it is assumed that hospital prescribing and dispensing is appropriate for costing and therefore eMit costs are preferred when available, followed by BNF costs.

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 194. 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 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 market share)	CMU eMit
Mycophenolate mofetil	50 × 500 mg = £9.17 100 × 250 mg = £10.94	g	£0.3774 (based on 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 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 market share)	CMU eMit

Dialysis

Dialysis access surgery costs were estimated per procedure (Table 195) and ongoing dialysis costs (i.e., the cost of dialysis sessions) were estimated per quarter year cycle.

Table 195. Unit costs of dialysis access surgery

Procedure	HRG4 currency		Unit cost
		2013/14 prices	2014/15 prices
Haemodialysis access surgery	YQ42Z: Open Arteriovenous Fistula, Graft or Shunt Procedures	£1,915	£1,946
Haemodialysis temporary access surgery	YR41A: Insertion of Tunnelled Central Venous Catheter, 19 years and over	£810	£823
Peritoneal dialysis access surgery	LA05Z: Renal Replacement Peritoneal Dialysis Associated Procedures	£1,083	£1,101

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 currencies 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.

Acute rejection

Costing acute rejection is challenging because although the initial treatment pathway for T-cell mediated acute rejection (which is the most common) is fairly standardised (bolus intravenous methylprednisolone and reassessment of immunosuppressive agent dosage) there is a great amount of variation in treatment if the acute rejection is steroid-resistant and/or antibody-mediated. It is also not clear how many acute rejection episodes require hospitalisation and/or dialysis.

A microcosting study was conducted by Ling, Pandit and Bennett for Bristol-Myers Squibb in which 11 UK renal consultants from nine centres completed a questionnaire estimating resource use for an average transplant patient.[409] This study was submitted by Bristol-Myers Squibb as part of the technology appraisal.

With regards acute rejection a unit cost was estimated by considering the following possible costs:

- Inpatient stay
- Additional clinic visits
- Laboratory tests
- First-line therapies
    - Methylprednisolone
    - Prednisolone
- Second-line therapies
    - ATG

- IV immunoglobulin
- OKT3
- Plasma exchange
- Rituximab

The estimated cost for an acute rejection episode was £3,217 in 2009 GBP, of which £615 was first-line treatment (all people), £798 was second-line treatment (significantly more expensive but only required by a small proportion of people), £797 was extra clinic visits and £1,007 was hospitalisation.

This unit cost was inflated to £3,557 in 2014/15 prices for use in the model.

Alternative unit costs were considered as follows:

- Astellas assumed that people with steroid-sensitive acute rejection (80%) would receive four days of therapy with IV methylprednisolone (500 mg/day) at a cost of £38.40 while people with steroid-resistant acute rejection (20%) would receive 10 days of rabbit ATG at a dose of 1.5 mg/kg/day and incur the cost "Acute kidney injury without [comorbidities or complications]" from NHS Reference Costs (total cost for steroid-resistant acute rejection = £8,535). The average cost of an acute rejection episode was therefore estimated to be £1,738. It was judged that the cost of treating steroid-sensitive acute rejection had likely been underestimated as there were no costs included for diagnosis, hospitalisation or intravenous administration and as such the estimated average cost of £1,738 may be underestimated.
- Novartis assumed a cost of £1,725 based on inflating the cost of acute rejection in McEwan et al. 2005[332] from 2003 to 2013 costs. The original cost included two days' hospitalisation for all people, increased immunosuppression using tacrolimus, mycophenolate mofetil and methylprednisolone for 33% of people and muromonab-CD3 for 5% of people. Given how old the cost estimate is, and that more therapies are used now beyond muromonab-CD3 for steroid-resistant acute rejection, it was judged that this cost estimate might not be applicable to current practice.

New-onset diabetes after transplantation

Recent studies of costs of diabetes to the NHS, such as Hex et al. (2012)[410] or cost-utility studies such as Davies et al. (2012),[411] Gillies et al. (2008)[412] demonstrate that the cost of complications associated with diabetes far outweigh the direct treatment costs. As such, we believe it important to include these costs within the model, particularly as this allows us to capture the additional costs of CVD associated with diabetes.

In their submission, Astellas cost annually for Metformin, applied only to those with a functioning graft. By comparing this figure to the dose recommendations in the BNF, this value forms a good basis for treatment costs. Treatment costs for diabetes are also likely to increase as more people become insulin dependent, but the data on how many people become insulin dependent and when is poor. Furthermore, the total cost of diabetes must include both treatment and complications costs. As the cost of complications far outweighs the costs of treatment for diabetes, we believe the inclusion of an insulin cost would not make a significant difference to the cost-effectiveness results and we therefore do not account for it in the model.

BMS used the annual cost of diabetes of £1,174, taken from Currie et al. 2010[413] and inflated to 2014 prices. This reflects the annual per patient cost of all prescriptions and consultations accrued by the diabetic population. It is not clear whether this includes renal costs. It is also reflective of cost to the NHS per year, as opposed to annual per patient cost, reflective of their lifetime costs. We therefore considered alternative sources for our diabetes costs.

One possible source is Gillies et al. 2008,[412] which calculates an annual cost of clinically detected Type 2 diabetes to be £2,756 (2006 costs). This value comes from the UKPDS data reported in Clarke et al. 2005 and inflated to 2006 prices. These costs seem to be outdated and were not explicit about whether renal transplantation costs are included, so we identified a more recent paper on costs of complications associated with diabetes from the UKPDS (Alva et al. 2014[414]) via personal communication with Professor Alistair Gray of the University of Oxford. This study follows the original UKPDS cohort since the closing of the intervention in 1997 to 2007 and includes ten years of follow up of over 3,000 people with Type 2 diabetes. Renal disease was not included in the list of complications, but it did include several complications associated with CVD. The average age of the population is slightly higher than that of the people in our model (63 as opposed to 50) and as they are no longer newly diagnosed people, this may make costs higher than expected for the first few cycles of the model. However, given the size of the trial and the recentness of the data, we believe this

source to be appropriate. From the Supplementary Tables 4 and 5, the average annual per patient costs of complications across the study period were given at 2012 prices as £1,352 for inpatient costs (standard deviation £5,364) and £676 (standard deviation £1,081) for non-inpatient costs. This demonstrates both the size of these costs compared to the cost of treatment of diabetes and also the variation in the cost of diabetes complications.

Dyslipidaemia

Statin acquisition costs for the treatment of dyslipidaemia are given in Table 196 and medical management costs are given in Table 197.

Table 196. 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 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 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 market share)	CMU eMit

Table 197. 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[397]: 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 198. Costs for CMV prophylaxis (valganciclovir) are clearly much higher than costs for PCP and UTI prophylaxis.

Table 198. 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

Ling, Pandit and Bennett (in the microcosting study referred to in the section Acute rejection, page 458) estimated the cost of CMV infection treatment to be £2,721 in 2009 GBP. This was inflated to £3,009 in 2014/15 prices for use in the model.

Alternative unit costs were considered as follows:

- Astellas assume a unit cost of £1,863 based on IV ganciclovir induction for 14–21 days followed by IV ganciclovir maintenance for eight weeks. They only appear to have included drug acquisition costs for this schedule and not administration costs, which would be substantial. It is possible that oral valganciclovir could be used for maintenance instead of IV ganciclovir reducing the administration costs in this period but there would still be 14–21 days of administration costs excluded from this estimate. It was judged that £1,863 is likely to be an underestimate of the true cost of CMV infection.

- Novartis assume a unit cost of £45 based on a GP visit on presentation of symptoms. This appears to be a significant underestimation of the true cost of CMV infection.

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 199. Drug acquisition costs for anaemia

Agent	Pack details	Units	Unit cost	Source
Epoetin alfa (Binocrit®)	1,000 IU = £4.33 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	Per 1,000 IU	£4.33 (based on 1,000 prefilled syringe)	BNF 68

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 patient is estimated to require 10 days inpatient stay).[415]

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 200). 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 200. 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 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,[415] as shown in Table 201.

Table 201. Unit costs of 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,[416] by mapping from OPCS-4 code M026 (Excision of rejected transplanted kidney) to groups LB60, LB61, LB62 and LB63 (Table 202). The average cost (weighted by activity) was £4,886 in 2013/14 prices which was inflated to £4,966 in 2014/15 prices for the model.

Table 202. Reference costs informing the unit cost of explant surgery

HRG4	Activity	Unit cost (2013/14 prices)	Total cost (2013/14 prices)
LB61C: Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over, with CC Score 10+	697	£8,175.72	£5,698,474
LB61D: Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over, with CC Score 7-9	796	£5,593.30	£4,452,263
LB61E: Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over, with CC Score 4-6	1661	£4,984.97	£8,280,041
LB61F: Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over, with CC Score 2-3	2391	£4,123.49	£9,859,272
LB61G: Major, Open or Percutaneous, Kidney or Ureter Procedures, 19 years and over, with CC Score 0-1	3947	£3,694.03	£14,580,351
LB62C: Major Laparoscopic, Kidney or Ureter Procedures, 19 years and over, with CC Score 3+	962	£6,445.46	£6,200,531
LB62D: Major Laparoscopic, Kidney or Ureter Procedures, 19 years and over, with CC Score 0-2	3860	£5,404.85	£20,862,707

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 203).

Table 203. 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.[353] 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 204). 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 204. 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 205. 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		£15,772.38	

Table 206. 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	£835.06	£848.72
Living donor costs	See Table 203	£8,770.60	£8,914.05
Deceased donor costs	See above	£9,868.92	£10,142.05
Transplant surgery	See Table 205	£15,772.38	£16,030.35

7.3.7. Summary of model parameters

Appendix 10 details base case values, sources and PSA distributions for parameters in the model.

7.3.8. Model verification

The decision model was tested by an independent academic decision modeller (Andy Salmon) twice, once following development of the deterministic base case and once following the addition of the probabilistic analyses. Extreme value testing and other black box testing techniques were applied to ensure the model performed as expected. The testing checklist was also applied by TS following the addition of the probabilistic analyses as an additional check on correct implementation.

7.4. Results

We first present the base case analysis, which we believe to be closest to the NICE reference case. Deterministic results for the base case analysis are given in Section 7.4.1.1 (page 470) and probabilistic results are given in Section 7.4.1.2 (page 481).

Next we present scenario analyses which explore structural and other uncertainties in the economic assessment. Structural uncertainty in the extrapolation of graft survival is explored in two scenario analyses in Section 7.4.2.1 (page 501). Although it is believed that unit costs for drug acquisition have been identified appropriately and in line with the reference case, we

also explore the impact of using list prices for all drugs, and conduct a two-way threshold analysis on costs relating to belatacept in Section 7.4.2.2 (page 515).

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

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

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

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

Note that throughout costs and ICERs are reported rounded to the nearest £1 and QALYs are reported to four decimal places. This should not be taken as an indication of the precision of these estimates but to allow for third-party checking of the accuracy of calculations.

7.4.1. Base case analysis

7.4.1.1. Deterministic results

Induction agents

We present the cost-effectiveness of induction agents basiliximab and rabbit ATG and the comparator of no induction in the context of three different maintenance regimens:

- Ciclosporin, azathioprine and corticosteroids

- Ciclosporin, mycophenolate mofetil and corticosteroids
- Tacrolimus, mycophenolate mofetil and corticosteroids

Note that while other regimens including basiliximab are modelled (BAS+SRL+MMF, BAS+BEL+MMF, BAS+CSA+MPS) these cannot be meaningfully compared to any other regimens to estimate the cost-effectiveness of basiliximab.

Summary cost-effectiveness results are given in Table 207.

Table 207. Summary of cost-effectiveness results for induction agents

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	£102,320	—	10.7486	—	Dominated	-0.3370	-0.2761
Basiliximab	£98,667	-£3,653	10.9029	+0.1544	—	—	—
Rabbit ATG	£101,751	+£3,084	10.9250	+0.0221	£139,636	-0.1321	-0.0807
With CSA+MMF						*vs. Basiliximab*	
No induction	£98,157	—	10.8925	—	Dominated	-0.2573	-0.2156
Basiliximab	£95,654	-£2,503	11.0247	+0.1322	—	—	—
Rabbit ATG	£99,231	+£3,576	11.0344	+0.0097	£368,853	-0.1691	-0.1095
With TAC+MMF						*vs. Basiliximab*	
No induction	£92,827	—	10.8595	—	Dominated	-0.2301	-0.1962
Basiliximab	£90,794	-£2,033	10.9880	+0.1285	—	—	—
Rabbit ATG	£94,538	+£3,744	11.0160	+0.0281	£133,329	-0.1591	-0.0967

Basiliximab

Basiliximab was compared to no induction and to rabbit ATG in three comparisons. In all three comparisons basiliximab was predicted to dominate no induction and to be less costly and less effective than rabbit ATG. The ICER of rabbit ATG versus basiliximab was above £100,000 per QALY in all three comparisons and therefore basiliximab is predicted to be cost-effective at £20,000 and £30,000 per QALY.

Rabbit ATG

Rabbit ATG was compared to no induction and to basiliximab in three comparisons. In all three comparisons rabbit ATG was predicted to be the most effective agent. When used in combination with CSA+AZA, rabbit ATG was predicted to be less costly than no induction, but when used in combination with CSA+MMF or TAC+MMF rabbit ATG was predicted to be the most costly agent. Since no induction was dominated by basiliximab the relevant comparator in all comparisons was basiliximab. The ICER of rabbit ATG versus basiliximab was above £100,000 per QALY in all three comparisons and therefore rabbit ATG is not predicted to be cost-effective at £20,000 and £30,000 per QALY.

As shown in Table 238 (in Appendix 9, page 733), rabbit ATG induction results in greater induction therapy costs than basiliximab and greater costs of infection prophylaxis (since KTRs at intermediate risk of CMV require prophylaxis if receiving rabbit ATG induction). These cost increases are partially offset by a reduction in costs of acute rejection treatment (due to reduced incidence of acute rejection). Rabbit ATG is predicted to give marginally greater life expectancy than basiliximab in all comparisons (see Table 239 in Appendix 9, page 734) and this is the primary reason for rabbit ATG being predicted to be more effective.

Summary

In all comparisons no induction was dominated by basiliximab and was also dominated by rabbit ATG when in combination with ciclosporin, azathioprine and corticosteroids.

Basiliximab was the only cost-effective induction agent in all comparisons.

Rabbit ATG was more costly and more effective than basiliximab in all comparisons. The ICERs of rabbit ATG versus basiliximab were in every case significantly above the NICE threshold range of £20,000 to £30,000 per QALY.

Maintenance agents

We present the cost-effectiveness results for the following maintenance agents:

- Immediate-release tacrolimus (TAC);
- Prolonged-release tacrolimus (TAC-PR);
- Mycophenolate mofetil (MMF);
- Mycophenolate sodium (MPS);
- Sirolimus (SRL);
- Everolimus (EVL);
- Belatacept (BEL).

These are compared to each other as appropriate and also to ciclosporin (CSA) or azathioprine (AZA). All maintenance agents were modelled with concomitant treatment which would be corticosteroids plus mycophenolate mofetil, azathioprine, ciclosporin or immediate-release tacrolimus according to the evidence base plus optional induction therapy (basiliximab or rabbit ATG). Comparisons are made holding all concomitant treatments equal. Summary results are given in Table 208.

Table 208. Summary of cost-effectiveness results for maintenance agents

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With MMF						*vs. TAC*	
TAC-PR	£111,499	—	10.6172	—	Dominated	-1.1759	-0.8647
TAC	£92,827	-£18,672	10.8595	+0.2423	—	—	—
CSA	£98,157	+£5,330	10.8925	+0.0330	£161,408	-0.2335	-0.1446
With AZA						*vs. TAC*	
CSA	£102,320	—	10.7486	—	Dominated	-0.5197	-0.3786
TAC	£93,851	-£8,469	10.8448	+0.0963	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£114,554	—	10.9010	—	Dominated	-1.2749	-0.8789
TAC	£90,794	-£23,760	10.9880	+0.0869	—	—	—
CSA	£95,654	+£4,860	11.0247	+0.0367	£132,272	-0.2063	-0.1253
BEL	£235,490	+£139,836	11.2941	+0.2694	£519,094	-6.9287	-4.5171
With rATG+MMF						*vs. TAC*	
TAC	£94,538	—	11.0160	—	—	—	—
CSA	£99,231	+£4,693	11.0344	+0.0184	£255,592	-0.2163	-0.1381
With CSA						*vs. MMF*	
AZA	£102,320	—	10.7486	—	Dominated	-0.3521	-0.2827
MMF	£98,157	-£4,163	10.8925	+0.1439	—	—	—
EVL	£176,788	+£78,631	10.9376	+0.0451	£1,743,739	-3.8864	-2.5759
With TAC						*vs. MMF*	
SRL	£126,147	—	10.5773	—	Dominated	-1.9481	-1.3928
AZA	£93,851	-£32,296	10.8448	+0.2675	Dominated	-0.0659	-0.0488
MMF	£92,827	-£1,024	10.8595	+0.0147	—	—	—

Table 208. 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 BAS+CSA						*vs. MMF*	
AZA	£98,667	—	10.9029	—	Dominated	-0.2724	-0.2222
MMF	£95,654	-£3,013	11.0247	+0.1218	—	—	—
MPS	£112,045	+£16,391	11.1377	+0.1130	£145,072	-0.7066	-0.4334
With rATG+CSA						*vs. MMF*	
AZA	£101,751	—	10.9250	—	Dominated	-0.2354	-0.1934
MMF	£99,231	-£2,521	11.0344	+0.1094	—	—	—

Immediate-release tacrolimus

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

When used in combination with mycophenolate mofetil and corticosteroids, immediate-release tacrolimus dominated prolonged-release tacrolimus and was less costly and less effective than ciclosporin. The ICER of ciclosporin versus immediate-release tacrolimus was £161,408 per QALY and therefore immediate-release tacrolimus was the only cost-effective agent in this comparison at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

When used in combination with azathioprine and corticosteroids, immediate-release tacrolimus dominated ciclosporin.

When used in combination with basiliximab induction, mycophenolate mofetil and corticosteroids, immediate-release tacrolimus dominated sirolimus and was less costly and less expensive than ciclosporin and belatacept. The ICERs for ciclosporin and belatacept in this comparison were £132,272 and £519,094 per QALY respectively and therefore immediate-release tacrolimus was the only cost-effective agent in this comparison at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

When used in combination with rabbit ATG induction, mycophenolate mofetil and corticosteroids, immediate-release tacrolimus was less costly and less effective than ciclosporin. The ICER of ciclosporin was £255,592 per QALY and therefore immediate-release tacrolimus was the only cost-effective agent in this comparison at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

In three comparisons (all with mycophenolate mofetil), immediate-release tacrolimus was predicted be less effective than ciclosporin. In all comparisons, however, immediate-release tacrolimus was predicted to result in greater life expectancy and more years with functioning graft (see Table 239 in Appendix 9, page 734). The QALY loss arises because of the reduction in health-related quality of life in KTRs who develop NODAT; 10.6% of KTRs are predicted to develop NODAT with immediate-release tacrolimus versus 5.0% of KTRs for ciclosporin. If the utility decrement for NODAT is removed (and NODAT therefore only affects costs, graft survival and death with functioning graft), then immediate-release tacrolimus is

more effective than ciclosporin in all comparisons and therefore is dominant (see Table 243 in Appendix 9, page 738).

Prolonged-release tacrolimus

Prolonged-release tacrolimus was compared to ciclosporin and immediate-release tacrolimus in combination with mycophenolate mofetil and corticosteroids. Prolonged-release tacrolimus was dominated by both ciclosporin and immediate-release tacrolimus in this comparison.

Mycophenolate mofetil

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

Mycophenolate mofetil dominated azathioprine in all four comparisons.

When used in combination with immediate-release tacrolimus and corticosteroids, mycophenolate mofetil dominated sirolimus.

When used in combination with ciclosporin and corticosteroids, mycophenolate mofetil was less costly and less effective than everolimus. The ICER of everolimus was £1,743,739 per QALY and therefore mycophenolate mofetil was the only cost-effective agent in this comparison at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

When used in combination with basiliximab induction, ciclosporin and corticosteroids, mycophenolate mofetil was less costly and less expensive than mycophenolate sodium. The ICER of mycophenolate sodium was £145,072 per QALY and therefore mycophenolate mofetil was the only cost-effective agent in this comparison at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Mycophenolate sodium

Mycophenolate sodium was compared to azathioprine and mycophenolate mofetil in combination with basiliximab induction, ciclosporin and corticosteroids. Mycophenolate sodium was more costly and more effective than azathioprine and mycophenolate mofetil. The ICER of mycophenolate sodium was £145,072 per QALY and therefore mycophenolate sodium was not cost-effective at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Mycophenolate sodium was considerably more costly than mycophenolate mofetil, with discounted maintenance immunosuppression costs more than double those of mycophenolate mofetil, although there were some predicted savings in dialysis expenditure (see Table 238 in Appendix 10, page 733). Mycophenolate sodium was predicted to lead to increased time with functioning graft and increased life expectancy versus mycophenolate mofetil, which is why it was predicted to give increased QALYs (see Table 239 in Appendix 10, page 733).

Sirolimus

Sirolimus was compared to ciclosporin, immediate-release tacrolimus and belatacept in one comparison (in combination with basiliximab induction, mycophenolate mofetil and corticosteroids) and to azathioprine and mycophenolate mofetil in one comparison (in combination with immediate-release tacrolimus and corticosteroids).

Sirolimus was dominated by ciclosporin and tacrolimus in the first comparison and was dominated by azathioprine and mycophenolate mofetil in the second comparison.

Everolimus

Everolimus was compared to azathioprine and mycophenolate mofetil in combination with ciclosporin and corticosteroids. Everolimus was more costly and more effective than azathioprine and mycophenolate mofetil. The ICER of everolimus was £1,743,739 per QALY and therefore everolimus was not cost-effective at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Belatacept

Belatacept was compared to ciclosporin, immediate-release tacrolimus and sirolimus in combination with basiliximab induction, mycophenolate mofetil and corticosteroids. Belatacept was more costly and more effective than all comparators. The ICER of belatacept was £519,094 per QALY and therefore belatacept was not cost-effective at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Summary

Only immediate-release tacrolimus and mycophenolate mofetil were cost-effective at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Prolonged-release tacrolimus and sirolimus were dominated in their relevant comparisons while mycophenolate sodium, everolimus and belatacept were all the most costly and most effective treatment in their relevant comparisons, but with ICERs significantly above £30,000 per QALY.

Comparing all regimens

When all regimens are simultaneously compared, the following regimens are dominated or extended dominated (if indicated):

- TAC+SRL
- TAC-PR+MMF
- CSA+AZA
- TAC+AZA
- TAC+MMF
- CSA+MMF
- BAS+SRL+MMF
- BAS+CSA+AZA
- rATG+CSA+AZA
- CSA+EVL
- rATG+TAC+MMF (extended dominated)
- rATG+CSA+MMF (extended dominated)

Four regimens were neither dominated nor extended dominated and therefore lay on the cost-effectiveness frontier and the cost-effectiveness results for these are presented in Table

209. BAS+TAC+MMF was predicted to be the only cost-effective regimen at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Table 209. Cost-effectiveness of all regimens on the cost-effectiveness frontier

Regimen	Discounted costs		Discounted QALYs		ICER	INHB	
	Total	Inc.	Total	Inc.		£20k	£30k
BAS+TAC+MMF	£90,794	—	10.9880	—	—	—	—
BAS+CSA+MMF	£95,654	+£4,860	11.0247	+0.0367	£132,272	-0.2063	-0.1253
BAS+CSA+MPS	£112,045	+£16,391	11.1377	+0.1130	£145,072	-0.9128	-0.5586
BAS+BEL+MMF	£235,490	+£123,445	11.2941	+0.1564	£789,291	-6.9287	-4.5171

Additional results

Additional results for the deterministic base case (including disaggregated discounted costs and additional clinical outcomes) can be found in Appendix 10.

7.4.1.2. Probabilistic results

The PenTAG model was run for 10,000 PSA iterations. Non-linearities in models often manifest in substantially different results between probabilistic and deterministic analyses. Figure 95 demonstrates that there are no significant discrepancies in terms of total costs for each regimen. Figure 96 indicates that there are some discrepancies in terms of total QALYs for each regimen between the probabilistic and deterministic analyses.

Figure 95. Comparison of deterministic and probabilistic costs in PenTAG model

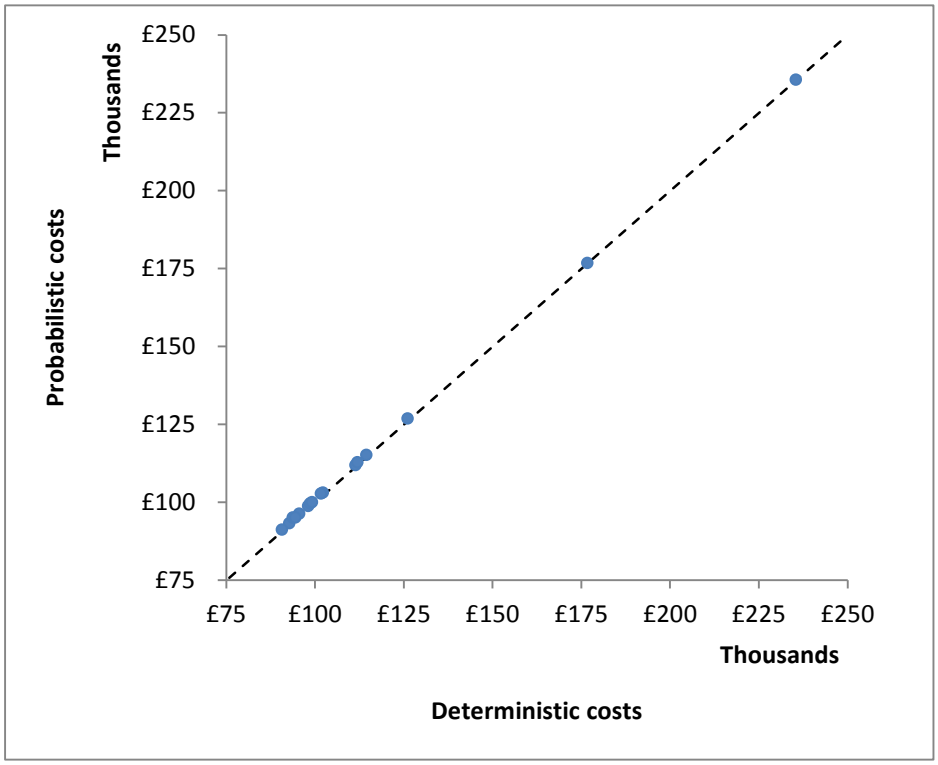
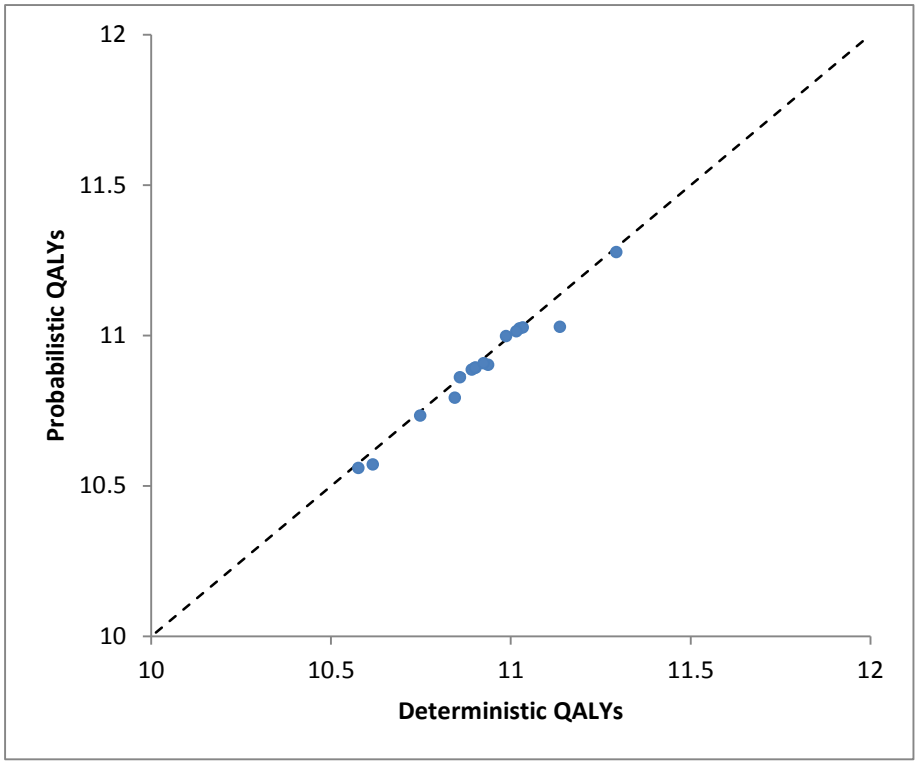


Figure 96. Comparison of deterministic and probabilistic QALYs in PenTAG model



The most significant outlier appears to be BAS+CSA+MPS+CCS, which is predicted to result in 11.1377 QALYs in the deterministic analysis but only 11.0001 in the probabilistic analysis. It was ascertained that this outlier effect is due to the significant uncertainty in the probability of mortality within the first 12 months for this regimen – the 95% CI of the odds ratio of mortality for MPS versus MMF is 0.058–7.23. When the probability of mortality drawn from the PSA distribution is extremely low the regression formulae for estimating the appropriate hazard ratio for death with functioning graft perform badly, and in some cases even a hazard ratio of zero results in above target mortality due to the mortality following graft loss. Noting that in the deterministic base case MPS was not cost-effective at £20,000 or £30,000 per QALY (the ICER of MPS versus MMF was over £100,000 per QALY) we have not attempted to compensate for this discrepancy in our analyses.

Induction agents

Probabilistic cost-effectivess results for induction agents (Table 210) were not significantly altered from the deterministic results (Table 207). No induction continued to be dominated by basiliximab in all three comparisons and by rabbit ATG when in combination with CSA+AZA. Rabbit ATG continued to be the most effective agent but with ICERs still over £100,000 per QALY, rabbit ATG is still not predicted to be cost-effective at £20,000 and £30,000 per QALY.

Table 210. Summary of probabilistic cost-effectiveness results for induction agents

Induction agent	Discounted costs		Discounted QALYs		ICER	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	£103,240	—	10.7343	—	Dominated	-0.3356	-0.2764	0.22%	0.13%
Basiliximab	£99,690	-£3,549	10.8924	+0.1581	—	—	—	77.21%	72.65%
Rabbit ATG	£102,922	+£3,232	10.9086	+0.0161	£200,329	-0.1454	-0.0916	22.57%	27.22%
With CSA+MMF						*vs. Basiliximab*			
No induction	£98,907	—	10.8874	—	Dominated	-0.2620	-0.2204	0.53%	0.30%
Basiliximab	£96,409	-£2,498	11.0245	+0.1371	—	—	—	84.48%	80.60%
Rabbit ATG	£100,091	+£3,682	11.0276	+0.0031	£1,184,805	-0.1810	-0.1196	14.99%	19.10%
With TAC+MMF						*vs. Basiliximab*			
No induction	£93,301	—	10.8623	—	Dominated	-0.2377	-0.2042	0.79%	0.47%
Basiliximab	£91,287	-£2,013	10.9994	+0.1371	—	—	—	85.56%	80.07%
Rabbit ATG	£95,142	+£3,854	11.0147	+0.0153	£251,653	-0.1774	-0.1132	13.65%	19.46%

Basiliximab

Basiliximab was predicted to dominate no induction in all three comparisons (as in the deterministic results). Basiliximab was predicted to be less costly and less effective than rabbit ATG in all comparisons but with the ICERs of rabbit ATG now over £200,000 per QALY, basiliximab is predicted to be the only cost-effective agent at £20,000 and £30,000 per QALY. Basiliximab was cost-effective at £20,000 per QALY in 77.2–85.6% of PSA iterations across comparisons and at £30,000 per QALY in 72.7–80.6% of iterations.

Rabbit ATG

Rabbit ATG was predicted to dominate no induction when used in combination with CSA+AZA and was predicted to be more costly and more effective than no induction when used in combination with CSA+MMF or TAC+MMF. Rabbit ATG was predicted to be more costly and more effective than basiliximab in all comparisons but the relevant ICERs for rabbit ATG (versus basiliximab) were over £200,000 per QALY, and therefore rabbit ATG is not predicted to be cost-effective at £20,000 to £30,000 per QALY. Rabbit ATG was cost-effective at £20,000 per QALY in 13.7–22.6% of PSA iterations across comparisons and at £30,000 per QALY in 19.1–27.2% of iterations.

Cost-effectiveness acceptability curves

Cost-effectiveness acceptability curves are shown in Figure 97, Figure 98 and Figure 99 for the three comparisons. While these have not been presented as cost-effectiveness acceptability frontiers (in which only the regimen with the greatest expected net health benefit is shown for each cost-effectiveness threshold), the only effect this would have would be to remove the curves for no induction and rabbit ATG, since basiliximab is predicted to give the greatest expected net health benefit across the cost-effectiveness threshold range explored (£1,000 to £50,000 per QALY).

The cost-effectiveness acceptability curves suggest the possibility of cross-over of basiliximab and rabbit ATG at cost-effectiveness thresholds above the range explored, which would be consistent with the ICERs from the mean probabilistic results.

Figure 97. Cost-effectiveness acceptability curves for induction agents in combination with ciclosporin, azathioprine and corticosteroids

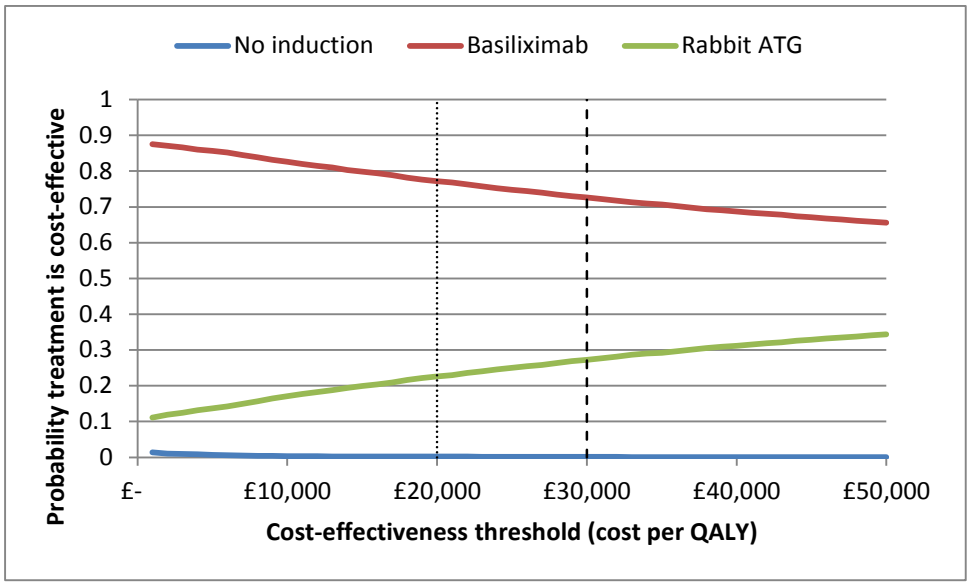


Figure 98. Cost-effectiveness acceptability curves for induction agents in combination with ciclosporin, mycophenolate mofetil and corticosteroids

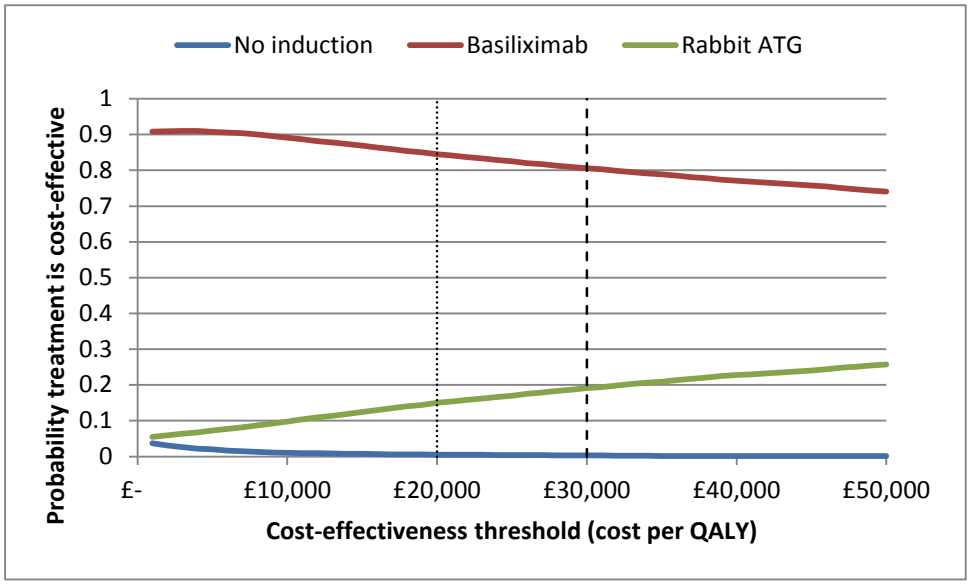
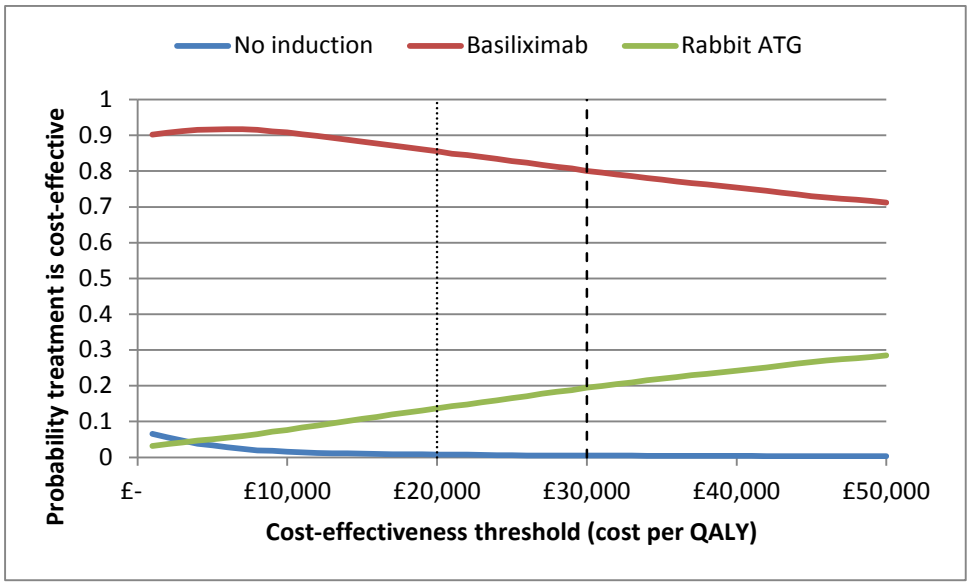


Figure 99. Cost-effectiveness acceptability curves for induction agents in combination with immediate-release tacrolimus, mycophenolate mofetil and corticosteroids



Summary

Basiliximab is predicted to be cost-effective with an error probability of 14.4–22.8% (cost-effectiveness threshold of £20,000 per QALY) to 19.9–27.3% (cost-effectiveness threshold of £30,000 per QALY). No induction and rabbit ATG are predicted not to be cost-effective.

Maintenance agents

A summary of cost-effectiveness results in the probabilistic analysis are given in Table 211. All treatments which were dominated in the deterministic analysis remain dominated in the probabilistic analysis. In addition, BAS+CSA+MPS is now predicted to be dominated by BAS+CSA+MMF, where in the deterministic analysis it was more costly and more effective with an ICER of over £100,000 per QALY. The treatment which was cost-effective at £20,000 and £30,000 per QALY in each comparison in the deterministic analysis remains cost-effective in the probabilistic analysis.

Table 211. Summary of probabilistic cost-effectiveness results for maintenance agents

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Inc.	Total	Inc.		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
With MMF						*vs. TAC*			
TAC-PR	£112,009	—	10.5756	—	Dominated	-1.2222	-0.9103	0.00%	0.00%
TAC	£93,301	-£18,709	10.8623	+0.2867	—	—	—	87.92%	82.36%
CSA	£98,907	+£5,606	10.8874	+0.0250	£223,855	-0.2553	-0.1618	12.08%	17.64%
With AZA						*vs. TAC*			
CSA	£103,240	—	10.7343	—	Dominated	-0.4600	-0.3260	5.42%	7.42%
TAC	£95,203	-£8,036	10.7925	+0.0581	—	—	—	94.58%	92.58%
With BAS+MMF						*vs. TAC*			
SRL	£115,267	—	10.8936	—	Dominated	-1.3048	-0.9051	0.00%	0.00%
TAC	£91,287	-£23,980	10.9994	+0.1058	—	—	—	86.91%	81.76%
CSA	£96,409	+£5,121	11.0245	+0.0251	£204,063	-0.2310	-0.1456	13.09%	18.24%
BEL	£235,722	+£139,313	11.2796	+0.2551	£546,136	-6.9415	-4.5343	0.00%	0.00%
With rATG+MMF						*vs. TAC*			
TAC	£95,142	—	11.0147	—	—	—	—	87.51%	83.29%
CSA	£100,091	+£4,949	11.0276	+0.0129	£384,013	-0.2346	-0.1521	12.49%	16.71%

Table 211. Summary of probabilistic cost-effectiveness results for maintenance agents (cont.)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Inc.	Total	Inc.		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
With CSA						*vs. MMF*			
AZA	£103,240	—	10.7343	—	Dominated	-0.3697	-0.2975	8.82%	7.81%
MMF	£98,907	-£4,333	10.8874	+0.1531	—	—	—	91.18%	92.19%
EVL	£177,034	+£78,127	10.9018	+0.0144	£5,424,605	-3.8920	-2.5898	0.00%	0.00%
With TAC						*vs. MMF*			
SRL	£127,041	—	10.5608	—	Dominated	-1.9886	-1.4262	0.00%	0.00%
AZA	£95,203	-£31,838	10.7925	+0.2317	Dominated	-0.1650	-0.1333	36.79%	36.18%
MMF	£93,301	-£1,903	10.8623	+0.0699	—	—	—	63.21%	63.82%
With BAS+CSA						*vs. MMF*			
AZA	£99,690	—	10.8924	—	Dominated	-0.2961	-0.2414	12.50%	11.14%
MPS	£112,895	+£13,205	11.0200	+0.1276	Dominated	-0.8288	-0.5540	0.10%	0.78%
MMF	£96,409	-£16,486	11.0245	+0.0045	—	—	—	87.40%	88.08%
With rATG+CSA						*vs. MMF*			
AZA	£102,922	—	10.9086	—	Dominated	-0.2606	-0.2134	14.96%	13.39%
MMF	£100,091	-£2,831	11.0276	+0.1190	—	—	—	85.04%	86.61%

Immediate-release tacrolimus

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

In all comparisons immediate-release tacrolimus was the least costly intervention. It dominated prolonged-release tacrolimus when used in combination with MMF; it dominated ciclosporin when used in combination with AZA; and, it dominated sirolimus when used in combination with BAS+MMF. When used in combination with MMF or BAS+MMF or rATG+MMF, immediate-release tacrolimus was less effective than ciclosporin but the ICERs of ciclosporin versus immediate-release tacrolimus were over £200,000 per QALY. Immediate-release tacrolimus was less costly and less effective than belatacept when used in combination with BAS+MMF but the relevant ICER of belatacept (versus ciclosporin) was over £500,000 per QALY.

In all comparisons, immediate-release tacrolimus was predicted to be cost-effective at £20,000 to £30,000 per QALY. The probability of immediate-release tacrolimus being cost-effective (i.e., giving the greatest net health benefit in each comparison) at £20,000 and £30,000 per QALY ranged from 81.8% to 94.6%.

Prolonged-release tacrolimus

Prolonged-release tacrolimus was compared to immediate-release tacrolimus and ciclosporin in combination with MMF. Prolonged-release tacrolimus was predicted to be dominated by immediate-release tacrolimus and ciclosporin and therefore not predicted to be cost-effective at any cost-effectiveness threshold. The probability of prolonged-release tacrolimus being cost-effective was 0.0% at both £20,000 and £30,000 per QALY.

Mycophenolate mofetil

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

Mycophenolate mofetil was predicted to dominate azathioprine in all comparisons, and to dominate sirolimus when used in combination with TAC, and to dominate mycophenoalte sodium when used in combination with BAS+CSA. Mycophenolate mofetil was predicted to

be less costly and less effective than everolimus when used in combination with CSA, but the ICER of everolimus (versus mycophenolate mofetil) was over £5,000,000 per QALY and therefore mycophenolate mofetil was predicted to be cost-effective at £20,000 to £30,000 per QALY.

In all comparisons, mycophenolate mofetil was predicted to be cost-effective at £20,000 to £30,000 per QALY. The probability of mycophenolate mofetil being cost-effective at £20,000 and £30,000 per QALY ranged from 63.2% to 92.2% across comparisons.

Mycophenolate sodium

Mycophenolate sodium was compared to mycophenolate mofetil and azathioprine in combination with BAS+CSA. Mycophenolate sodium was predicted to be dominated by mycophenolate mofetil and therefore was not predicted to be cost-effective at any cost-effectiveness threshold. The probability of mycophenolate sodium being cost-effective was 0.1% at £20,000 per QALY and 0.8% and £30,000 per QALY.

Sirolimus

Sirolimus was compared to immediate-release tacrolimus, belatacept and ciclosporin in combination with BAS+MMF. Sirolimus was predicted to be dominated by immediate-release tacrolimus and ciclosporin and therefore not predicted to be cost-effective at any cost-effectiveness threshold. The probability of sirolimus being cost-effective in combination with BAS+MMF was 0.0% at both £20,000 and £30,000 per QALY.

Sirolimus was also compared to mycophenolate mofetil and azathioprine in combination with TAC. Sirolimus was predicted to be dominated by mycophenolate mofetil and azathioprine and therefore not predicted to be cost-effective at any cost-effectiveness threshold. The probability of sirolimus being cost-effective in combination with TAC was 0.0% at both £20,000 and £30,000 per QALY.

Everolimus

Everolimus was compared to mycophenolate mofetil and azathioprine in combination with CSA. Everolimus was predicted to be more costly and more effective than all comparators. The relevant ICER for everolimus (versus mycophenolate mofetil) was over £5,000,000 per QALY and therefore everolimus was not predicted to be cost-effective at £20,000 to £30,000

per QALY. The probability of everolimus being cost-effective was 0.0% at both £20,000 and £30,000 per QALY.

Belatacept

Belatacept was compared to immediate-release tacrolimus, sirolimus and ciclosporin in combination with BAS+MMF. Belatacept was predicted to be more costly and more effective than all comparators. The relevant ICER for belatacept (versus ciclosporin) was over £500,000 per QALY and therefore belatacept was not predicted to be cost-effective at £20,000 to £30,000 per QALY. The probability of belatacept being cost-effective was 0.0% at both £20,000 and £30,000 per QALY.

Cost-effectiveness acceptability curves

Figure 100 to Figure 107 show the cost-effectiveness acceptability curves (CEACs) for maintenance agents in the probabilistic analysis. As for induction agents, we have not presented these as cost-effectiveness acceptability frontiers because the agent with the highest probability of being cost-effective also gives the greatest expected net health benefit in the range explored.

Figure 100. CEACs for maintenance agents (CSA, TAC and TAC-PR) in combination with MMF

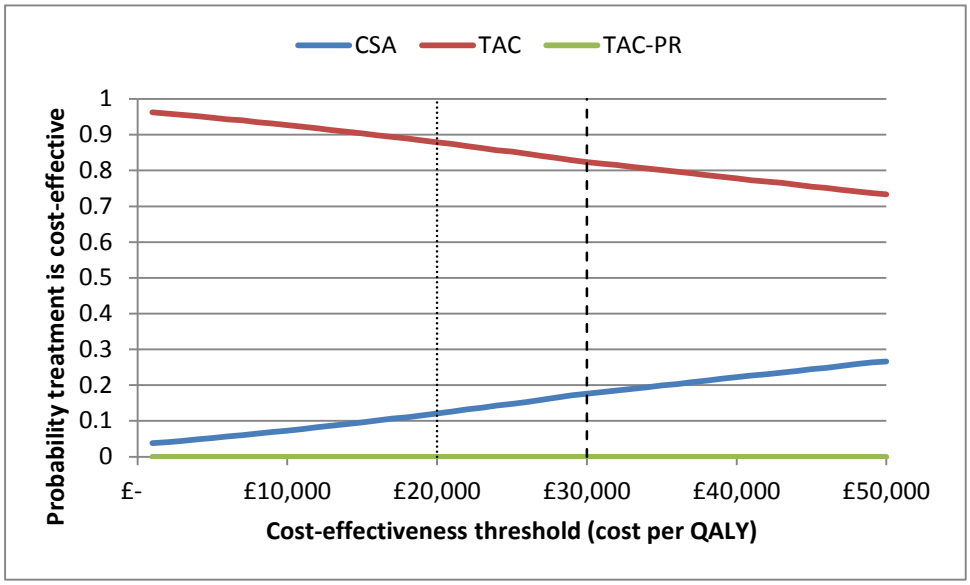


Figure 101. CEACs for maintenance agents (CSA and TAC) in combination with AZA

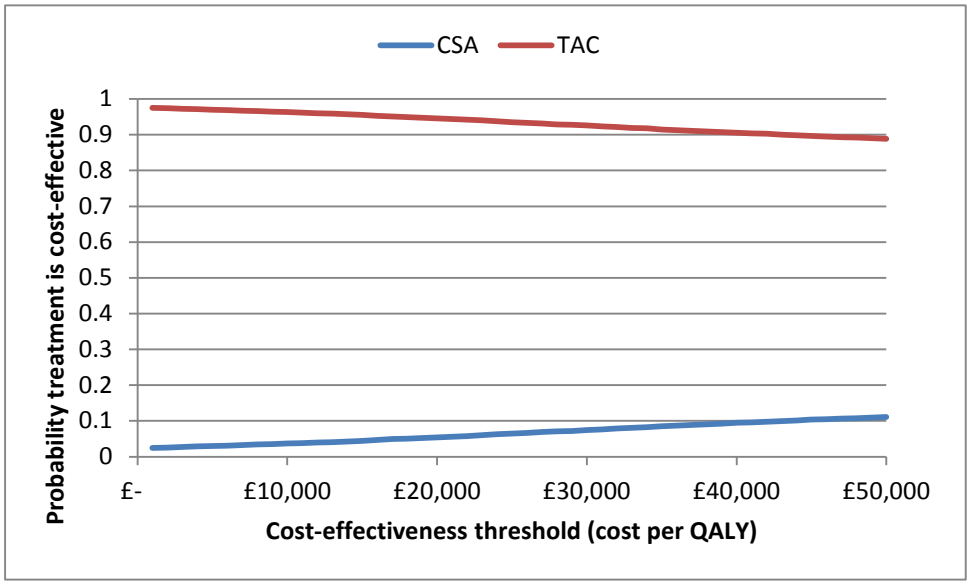


Figure 102. CEACs for maintenance agents (CSA, TAC, SRL and BEL) in combination with BAS+MMF

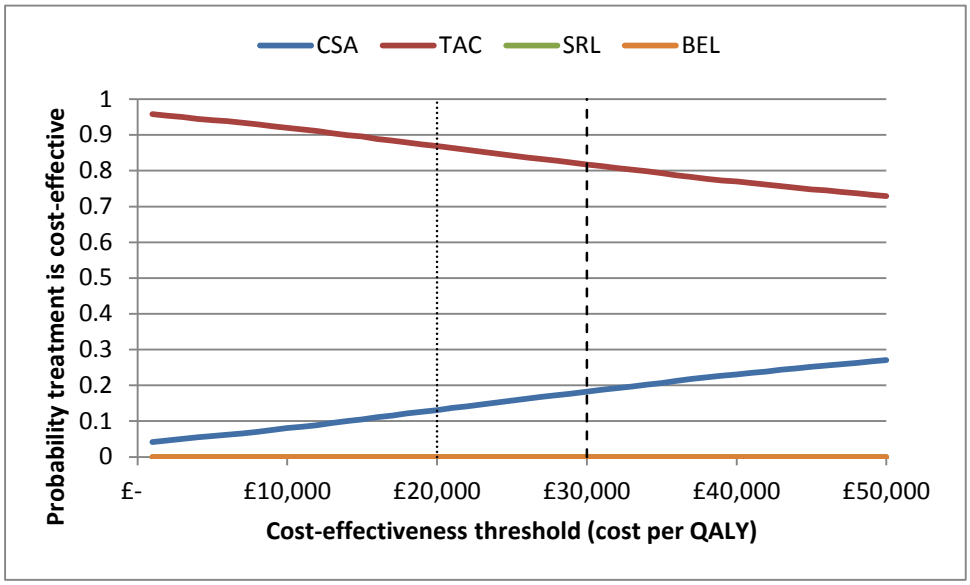


Figure 103. CEACs for maintenance agents (CSA and TAC) in combination with rATG+MMF

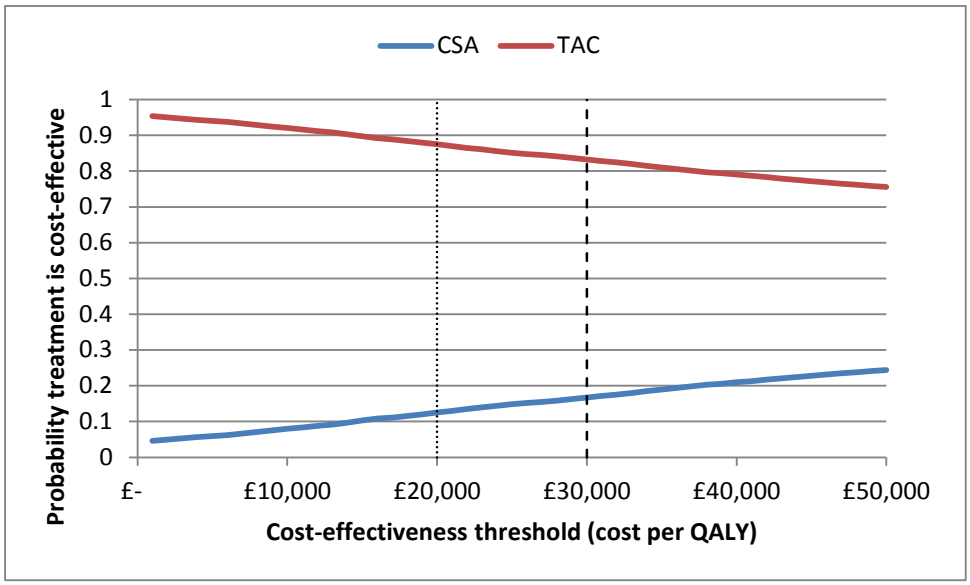


Figure 104. CEACs for maintenance agents (AZA, MMF and EVL) in combination with CSA

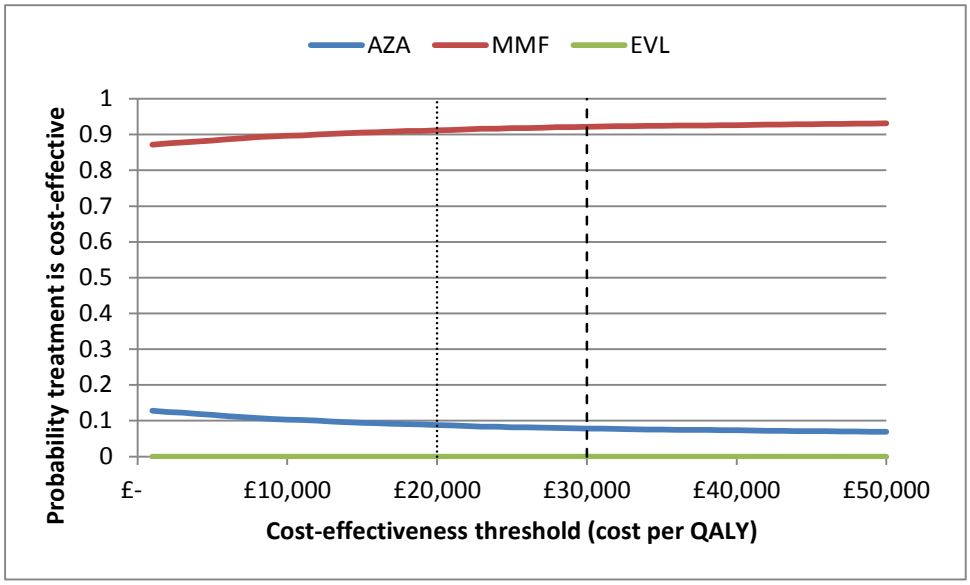


Figure 105. CEACs for maintenance agents (AZA, MMF and SRL) in combination with TAC

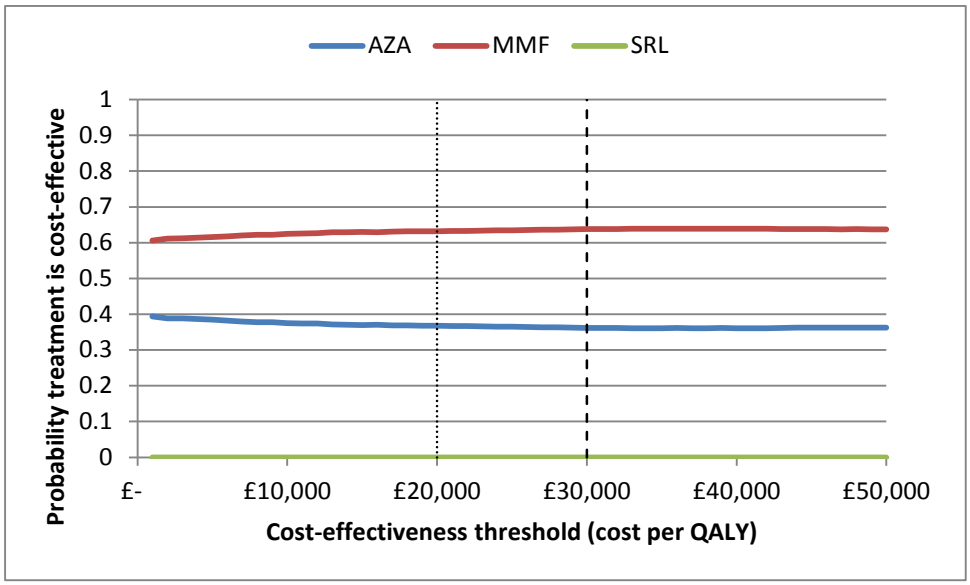


Figure 106. CEACs for maintenance agents (AZA, MMF and MPS) in combination with BAS+CSA

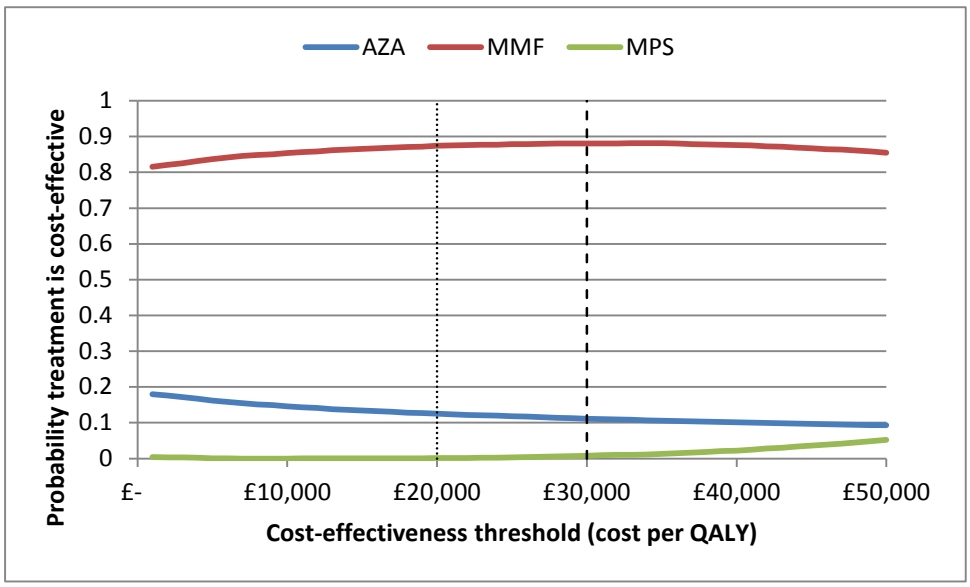
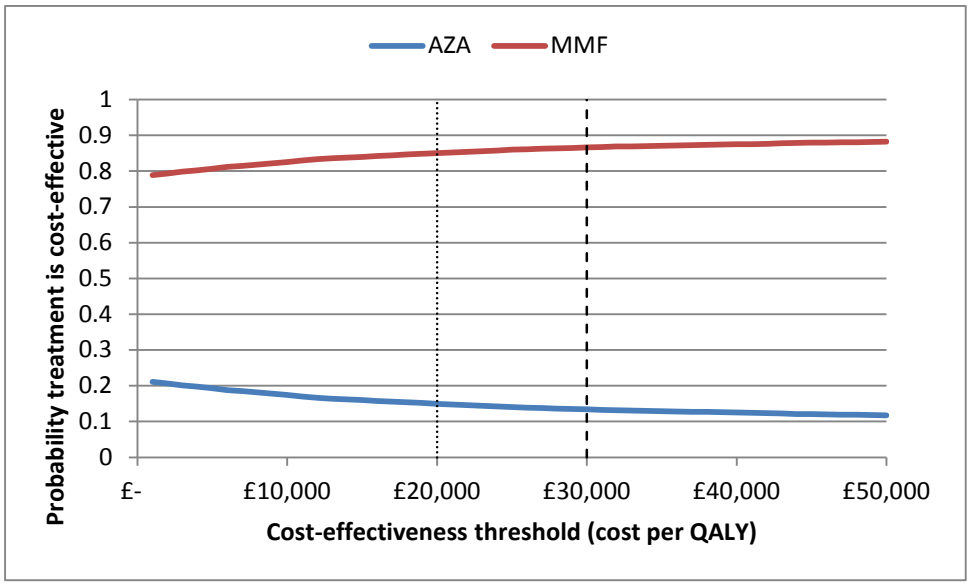


Figure 107. CEACs for maintenance agents (AZA and MMF) in combination with rATG+CSA



Summary

As in the deterministic analysis only immediate-release tacrolimus and mycophenolate mofetil were cost-effective at cost-effectiveness thresholds between £20,000 and £30,000 per QALY.

Prolonged-release tacrolimus, mycophenolate sodium and sirolimus were dominated in their relevant comparisons while everolimus and belatacept were all the most costly and most effective treatment in their relevant comparisons, but with ICERs significantly above £30,000 per QALY.

Comparing all regimens

When all regimens are compared simultaneously all regimens are dominated or extended dominated (rATG+TAC+MMF, rATG+CSA+MMF) except for BAS+TAC+MMF, BAS+CSA+MMF and BAS+BEL+MMF, which lie on the cost-effectiveness frontier. BAS+CSA+MPS is not predicted to be on the cost-effectiveness frontier in the probabilistic analysis whereas it was in the deterministic analysis. As explained in Section 7.4.1.2 (page 481) this may be due to a downward bias on probabilistic QALYs versus deterministic QALYs for this regimen due to non-linearities. The cost-effectiveness results for the regimens on the cost-effectiveness frontier are given in Table 212.

These results indicate that there is a 69.6–73.0% probability that a regimen on the cost-effectiveness frontier gives the maximum net health benefit at £20,000 to £30,000 per QALY. The probability that BAS+TAC+MMF gives the maximum net health benefit is 64.3% at £20,000 per QALY and 57.6% at £30,000 per QALY.

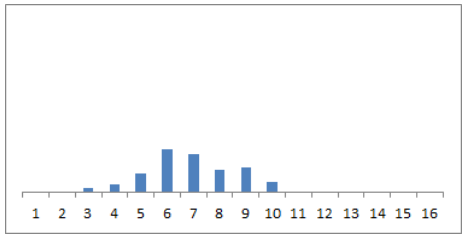
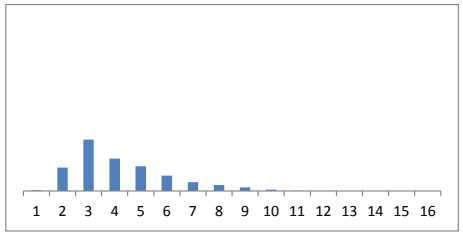
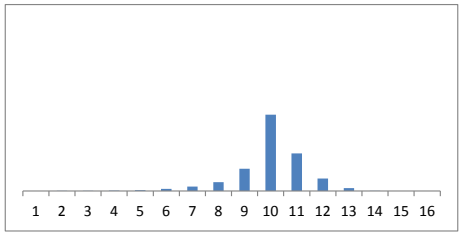
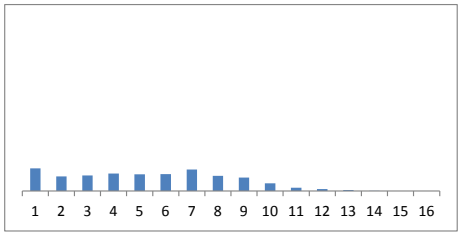
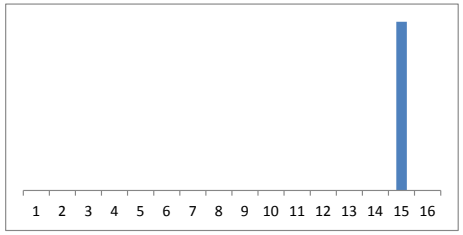
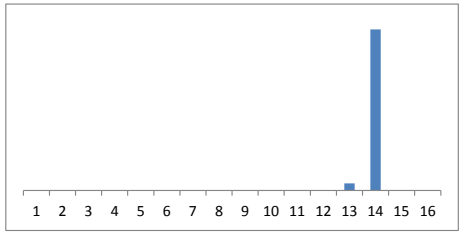
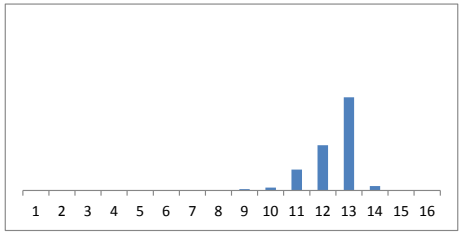
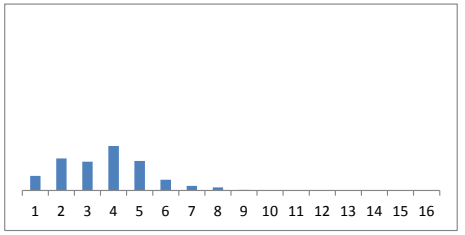
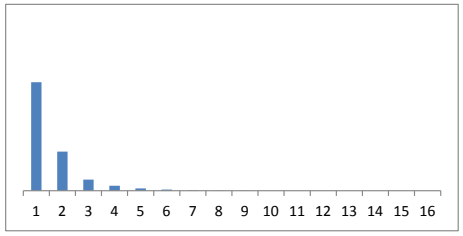
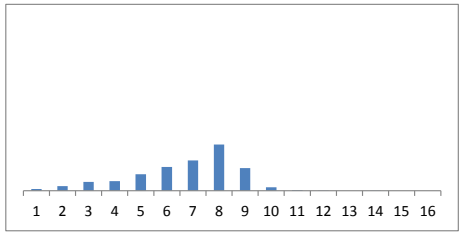
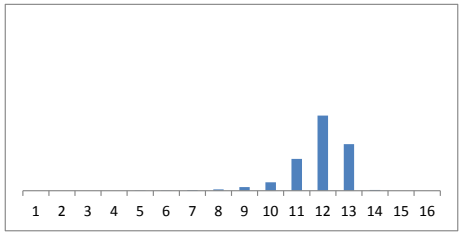
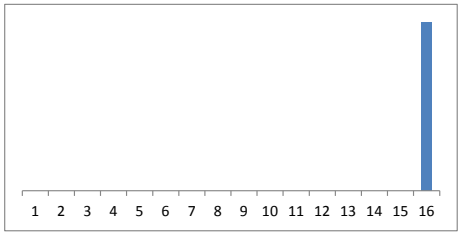
Table 212 also presents the cost-effectiveness results for regimens not on the cost-effectiveness frontier. All incremental costs and QALYs and INHBs are versus BAS+TAC+MMF. All these regimens are by definition dominated or extended dominated, although not in every case by BAS+TAC+MMF. Interestingly, at £20,000 per QALY there are two regimens not on the cost-effectiveness frontier (TAC+AZA and rATG+TAC+MMF) which are predicted to be more likely to be cost-effective than BAS+CSA+MMF and BAS+BEL+MMF (which are both on the frontier).

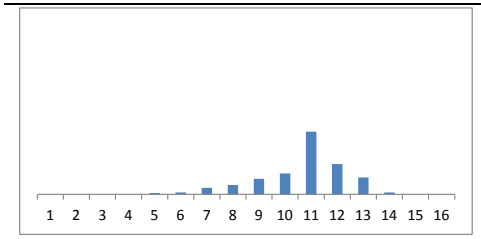
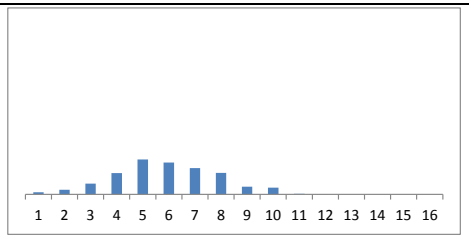
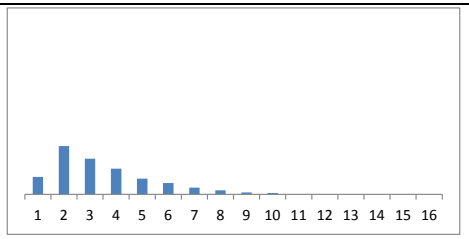
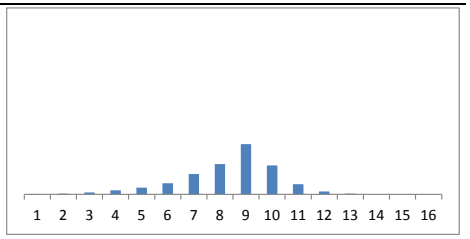
It is known that when the cost-effectiveness of an intervention is highly uncertain it can result in a flatteringly high probability of being cost-effective. A graphical representation which helps to identify this phenomenon is the rankogram,[417] which plots the probability distribution for the rank of an intervention according to a certain measure. We present rankograms of the net health benefit at £20,000 per QALY for all 16 regimens in Table 213. These suggest that the ranks of CSA+AZA, CSA+EVL, TAC+SRL, TAC-PR+MMF, BAS+TAC+MMF, BAS+SRL+MMF and BAS+BEL+MMF are fairly well or extremely well estimated (little dispersion in rank probability distribution) whereas the ranks for other regimens are less well estimated. The mean rank can also be calculated and is also presented in Table 213, demonstrating that the regimen with the greatest expected rank is BAS+TAC+MMF.

Table 212. Probabilistic cost-effectiveness results when all regimens are compared simultaneously

Regimen	Discounted costs		Discounted QALYs		ICER	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY	£20k/QALY	£30k/QALY
Regimens on the cost-effectiveness frontier									
BAS+TAC+MMF	£91,287	—	10.9994	—	—	—	—	64.34%	57.56%
BAS+CSA+MMF	£96,409	+£5,121	11.0245	+0.0251	£204,063	-0.2310	-0.1456	8.65%	12.02%
BAS+BEL+MMF	£235,722	+£139,313	11.2796	+0.2551	£546,136	-6.9415	-4.5343	0.00%	0.00%
				Probability a regimen on the cost-effectiveness frontier is cost-effective				72.99%	69.58%
Regimens not on the cost-effectiveness frontier									
TAC+SRL	+£127,041	+£35,754	10.5608	-0.4386	Dominated	-2.2263	-1.6304	0.00%	0.00%
TAC-PR+MMF	+£112,009	+£20,722	10.5756	-0.4238	Dominated	-1.4599	-1.1145	0.00%	0.00%
CSA+AZA	+£103,240	+£11,952	10.7343	-0.2651	Dominated	-0.8627	-0.6635	0.00%	0.00%
TAC+AZA	+£95,203	+£3,916	10.7925	-0.2069	Dominated	-0.4027	-0.3375	13.48%	11.30%
TAC+MMF	+£93,301	+£2,013	10.8623	-0.1371	Dominated	-0.2377	-0.2042	0.49%	0.29%
CSA+MMF	+£98,907	+£7,619	10.8874	-0.1120	Dominated	-0.4930	-0.3660	0.06%	0.04%
BAS+CSA+AZA	+£99,690	+£8,403	10.8924	-0.1070	Dominated	-0.5271	-0.3871	1.02%	1.24%
BAS+SRL+MMF	+£115,267	+£23,980	10.8936	-0.1058	Dominated	-1.3048	-0.9051	0.00%	0.00%
CSA+EVL	+£177,034	+£85,747	10.9018	-0.0976	Dominated	-4.3850	-2.9559	0.00%	0.00%
rATG+CSA+AZA	+£102,922	+£11,634	10.9086	-0.0908	Dominated	-0.6726	-0.4786	0.29%	0.40%
rATG+TAC+MMF	+£95,142	+£3,854	11.0147	0.0153	Extended dominated	-0.1774	-0.1132	10.38%	14.50%
BAS+CSA+MPS	+£112,895	+£21,607	11.0200	0.0206	Dominated	-1.0597	-0.6996	0.01%	0.13%
rATG+CSA+MMF	+£100,091	+£8,804	11.0276	0.0282	Extended dominated	-0.4120	-0.2652	1.28%	2.52%
				Probability a regimen not on the cost-effectiveness frontier is cost-effective				27.01%	30.42%

Table 213. Rankograms of net health benefit at £20,000 per QALY for each regimen

Regimen (mean rank)			
CSA+MMF (6.9)	TAC+MMF (4.2)	CSA+AZA (10.0)	TAC+AZA (5.4)
			
CSA+EVL (15.0)	TAC+SRL (14.0)	TAC-PR+MMF (12.4)	BAS+CSA+MMF (3.7)
			
BAS+TAC+MMF (1.6)	BAS+CSA+AZA (6.7)	BAS+SRL+MMF (11.9)	BAS+BEL+MMF (16.0)
			
BAS+CSA+MPS (10.7)	rATG+CSA+MMF (5.9)	rATG+TAC+MMF (3.5)	rATG+CSA+AZA (8.3)

Regimen (mean rank)			
			

7.4.2. Scenario analyses

7.4.2.1. Graft survival structural scenario analyses

Eliminating graft survival differences after a certain time

To explore what impact the model for death-censored graft survival had on cost-effectiveness a scenario analysis was conducted in which after *N* years the hazard rate of death-censored graft loss was equalised for all regimens (set equal to the baseline hazard function). This is equivalent to the conditional graft survival from time *N* years being identical across the regimens.

N was varied from 1 to 20; the base case is effectively *N* = 50. When *N* = 1 it is therefore assumed that acute rejection, eGFR and NODAT do not affect graft survival after 1 year and that long-term graft survival is determined solely by graft survival at 1 year. As *N* increases the surrogate relationship from acute rejection, eGFR and NODAT to graft survival is strengthened towards the base case.

Figure 108 shows the net health benefit of all regimens as *N* is varied from 1 to 20. Figure 109 shows a close up of the regimens with high net health benefit (BAS+CSA+MPS, TAC-PR+MMF, BAS+SRL+MMF, TAC+SRL, CSA+EVL and BAS+BEL+MMF are not visible in this figure).

Figure 108. Net health benefit of regimens as duration of surrogate effect on graft survival is varied

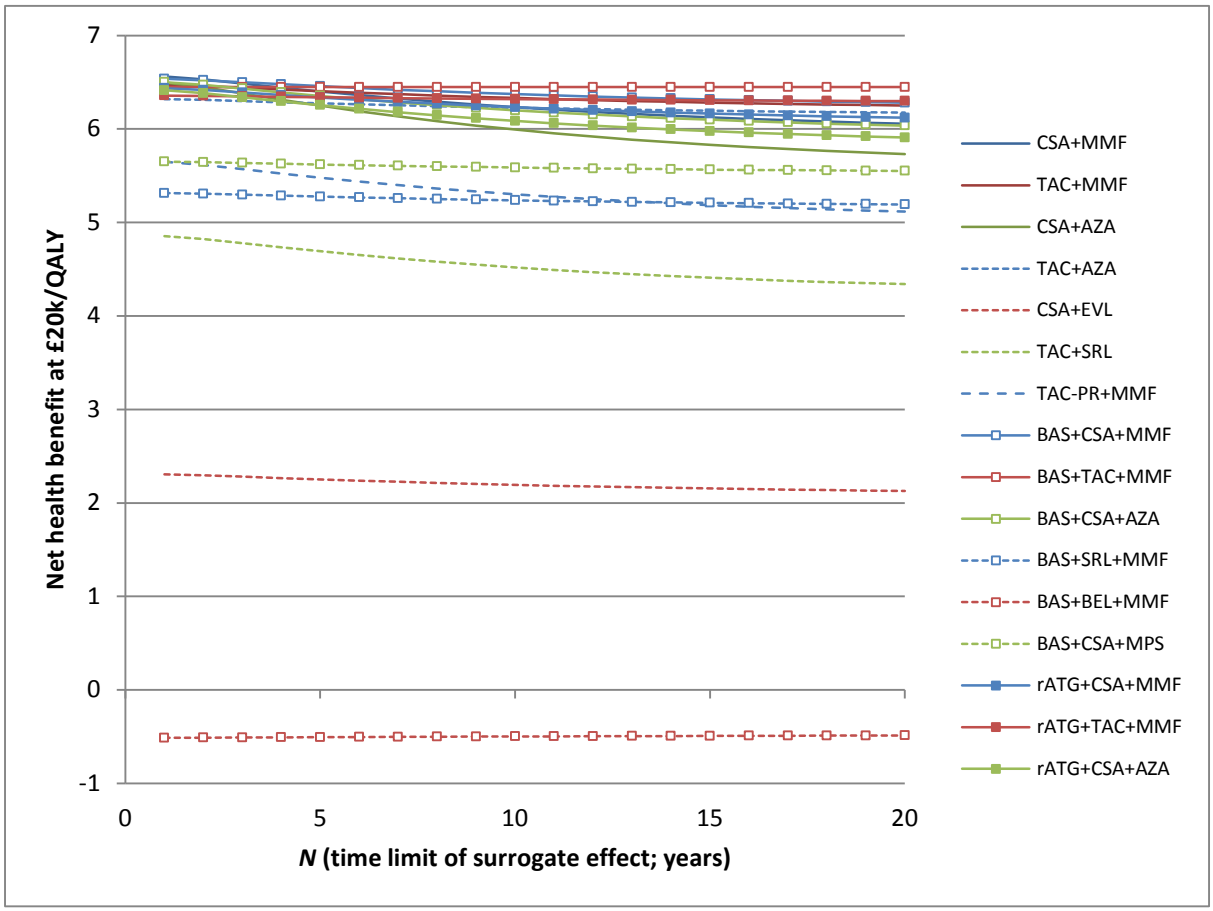


Figure 109. Net health benefit of regimens as duration of surrogate effect on graft survival is varied (close up)

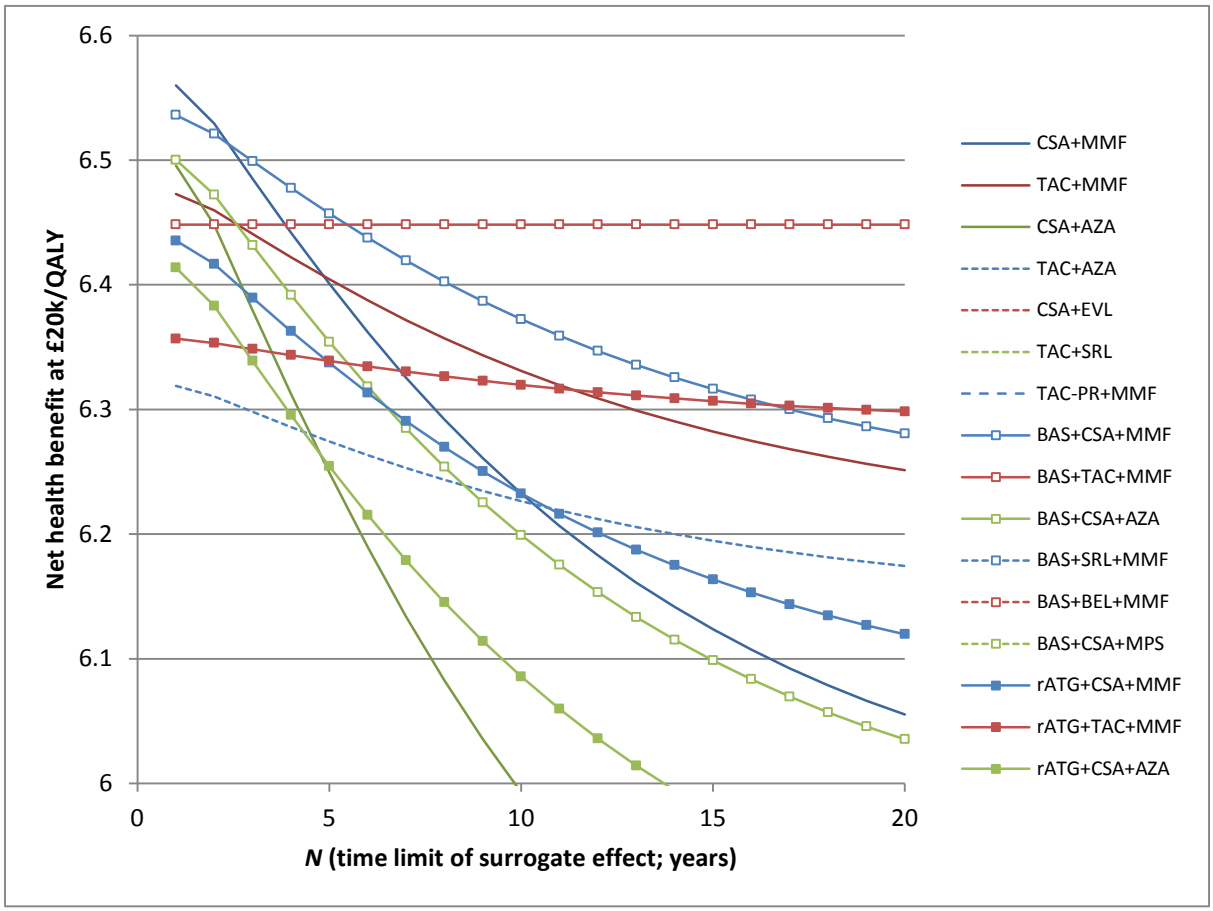


Table 214 and Table 215 respectively indicate the ranges of *N* for which induction and maintenance agents are cost-effective (i.e., give the greatest net health benefit in each comparison).

Table 214. Range of *N* for which each induction agent is cost-effective

Induction agent	Range of *N* for which induction agent is cost-effective	
	£20k/QALY	**£30k/QALY**
With CSA+AZA		
No induction	N/A	N/A
Basiliximab	1–20	1–20
Rabbit ATG	N/A	N/A
With CSA+MMF		
No induction	1–2	1
Basiliximab	3–20	2–20
Rabbit ATG	N/A	N/A
With TAC+MMF		
No induction	1–2	1
Basiliximab	3–20	2–20
Rabbit ATG	N/A	N/A

Table 214 indicates that for no value of *N* from 1–20 was rabbit ATG cost-effective at £20,000 or £30,000 per QALY. When in combination with CSA+AZA, basiliximab was cost-effective at £20,000 and £30,000 per QALY for all values of *N* from 1–20. When in combination with CSA+MMF or TAC+MMF basiliximab was cost-effective at £20,000 per QALY for *N* = 3 to 20 and at £30,000 per QALY for *N* = 2 to 20, with no induction being cost-effective for *N* = 1 or 2 (£20,000 per QALY) and *N* = 1 (£30,000 per QALY).

Table 215. Range of *N* for which each maintenance agent is cost-effective

Maintenance agent	Range of *N* for which maintenance agent is cost-effective	
	£20k/QALY	**£30k/QALY**
With MMF		
TAC-PR	N/A	N/A
TAC	5–20	8–20
CSA	1–4	1–7
With AZA		
CSA	1–4	1–5
TAC	5–20	6–20
With BAS+MMF		
SRL	N/A	N/A
TAC	6–20	9–20
CSA	1–5	1–8
BEL	N/A	N/A
With rATG+MMF		
TAC	5–20	8–20
CSA	1–4	1–7

Table 215. Range of *N* for which each maintenance agent is cost-effective (cont.)

Maintenance agent	Range of *N* for which maintenance agent is cost-effective	
	£20k/QALY	**£30k/QALY**
With CSA		
AZA	N/A	N/A
MMF	1–20	1–20
EVL	N/A	N/A
With TAC		
SRL	N/A	N/A
AZA	N/A	N/A
MMF	1–20	1–20
With BAS+CSA		
AZA	N/A	N/A
MMF	1–20	1–20
MPS	N/A	N/A
With rATG+CSA		
AZA	N/A	N/A
MMF	1–20	1–20

Table 215 indicates that TAC-PR, SRL, BEL, EVL and MPS were not cost-effective at £20,000 or £30,000 per QALY for any *N* from 1 to 20. MMF was cost-effective at £20,000 and £30,000 per QALY for all *N* from 1 to 20. For lower values of *N* (up to 4–8), CSA was cost-effective at £20,000 or £30,000 per QALY whereas for higher values (towards the base case), TAC was cost-effective at £20,000 and £30,000 per QALY.

As can be seen in Figure 109 once $N \geq 6$, BAS+TAC+MMF gives the greatest net health benefit. When $N < 6$, BAS+CSA+MMF, CSA+MMF, BAS+CSA+AZA, CSA+AZA and TAC+MMF give greater net health benefit than BAS+TAC+MMF for some N, although only BAS+CSA+MMF or CSA+MMF gives the greatest net health benefit for $N < 6$. Base case graft survival curves for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF are shown in Figure 110 and Figure 111.

Figure 110. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (base case)

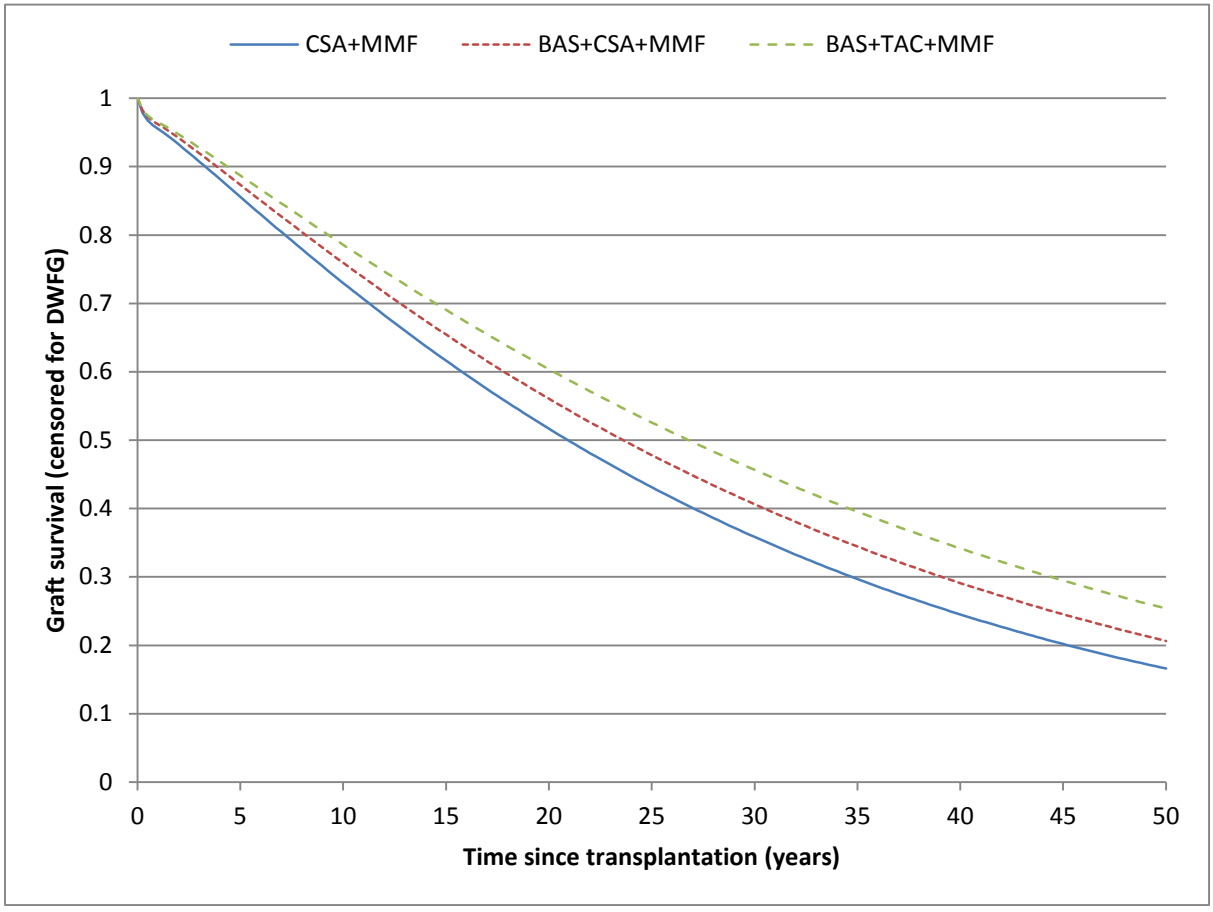
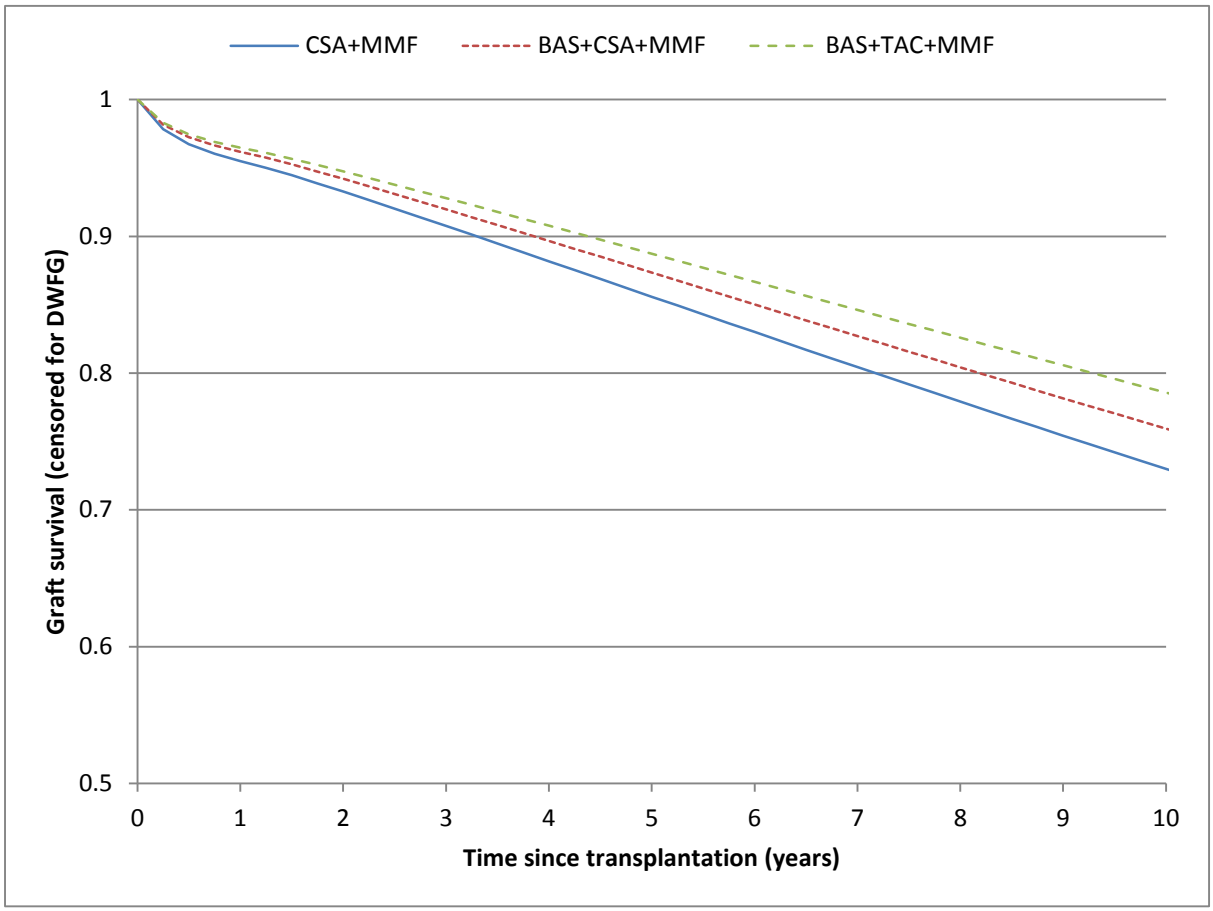


Figure 111. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (base case; close up 0–10 years)



When *N* = 5, BAS+CSA+MMF gives the greatest net health benefit and the graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF are shown in Figure 112 and Figure 113. As expected, by reducing the duration of the surrogate effect the graft survival curves diverge significantly less than in the base case.

Figure 112. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (*N* = 5)

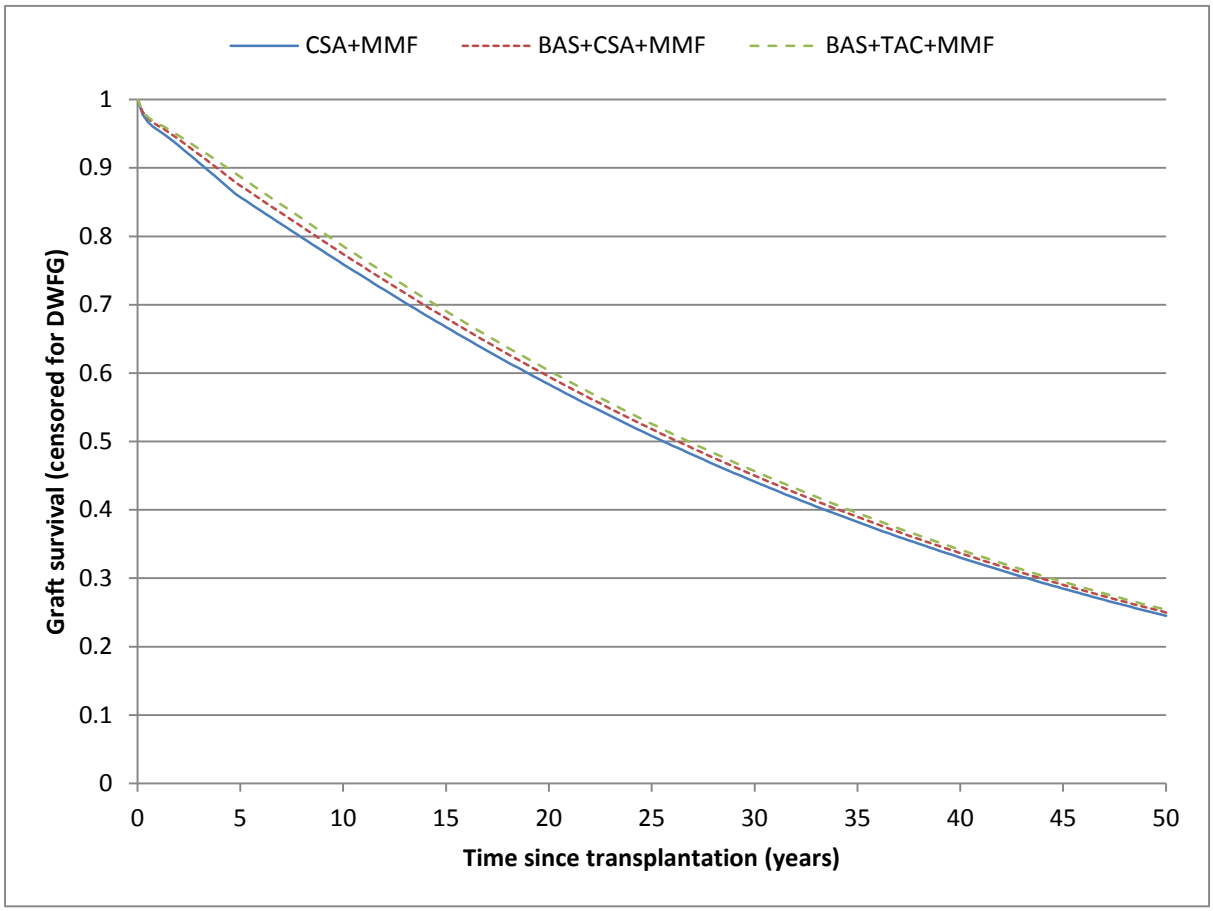
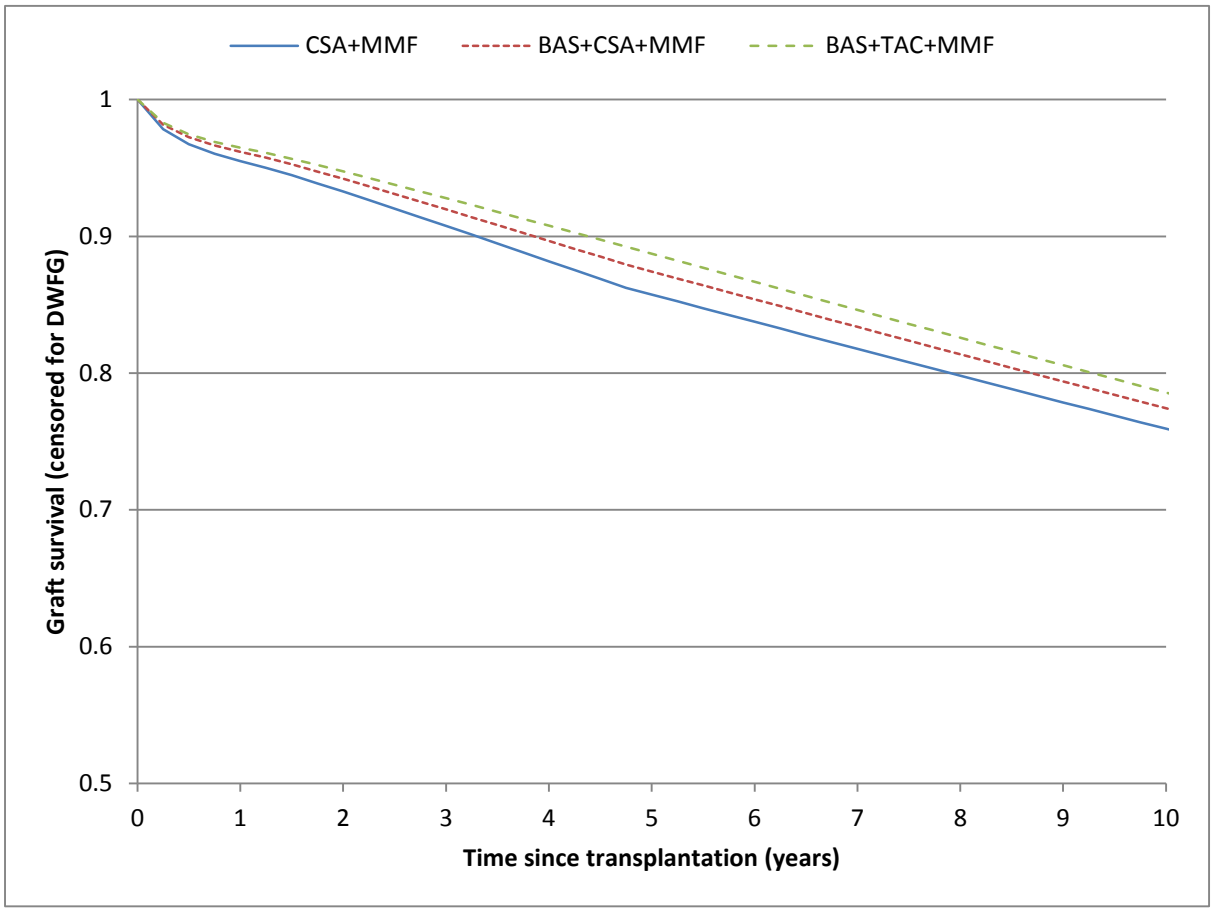


Figure 113. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (N = 5; close up 0–10 years)



When *N* = 2, CSA+MMF gives the greatest net health benefit and the graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF are shown in Figure 114 and Figure 115. As there is now only one year of graft survival difference extrapolated according to the surrogate relationship, the graft survival curves are virtually identical. In this scenario CSA+MMF gives the greatest net health benefit but it is noteworthy that the net health benefit of CSA+MMF is quite sensitive to *N* and even in this scenario only four regimens are predicted to give greater net health benefit than BAS+TAC+MMF: CSA+MMF, TAC+MMF, BAS+CSA+MMF and BAS+CSA+AZA.

Figure 114. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (N = 2)

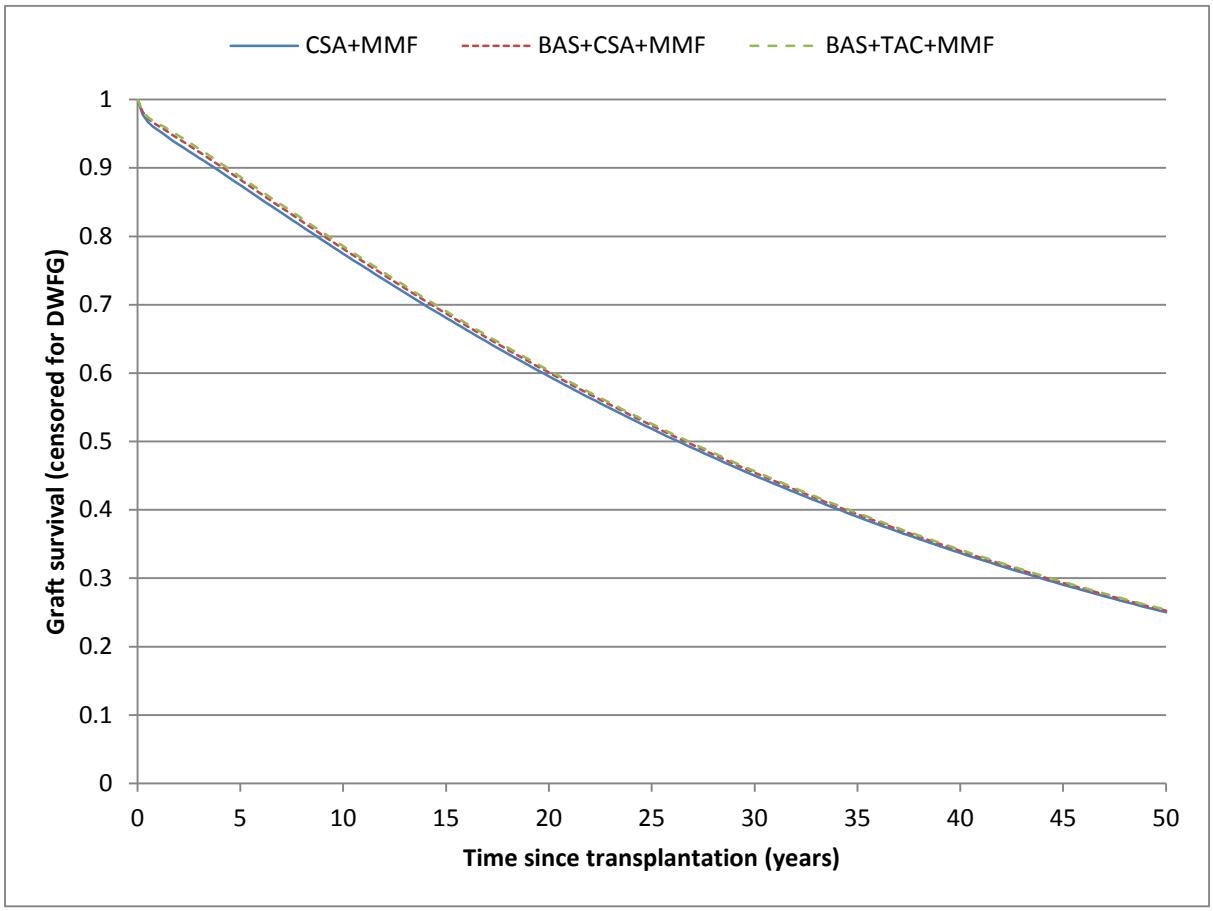
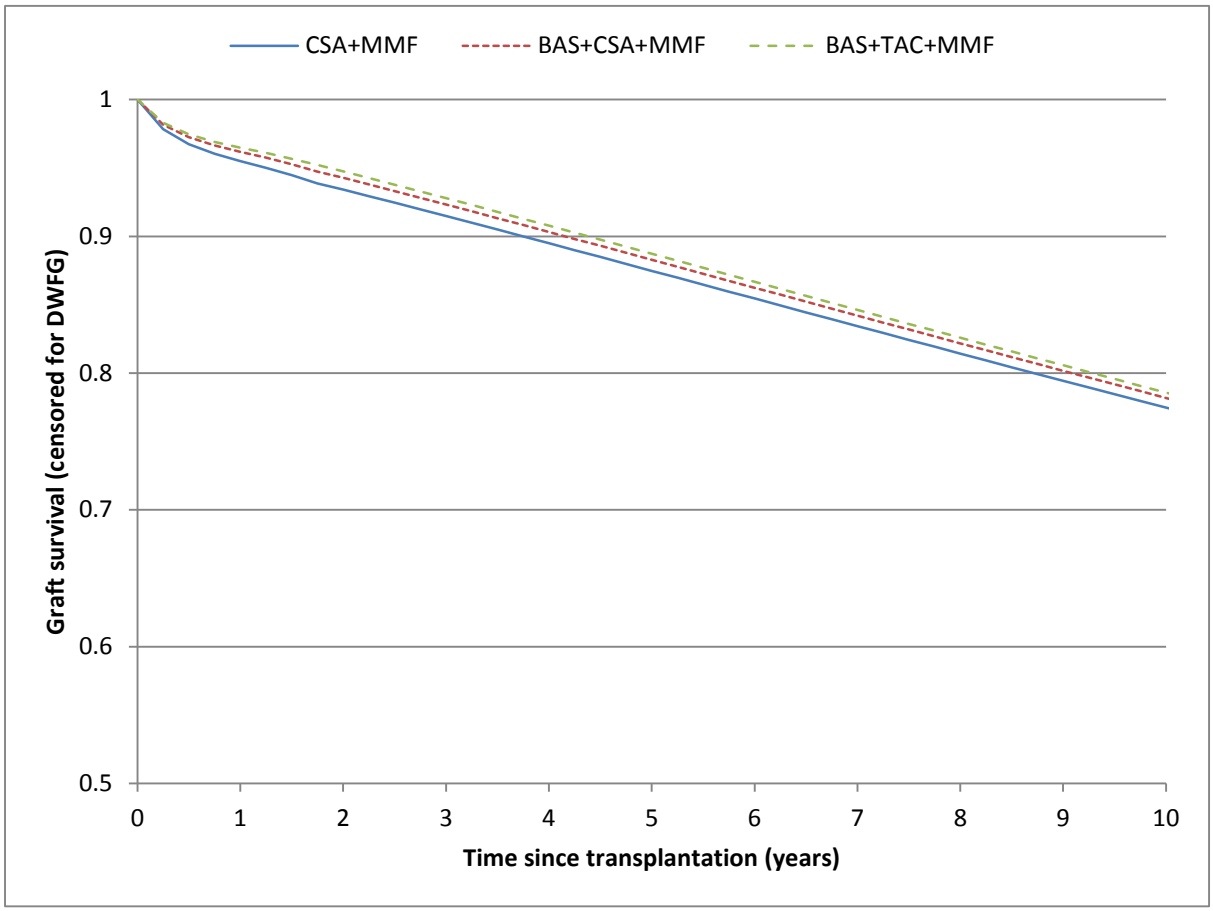


Figure 115. Death-censored graft survival for CSA+MMF, BAS+CSA+MMF and BAS+TAC+MMF (N = 2; close up 0–10 years)



Different gamma parameter for CNI-free regimens

It may be plausible that avoiding calcineurin inhibitors will prolong long-term graft survival by avoiding CNI nephrotoxicity. This possibility was investigated by reducing the gamma (γ) parameter in the Weibull model for graft survival (death-censored) for regimens without CNI, i.e., for BAS+SRL+MMF and BAS+BEL+MMF.

An offset was included for ln(γ) between −2 and 0 (equivalent to the base case). The incremental net health benefit for BAS+SRL+MMF and BAS+BEL+MMF versus BAS+TAC+MMF was calculated (since TAC was predicted to be the only cost-effective agent in combination with BAS+MMF at cost-effectiveness thresholds between £20,000 and £30,000 per QALY). The INHB was calculated at both £20,000 and £30,000 per QALY. As shown in Figure 116 and Figure 117 there is a cross-over for SRL but not for BEL across the

range explored, suggesting that SRL could be cost-effective at £20,000 to £30,000 per QALY if long-term graft survival were significantly better than extrapolated in the base case.

Figure 116. Incremental net health benefit (at £20,000 per QALY) of SRL and BEL versus TAC as gamma parameter of graft survival is varied

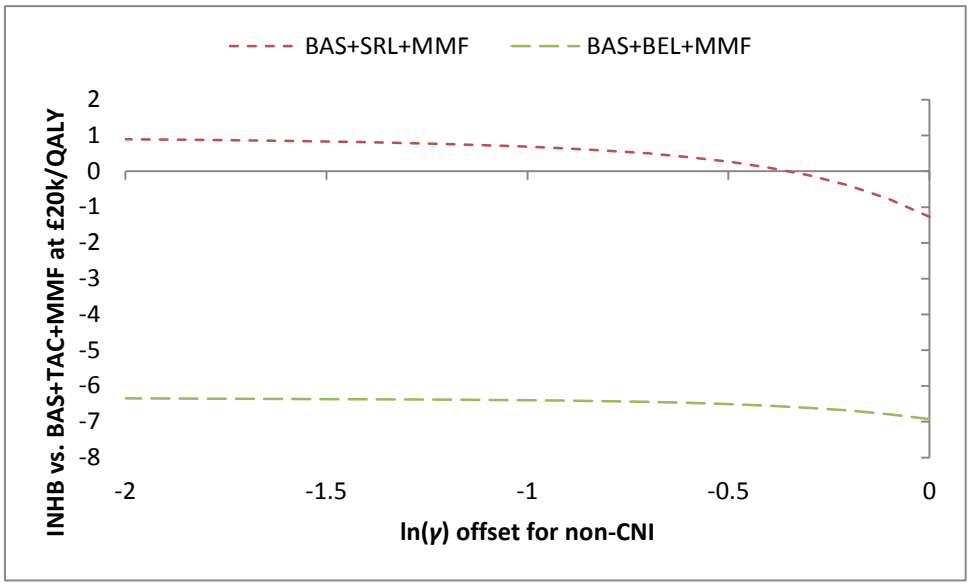
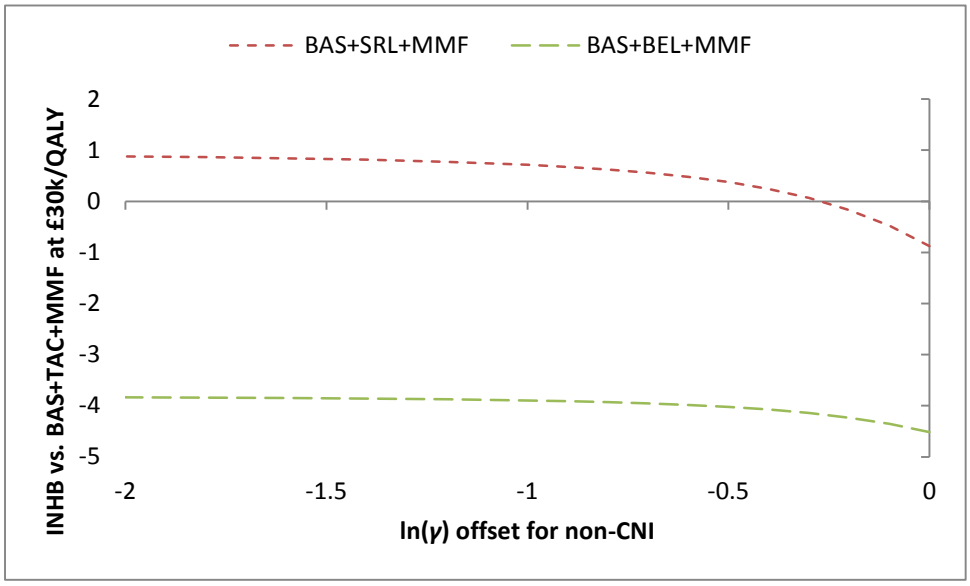


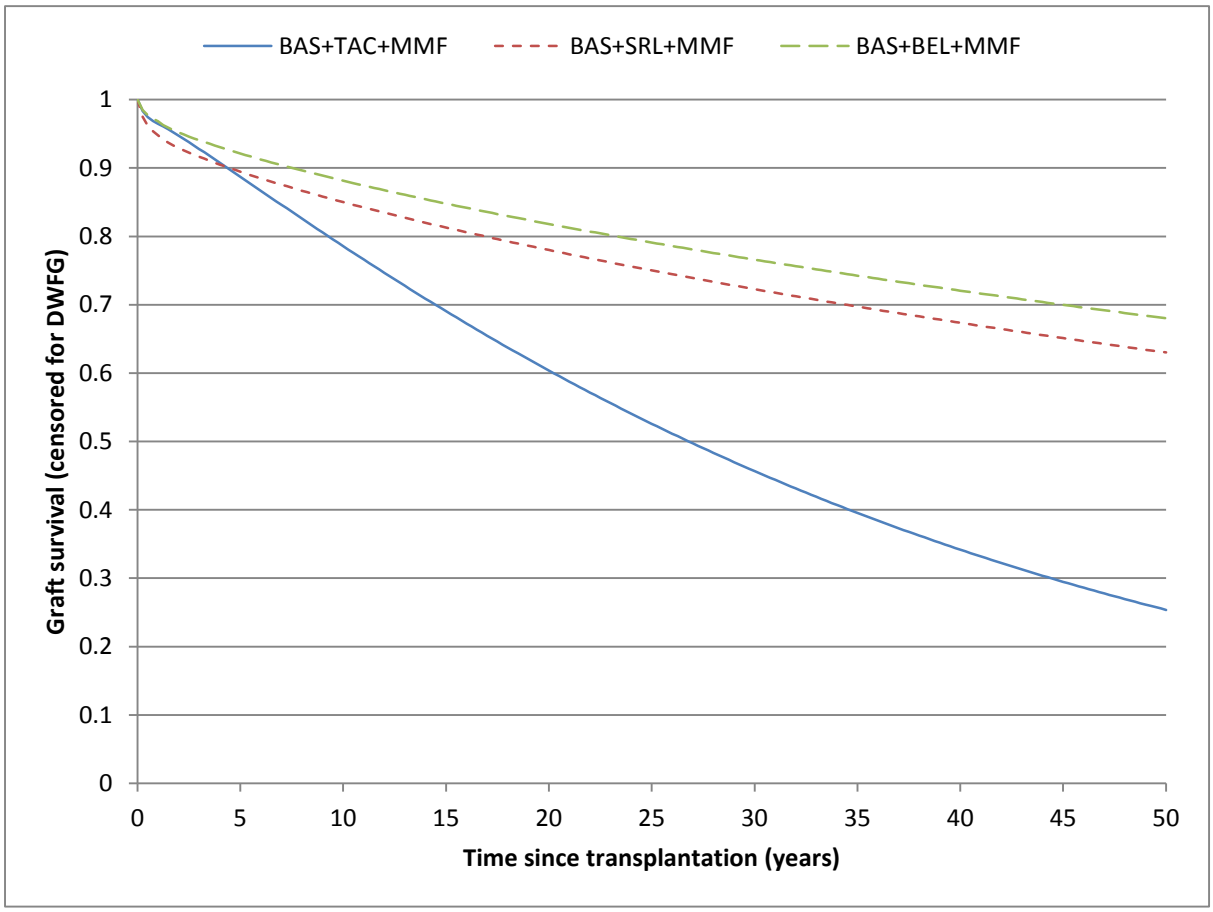
Figure 117. Incremental net health benefit (at £30,000 per QALY) of SRL and BEL versus TAC as gamma parameter of graft survival is varied



Cross-over at £20,000 per QALY occurs for SRL with a ln(γ) offset of −0.3477 (corresponding to γ=0.781), which leads to a reduction in total discounted costs from £114,554 to £100,055 and an increase in total discounted QALYs from 10.9010 to 11.4509.

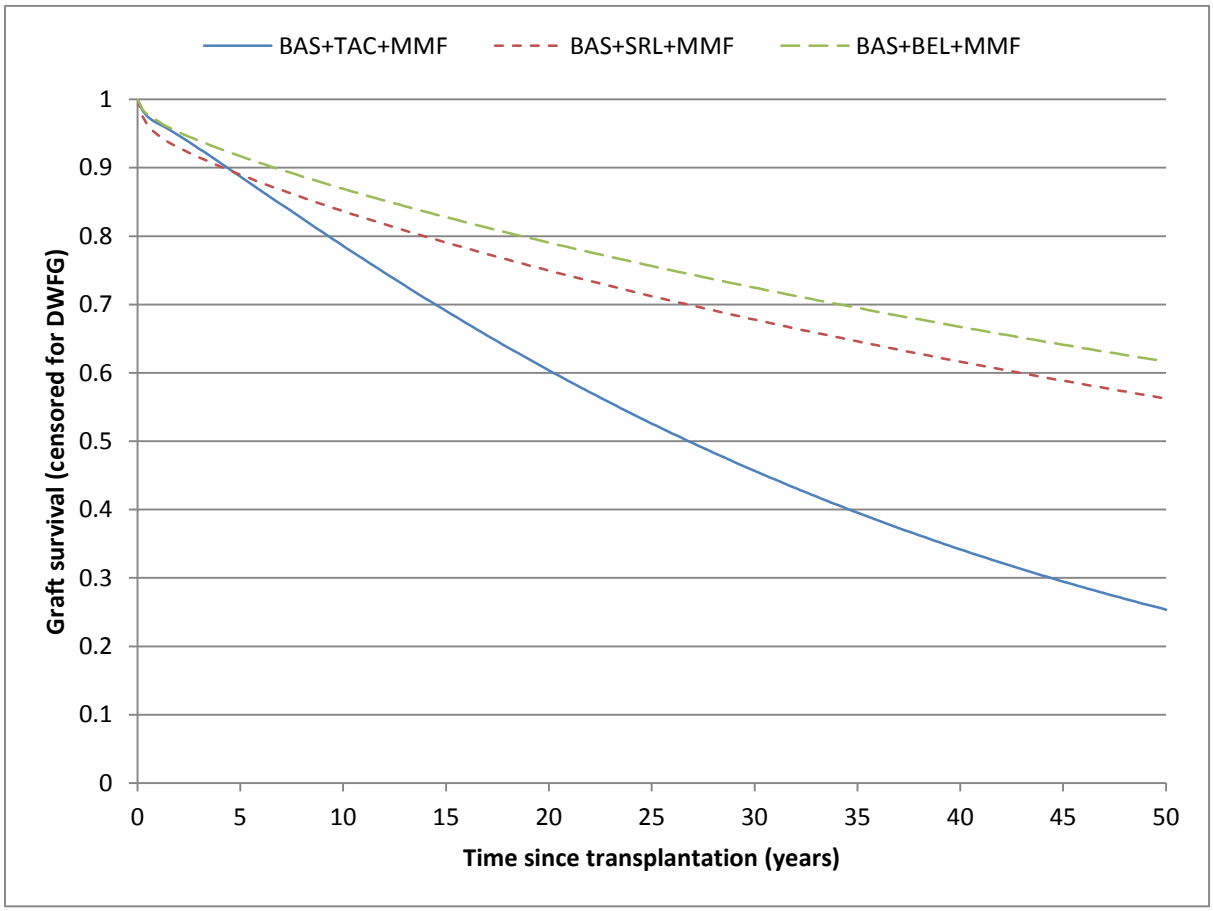
Death-censored graft survival in this scenario is shown in Figure 118. In this scenario TAC and SRL are equally cost-effective at £20,000 per QALY but BEL is not cost-effective.

Figure 118. Death-censored graft survival when non-CNI gamma parameter for graft survival is 0.781 for SRL and BEL versus 1.105 for TAC



Cross-over at £30,000 per QALY occurs for SRL with a ln(γ) offset of −0.27 (corresponding to γ=0.844), which leads to a reduction in total discounted costs to £102,219 and an increase in total discounted QALYs to 11.3688. Death-censored graft survival in this scenario is shown in Figure 119. In this scenario TAC and SRL are equally cost-effective at £30,000 per QALY but BEL is not cost-effective.

Figure 119. Death-censored graft survival when non-CNI gamma parameter for graft survival is 0.844 for SRL and BEL versus 1.105 for TAC



7.4.2.2. Cost-related scenario analyses

List prices for drug acquisition costs

A scenario analysis was conducted in which the drug acquisition costs (for immunosuppression, NODAT and dyslipidaemia) were taken from list prices (BNF 68) rather than the CMU eMit database.

Unit costs for CSA, TAC, AZA and MMF increased, which as expected increased the total costs for all regimens (since there were no regimens not including at least one of CSA, TAC, AZA and MMF).

The cost-effectiveness results for induction agents were only marginally affected (Table 216). No induction continued to be dominated by basiliximab and rabbit ATG continued to be

more costly and more effective than basiliximab with ICERs only marginally affected and all over £100,000 per QALY.

Table 216. Impact on cost-effectiveness of induction agents of using list prices for drug acquisition costs

Induction agent	Total costs (discounted) [Reference case]	Total QALYs (discounted)	ICER (cost per QALY) [Reference case]	INHB at £20k/QALY
With CSA+MMF				
No induction	£104,050 [£98,157]	10.8925	Dominated (BAS) [Dominated (BAS)]	— [—]
Basiliximab	£101,530 [£95,654]	11.0247	— [—]	0.2582 [0.2573]
Rabbit ATG	£105,118 [£99,231]	11.0344	£370,071 [£368,853]	0.0885 [0.0882]
With TAC+MMF				
No induction	£105,059 [£92,827]	10.8595	Dominated (BAS) [Dominated (BAS)]	— [—]
Basiliximab	£103,246 [£90,794]	10.9880	— [—]	0.2191 [0.2301]
Rabbit ATG	£107,009 [£94,538]	11.0160	£134,023 [£133,329]	0.0590 [0.0710]
With CSA+AZA				
No induction	£105,455 [£102,320]	10.7486	Dominated (BAS, rATG) [Dominated (BAS, rATG)]	— [—]
Basiliximab	£101,630 [£98,667]	10.9029	— [—]	0.3456 [0.3370]
Rabbit ATG	£104,720 [£101,751]	10.9250	£139,891 [£139,636]	0.2132 [0.2049]

The cost-effectiveness results for maintenance agents showed some marked differences from the reference case analysis (Table 217). In general the INHB (at £20,000 per QALY) of TAC versus CSA decreased, in some cases causing it to become negative. Likewise, in general, the INHB of MMF versus AZA decreased, in some cases causing it to become

negative. The cost-effectiveness of TAC-PR, SRL, EVL and MPS improved marginally but still none was predicted to be cost-effective in the range £20,000 to £30,000 per QALY. The cost-effectiveness of BEL was virtually unchanged with an ICER over £500,000 per QALY.

With a cost-effectiveness threshold in the range £20,000 to £30,000 per QALY the following changes were observed in cost-effectiveness:

- CSA instead of TAC was cost-effective in combination with MMF, BAS+MMF and rATG+MMF (TAC remained cost-effective in combination with AZA);
- AZA instead of MMF was cost-effective in combination with TAC (MMF remained cost-effective in combination with CSA, BAS+CSA and rATG+CSA).

Table 217. Impact on cost-effectiveness of maintenance agents of using list prices for drug acquisition costs

Maintenance agent	Total costs (discounted) [Reference case]	Total QALYs (discounted)	ICER (cost per QALY) [Reference case]	INHB at £20k/QALY
With MMF				
CSA	£104,050 [£98,157]	10.8925	— [£161,408]	— [—]
TAC	£105,059 [£92,827]	10.8595	Dominated (CSA) [—]	−0.0835 [0.2335]
TAC-PR	£116,617 [£111,499]	10.6172	Dominated (CSA, TAC) [Dominated (CSA, TAC)]	−0.9036 [−0.9424]
With AZA				
CSA	£105,455 [£102,320]	10.7486	Dominated (TAC) [Dominated (TAC)]	— [—]
TAC	£103,746 [£93,851]	10.8448	— [—]	0.1817 [0.5197]
With BAS+MMF				
CSA	£101,530 [£95,654]	11.0247	— [£132,272]	— [—]
TAC	£103,246	10.9880	Dominated (CSA)	−0.1226

Maintenance agent	Total costs (discounted) [Reference case]	Total QALYs (discounted)	ICER (cost per QALY) [Reference case]	INHB at £20k/QALY
	[£90,794]		[—]	[0.2063]
SRL	£119,604 [£114,554]	10.9010	Dominated (CSA, TAC) [Dominated (CSA, TAC)]	−1.0274 [−1.0687]
BEL	£241,432 [£235,490]	11.2941	£519,339 [£519,094]	−6.7257 [−6.7224]
With rATG+MMF				
CSA	£105,118 [£99,231]	11.0344	— [£255,592]	— [—]
TAC	£107,009 [£94,538]	11.0160	Dominated (CSA) [—]	−0.1129 [0.2163]
With CSA				
AZA	£105,455 [£102,320]	10.7486	Dominated (MMF) [Dominated (MMF)]	— [—]
MMF	£104,050 [£98,157]	10.8925	— [—]	0.2142 [0.3521]
EVL	£179,439 [£176,788]	10.9376	£1,671,840 [£1,743,739]	−3.5102 [−3.5343]
With TAC				
AZA	£103,746 [£93,851]	10.8448	— [Dominated (MMF)]	— [—]
MMF	£105,059 [£92,827]	10.8595	£89,518 [—]	−0.0510 [0.0659]
SRL	£134,712 [£126,147]	10.5773	Dominated (AZA, MMF) [Dominated (AZA, MMF)]	−1.8158 [−1.8823]
With BAS+CSA				
AZA	£101,630 [£98,667]	10.9029	Dominated (MMF) [Dominated (MMF)]	— [—]

Maintenance agent	Total costs (discounted) [Reference case]	Total QALYs (discounted)	ICER (cost per QALY) [Reference case]	INHB at £20k/QALY
MMF	£101,530 [£95,654]	11.0247	— [—]	0.1268 [0.2724]
MPS	£114,692 [£112,045]	11.1377	£116,491 [£145,072]	−0.4183 [−0.4341]
With rATG+CSA				
AZA	£104,720 [£101,751]	10.9250	— [Dominated (MMF)]	— [—]
MMF	£105,118 [£99,231]	11.0344	£3,638 [—]	0.0895 [0.2354]

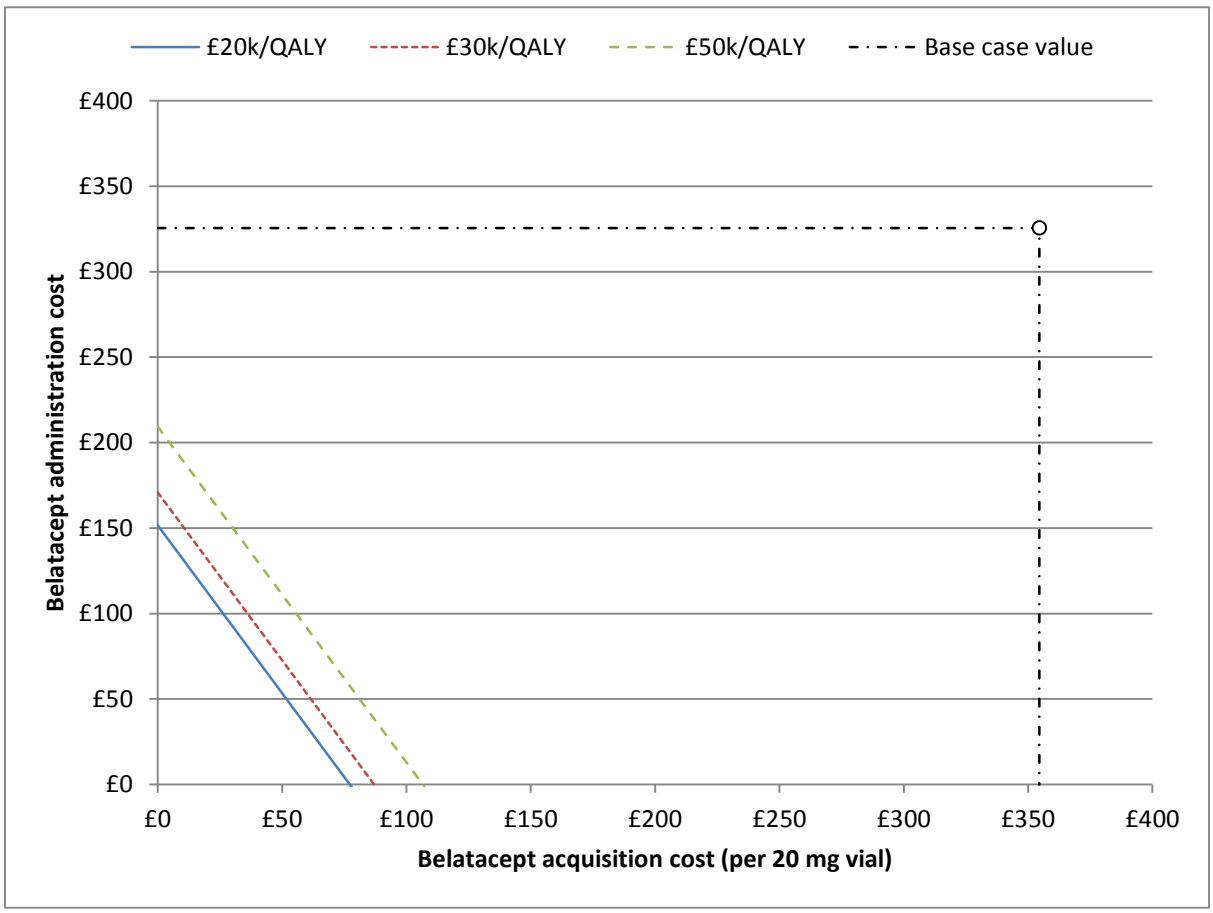
Threshold analysis on costs associated with belatacept

A two-way threshold analysis was conducted on the two costs associated with belatacept: drug administration and drug acquisition. It was found that the total discounted costs for BAS+BEL+MMF were exactly linearly dependent on both costs according to the following formula:

Cost(BAS+BEL+MMF) = 72,765.71 + 159.277×Cost(IV admin) + 312.721×Cost(Vial)

This formula was used to calculate the ICER of BAS+BEL+MMF versus BAS+TAC+MMF. ICER isolines (lines of constant ICER) are straight lines in the 2D plot of the costs of IV administration and belatacept vials, as shown in Figure 120.

Figure 120. Threshold analysis on costs associated with belatacept



The threshold analysis indicated that if the administration cost in the base case is assumed to be correct, BAS+BEL+MMF is not predicted to be cost-effective at £20,000 to £30,000 per QALY even at zero acquisition cost. Since the acquisition and administration costs are both NHS costs and are intrinsically related to treating the condition of interest with belatacept, both of these costs should be included in the reference-case analysis. The administration cost associated with belatacept is a genuine incremental cost associated with belatacept and not with other available treatments.[418] Even if administration costs are excluded for belatacept, BAS+BEL+MMF is not predicted to be cost-effective at £20,000 to £30,000 per QALY based on the current list price for drug acquisition. Bristol Myers Squibb argue for a cost of administration for belatacept of £153.57. At this cost of administration BAS+BEL+MMF is still not predicted to be cost-effective at £20,000 per QALY even at zero acquisition cost; the ICER of BAS+BEL+MMF in this case is £21,009 per QALY with zero acquisition cost and £383,166 per QALY with list price acquisition cost.

7.4.3. Comparison of PenTAG's model-based results with those in company submissions

Below we compare the main deterministic analyses from three of the company submissions with those produced by the independent Assessment Group (PenTAG). These have been selected to include the main maintenance treatments produced and evaluated by the three companies that provided model-based cost-effectiveness studies: prolonged-release tacrolimus versus immediate-release tacrolimus (Astellas), everolimus (Novartis), enteric-coated mycophenolate sodium (Novartis) and belatacept (BMS). While some of the PenTAG analyses contained a larger set of comparator treatments, they are generally comparable, especially after dominated comparators are excluded from the PenTAG analyses.

Overall, for comparisons with the above treatments and equivalent concomitant drugs, the PenTAG model led to lower estimations of discounted incremental costs (between 25% and 40% lower) than the company's analyses. This in large part reflects the lower estimates of incremental graft survival that resulted from our systematic review and network meta-analysis. And all of the models employed different assumptions to extrapolate from short-term trial outcomes to the long-term (25 to 50 years, depending on the model).

For reference, three larger tables at the end of this section compare the main cost parameters, effectiveness parameters and main cost and effectiveness results for the three companies' models and the PenTAG model (Table 222 to Table 224). These show, for example, that the PenTAG model assumptions tended to include fuller costing of the administration of the maintenance therapies, and more realistic (NHS reference cost) relatively lower annual costs of dialysis (except Novartis, who used similar costs for dialysis). Also, although applied differently in the models, the approximate utility difference between living with a functioning graft and living on dialysis was greater in the three company's analyses (typical difference of between ~0.25 to ~0.3) than in the PenTAG model (~0.2 difference). Overall, these particular differences in the company's models will tend to magnify the impact on QALYs of any incremental effectiveness differences which affect long-term graft survival, and also reduce their associated incremental cost.

7.4.3.1. PenTAG's and Astellas' analysis of IR- versus PR-tacrolimus

Table 218 (below) shows the company's and the assessment group's analysis of the cost-effectiveness of prolonged-release (PR-) with immediate-release (IR-) tacrolimus. The Astellas analysis estimates PR-tacrolimus to be both cheaper and more effective than IR-tacrolimus (i.e. PR 'dominates' IR-tacrolimus). This is the opposite result to the PenTAG analysis.

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 218. PenTAG's and Astellas' analysis compared

Maintenance agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG (assessment group)					
TAC-PR (+MMF)	£111,499	—	10.6172	—	Dominated
TAC (+MMF)	£92,827	-£18,672	10.8595	+0.2423	—
CSA (+MMF)	£98,157	+£5,330	10.8925	+0.0330	£161,408
Astellas					
TAC-PR	£118,907	-£11,211	8.2100	+0.2000	—
TAC	£130,118	—	8.0100	—	Dominated
CSA	Missing from Astellas' comparators				

7.4.3.2. PenTAG's and Novartis' analysis of everolimus and of enteric-coated mycophenolate sodium

Table 219 (below) shows the company's and the assessment group's analysis of the cost-effectiveness of everolimus and relevant comparators. Novartis conducted two analyses, with different comparators and doses of ciclosporin, and estimated that everolimus either dominates tacrolimus or, when compared to MMF, has an ICER of £59,696 per QALY. The PenTAG analysis (comparison with MMF shown) produces an ICER of over £1.7 million per QALY. Since azathioprine is dominated in the PenTAG analysis, and omitted from the Novartis analysis, both these ICERs are relative to the next most effective and cheaper treatment, MMF.

There is a modest difference in the incremental costs between the two analyses, with the Novartis analysis estimating the incremental cost of everolimus over MMF to be 25% lower than the PenTAG analysis (£59,354 versus £78,631). However, most of the difference in the ICER is explained by the Novartis analysis estimating a twenty-fold higher incremental QALYs between the two treatments (1 QALY versus 0.045 QALYs in the PenTAG analysis).

This large difference in incremental QALYs will be the combined result of a large number of differences in the parameter values and structural assumptions within each of the models, which lead to differences in incremental graft survival and incremental life-years. The undiscounted incremental time lived with a functioning graft between everolimus and MMF is 0.32 years from the PenTAG analysis and 5.17 years from the Novartis analysis. Correspondingly, the incremental overall survival (life-years) is 0.09 years from the PenTAG analysis but 1.76 years from the Novartis analysis. These differences in incremental graft and overall survival are in turn likely to be mainly due to the use by Novartis of rates of acute and chronic rejection from single arms of different individual trials (Tedesco Silva et al 2010 for everolimus, Vitko et al 2004 for chronic rejection[141 419]), versus less clear evidence of such large effect differences for acute rejection or graft survival from the PenTAG mixed treatment comparison).

Table 219. PenTAG's and Novartis' analysis of everolimus compared

Agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG					
AZA	£102,320	—	10.7486	—	Dominated
MMF	£98,157	-£4,163	10.8925	+0.1439	—
EVL	£176,788	+£78,631	10.9376	+0.0451	£1,743,739
Novartis					
AZA	*Missing from Novartis comparators*				
MMF	£76,826		7.8900		
EVL	£136,180	+£59,354	8.8900	+1.0000	£59,354

Both these analyses are of these drugs in a regimen with ciclosporin and corticosteroids

Table 220 (below) shows the Novartis and the assessment group's analysis of the cost-effectiveness of MPS and relevant comparators. While the Novartis analysis estimates at a favourable ICER for its own product, of £13,235 per QALY, our analysis produces an ICER of £145,072 per QALY. Since, again, azathioprine is dominated in the PenTAG analysis, and omitted from the Novartis analysis, both these ICERs are relative to the next most effective and cheaper treatment, MMF.

There is a modest difference in the incremental costs between the two analyses, with the Novartis analysis estimating the incremental cost of MPS over MMF to be 35% lower than the PenTAG analysis (£10,588 versus £16,391). However, most of the difference in the ICER is explained by the Novartis analysis estimating a seven-fold higher incremental QALYs between the two treatments (0.80 versus 0.113 QALYs).

This large difference in incremental QALYs will be the combined result of a large number of differences in the parameter values and structural assumptions within each of the models, which lead to differences in incremental graft survival and incremental life-years. The undiscounted incremental time lived with a functioning graft between MPS and MMF is 0.4 years from the PenTAG analysis and 4.66 years from the Novartis analysis. Similarly, the incremental overall survival (life-years) is 0.24 years from the PenTAG analysis but 4.66 years from the Novartis analysis.

For informing the effectiveness of the drugs on BPAR, mortality, graft loss and renal function, the PenTAG analysis uses meta-analysis of direct head-to-head trials of the two comparators (Ciancio et al 2008 and Salvadori et al 2001.[130 141 269 419]

Table 220. PenTAG's and Novartis' analyses of MPS compared

Agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG					
AZA	£98,667	—	10.9029	—	Dominated
MMF	£95,654	-£3,013	11.0247	+0.1218	—
MPS	£112,045	+£16,391	11.1377	+0.1130	£145,072
Novartis					
AZA	*Missing from Novartis comparators*				
MMF	£76,771	—	7.89	—	—
MPS	£87,359	+£10,588	8.69	+0.8000	£13,235

7.4.3.3. PenTAG's and BMS's analysis of belatacept

Table 221 (below) shows the company's and the assessment group's analysis of the cost-effectiveness of belatacept and relevant comparators. While the BMS analysis estimates an ICER for belatacept, of £95,068 per QALY (compared with tacrolimus), our analysis produces an ICER of £519,094 per QALY (compared with ciclosporin).

There is a large absolute difference in the incremental costs between the two analyses, with the BMS analysis estimating the incremental cost of belatacept to be £47,620 (34%) lower than the PenTAG analysis (£92,216 versus £139,836). This will in part be due to the PenTAG model using costs for the IV administration of belatacept approximately twice those of the BMS analysis, and the BMS model using an unusually high annual cost for dialysis (£43,586 – about £19,000 more than the NHS reference cost). However, most of the difference in the ICER is explained by the BMS analysis estimating a nearly four-fold higher incremental QALYs between the relevant treatments (0.97 versus 0.269 QALYs).

This difference in incremental QALYs will be the combined result of a large number of differences in the parameter values and structural assumptions within each of the models, which lead to differences in incremental graft survival and incremental life-years. The undiscounted incremental time lived with a functioning graft between Belatacept and TAC/CSA is 0.95 years from the PenTAG analysis and 1.51 years from the BMS analysis. Similarly, the incremental overall survival (life-years) is 0.57 years from the PenTAG analysis 1.51 years from the BMS analysis. These differences in incremental graft and overall survival are in turn likely to be due to the BMS analysis relying on: a much longer assumed time between graft failure and re-transplantation (16.5 years, vs 5 years time-to-

retransplantation (or death in the PenTAG analysis)); assumed linear changes in GFR within the functioning graft state determining long-term outcomes, and; long-term transition probabilities being based on US cohort data (not UK registry data, as in the PenTAG analysis).

Table 221. PenTAG's and BMS' analysis of belatacept compared

Agent	Discounted costs		Discounted QALYs		ICER
	Total	Incremental	Total	Incremental	
PenTAG					
SRL	£114,554	—	10.9010	—	Dominated
TAC	£90,794	-£23,760	10.9880	+0.0869	—
CSA	£95,654	+£4,860	11.0247	+0.0367	£132,272
BEL	£235,490	+£139,836	11.2941	+0.2694	£519,094
BMS					
TAC	£205,502	+£1,215	6.53	0.36	£3,375
CSA	£204,287	—	6.17		
BEL	£296,503	+£92,216	7.14	0.97	£95,068

Table 222. Major cost elements in the different analyses (£)

Cost parameter	Astellas[1]	BMS[2,3]	Novartis[1,3]	PenTAG
Tacrolimus therapy (per year)	4,255 [4]	3,937 (1st year) 2,821 (2nd year+)[9]	5,283	With AZA: 1,816 (1st year) 1,196 (2nd and 3rd year) 1,063 (4th year+) With MMF: 1,378 (1st year) 1,063 (2nd year+)
Tacrolimus administration	0	386 (1st year) 89 (2nd year)[9]	0	1,114 (1st year) 374 (2nd year) 107 (3rd year+)
MMF therapy (per year)	2,402 [5]	0 [8]	282 [11]	With TAC 249 (1st year) 202 (2nd year+) With CSA 259 (1st year) 230 (2nd year+) With SRL 248 (1st year) 202 (2nd year+) With BEL 276
Cyclosporine therapy	N/A[6]	1,971 (1st year) 1,562 (2nd year+)[9]	839 (1st year) 694 (2nd year+)	With AZA 1,649 (1st year) 1,233 (2nd and 3rd year) 1,195 (4th year+) With MMF/MPS 1,374 (1st year) 1,187 (2nd year+)
Cyclosporine administration	0	386 (1st year) 90 (2nd year)[9]	0	1,114 (1st year) 374 (2nd year) 107 (3rd year+)
Belatacept (per year)	10,966 (1st year) 6,480 (2nd year+)	13,472 (1st year) 9,217 (2nd year+)	N/A	12,812 (1st year) 8,849 (2nd year+)

Cost parameter	Astellas[1]	BMS[2,3]	Novartis[1,3]	PenTAG
Belatacept administration	0	2,457 (1st year) 1,996 (2nd year+)	N/A	4,728 (1st year) 4,246 (2nd year+)
Corticosteroids	178	0 [8]	285	20
Acute rejection (event)	1,738	3,483	1,725	3,557
Dialysis (per year)	38,387[7]	43,586[10]	22,877	24,372 (HD) 24,000 (PD) 24,314 (Mix, age 45–54)
Re-transplantation	25,953	25,908	17,736	16,030 (procedure) 1,226 (work-up)
Re-transplantation: Organ procurement	0	12,954	0	8,914 (live donor) 10,142 (deceased donor)

[1] Adopted a 70 kg weight for representative patient in the model. The cost of Basilliximab induction (20 mg within 2 hour before transplantation and at 4 days post-transplant, BNF 2014 prices, £1,685) was included in all arms. [2] Adopted a 75 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] Prograf. [5] 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. [6] Astellas does not evaluate cyclosporine 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.[7] From Beaudet et al. Beaudet et al. 2011 [8] BMS model did not include costs of concomitant medications in the triple therapy regimen for any treatment arm. [9] The BMS submission reports a cost (of drug acquisition or drug administration) for the second year that is different from the cost for the third and subsequent years but the model spreadsheet adopts the price given for the third year in the submission as the price of the second and subsequent years. The figure presented here is the one adopted by the model. [10] From Baboolal et al. Baboolal et al. 2008. [11] Based on 1 g daily starting within 72 h of transplantation, valued at £9.65 price for 500mg, 50 tab pack from Commercial Medicines Unit (CMU) Electronic Market Information Tool (E-MIT), 2014. [12] From supporting evidence of NICE guidance cg135 (NICE 2011).

Table 223. Key effectiveness assumptions and outcomes in economic models compared

Effectiveness parameter	Astellas[1]	BMS[2]	Novartis[2]	Assessment Group (PenTAG)
Time to graft failure (median)	Without BCAR at 12 months: 23 years With BCAR at 12 months: >25 years[3]	initial GFR 2 15.0 years initial GFR3a 11.5 years initial GFR3b 7.0 years initial GFR 4 2.5 years	Everolimus: 15.8 years MPS: 21.3 years MMF + Cs: 7.2 years Tac + Cs: 8.3 years	(To nearest 0.25 years) CSA+MMF: 13.75 y TAC+MMF: 14.75 y CSA+AZA: 12.75 y TAC+AZA: 14.50 y CSA+EVL: 14.50 y TAC+SRL: 12.75 y TAC-PR+MMF: 13.25 y BAS+CSA+MMF: 14.75 y BAS+TAC+MMF: 15.50 y BAS+CSA+AZA: 13.75 y BAS+SRL+MMF: 14.75 y BAS+BEL+MMF: 16.50 y BAS+CSA+MPS: 15.50 y rATG+CSA+MMF: 14.75 y rATG+TAC+MMF: 15.50 y rATG+CSA+AZA: 13.75 y
Time to transplantation from graft failure (mean unless otherwise stated)	3.5 years (median)	16.5 years[4]	3 years (SD 1)	Mean time to transplantation or death following failure of initial graft 4.97 years (range 4.87–5.06)
Annual change in GFR	N/A	-3 (4th year+)	-1.66 (2nd year) -2.68 (3rd year+)	N/A
Utility of functioning graft –first transplant	0.71	0.49-0.64 (depending on GFR stage)	0.49-0.64 (depending on GFR stage)	0.815 (age 50) 0.786 (age 60) 0.755 (age 70) 0.723 (age 80)

Effectiveness parameter	Astellas[1]	BMS[2]	Novartis[2]	Assessment Group (PenTAG)
Utility of functioning graft - 2nd+ transplants	0.71	0.59	0.49-0.64 (depending on GFR stage)	As 1st
Utility of dialysis state	0.459	0.28	0.28	Haemodialysis 0.591 (age 50) 0.562 (age 60) 0.531 (age 70) 0.499 (age 80) Peritoneal dialysis 0.604 (age 50) 0.575 (age 60) 0.544 (age 70) 0.562 (age 80)

[1]Model was driven by surrogate marker of acute rejection [2]Models driven by GFR change over time. [3] Modelled time horizon was 25 years, by which point 53.9% of those with BCAR in the first twelve months still had their initial graft functioning. [4] This value was derived by the company from an exponential survival model (Levy et al. 2014) with predicted hazard rate for a person of average age 40.3 (BMS submission model excel file). The model had been estimated on USRDS data for a sample of Medicare-covered kidney transplant recipients (no information on sample characteristics were provided), which means that the model predictions are likely to be out of the age range of the sample on which the model was estimated.

Table 224. Results of the model-based analyses compared

Model	Regimens compared	Functioning first graft (years)	Functioning graft (years)	Years with Graft loss/dialysis	Life years	QALYs*	Costs (£)*	ICER Incremental cost per QALY
Astellas	Tacrolimus TD (+MMF+St)	15.10	15.40	2.44	17.88	8.01	130,118	TAC vs. SIRI:
	Sirolimus I (+MMF+St)	15.05	15.36	2.46	17.82	7.99	104,905	1,651,801
	Everolimus (+MMF+St)	15.03	15.34	2.46	17.80	7.99	142,995	TAC vs. SIRII:
	Sirolimus II (+MMF+St)	14.90	15.22	2.51	17.73	7.94	119,371	170,681
	Belatacept (+MMF+St)	14.88	15.20	2.52	11.72	7.94	163,740	
	Tacrolimus TC# (+MMF+St)	15.76	16.03	2.16	18.19	8.21	118,907	TAC TD dominates
	Tacrolimus OD# (+MMF+St)	15.10	15.40	2.44	17.88	8.01	130,118	
Assessment Group (PenTAG)	Tacrolimus TD (+ MMF + St)	16.49	19.32	3.03	22.36	10.86	92,827	No PenTAG analysis compared everolimus with belatacept
	Everolimus (+ CSA + St)	16.39	19.32	3.13	22.44	10.94	176,788	
	Belatacept (Bas+ MMF + St)	18.01	20.50	2.70	23.21	11.29	235,490	
	Tacrolimus OD# (+MMF+ St)	16.49	19.32	3.03	22.36	10.86	92,827	TAC OD dominates
	Tacrolimus TD# (+MMF+St)	15.24	18.46	3.39	21.85	10.62	111,499	
BMS	Belatacept + ? (not stated)	13.39	14.53	5.00	19.53	7.14	296,503	Belatacept vs. Tac:
	Tacrolimus + ? (not stated)	11.89	13.04	4.98	18.02	6.53	205,502	149,182
	Ciclosporin + ? (not stated)	10.80	12.05	5.33	17.38	6.17	204,287	Tac vs Cs 3,375
Assessment Group (PenTAG)	Belatacept + (MMF + St)	18.01	20.50	2.70	23.21	11.29	235,490	Belatacept vs. Tac:
	Tacrolimus + (MMF + St)	17.28	19.85	2.79	22.64	10.99	90,794	*£472,708***
	Ciclosporin + (MMF + St)	16.67	19.55	3.08	22.64	11.02	95,654	CsA vs TAC £132,272
Novartis**	Everolimus + ciclosporin (low dose)	14.28	14.98	10.73	25.71	8.86	135,358	Everolimus dominant
	Tacrolimus+ MMF	9.92	9.94	13.45	23.39	7.37	140,972	
	Everolimus + ciclosporin (low dose)	13.91	14.34	11.46	25.80	8.89	136,180	MM+CsA vs EVE+CsA: £59,696 (deterministic) >£200,000 (probabilistic)
	MMF + ciclosporin	9.03	9.17	15.01	24.04	7.89	76,826	

Model	Regimens compared	Functioning first graft (years)	Functioning graft (years)	Years with Graft loss/dialysis	Life years	QALYs*	Costs (£)*	ICER Incremental cost per QALY
	MPS + ciclosporin	15.97	16.01	9.47	25.48	8.69	87,359	MPS+CsA vs. MMF+CsA: £13,209 (deterministic) ~£29,000 (probabilistic)
	MMF + ciclosporin	9.43	9.35	14.77	24.17	7.89	76,771	
Assessment Group (PenTAG)	Everolimus + ciclosporin (low dose)	16.39	19.32	3.13	22.44	10.9376	176,788	EVE+CsA vs MMF+CsA: £1,743,739
	Tacrolimus+ MMF	15.82	19.00	3.35	22.44	10.8925	98,157	
	EC-MPS + MMF	17.24	19.55	3.13	22.88	11.1377	112,045	MPS vs. MMF+Cs: £145,072
	MMF + ciclosporin	16.67	19.95	2.84	22.64	11.0247	95,654	

* Discounted at 3.5% per year. ** The number of years with a functioning graft, years with a functioning first graft for the Novartis model were obtained in separate model runs by manipulating the parameter values to obtain the respective figures, since the model did not produce these outputs. This made the calculation unreliable, since with each run different results are obtained for the same output, as evidenced by comparing the figures for MMF + cyclosporine where the number of years with a functioning graft for the first graft is larger, 9.43, than the total number of years with a functioning graft, 9.35. # tacrolimus OD = once daily (prolonged release); TD = twice daily (immediate release)

8. Discussion

8.1. Statement of principal findings

8.1.1. Aim

This remit for this report was to review and update the evidence used to inform the current NICE guidance (TA85) on the clinical and cost-effectiveness of immunosuppressive therapies in adult renal transplantation. The current guidance is Woodroffe et al. 2005. [60] 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.

8.1.2. Clinical effectiveness systematic review

Previous technology assessment for NICE

The previous assessment (TA85) in 2002 found that basiliximab, tacrolimus and MMF consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy (e.g. dual or triple combination therapy for induction and/or maintenance including CSA, AZA and CCS). The independent use of basiliximab, tacrolimus and MMF was associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%). However, the effects of these drugs did not appear to be additive (e.g. benefit of tacrolimus with adjuvant MMF was 5% reduction in acute rejection rate compared with 15% reduction with adjuvant AZA). Thus, the addition of one of these drugs to a baseline immunosuppressant regimen was likely to affect adversely the incremental cost-effectiveness of the addition of another.

Important gaps in the evidence were identified concerning the impact of the newer immunosuppressants on long-term graft loss and patient survival. The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost-effectiveness on the newer immunosuppressants contingent on modelling based on extrapolations from short-term trial outcomes.

Updated systematic review

In total, 68 new RCTs were included in the clinical effectiveness review presented in this report, with an additional 21 RCTs meeting our inclusion criteria from the previous assessment.

For the head-to-head comparisons of **induction therapies**, from 0.5 years to 10 years post-transplant, we found no evidence to suggest that BAS or rATG are more effective than placebo, no induction or each other in reducing the odds of mortality (overall survival). Similarly, for graft loss, we found no evidence of a statistically significant difference for BAS or rATG vs placebo, no induction or each other.

We found evidence to suggest that rATG and BAS are more effective than placebo or no induction at reducing BPAR (rATG at 1 yr, OR 0.34, 95%CI 0.22 to 0.52, I^2 8.9%; BAS at 1 yr, OR 0.53, 95% CI 0.40 to 0.70, I^2 0.0%). A statistically significant difference was found for the severity of BPAR, comparing BAS vs rATG, where BAS was associated with lower odds of Banff 3, the most severe classification of acute rejection (1 year, OR 0.04, 95%CI 0.00 to 0.65).

We found no evidence that any **maintenance therapies** were preferable to others in terms of mortality.

For **graft loss** outcomes reported by maintenance studies, we found evidence that at five years that BEL+MMF may be superior to CSA+MMF (OR 0.40, 95%CI 0.19 to 0.87, I^2 0.0%). At 0.5 years, there are greater odds of reduced graft loss for CSA+MMF as compared to CSA+AZA (OR 0.58, 95%CI 0.04 to 0.59, I^2 72.2%).

Several treatments showed a beneficial effect with regard to reducing **BPAR**, although this varied across time points. For all the following comparisons, the arm containing TAC displayed lower odds of BPAR:

- TAC+AZA vs CSA+AZA (0.5 years OR 0.50 95%CI 0.32 to 0.79, I2 50.1%; 1 year OR 0.50, 95%CI 0.39 to 0.64, I2 8.1%; 4 years OR 0.38, 95%CI 0.25 to 0.57);
- TAC+MMF vs CSA+AZA (0.5 year OR 0.64, 95%CI 0.41 to 0.98; 1 year OR 0.35, 95% CI 0.15 to 0.82);
- TAC+MMF vs CSA+MMF (1 year OR 0.59, 95%CI 0.37 to 0.94, I^2 19.3%);

- TAC+MMF vs SRL+MMF (1 year OR 0.32, 95%CI 0.12 to 0.87, I^2 0.0%);
- TAC+SRL vs TAC+MMF (0.5 years OR 0.65 95%CI 0.44 to 0.96).

For CSA+MMF vs CSA+AZA, at 0.5 years and one year, there is statistically significant evidence to suggest MMF is more effective (0.5 years OR 0.50, 95%CI 0.35 to 0.72, I^2 35.1%).

TAC is also associated with a higher level of **graft function** for the following regimens:

- TAC+MMF vs CSA+MMF (at 3 years, eGFR WMD 4.60 ml/min, 95%CI 1.35 to 7.85);
- TAC+MMF vs TAC PR+MMF (at 0.5 years, eGFR WMD 1.90 ml/min, 95%CI 1.70 to 2.10);
- TAC+SRL vs CSA+SRL (at 0.5 years, eGFR MD 6.35 ml/min, p<0.0001; 1 year MD 5.25, p=0.0004).

For MMF+TAC vs MPS+TAC, MPS at 1 year and 3 years is more effective (1 year, MD 1.9 ml/min, p<0.0001; 3 years eGFR MD 0.5 ml/min, p=0.0016). BEL appears more effective at one year and three years for BEL+MMF vs CSA+MMF (1 year, eGFR WMD 7.83 ml/min, 95%CI 1.57 to 4.10, I^2 73.6%; 3 years WMD 16.08 ml/min, 95%CI 5.59 to 26.56, I^2 89.5%) however, heterogeneity across studies is substantial. Where there are two comparisons involving SRL and CSA, the regimen including MMF suggests CSA to be more beneficial up to five years (5 years, eGFR WMD 9.10 ml/min, 95%CI 1.68 to 16.52), yet in contrast, the regimen including AZA suggests SRL to be more effective (1 year, eGFR MD 10.8 ml/min, p<0.0001).

Time to BPAR is generally poorly reported and therefore challenging to form a conclusion. Again, TAC+AZA vs CSA+AZA shows conflicting results for two studies, however, the statistically significant result in one of the two studies suggests that BPAR is achieved more quickly for participants receiving TAC rather than CSA (MD 24 days, p=0.0033). This is also true for TAC+MMF vs CSA+MMF (MD 46.7 days, p<0.0001). Where SRL+TAC and MMF+TAC are compared, a reduced time to BPAR is seen for MMF (MD 48.6 days, p=0.0017). For SRL+MMF vs CSA+MMF, one of three studies demonstrates a statistically significant difference in favour of CSA (MD 38 days, p=0.0035), however, the other two studies show no difference.

BPAR severity. For TAC+AZA vs CSA+AZA, there are lower odds of the more severe BPAR for the arm containing TAC, although there is substantial heterogeneity across studies (Banff 3 OR 0.28, 95%CI 0.12 to 0.66). Similarly, for TAC+MMF vs TAC PR+MMF, TAC has a lower proportion of people experiencing the more severe BPAR of Banff 3 (OR 0.11, 95%CI 0.01 to 0.87, I^2 0.0%).

Following **network meta-analysis** for **induction therapy**, there is no evidence to suggest BAS or ATG are more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality. ATG and BAS were both estimated to be more effective than placebo/no induction, with ATG being more effective than BAS at reducing BPAR. There is evidence to suggest that BAS is more effective than placebo/no induction for increasing graft function.

With regard to **maintenance therapy**, the network meta-analysis showed none of the maintenance regimens performed consistently well on all four outcomes and a great deal of heterogeneity was noted:

- No evidence was found to suggest that one treatment was any more effective at reducing the odds of graft loss than any other treatment.

- There is evidence to suggest that BEL+MMF is more effective at reducing the odds of mortality than TAC+MMF and SRL+MMF, but no other treatments are estimated to be any more effective at reducing mortality than any other treatment.

- MMF+CSA, TAC+MMF and SRL+TAC are estimated to be more effective than CSA+AZA and EVL+MPS at reducing the odds of BPAR. In addition,TAC+AZA and EVL+CSA are also estimated to be more effective than and CSA+AZAat reducing the odds of BPAR. However, apart from CSA+AZA and EVL+MPS performing poorly in some comparisons, it is difficult to say that any one treatment is more effective at reducing BPAR than another as the 95% CIs are very wide.

- Similarly, a number of treatments TAC+AZA, TAC+MMF and BEL+MMF, are estimated to be more effective than CSA+AZA and MMF+CSA at increasing graft function. In addition, SRL+AZA is estimated to be more effective than CSA+AZA at increasing graft function. However, due to the limited direct evidence informing many of the comparisons and the 95% CIs being very wide, we can only conclude that CSA+AZA and MMF+CSA are performing poorly in some comparisons.

Overall, we found that despite the volume of evidence, there is little impact on effectiveness conclusions from the head-to-head comparisons, particularly for graft loss and mortality. However, this may be a reflection of the lack of long term data since very few studies reported all outcomes beyond one year, and also the frequently substantial level of heterogeneity across studies. Furthermore, the quality of trials was variable and, due to reporting omissions, it was difficult to make a general assessment regarding quality.

8.1.3. Economic evaluations

8.1.3.1. Published economic evaluations

- There is limited evidence on costs and benefits of induction regimens, as studies are typically economic evaluations conducted alongside single-centre randomised controlled trials or 1 year duration or less, involving small samples and reporting insufficient data in order to evaluate their generalisability.

- Studies of initial and maintenance immunosuppression are all sponsored by the industry or conducted by a person affiliated to them (except for the analysis by the Birmingham assessment group who reviewed the evidence on behalf of NICE during the previous appraisal on the topic)

- Studies of initial and maintenance immunosuppression typically use a biomarker as a surrogate to extrapolate outcomes from randomised controlled trials of 1-3 year duration to the long term (i.e. 10 to 50 years after initial transplantation)

- Since the previous NICE appraisal, the main development in economic evaluation modelling of immunosuppressive regimens is the use of renal function as a surrogate outcome in addition to acute rejection for extrapolating trial efficacy outcomes to long term graft and patient survival

- In addition, new evidence has emerged that changes in renal function directly impact on current health related quality of life and costs and this is now recognised by the more recently published models

- In the UK, however, only one study of initial and maintenance immunosuppression has accounted for these methodological developments but it suffers from a lack of a

systematic approach to evidence synthesis on the efficacy of relevant UK treatments in routine use.

- Evidence from other countries is of questionable generalizability due to inadequate reporting or the regimens being compared

- A new study would fill a gap the evidence base required to inform NHS decision making by adopting a systematic approach to evidence synthesis on all relevant comparators, from an independent standpoint and incorporating the latest methodological developments and evidence on the topic.

8.1.3.2. Company submissions

- Three models of initial and maintenance immunosuppression in adult patients were submitted to NICE: Astellas, Novartis and BMS.

- The analysis by Astellas compared tacrolimus (Prograf) with sirolumus CNI avoidance, sirolimus CNI minimisation, belatacept, and everolimus. In addition it presented a comparison of tacrolimus once-daily extended release (Advagraf) and two-daily immediate release (Prograf formulations).

- The study found that Prograf is cost-effective against belatacept and everolimus, but it was not cost-effective relative to the sirolimus regimens, against which it found ICERs >£100,000 per QALY. In turn, Advagraf was found to cost less and generate more QALYs than Prograf.

- The analysis by Astellas was found to be flawed due to the structure and the implementation of the model used to extrapolate short term efficacy differences between the regimens compared; that is, the model did not account for the effect of regimens on renal function, and the Markov model included errors in the way the incidence of re-transplantations was modelled

- Also, it is questionable whether the Sirolimus regimens apply to the general kidney transplant patient population modelled by Astellas

- Novartis presented the results of pairwise comparisons between everolimus (in combination with reduced dose ciclosporin and steroids) and tacrolimus or ciclosporin (each combined with MMF and steroids). In addition it presented an analysis of EC-

MPS (combined with standard dose ciclosporin and steroids) vs ciclosporin (with MMF and steroids). Outcomes were modelled over a 50-year time horizon.

- Novartis found that everolimus was cost-effective against tacrolimus and ciclosporin. However, when results accounted for uncertainty in parameter estimates, everolimus was borderline cost-effective (as evidence by the ICER against cyclosporine being in the vicinity of £30,000 per QALY).

- The analysis of MPS found it not to be cost-effective relative to cyclosporine.

- The analyses by Novartis were likely to be biased due to the lack of a systematic approach to the identification of evidence on efficacy, and also, due to the assumptions built in the model used to predict long term graft and patient survival from short term efficacy outcomes; the differences in efficacy between the regimens compared were derived from indirect comparisons of outcomes in trail arms from single studies; the model assumed that the rate of chronic rejection at 12 months post-transplant for each therapy applied throughout the modelled time horizon, independently from acute rejection and renal function outcomes.

- BMS compared belatacept with tacrolimus and ciclosporin, over a 40-year time horizon, using mixed treatment comparisons to estimate the efficacy of each regimen at 36 months. A model was then used to extrapolate from this endpoint to 40 years.

- The analyses found belatacept was not cost-effective, and the company produced additional 'subgroup analyses' by selecting a group of patients at high risk of short graft survival for which belatacept may be more economically attractive. Selecting patients in this way may be impractical in routine practice, as it is by definition outcome dependent (unknown immediately after transplant). The company also performed subgroup analysis based on patient weight; in patients with bodyweight >90kg belatacept was found to be cost-effective

- The analysis by BMS was strengthened by the use of observational data on resource utilisation data which was analysed as a function of renal function.

- Although BMS adopted the more advanced techniques to model long term graft and patient survival, including information on renal function and acute rejection in a prognostic model, its analyses were found to be biased due to the use of surrogate-

based models of patient and graft survival estimated from US data; these were found to differ from graft survival outcomes in the UK kidney transplant patient population. There were other limitations which related to how the impact on HRQoL and costs of changes in renal function were measured, as well as how the surrogate-long term outcome model was used to derive the transition probabilities in the model.

- Due to the listed limitations of the industry analyses, an independent de novo analysis is warranted which synthesises the evidence base on effectiveness outcomes and combines them with observational routinely available data on long term outcomes of UK kidney transplant patients with a decision analysis model from the NHS and personal social services perspective.

8.1.3.3. PenTAG economic assessment

Previous appraisal

The previous appraisal (TA85) considered the cost-effectiveness of basiliximab, daclizumab, [immediate-release] tacrolimus, mycophenolate mofetil and sirolimus. Briefly, the Appraisal Committee considered that:

- Basiliximab and [immediate-release] tacrolimus would likely be cost-effective (versus no induction and ciclosporin respectively)

- Mycophenolate mofetil was unlikely to be cost-effective in the general setting (versus azathioprine) but was likely to be cost-effective in settings where a reduction in ciclosporin dose is required

- Sirolimus in combination with corticosteroids should be considered as an option where proven intolerance to calcineurin inhibitors necessitates their complete withdrawal.

Update

In this update review we have a slightly different set of interventions under consideration, due to the removal of daclizumab and the addition of rabbit ATG as induction, prolonged-release tacrolimus, mycophenolate sodium, everolimus and belatacept.

We have constructed an independent economic model which incorporates current costs, evidence published since the previous appraisal and an updated surrogate relationship which additionally takes into account graft function following transplantation.

We present our principal findings for each intervention separately, summarising the findings from deterministic and probabilistic analyses and relevant scenario analyses.

Induction agents

Basiliximab

Basiliximab is predicted to be cost-effective at £20,000 to £30,000 per QALY in the deterministic analysis and the probabilistic analysis. Basiliximab was cost-effective at £20,000 per QALY in 77.2–85.6% of PSA iterations across comparisons and at £30,000 per QALY in 72.7–80.6% of iterations.

When the duration of the surrogate effect on graft survival was reduced, basiliximab gradually became less cost-effective. When in combination with ciclosporin and azathioprine, basiliximab remained cost-effective versus no induction at £20,000 and £30,000 per QALY. When followed by ciclosporin or immediate-release tacrolimus and mycophenolate mofetil, basiliximab was no longer cost-effective at £20,000 per QALY when the duration of surrogate effect was limited to zero or one year, but was cost-effective at £30,000 per QALY unless the surrogate effect was eliminated.

Adopting list prices for drug acquisition instead of average NHS acquisition costs (from the Commercial Medicines Unit eMit database) did not materially affect the cost-effectiveness of basiliximab.

Rabbit ATG

Rabbit ATG is not predicted to be cost-effective at £20,000 to £30,000 per QALY in the deterministic analysis or the probabilistic analysis. Rabbit ATG was cost-effective at £20,000 per QALY in 13.7–22.6% of PSA iterations across comparisons and at £30,000 per QALY in 19.1–27.2% of iterations.

When the duration of surrogate effect on graft survival was varied from 0 to 19 years, at no point was rabbit ATG cost-effective at £20,000 to £30,000 per QALY in any of the three comparisons.

Adopting list prices for drug acquisition instead of average NHS acquisition costs did not materially affect the cost-effectiveness of rabbit ATG.

Summary

Basiliximab is predicted to be cost-effective at £20,000 to £30,000 per QALY, whereas rabbit ATG is not.

Maintenance agents

Immediate-release tacrolimus

Immediate-release tacrolimus is predicted to be cost-effective at £20,000 to £30,000 per QALY in the deterministic and probabilistic sensitivity analyses across all comparisons. The probability of immediate-release tacrolimus being cost-effective at £20,000 and £30,000 per QALY ranged from 81.8% to 94.6%.

When the duration of surrogate effect on graft survival was reduced either immediate-release tacrolimus or ciclosporin was cost-effective at £20,000 or £30,000 per QALY. Ciclosporin was cost-effective when the surrogate effect was shorter whereas immediate-release tacrolimus was cost-effective when the surrogate effect lasted longer.

Adopting list prices instead of average NHS acquisition costs resulted in immediate-release tacrolimus no longer being cost-effective at £20,000 or £30,000 per QALY when used in combination with mycophenolate mofetil (ciclosporin was instead cost-effective) but remaining cost-effective when used in combination with azathioprine.

Prolonged-release tacrolimus

Prolonged-release tacrolimus is not predicted to be cost-effective at £20,000 or £30,000 per QALY in any analyses (including scenario analyses). The probability of prolonged-release tacrolimus being cost-effective was 0.0% at £20,000 and £30,000 per QALY.

Mycophenolate mofetil

Mycophenolate mofetil is predicted to be cost-effective at £20,000 and £30,000 per QALY in the deterministic and probabilistic analyses. The probability of mycophenolate mofetil being cost-effective at £20,000 and £30,000 per QALY ranged from 63.2% to 92.2% across comparisons.

The cost-effectiveness of mycophenolate mofetil was robust to structural scenario analyses.

Adopting list prices instead of average NHS acquisition costs resulted in mycophenolate mofetil no longer being cost-effective at £20,000 or £30,000 per QALY when used in combination with immediate-release tacrolimus (azathioprine instead was cost-effective) but remaining cost-effective when used in combination with ciclosporin.

Mycophenolate sodium

Mycophenolate sodium is not predicted to be cost-effective at £20,000 or £30,000 per QALY in any analyses (including scenario analyses). The probability of mycophenolate sodium being cost-effective was 0.1% at £20,000 per QALY and 0.8% and £30,000 per QALY.

Sirolimus

Sirolimus is not predicted to be cost-effective at £20,000 or £30,000 per QALY in the deterministic or probabilistic analyses whether in combination with immediate-release tacrolimus or in combination with basiliximab induction and mycophenolate mofetil. The probability of sirolimus being cost-effective in either combination was 0.0% at £20,000 and £30,000 per QALY.

A threshold analysis was conducted in which the gamma parameter of the Weibull distribution for death-censored graft survival was allowed to vary independently for regimens not including calcineurin inhibitors. Sirolimus was included in one of the two affected regimens (BAS+SRL+MMF). The threshold analysis indicated that there are values for gamma for which sirolimus is cost-effective at £20,000 or £30,000 per QALY, but these result in markedly different survival curves for sirolimus versus immediate-release tacrolimus, for which we are aware of no supporting high-quality evidence.

Other scenario analyses did not lead to sirolimus becoming cost-effective at £20,000 or £30,000 per QALY.

Everolimus

Everolimus is not predicted to be cost-effective at £20,000 or £30,000 per QALY in any analyses (including scenario analyses). The probability of everolimus being cost-effective was 0.0% at £20,000 and £30,000 per QALY.

Belatacept

Belatacept is not predicted to be cost-effective at £20,000 or £30,000 per QALY in the deterministic or probabilistic analyses. The probability of belatacept being cost-effective was 0.0% at £20,000 and £30,000 per QALY.

A threshold analysis was conducted in which the gamma parameter of the Weibull distribution for death-censored graft survival was allowed to vary independently for regimens not including calcineurin inhibitors. Belatacept was included in one of the two affected regimens (BAS+BEL+MMF). The threshold analysis suggested that no value of gamma would enable belatacept to be cost-effective at £20,000 or £30,000 per QALY.

Another threshold analysis was conducted to investigate the impact of the administration and acquisition costs of belatacept on cost-effectiveness. With the base case cost of administration belatacept is not cost-effective at £20,000 or £30,000 per QALY even at zero acquisition cost. With the list price for acquisition cost belatacept is similarly not cost-effective at £20,000 or £30,000 per QALY even at zero administration cost.

Other scenario analyses did not lead to belatacept being cost-effective at £20,000 or £30,000 per QALY.

Summary

Base case deterministic and probabilistic results suggest that at cost-effectiveness thresholds between £20,000 and £30,000 per QALY only basiliximab, immediate-release tacrolimus and mycophenolate mofetil are likely to be cost-effective.

When structural uncertainty about the surrogate relationship for graft survival was explored it was found that when the surrogate relationship was weakened, no induction became cost-effective instead of basiliximab and ciclosporin became cost-effective instead of immediate-release tacrolimus. Mycophenolate mofetil remained cost-effective throughout.

Another structural uncertainty analysis investigating the possibility that CNI-free regimens could prolong graft survival found that a regimen containing sirolimus could become cost-effective at £20,000 or £30,000 per QALY but required potentially implausible gains in graft survival. The analysis also found that belatacept could not become cost-effective at £20,000 or £30,000 per QALY despite the same potentially implausible gains in graft survival.

When list prices were adopted instead of average NHS acquisition costs (despite this being considered a deviation from the reference case) ciclosporin was cost-effective instead of tacrolimus in some comparisons and azathioprine was cost-effective instead of mycophenolate in some comparisons.

Pre-specified subgroup analyses were not possible based on the randomised controlled trials included in the systematic review of clinical effectiveness and therefore have not been conducted.

8.1.3.4. Comparison between PenTAG model and company models

We compared the main deterministic analyses from three of the company submissions with those produced by the independent Assessment Group (PenTAG). These assessed the cost-effectiveness of: prolonged-release tacrolimus versus immediate-release tacrolimus (Astellas), everolimus (Novartis), enteric-coated mycophenolate sodium (Novartis) and belatacept (BMS). While some of the PenTAG analyses contained a larger set of comparator treatments, they were generally comparable after dominated comparators were excluded from the PenTAG analyses.

Overall, the PenTAG analyses of cost-effectiveness were considerably less favourable than the company analyses of their own products. This could mostly be attributed to: the company analyses basing their effectiveness assumptions on the results of specific RCTs (rather than meta-analysis), combined with using different surrogate endpoints and/or US cohort data to extrapolate long-term outcomes such as graft survival.

The economic modelling by PenTAG tended to include fuller costing of the administration of the maintenance therapies, and more realistic relatively lower annual costs of dialysis (except Novartis). Also, the utility difference between living with a functioning graft and living on dialysis was generally greater in the three company's analyses (typical difference of between ~0.25 to ~0.3) than in the PenTAG model (~0.2 difference). Overall, these

differences in the company's models will tend to magnify the impact on QALYs of any incremental effectiveness differences which affect long-term graft survival, and also reduce their associated incremental cost.

8.2. Strengths and limitations

8.2.1. Systematic review of studies of effectiveness

The strengths of this systematic review are that is was conducted by an independent research team using the latest evidence.

There are a number of limitations:

- Due to level of reporting detail, we were unable to perform subgroup analysis according to donor or HLA matching.
- Study design and participant characteristics varied widely across studies, leading to substantial heterogeneity
- The 89 included RCTs were of variable quality, but all appear to be flawed. However, due to reporting omissions, for most of the trials it was difficult to make a general assessment regarding quality. The quality appraisal should, therefore, be noted with caution
- Very few trials reported longer term follow up, with the majority reporting data at one year.

8.2.2. Economic modelling by PenTAG

Strengths

- This is an analysis conducted by an independent academic group, adhering to the NICE reference case where possible
- All interventions and relevant comparators allowable are included and evaluated for cost-effectiveness (see Table 225)

Table 225. Immunosuppressive agents evaluated for cost-effectiveness in PenTAG analysis and industry submissions

Agent	PenTAG	Astellas	Bristol Myers Squibb	Novartis	TA85
Basiliximab	Y	N	N	N	Y
Rabbit ATG	Y	N	N	N	N
(No induction)	Y	N	N	N	Y
Immediate-release tacrolimus	Y	Y	Y	P	Y
Prolonged-release tacrolimus	Y	Y	N	N	N
Mycophenolate mofetil	Y	N	N	Y	Y
Mycophenolate sodium	Y	N	N	Y	N
Sirolimus	Y	Y	N	N	Y
Everolimus	Y	Y	N	Y	N
Belatacept	Y	Y	Y	N	N
Ciclosporin	Y	N	Y	P	Y
Azathioprine	Y	N	N	N	Y

Key Y, yes; N, no; P, partial

- The natural history of disease (e.g., graft survival, death with functioning graft, mortality while receiving dialysis) is based on UK data, either published by the UK Renal Registry in their annual reports or from new analyses of the UK Transplant Registry dataset

- Relative effectiveness parameters are taken directly from the results of the systematic review of clinical effectiveness when possible (including for key outcomes of graft survival, patient survival, post-transplantation graft function and acute rejection) and when not possible are synthesised from data reported in randomised controlled trials included in the systematic review

- The prognostic significance of acute rejection, post-transplantation graft function and new-onset diabetes after transplantation on outcomes is incorporated into the analysis

- 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 where available)

- Dosing of immunosuppressive agents is based on recent randomised controlled trials and for many included tapering to low levels as would be targeted in clinical practice

- A probabilistic sensitivity analysis is presented to reflect the potential impact of parameter uncertainty

- Structural uncertainty in the modelling of graft survival is addressed through scenario analyses

Limitations

- We have not modelled eGFR for regimens except at 12 months; the Novartis and Bristol Myers Squibb analyses both estimated eGFR over time and used CKD stages (defined by eGFR intervals) to drive certain costs and health-related quality of life; the Bristol Myers Squibb analysis in particular predicts significantly greater costs in more advanced CKD stages, although it is considered likely that both the absolute eGFR and the trajectory of eGFR for a patient will determine the level of monitoring and therefore the level of monitoring for CKD stage 4 patients in 24–36 months after transplantation may not be a good reflection of the level of monitoring for patients reaching CKD stage 4 much later (with a much shallower trajectory); in the absence of evidence that any agent or regimen leads to greater time in higher or lower eGFR ranges other than by extension of graft survival we consider that our model adequately incorporates the clinical importance of eGFR through the surrogate relationship with graft survival and that modelling eGFR further in the model would be rather speculative and unlikely to lead to significant differences in cost-effectiveness.

- We have not included any analysis of the cost-effectiveness of reducing or eliminating corticosteroids, although in many studies informing the model the corticosteroid dose was heavily tapered for long-term maintenance; since the cost of corticosteroids is minimal this would be very unlikely to affect cost-effectiveness results.

- We did not include NHS funded transport costs for haemodialysis, which may constitute around 10% of the total cost of haemodialysis provision; inclusion of transport costs would increase the overall cost of haemodialysis and make regimens with less time dependent on dialysis more cost-effective .

- We did not include any treatment discontinuation or switching except following graft loss; published randomised controlled trials suggest that treatment switching is usually towards immediate-release tacrolimus and mycophenolate mofetil.

- We did not differentiate between different severity of acute rejection, i.e., if any regimen results in less severe acute rejection (but no fewer) episodes this will not be reflected and the cost-effectiveness will be underestimated.

- We applied hazard ratios for graft survival based on eGFR at 12 months which were only intended for extrapolation to four years, although justifications are given for not using the hazard ratios intended for further extrapolation.

- We assumed independence of acute rejection, NODAT and eGFR at 12 months within each regimen; if, for example, patients experiencing acute rejection in the first 12 months are likely to have a lower eGFR at 12 months than patients not experiencing acute rejection then there will be second order error in the estimated hazard ratio for each regimen (in this example an overrepresentation of patients with acute rejection and high eGFR and patients without acute rejection and with low eGFR and an underrepresentation of patients with acute rejection and low eGFR and patients without acute rejection and with high eGFR); at the aggregate level acute rejection, NODAT and eGFR were estimated according to randomised controlled trials included in the systematic review and therefore correlation of these at the aggregate level across regimens would be possible and would be represented in the model.

- We did not include continuing immunosuppression following graft loss (which may happen in clinical settings).

- We combined estimates of incremental renal function between comparators based on different measurements of graft function (measured GFR, MDRD estimated GFR, Cockcroft-Gault CrCl and measured CrCl).

- We assumed that a proportional hazards model for graft survival is appropriate, where it is possible that certain regimens may result in qualitatively different survival curves, e.g., due to absence of CNI nephrotoxicity in CNI sparing regimens; we conducted a scenario analysis which demonstrated that markedly (and perhaps

implausibly) different survival curves would be required for cost-effectiveness to be demonstrated.

- We modelled de novo sirolimus with basiliximab induction and mycophenolate mofetil rather than including initial ciclosporin medication and delayed sirolimus initiation, although this may be common in clinical practice while surgical wounds heal; including delayed sirolimus initiation would slightly reduce costs and improve cost-effectiveness of the BAS+SRL+MMF regimen.

- We made no attempt to explicitly model adherence to immunosuppressive medication due to the absence of evidence on this outcome in RCTs included in the systematic review of clinical effectiveness; there is some evidence that non-adherence is a cause of late acute rejection and graft loss, but at this time any gains in clinical effectiveness owing to improved adherence attributable to any individual agent or regimen are considered to be speculative.

- It was assumed that there would be no treatment interactions between induction and maintenance therapies affecting clinical effectiveness outcomes. It is, however, known, for example, that there is a pharmacokinectic interaction between basiliximab and MMF which results in prolonged basiliximab half-life.

- Due to inconsistent reporting of adverse events in randomised controlled trials included in our systematic review only a few 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. Cardiovascular disease was included as a potential sequelae of NODAT (inpatient and non-inpatient costs and increased rate of death with functioning graft) but was not included otherwise (including as a sequelae of dyslipidaemia).

8.2.3. Economic modelling in the company submissions

8.3. Uncertainties

- Long-term outcomes from RCTs are seldom reported so it has not been possible to externally validate the predicted survival differences between regimens.

- No evidence has been identified on the influence of the induction or maintenance therpaies on HRQoL.
- RCTs identified in the systematic review have not provided evidence to support subgroup analyses.
- The costs for diabetes are highly uncertain, especially as the costs relate to the general diabetic population rather than transplant recipients with NODAT.
- 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).

9. Conclusions

The systematic review and meta-analyses of the clinical effectiveness of the two induction agents found both ATG and BAS were more effective than placebo/no induction at reducing BPAR, with ATG being more effective than BAS. However, the review found no evidence to suggest either BAS or ATG were more effective than placebo/no induction or each other in reducing the odds of graft loss or mortality.

Overall, the systematic review and meta-analyses of the clinical effectiveness of the maintenance agents found that none of the maintenance regimens were consistently better on all four outcomes: mortality, graft loss, graft function and BPAR. However, for a number of pair-wise comparisons of different regimens, the one containing TAC had lower odds of BPAR and a higher level of graft function than the other regimen.

The cost-effectiveness analyses suggest that only a regimen of basiliximab induction followed by maintenance with immediate-release tacrolimus and mycophenolate mofetil would be cost-effective at £20,000 to £30,000 per QALY.

9.1.1. Implications for service provision

The immunosuppressive regimen of basiliximab induction followed by maintenance with immediate-release tacrolimus, mycophenolate mofetil (with or without corticosteroids) is in common usage within most of the NHS at present.

If only these interventions were to be recommended then there would probably be little implication for service provision.

9.2. Suggested research priorities

New research in the following areas could reduce the uncertainty noted:

- Good quality longer term RCTs to include HRQoL as an outcome and sufficiently powered for subgroup analysis by sex, donor type, and HLA matching
- Improved reporting of trials would be beneficial, in particular, reporting of randomization methods and withdrawal, drop-outs and loss to follow-up

10. References

1. Drey N, Roderick P, Mullee M, et al. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. American Journal of Kidney Diseases 2003;**42**(4):677-84.

2. KDIGO: Kidney Disease Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation 2009;**9**:S1–S157.

3. UK Renal Registry. UK Renal Registry 16th Annual Report: Chapter 2 UK RRT Prevalence in 2012: National and Centre-specific Analyses. In: UK Renal Registry, ed.: UK Renal Registry,, 2013.

4. Merion RM, Ashby VB, Wolfe RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. Jama-Journal of the American Medical Association 2005;**294**(21):2726-33.

5. Ojo AO, Hanson JA, Meier-Kriesche HU, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. Journal of the American Society of Nephrology 2001;**12**(3):589-97.

6. Bhowmik DM, Dinda AK, Mahanta P, et al. The evolution of the Banff classification schema for diagnosing renal allograft rejection and its implications for clinicians. Indian Journal of nephrology 2010;**20**:2-8.

7. Pascual M, Theruvath T, Kawai T, et al. Medical progress - Strategies to improve long-term outcomes after renal transplantation. New England Journal of Medicine 2002;**346**:580-90.

8. Webster A, Woodroffe RC, Taylor RS, et al. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. Cochrane database of systematic reviews (Online) 2005:CD003961.

9. Butler J, Roderick P, Mullee M, et al. Frequency and impact of nonadherence to immunosuppression after renal transplantation: A systematic review. Transplantation. 2004;**77**:769-89.

10. NHS Kidney Care. Kidney Disease: Key Facts and Figures: NHS Kidney Care, 2010.

11. NHS Blood and Transplant. Annual report on kidney transplantation report for 2013/2014 (1 April 2004 - 31 March 2014): NHS Blood and Transplant, 2014.

12. NHS Blood and Transplant. Organ Donation and Transplantation. Annual Acitivity Report 2012-2013.: NHS Blood and Transplant,, 2013:140.

13. NHS Blood and Transplant. Organ Donation and Transplantation - Activity figures for the UK as at 12 April 2013: NHS Blood and Transplant,.

14. Orr A, Willis S, Holmes M, et al. Living with a kidney transplant - A qualitative investigation of quality of life. J Health Psychol 2007;**12**(4):653-62.

15. Apostolou T, Hutchison AJ, Boulton AJM, et al. Quality of life in CAPD, transplant, and chronic renal failure patients with diabetes. Renal Failure 2007;**29**:189-97.

16. Balaska A, Moustafellos P, Gourgiotis S, et al. Changes in health-related quality of life in Greek adult patients 1 year after successful renal transplantation. Experimental and Clinical Transplantation 2006;**4**:521-24.

17. Bremer BA, Mccauley CR, Wrona RM, et al. Quality of Life in End-Stage Renal-Disease - a Reexamination. American Journal of Kidney Diseases 1989;**13**(3):200-09.

18. Dale PL, Hutton J, Elgazzar H. Utility of health states in chronic kidney disease: A structured review of the literature. Current Medical Research and Opinion 2008;**24**:193-206.

19. Evans RW, Manninen DL, Garrison LP, et al. The Quality of Life of Patients with End-Stage Renal-Disease. New England Journal of Medicine 1985;**312**(9):553-59.

20. Morris PLP, Jones B. Transplantation Versus Dialysis - a Study of Quality of Life. Transplantation Proceedings 1988;**20**(1):23-26.

21. Morris PLP, Jones B. Life Satisfaction across Treatment Methods for Patients with End-Stage Renal-Failure. Med J Australia 1989;**150**(8):428-32.

22. Nourbala MH, Hollisaaz MT, Nasiri M, et al. Pain Affects Health-Related Quality of Life in Kidney Transplant Recipients. Transplantation Proceedings 2007;**39**:1126-29.

23. Seedat YK, Macintosh CG, Subban JV. Quality-of-Life for Patients in an End-Stage Renal-Disease Program. S Afr Med J 1987;**71**(8):500-04.

24. Simmons RG, Anderson CR, Abress LK. Quality-of-Life and Rehabilitation Differences among 4 End-Stage Renal-Disease Therapy Groups. Scandinavian Journal of Urology and Nephrology 1990:7-22.

25. Sureshkumar KK, Patel BM, Markatos A, et al. Quality of life after organ transplantation in type 1 diabetics with end-stage renal disease. Clinical Transplantation 2006;**20**:19-25.

26. Overbeck I, Bartels M, Decker O, et al. Changes in quality of life after renal transplantation. Transplantation Proceedings 2005;**37**:1618-21.

27. Yildirim A. The importance of patient satisfaction and health-related quality of life after renal transplantation. Transplantation Proceedings 2006;**38**(9):2831-34.

28. The British Transplantation Society. Management of the failing kidney transplant: The British Transplantation Society, 2013.

29. Lamping DL, Constantinovici N, Roderick P, et al. Clinical outcomes, quality of life, and costs in the North Thames Dialysis Study of elderly people on dialysis: a prospective cohort study. Lancet 2000;**356**(9241):1543-50.

30. Bakewell AB, Higgins RM, Edmunds ME. Quality of life in peritoneal dialysis patients: Decline over time and association with clinical outcomes. Kidney International 2002;**61**(1):239-48.

31. Ardine de Wit G, Ramsteijn PG, Charro FT. Economic evaluation of end stage renal disease treatment (Structured abstract). NHS Economic Evaluation Database (NHSEED) 1998; (3). http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-21998008203/frame.html.

32. UK Renal Registry. UK Renal Registry 17th Annual Report: Appendix C Renal Services Descried for Non-Physicians: UK Renal Registry,, 2014.

33. NHS England. NHS Standard contract for adult kidney transplant service NHS England,, 2013.

34. White C A HD, Akbari A, Garland J, Knoll G A. Performance of creatinine-based estimates of GFR in kidney transplant recipients: a systematic review American Journal of Kidney Diseases 2008;**51**(6):1005-15.

35. Department of Health. The National Service Framework for Renal Services. Part one: Dialysis and Transplantation, 2004.

36. Su XM, Zenios SA, Chakkera H, et al. Diminishing significance of HLA matching in kidney transplantation. American Journal of Transplantation 2004;**4**(9):1501-08.

37. Trebern-Launay K, Foucher Y, Giral M, et al. Poor Long-Term Outcome in Second Kidney Transplantation: A Delayed Event. Plos One 2012;**7**(10).

38. Redfield RR GM, Rodriguez E, Wood A, Abt PL, Levine MH. Graft and patient survival outcomes of a third kidney transplant. Transplantation 2015;**99**(2):416-23.

39. Kerr M, Bray B, Medcalf J, et al. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrology Dialysis Transplantation 2012;**27**:73-80.

40. Baker R, Jardine A, Andrews P. Renal Association Clinical Practice Guideline on Post-operative Care of the Kidney Transplant Recipient. Nephron Clinical Practice 2011;**118**:C311-C47.

41. Chamberlain G, Baboolal K, Bennett H, et al. The Economic Burden of Posttransplant Events in Renal Transplant Recipients in Europe. Transplantation 2014;**97**(8):854-61.

42. National Institute for Health and Care Excellence. Renal transplantation - immuno-suppressive regimens (adults) (TA85). London: NICE, 2004.

43. Gordon EJ, Ladner DP, Caicedo JC, et al. Disparities in Kidney Transplant Outcomes: A Review. Seminars in Nephrology 2010;**30**(1):81-89.

44. Meier-Kriesche HU, Port FK, Ojo AO, et al. Effect of waiting time on renal transplant outcome. Kidney International 2000;**58**(3):1311-17.

45. Metzger RA, Delmonico FL, Feng S, et al. Expanded criteria donors for kidney transplantation. American Journal of Transplantation 2003;**3**:114-25.

46. Wu C, Evans I, Joseph R, et al. Comorbid conditions in kidney transplantation: Association with graft and patient survival. Journal of the American Society of Nephrology 2005;**16**(11):3437-44.

47. Laftavi MR, Patel SK, Feng L, et al. African American (AA) renal transplant recipients (RTR) require higher tacrolimus (TAC) doses to achieve target levels compared to white (W) RTR: Does clotrimazole help? American Journal of Transplantation 2012;**12**:299-300.

48. Neylan JF. Immunosuppressive therapy in high-risk transplant patients - Dose-dependent efficacy of mycophenolate mofetil in African-American renal allograft recipients. Transplantation 1997;**64**(9):1277-82.

49. Neylan J. Effect of race on efficacy and safety of sirolimus vs azathioprine +standard immunotherapy in renal transplantation. Transplantation 1999;**67**:S237A.

50. Nottingham University Hospitals NHS Trust. Kidney Transplant Protocol. Secondary Kidney Transplant Protocol 2013.
https://www.nuh.nhs.uk/handlers/downloads.ashx?id=40176.

51. Muthusamya ASRV, A. C. Sinhaa, S. Roya, D. Elkera, D. E. Frienda, P. J. Alemtuzumab induction and steroid-free maintenance immunosuppression in pancreas transplantation. American Journal of Transplantation 2008;**8**:2126-31.

52. Royal Infirmary of Edinburgh. EdRen Handbook: Renal Transplant protocols. Secondary EdRen Handbook: Renal Transplant protocols 2007.
http://renux.dmed.ed.ac.uk/edren/intranet/TPHdbkFeb07.pdf.

53. Krämer BK, Klinger M, Wlodarczyk Z, et al. Tacrolimus combined with two different corticosteroid-free regimens compared with a standard triple regimen in renal transplantation: one year observational results. Clinical Transplantation 2010; 24(1).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/321/CN-00762321/frame.html.

54. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). American Journal of Transplantation 2010; 10(3).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/173/CN-00761173/frame.html.

55. Larsen CP, Grinyo J, Medina-Pestana J, et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. Transplantation 2010; 90(12).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/418/CN-00782418/frame.html.

56. Vincenti F, Larsen CP, Alberu J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. American Journal of Transplantation 2012; 12(1).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/516/CN-00814516/frame.html.

57. Rostaing L, Vincenti F, Grinyo J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: Results from the long-term extension of the BENEFIT study. American Journal of Transplantation 2013; 13(11).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/073/CN-00909073/frame.html.

58. Bristol Myers Squibb. Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85); Belatacept submission of evidence, 2014.

59. Department of Health. NHS reference costs 2013 to 2014: Department of Health, 2014.

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

61. NHS Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in healthcare*. York, 2009.

62. Dias SW, N. Sutton, A. Ades, A. NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and netwrok meta-analysis of randomised controlled trials. In: National Institute for Health Care Excellence Decision Support Unit, ed. London: NICE, 2011.

63. Dias SW, N. Sutton, A. Caldwell, D. Lu, G. Ades, A. NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials. . In: National Institute for Health Care Excellence Decision Support Unit, ed. London: NICE, 2011.

64. Ades AC, D. Reken, S. Welton, N. Sutton, A. Dias, S. NICE DSU Technical Support Document 7: Evidence synthesis of treatment efficacy in decision making: A reviewer's checklist. In: National Institute for Health Care Excellence Decision Support Unit, ed. London: NICE, 2012.

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

66. Nashan B, Moore R, Amlot P, et al. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. Lancet 1997;**350**(9086):1193-8.

67. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. Transplantation 1999;**67**(2):276-84.

68. Ponticelli C, Yussim A, Cambi V, et al. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. Transplantation 2001;**72**(7):1261-7.

69. Lawen JG, Davies EA, Mourad G, et al. Randomized double-blind study of immunoprophylaxis with basiliekimab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. Transplantation 2003;**75**:37-43.

70. Salvadori M. Long term administration of enteric-coated mycophenolate sodium (EC-MPS, myfortic) is safe in kidney transplant patients. [abstract no: P194]. Transplantation 2004; 78(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/132/CN-00583132/frame.html.

71. Vincenti F, Larsen C, Durrbach A, et al. Costimulation blockade with belatacept in renal transplantation. New England Journal of Medicine 2005; 353(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/045/CN-00524045/frame.html.

72. Krämer BK, Charpentier B, Bäckman L, et al. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. American Journal of Transplantation 2010;**10**(12):2632-43.

73. van Duijnhoven EM, Christiaans MH, Boots JM, et al. Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus versus cyclosporine-based immunosuppression. J Am Soc Nephrol 2002;**13**(1):213-20.

74. Waller JR, Murphy GJ, Metcalfe MS, et al. Primary immunosuppression with tacrolimus is associated with a reduction in renal allograft fibrosis compared with neoral therapy. Transplantation Proceedings 2002;**34**:1587-8.

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

76. Tuncer M, Gürkan A, Erdo?an O, et al. Mycophenolate mofetil in renal transplantation: five years experience. Transplantation proceedings 2002; 34(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/123/CN-00422123/frame.html.

77. Soleimani AR, Kamkar I, Nikoueinejad H, et al. Comparison of Cyclosporine and Sirolimus Effects on Serum Creatinine Level Over Five Years After Kidney Transplantation. Transplantation Proceedings 2013;**45**:1644-47.

78. Schaefer HM, Kizilisik AT, Feurer I, et al. Short-term results under three different immunosuppressive regimens at one center. Transplantation Proceedings 2006; 38(10). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/343/CN-00577343/frame.html.

79. Smith MP, Newstead CG, Ahmad N, et al. Poor tolerance of sirolimus in a steroid avoidance regimen for renal transplantation. Transplantation 2008; 85(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/404/CN-00638404/frame.html.

80. Vitko S, Wlodarczyk Z, Kyllönen L, et al. Tacrolimus combined with two different dosages of sirolimus in kidney transplantation: results of a multicenter study. American journal of transplantation 2006; 6(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/545/CN-00562545/frame.html.

81. Bingyi S, Yeyong Q, Ming C, et al. Randomised trial of simulect versus placebo for control of acute rejection in renal allograft recipients. Transplantation Proceedings 2003;**35**:192-4.

82. Charpentier B. Induction versus noninduction protocols in anti-calcineurin-based immunosuppression. Transplantation Proceedings 2001;**33**(7–8):3334-36.

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

84. Samsel R, Pliszczy?ski J, Chmura A, et al. Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients--long term results. Annals of Transplantation 2008; 13(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/384/CN-00638384/frame.html.

85. Sheashaa HA, Hamdy AF, Bakr MA, et al. Long-term evaluation of single bolus high dose ATG induction therapy for prophylaxis of rejection in live donor kidney transplantation. International Urology and Nephrology 2008; 40(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/302/CN-00647302/frame.html.

86. Kyllönen LE, Eklund BH, Pesonen EJ, et al. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. Transplantation 2007; 84(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/081/CN-00707081/frame.html.

87. Albano L, Banas B, Klempnauer JL, et al. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. Transplantation 2013; 96(10). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/107/CN-00959107/frame.html.

88. Charpentier B, Rostaing L, Berthoux F, et al. 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 2003;**75**:844-51.

89. Brennan DC, Daller JA, Lake KD, et al. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. New England Journal of Medicine 2006; 355(19). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/547/CN-00573547/frame.html.

90. Lebranchu Y, Bridoux F, Buchler M, et al. Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. American Journal of Transplantation 2002;**2**:48-56.

91. Mourad G, Rostaing L, Legendre C. Assessment of two strategies of neoral® administration, early versus delayed, on renal function and efficacy in de novo renal transplant patients receiving myfortic®, steroids and anti-il2r antibodies: 6 months interim results. [abstract]. Transplantation 2004; 78(2 Suppl). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/366/CN-00509366/frame.html.

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

93. Schleibner S, Krauss M, Wagner K, et al. FK 506 versus cyclosporin in the prevention of renal allograft rejection — European pilot study: six-week results. Transplant International 1995;**8**(2):86-90.

94. Laskow DA, Vincenti F, Neylan JF, et al. An open-label, concentration-ranging trial of FK506 in primary kidney transplantation: a report of the United States Multicenter FK506 Kidney Transplant Group. Transplantation 1996;**62**(7):900-5.

95. Vincenti F, Laskow DA, Neylan JF, et al. One-year follow-up of an open-label trial of FK506 for primary kidney transplantation. A report of the U.S. Multicenter FK506 Kidney Transplant Group. Transplantation 1996;**61**(11):1576-81.

96. Mayer AD, Dmitrewski J, Squifflet JP, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. Transplantation 1997;**64**(3):436-43.

97. Mayer AD. Four-year follow-up of the European Tacrolimus Multicenter Renal Study. Transplantation Proceedings 1999;**31**(7):27-28.

98. Mayer AD. Chronic rejection and graft half-life: five-year follow-up of the European Tacrolimus Multicenter Renal Study. Transplantation Proceedings 2002;**34**:1491-2.

99. Radermacher J, Meiners M, Bramlage C, et al. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. Transplant international : official journal of the European Society for Organ Transplantation 1998;**11**(1):3-10.

100. Jarzembowski T, Panaro F, Raofi V, et al. Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant. Transplant International 2005; 18(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/538/CN-00513538/frame.html.

101. Baboolal K, Jones GA, Janezic A, et al. Molecular and structural consequences of early renal allograft injury. Kidney International 2002;**61**:686-96.

102. Campos HH, Abbud Filho M. One-year follow-up of a Brazilian randomized multicenter study comparing tacrolimus versus cyclosporine in kidney transplantation. Transplantation proceedings 2002; 34(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/858/CN-00406858/frame.html.

103. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: A randomised multicentre study. Lancet 2002;**359**:741-46.

104. Krämer BK, Montagnino G, Castillo D, et al. Efficacy and safety of tacrolimus compared with cyclosporin A microemulsion in renal transplantation: 2 year follow-up results. Nephrology, dialysis, transplantation 2005; 20(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/990/CN-00512990/frame.html.

105. Kramer BK, Castillo D, Margreiter R, et al. Efficacy and safety of tacrolimus compared with ciclosporin A in renal transplantation: three-year observational results. Nephrology Dialysis Transplantation 2008; 23(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/820/CN-00653820/frame.html.

106. Murphy GJ, Waller JR, Sandford RS, et al. Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. British Journal of Surgery 2003;**90**:680-6.

107. Töz H, Sen S, Sezi M, et al. Comparison of tacrolimus and cyclosporin in renal transplantation by the protocol biopsies. Transplantation proceedings 2004; 36(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/115/CN-00489115/frame.html.

108. Hardinger KL, Bohl DL, Schnitzler MA, et al. A randomized, prospective, pharmacoeconomic trial of tacrolimus versus cyclosporine in combination with thymoglobulin in renal transplant recipients. Transplantation 2005; 80(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/065/CN-00523065/frame.html.

109. Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. American Journal of

Transplantation 2005; 5(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/723/CN-00513723/frame.html.

110. The Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomised clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. Transplantation 1996;**61**(7):1029 - 37.

111. Mathew T. A blinded, long-term, randomized multicentre study of mycophenolate mofetil in cadaveric renal transplantation: Results at three years. Transplantation 1998;**65**(11):1450-54.

112. Clayton PA, McDonald SP, Chapman JR, et al. Mycophenolate versus azathioprine for kidney transplantation: a 15-year follow-up of a randomized trial. Transplantation 2012; 94(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/737/CN-00859737/frame.html.

113. Sadek S, Medina J, Arias M, et al. Short-term combination of mycophenolate mofetil with cyclosporine as a therapeutic option for renal transplant recipients: A prospective, multicenter, randomized study. Transplantation 2002;**74**:511-17.

114. Merville P, Berge F, Deminiere C, et al. Lower incidence of chronic allograft nephropathy at 1 year post-transplantation in patients treated with mycophenolate mofetil. American Journal of Transplantation 2004;**4**:1769-75.

115. Remuzzi G, Cravedi P, Costantini M, et al. Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. Journal of the American Society of Nephrology : JASN 2007; 18(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/948/CN-00617948/frame.html.

116. Remuzzi G, Lesti M, Gotti E, et al. Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. Lancet 2004;**364**:503-12.

117. Wlodarczyk Z, Walaszewski J, Perner F, et al. Steroid withdrawal at 3 months after kidney transplantation: a comparison of two tacrolimus-based regimens. Transplant International 2005; 18(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/779/CN-00513779/frame.html.

118. Wlodarczyk Z, Walaszewski J, Perner F, et al. Freedom from rejection and stable kidney function are excellent criteria for steroid withdrawal in tacrolimus-treated kidney transplant recipients. Annals of Transplantation 2002;**7**:28-31.

119. Vacher-Coponat H, Moal V, Indreies M, et al. A randomized trial with steroids and antithymocyte globulins comparing cyclosporine/azathioprine versus tacrolimus/mycophenolate mofetil (CATM2) in renal transplantation. Transplantation 2012; 93(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/336/CN-00860336/frame.html.

120. Zadrazil J, Horak P, Strebl P, et al. 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. Biomedical papers of the Medical

Faculty of the University Palacký, Olomouc, Czechoslovakia 2012; 156(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/320/CN-00880320/frame.html.

121. Hernández D, Miquel R, Porrini E, et al. Randomized controlled study comparing reduced calcineurin inhibitors exposure versus standard cyclosporine-based immunosuppression. Transplantation 2007; 84(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/221/CN-00612221/frame.html.

122. Rowshani AT, Scholten EM, Bemelman F, et al. No difference in degree of interstitial Sirius red-stained area in serial biopsies from area under concentration-over-time curves-guided cyclosporine versus tacrolimus-treated renal transplant recipients at one year. Journal of the American Society of Nephrology : JASN 2006; 17(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/558/CN-00561558/frame.html.

123. Yang HC, Holman MJ, Langhoff E, et al. Tacrolimus/"low-dose" mycophenolate mofetil versus microemulsion cyclosporine/"low-dose" mycophenolate mofetil after kidney transplantation--1-year follow-up of a prospective, randomized clinical trial. Transplant Proc 1999;**31**(1-2):1121-4.

124. Ulsh PJ, Yang HC, Holman MJ, et al. New strategies using 'low-dose' mycophenolate mofetil to reduce acute rejection in patients following kidney transplantation. Journal of transplant coordination : official publication of the North American Transplant Coordinators Organization (NATCO) 1999;**9**(2):114-8.

125. Weimer R, Susal C, Yildiz S, et al. Post-transplant sCD30 and neopterin as predictors of chronic allograft nephropathy: Impact of different immunosuppressive regimens. American Journal of Transplantation 2006;**6**:1865-74.

126. Weimer R, Susal C, Yildiz S, et al. sCD30 and neopterin as risk factors of chronic renal transplant rejection: impact of cyclosporine A, tacrolimus, and mycophenolate mofetil. Transplantation Proceedings 2005; 37(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/732/CN-00550732/frame.html.

127. Wlodarczyk Z, Squifflet JP, Ostrowski M, et al. Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial. American Journal of Transplantation 2009; 9(11). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/422/CN-00734422/frame.html.

128. Tsuchiya T, Ishida H, Tanabe T, et al. Comparison of pharmacokinetics and pathology for low-dose tacrolimus once-daily and twice-daily in living kidney transplantation: prospective trial in once-daily versus twice-daily tacrolimus. Transplantation 2013; 96(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/158/CN-00874158/frame.html.

129. Oh CH, K. H. Lee, J. S. Cho, H. R. Kim, Y.S. Safety and Efficacy of Conversion from Twice-Daily Tacrolimus to Once-Daily Tacrolimus One Month after Transplantation: Randomized Controlled Trial in Adult Renal Transplantation. Yonsei Medical Journal 2014;**55**:1341-47.

130. Ciancio G, Burke GW, Gaynor JJ, et al. Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplant recipients given tacrolimus and daclizumab/thymoglobulin: one year follow-up. Transplantation 2008; 86(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/609/CN-00640609/frame.html.

131. Ciancio G, Gaynor JJ, Zarak A, et al. Randomized trial of mycophenolate mofetil versus enteric-coated mycophenolate sodium in primary renal transplantation with tacrolimus and steroid avoidance: four-year analysis. Transplantation 2011; 91(11). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/087/CN-00787087/frame.html.

132. Salvadori M, Holzer H, De Mattos A, et al. Enteric-Coated Mycophenolate Sodium is Therapeutically Equivalent to Mycophenolate Mofetil in de novo Renal Transplant Patients. American Journal of Transplantation 2004;**4**:231-36.

133. Vincenti F. Costimulation blockade with belatacept in renal transplantation - Reply. New England Journal of Medicine 2005;**353**:2086-86.

134. Vincenti F, Blancho G, Durrbach A, et al. Five-year safety and efficacy of belatacept in renal transplantation. Journal of the American Society of Nephrology : JASN 2010;**21**(9):1587-96.

135. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). American Journal of Transplantation 2010; 10(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/172/CN-00761172/frame.html.

136. Pestana JO, Grinyo JM, Vanrenterghem Y, et al. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. American Journal of Transplantation 2012; 12(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/889/CN-00832889/frame.html.

137. Charpentier B, Medina Pestana JO, M CR, et al. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. American Journal of Transplantation 2013; 13(11). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/070/CN-00909070/frame.html.

138. Ferguson R, Grinyó J, Vincenti F, et al. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. American Journal of Transplantation 2011; 11(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/567/CN-00779567/frame.html.

139. Lorber MI, Mulgaonkar S, Butt KM, et al. Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. Transplantation 2005; 80(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/431/CN-00523431/frame.html.

140. Vítko S, Klinger M, Salmela K, et al. Two corticosteroid-free regimens-tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil-in comparison with a standard triple regimen in renal transplantation: results of the Atlas study. Transplantation 2005; 80(12). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/602/CN-00532602/frame.html.

141. Vitko S, Margreiter R, Weimar W, et al. Everolimus (certican) 12-month safety and efficacy versus mycophenolate mofetil in de Novo renal transplant recipients. Transplantation 2004;**78**:1532-40.

142. Vítko S, Margreiter R, Weimar W, et al. Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients.

American Journal of Transplantation 2005; 5(10). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/189/CN-00530189/frame.html.

143. Takahashi K, Uchida K, Yoshimura N, et al. Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. Transplantation Research 2013; 2(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/417/CN-00960417/frame.html.

144. Chadban S, Eris J, Russ G, et al. Enteric-coated mycophenolate sodium in combination with full dose or reduced dose cyclosporine, basiliximab and corticosteroids in Australian de novo kidney transplant patients. Nephrology (Carlton, Vic) 2013; 18(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/388/CN-00878388/frame.html.

145. Tedesco-Silva H, Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. American Journal of Transplantation 2010;**10**(6):1401-13.

146. Bertoni E, Larti A, Rosso G, et al. Good outcomes with cyclosporine very low exposure with everolimus high exposure in renal transplant patients. Journal of Nephrology 2011; 24(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/785/CN-00812785/frame.html.

147. Budde K, Becker T, Arns W. 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 2011;**377**:2006.

148. Budde K, Lehner F, Sommerer C, et al. Conversion from cyclosporine to everolimus at 4.5 months posttransplant: 3-year results from the randomized ZEUS study. American Journal of Transplantation 2012; 12(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/333/CN-00840333/frame.html.

149. Liefeldt L, Brakemeier S, Glander P, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. American Journal of Transplantation 2012; 12(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/495/CN-00836495/frame.html.

150. Mjörnstedt L, Sørensen SS, Zur Mühlen B, et al. Improved renal function after early conversion from a calcineurin inhibitor to everolimus: a randomized trial in kidney transplantation. American Journal of Transplantation 2012; 12(10). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/549/CN-00879549/frame.html.

151. Barsoum RS, Morsey AA, Iskander IR, et al. The Cairo kidney center protocol for rapamycin-based sequential immunosuppression in kidney transplant recipients: 2-year outcomes. Experimental and Clinical Transplantation 2007; 5(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/551/CN-00647551/frame.html.

152. Stallone G, Di Paolo S, Schena A, et al. Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. Journal of the American Society of Nephrology 2004;**15**:228-33.

153. Anil Kumar MS, Heifets M, Fyfe B, et al. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney

transplantation monitored by surveillance biopsy. Transplantation 2005; 80(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/341/CN-00583341/frame.html.

154. Mendez R, Gonwa T, Yang HC, et al. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 1 year. Transplantation 2005; 80(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/678/CN-00523678/frame.html.

155. Gonwa T, Mendez R, Yang HC, et al. Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: Results at 6 months. Transplantation 2003;**75**:1213-20.

156. Sampaio EL, Pinheiro-Machado PG, Garcia R, et al. Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen. Clinical Transplantation 2008; 22(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/808/CN-00630808/frame.html.

157. Gelens MA, Christiaans MH, Heurn EL, et al. High rejection rate during calcineurin inhibitor-free and early steroid withdrawal immunosuppression in renal transplantation. Transplantation 2006; 82(9). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/689/CN-00573689/frame.html.

158. Gallon L, Perico N, Dimitrov BD, et al. Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression comparing sirolimus vs. MMF. American Journal of Transplantation 2006; 6(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/092/CN-00571092/frame.html.

159. Chhabra D, Skaro AI, Leventhal JR, et al. Long-term kidney allograft function and survival in prednisone-free regimens: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. Clinical Journal of the American Society of Nephrology 2012; 7(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/793/CN-00842793/frame.html.

160. Van Gurp E, Bustamante J, Franco A, et al. Comparable Renal Function at 6 Months with Tacrolimus Combined with Fixed-Dose Sirolimus or MMF: Results of a Randomized Multicenter Trial in Renal Transplantation. Journal of transplantation 2010.

161. Noris M, Casiraghi F, Todeschini M, et al. Regulatory T cells and T cell depletion: role of immunosuppressive drugs. Journal of the American Society of Nephrology : JASN 2007; 18(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/313/CN-00644313/frame.html.

162. Ruggenenti P, Perico N, Gotti E, et al. Sirolimus versus cyclosporine therapy increases circulating regulatory T cells, but does not protect renal transplant patients given alemtuzumab induction from chronic allograft injury. Transplantation 2007; 84(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/798/CN-00620798/frame.html.

163. Lebranchu Y, Thierry A, Toupance O, et al. Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. American Journal of Transplantation 2009; 9(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/174/CN-00703174/frame.html.

164. Servais A, Meas-Yedid V, Toupance O, et al. Interstitial fibrosis quantification in renal transplant recipients randomized to continue cyclosporine or convert to sirolimus. American

Journal of Transplantation 2009; 9(11).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/262/CN-00730262/frame.html.

165. Lebranchu Y, Thierry A, Thervet E, et al. Efficacy and safety of early cyclosporine conversion to sirolimus with continued MMF-four-year results of the Postconcept study. American Journal of Transplantation 2011; 11(8).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/413/CN-00810413/frame.html.

166. Joannidès R, Monteil C, Ligny BH, et al. Immunosuppressant regimen based on sirolimus decreases aortic stiffness in renal transplant recipients in comparison to cyclosporine. American Journal of Transplantation 2011; 11(11).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/301/CN-00814301/frame.html.

167. Büchler M, Caillard S, Barbier S, et al. Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin, mycophenolate mofetil and a 6-month course of steroids. American journal of transplantation 2007; 7(11).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/369/CN-00619369/frame.html.

168. Lebranchu Y, Snanoudj R, Toupance O, et al. Five-year results of a randomized trial comparing De Novo sirolimus and cyclosporine in renal transplantation: The Spiesser study. American Journal of Transplantation 2012; 12(7).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/309/CN-00904309/frame.html.

169. Joannides R, Etienne I, Iacob M, et al. Comparative effects of sirolimus and cyclosporin on conduit arteries endothelial function in kidney recipients. Transplant International 2010; 23(11). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/160/CN-00792160/frame.html.

170. Durrbach A, Rostaing L, Tricot L, et al. Prospective comparison of the use of sirolimus and cyclosporine in recipients of a kidney from an expanded criteria donor. Transplantation 2008; 85(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/408/CN-00630408/frame.html.

171. Kreis HC, J. Land, W. Wramner, L. Squifflet, J. Abramawicz, D. . Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejectionin renal allograft recipients. Transplantation 2000;**69**(1252-1260).

172. Campistol JM, Holt DW, Epstein S, et al. Bone metabolism in renal transplant patients treated with cyclosporine or sirolimus. Transplant International 2005; 18(9).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/888/CN-00523888/frame.html.

173. Guba M, Pratschke J, Hugo C, et al. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: one-year analysis of a randomized multicenter trial. Transplantation 2010; 90(2).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/462/CN-00751462/frame.html.

174. Martinez-Mier G, Mendez-Lopez MT, Budar-Fernandez LF, et al. Living related kidney transplantation without calcineurin inhibitors: initial experience in a Mexican center. Transplantation 2006; 82(11).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/280/CN-00577280/frame.html.

175. Nafar M, Alipour B, Ahmadpoor P, et al. Sirolimus versus calcineurin inhibitor-based immunosuppressive therapy in kidney transplantation: a 4-year follow-up. Iranian Journal of Kidney Diseases 2012; 6(4).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/600/CN-00879600/frame.html.

176. Larsen C, Alberu J, Massari P, et al. 4-Year results from the long-term extension of the belatacept BENEFIT study. American Journal of Transplantation 2012;**12**:82.

177. Stegall MD, Larson TS, Prieto M, et al. Kidney transplantation without calcineurin inhibitors using sirolimus. Transplantation Proceedings 2003;**35**:125S-27S.

178. Heilman RL, Younan K, Wadei HM, et al. Results of a prospective randomized trial of sirolimus conversion in kidney transplant recipients on early corticosteroid withdrawal. Transplantation 2011; 92(7).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/585/CN-00810585/frame.html.

179. Heilman RL, Cortese C, Geiger XJ, et al. Impact of early conversion from tacrolimus to sirolimus on chronic allograft changes in kidney recipients on rapid steroid withdrawal. Transplantation 2012; 93(1).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/082/CN-00882082/frame.html.

180. Silva Jr HT, Felipe CR, Garcia VD, et al. Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. American Journal of Transplantation 2013;**13**:3155-63.

181. Hamdy AF, El-Agroudy AE, Bakr MA, et al. Comparison of sirolimus with low-dose tacrolimus versus sirolimus-based calcineurin inhibitor-free regimen in live donor renal transplantation. American Journal of Transplantation 2005; 5(10).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/190/CN-00530190/frame.html.

182. Hamdy AF, Bakr MA, Ghoneim MA. Long-term efficacy and safety of a calcineurin inhibitor-free regimen in live-donor renal transplant recipients. Journal of the American Society of Nephrology : JASN 2008; 19(6).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/312/CN-00638312/frame.html.

183. Hamdy AF, Bakr MA, Ghoneim MA. Proteinuria among primarily sirolimus treated live-donor renal transplant recipients' long-term experience. Experimental and Clinical Transplantation 2010; 8(4).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/967/CN-00783967/frame.html.

184. Charpentier B, Groth CG, Bäckman L, et al. Bicêtre hospital experience with sirolimus-based therapy in human renal transplantation: the Sirolimus European Renal Transplant Study. Transplantation proceedings 2003; 35(3 Suppl).
http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/744/CN-00456744/frame.html.

185. Groth CG, Backman L, Morales JM, et al. Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation 1999;**67**(7):1036-42.

186. Chen KH, Tsai MK, Lai IR, et al. Favorable results of concomitant tacrolimus and sirolimus therapy in Taiwanese renal transplant recipients at 12 months. Journal of the

Formosan Medical Association / Taiwan yi zhi 2008; 107(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/776/CN-00649776/frame.html.

187. Flechner SM, Glyda M, Cockfield S, et al. The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. American Journal of Transplantation 2011; 11(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/540/CN-00796540/frame.html.

188. Grinyo JM, Ekberg H, Mamelok RD, et al. The pharmacokinetics of mycophenolate mofetil in renal transplant recipients receiving standard-dose or low-dose cyclosporine, low-dose tacrolimus or low-dose sirolimus: the Symphony pharmacokinetic substudy. Nephrology Dialysis Transplantation 2009; 24(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/043/CN-00716043/frame.html.

189. Ekberg H, Mamelok RD, Pearson TC, et al. The challenge of achieving target drug concentrations in clinical trials: Experience from the symphony study. Transplantation 2009;**87**:1360-66.

190. Demirbas A, Hugo C, Grinyó J, et al. Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study. Transplant International 2009; 22(12). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/379/CN-00728379/frame.html.

191. Ekberg H, Bernasconi C, Nöldeke J, et al. Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphony study. Nephrology, dialysis, transplantation 2010; 25(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/872/CN-00759872/frame.html.

192. Frei U, Daloze P, Vítko S, et al. Acute rejection in low-toxicity regimens: clinical impact and risk factors in the Symphony study. Clinical Transplantation 2010; 24(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/943/CN-00772943/frame.html.

193. Claes K, Meier-Kriesche HU, Schold JD, et al. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. Nephrology, dialysis, transplantation 2012; 27(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/863/CN-00860863/frame.html.

194. Anil Kumar MS, Irfan Saeed M, Ranganna K, et al. Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. Transplant Immunology 2008; 20(1-2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/129/CN-00684129/frame.html.

195. Chadban SJ, Eris JM, Kanellis J, et al. A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. Transplant International 2014;**27**:302-11.

196. Cochrane C. *Cochrane handbook for Systematic Reviews of Interventions*. Wst Sussex, England: John Wiley & Sons Ltd, 2008.

197. Yao G, Albon E, Adi Y, et al. A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children (Structured abstract). Health Technology Assessment Database 2006; (1). http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32007000021/frame.html.

198. Cochrane Collaboration. *Cochrane handbook for Systematic Reviews of Interventions*. Wst Sussex, England: John Wiley & Sons Ltd, 2008.

199. Mourad G, Rostaing L, Legendre C, et al. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. Transplantation 2004;**78**:584-90.

200. Clayton P, McDonald S, Chapman J, et al. Mycophenolate vs azathioprine for kidney transplantation: 15 year follow-up of a randomized trial. Nephrology 2011;**16**:69.

201. Kumar N, Manimaran R, Williams C, et al. Tacrolimus preserves renal function better than cyclosporin at 10 years - long term results of a randomised controlled trial. American Journal of Transplantation 2009;**9**:200.

202. Kramer BK. Better tolerability and significantly higher freedom from acute rejection at 7 years with tacrolimus vs. cyclosporine-based immunosuppression in renal transplant recipients. NDT Plus 2010;**3**:iii284.

203. Durrbach A, Larsen CP, Medina Pestana J, et al. Belatacept vs cyclosporine in ECD kidney transplants: Two-year outcomes from the BENEFIT-EXT study. NDT Plus 2010;**3**:iii262.

204. Stallone G, Di Paolo S, Schena A, et al. Early withdrawal of cyclosporine A improves 1-year kidney graft structure and function in sirolimus-treated patients. Transplantation 2003;**75**:998-1003.

205. Flechner SM, Goldfarb D, Modlin C, et al. Kidney transplantation without calcineurin inhibitor drugs: A prospective, randomized trial of sirolimus versus cyclosporin. Transplantation 2002;**74**:1070-76.

206. Kreis H, Cisterne JM, Land W, et al. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 2000;**69**(7):1252-60.

207. Flechner SM, Friend PJ, Brockmann J, et al. Alemtuzumab induction and sirolimus plus mycophenolate mofetil maintenance for CNI and steroid-free kidney transplant immunosuppression. American Journal of Transplantation 2005;**5**:3009-14.

208. Mahe E, Morelon E, Lechaton S, et al. Acne in recipients of renal transplantation treated with sirolimus: Clinical, microbiologic, histologic, therapeutic, and pathogenic aspects. Journal of the American Academy of Dermatology 2006;**55**:139-42.

209. Larson TS, Dean PG, Stegall MD, et al. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. American Journal of Transplantation 2006; 6(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/544/CN-00562544/frame.html.

210. Dias SW, N. Sutton, A. Ades, A. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making. In: National Institute for Health Care Excellence Decision Support Unit, ed. London: NICE, 2011.

211. Alloway RR, Sadaka B, Trofe-Clark J, et al. A randomized pharmacokinetic study of generic tacrolimus versus reference tacrolimus in kidney transplant recipients. American

journal of transplantation 2012; 12(10). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/808/CN-00864808/frame.html.

212. Bloom RD, Trofe-Clark J, Wiland A, et al. A randomized, crossover pharmacokinetic study comparing generic tacrolimus vs. the reference formulation in subpopulations of kidney transplant patients. Clinical transplantation 2013; 27(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/041/CN-00911041/frame.html.

213. Connor A, Prowse A, MacPhee I, et al. Generic tacrolimus in renal transplantation: trough blood concentration as a surrogate for drug exposure. Transplantation 2012;**93**:e45-6.

214. Connor A, Prowse A, Newell P, et al. A single-centre comparison of the clinical outcomes at 6 months of renal transplant recipients administered Adoport or Prograf preparations of tacrolimus. Clinical Kidney Journal 2013;**6**:21-28.

215. Heavner MS, Tichy EM, Yazdi M, et al. Clinical outcomes associated with conversion from brand-name to generic tacrolimus in hospitalized kidney transplant recipients. American Journal of Health-System Pharmacy 2013;**70**:1507-12.

216. Marfo K, Aitken S, Akalin E. Clinical outcomes after conversion from brand-name tacrolimus (prograf) to a generic formulation in renal transplant recipients: a retrospective cohort study. P&T 2013;**38**:484-88.

217. McDevitt-Potter LM, Sadaka B, Tichy EM, et al. A multicenter experience with generic tacrolimus conversion. Transplantation 2011; 92(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/872/CN-00890872/frame.html.

218. Richards KR, Hager D, Muth B, et al. Tacrolimus Trough Level at Discharge Predicts Acute Rejection in Moderately Sensitized Renal Transplant Recipients. Transplantation 2014;**97**(10):986-91.

219. Rosenborg S, Nordstrom A, Almquist T, et al. Systematic conversion to generic tacrolimus in stable kidney transplant recipients. Clin Kidney J 2014;**7**(2):151-55.

220. Spence M M NLMHRLCJ. Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus in transplant recipients enrolled in an integrated health care system. Pharmacotherapy 2012;**32(11):981-987**.

221. Adoport -v- Prograf in de-novo renal transplants: single centre experience. Joint Congress of the British Transplantation Society & Renal Association; 2013; Bournemouth, UK.

222. Switching Prograf ® to generic tacrolimus (Adoport®) is safe and cost effective in renal and pancreas transplants. Joint Congress of the British Transplantation Society & Renal Association 2012; Glasgow, UK.

223. Chiu C, Miyashiro S. Pharmacist-managed conversion of Prograf to generic tacrolimus in kidney and liver transplant patients with stable allograft function. . Hawai'i Journal of Medicine and Public Health 2012;**7**(16):148-50.

224. Crowther BR, Dobie H, Brady R, et al. Conversion of Prograf (R) to Generic Tacrolimus in Stable Renal Transplant Recipients. American Journal of Transplantation 2012;**12**:203-03.

225. Dick TB, Raines AA, Van der Werf W, et al. Comparison of Dose Requirements of Sandoz (TM) Generic Tacrolimus with Brand Prograf (R) in Kidney Transplant Recipients. American Journal of Transplantation 2011;**11**:354-54.

226. Heldenbrand S, Jones GD, Bornhorst J, et al. Extended Comparison of Therapeutic Treatment Outcomes of De Novo Liver and Kidney Transplant Recipients with Generic Tacrolimus (Sandoz (TM)) or Brand Name (Prograf (R)). American Journal of Transplantation 2012;**12**:240-40.

227. Jogia P, Oskiera D, Booth S, et al. Generic Switch of Tacrolimus in Prevalent Kidney Transplant Recipients. American Journal of Transplantation 2013;**13**:226-26.

228. Kendrew P, Edey M, Bhandan S. An investigation into the differences between Adoport® and Prograf® in kidney transplant recipients. Joint Congress of the British Transplantation Society & Renal Association. Bournemouth, UK, 2013:69.

229. Qazi YA, Bolonesi R, Monis T, et al. Effect of Generic Tacrolimus on the Incidence of Acute Rejection in Kidney Transplant Recipients - A Single Center Experience. American Journal of Transplantation 2012;**12**:205-06.

230. Assessment of post transplantation results of adoport compared to prograf. A short sample study. Joint Congress of the British Transplantation Society & Renal Association; 2013; Bournemouth, UK.

231. Programmed switching of renal transplant recipients from branded to generic tacrolimus is safe, well-tolerated and cost-effective. Joint Congress of the British Transplantation Society & Renal Association 2013; Bournemouth, UK.

232. Siddiqi N, Lu A, Jones T, et al. Clinical and economic outcomes: De novo use of FDA-approved bioequivalent formulation of generic tacrolimus versus brand tacrolimus (Prograf). American Journal of Transplantation 2011;**11**:242.

233. Storey R, Hossain MA, Shrivastava S, et al. Tacrolimus Dosing in Renal Transplant Recipients Following Introduction of a Generic Preparation. Transplant International 2013;**26**:82-82.

234. Venkataramanan R, Raghu V, Momper J, et al. The effect of generic substitution of tacrolimus in liver and kidney transplant recipients. . Transplantation 2012;**94**(10S):748.

235. Wilcock M, Self P, Dickinson S, et al. Switching branded immunosuppressants in a stable renal transplant population: A single centre experience. International Journal of Pharmacy Practice 2013;**21**:72.

236. Marsen T. How Safe Is Conversion from Tacrolimus to Its Generic Drug?—A Single Center Experience. Open Journal of Nephrology 2012;**2**:72-77.

237. Silva HT, Yang HC, Abouljoud M, et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. American Journal of Transplantation 2007; 7(3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/674/CN-00577674/frame.html.

238. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. New England Journal of Medicine 2007; 357(25). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/906/CN-00621906/frame.html.

239. Abou-Jaoude MM, Irani-Hakime N, Ghantous I, et al. Cyclosporine microemulsion (Neoral) versus tacrolimus (FK506) as maintenance therapy in kidney transplant patients. Transplantation Proceedings 2003;**35**:2748-9.

240. Abou-Jaoude MM, Najm R, Shaheen J, et al. Tacrolimus (FK506) versus cyclosporine microemulsion (neoral) as maintenance immunosuppression therapy in kidney transplant recipients. Transplantation Proceedings 2005; 37(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/985/CN-00530985/frame.html.

241. Busque S, Shoker A, Landsberg D, et al. Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus neoral/mycophenolate mofetil/steroids in renal transplantation. Transplant Proc 2001;**33**(1-2):1266-7.

242. Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. Transplantation 2000;**69**:834-41.

243. Garcia DM, Gago JM, Mendiluce A, et al. Tacrolimus-Basiliximab versus cyclosporine-basiliximab in renal transplantation "De novo": Acute rejection and complications. Transplantation Proceedings 2003;**35**:1694-96.

244. Morris-Stiff G, Singh J, Ostrowski K, et al. Prospective randomized study comparing FK 506 (Prograf) and cyclosporine a (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: Interim report of the first 80 cases. Transplantation Proceedings 1998;**30**(4):1295-96.

245. Raofi V, Holman DM, Coady N, et al. A prospective randomized trial comparing the efficacy of tacrolimus versus cyclosporine in black recipients of primary cadaveric renal transplants. Am J Surg 1999;**177**(4):299-302.

246. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. American Journal of Transplantation 2007; 7(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/353/CN-00609353/frame.html.

247. Wang XH, Tang XD, Xu D. Tacrolimus vs CyA neoral in combination with MMF and steroids after cadaveric renal transplantation. Transplantation Proceedings 2000;**32**(7):1702-03.

248. White SA, Jain S, Williams ST, et al. Randomized trial comparing neoral and tacrolimus immunousuppression for recipients of renal transplants procured from different donor groups. Transplantation Proceedings 2000;**32**(3):600-00.

249. Williams S, White S, Jain S, et al. A randomised trial comparing Neoral (ciclosporin) and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. . British Journal of Surgery 1998;**86**(Supp 1):008.

250. Glotz D, Charpentier B, Abramovicz D, et al. Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. Transplantation 2010; 89(12). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/047/CN-00753047/frame.html.

251. Chhabra D, Alvarado A, Dalal P, et al. Impact of calcineurin-inhibitor conversion to mTOR inhibitor on renal allograft function in a prednisone-free regimen. American Journal of Transplantation 2013; 13(11). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/077/CN-00909077/frame.html.

252. Lo A, Egidi MF, Gaber LW, et al. Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. Transplantation 2004;**77**:1228-35.

253. Ciancio G, Burke GW, Gaynor JJ, et al. 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 2004;**77**:244-51.

254. Ciancio. 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 2004;**77**:1131-31.

255. Langer RM, Hené R, Vitko S, et al. Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation. Transplant International 2012; 25(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/687/CN-00880687/frame.html.

256. Chan L, Greenstein S, Hardy MA, et al. Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. Transplantation 2008; 85(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/496/CN-00638496/frame.html.

257. Favi E, Silvestrini N, Salerno MP, et al. Extended-release tacrolimus plus everolimus or micophenolate mofetil in deceased donor kidney transplant recipients: 6-month results of a prospective randomized clinical trial. American Journal of Transplantation 2012;**12**:42-43.

258. Ruiz JC, Sanchez Fructuoso A, Hernandez D, et al. Better renal function with early everolimus (EVL) introduction and calcineurin inhibitor (CNI) withdrawal at third month in kidney recipients at month 12: Results of the eric study. Transplant International 2011;**24**:112.

259. Abou-Jaoude MM, Ghantous I, Almawi WY. 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 2003;**39**:1095-100.

260. Cheung CY, Wong KM, Chan HW, et al. Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. Transplant International 2006; 19(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/403/CN-00566403/frame.html.

261. Egfjord M, Ladefoged J, Olgaard K. Similar frequency of acute rejection, graft-and patient survival in quadriple therapy with tacrolimus versus cyclosporin in combination with prednisone, mycophenolate mofetil, and ATGAM after renal allotransplantation [abstract]. XIXth International Congress of the Transplantation Society; 2002 Aug 25-30; Miami, FL 2002. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/359/CN-00583359/frame.html.

262. El Haggan W, Barthe N, Vendrely B, et al. One year evolution of bone mineral density in kidney transplant recipients receiving tacrolimus versus cyclosporine. Transplantation Proceedings 2002;**34**:1817-8.

263. Liu B, Lin ZB, Ming CS, et al. Randomized trial of tacrolimus in combination with mycophenolate mofetil versus cyclosporine with mycophenolate mofetil in cadaveric renal transplant recipients with delayed graft function. Transplantation Proceedings 2003;**35**:87-8.

264. Cost of medical care after renal transplantation comparing cyclosporine-mycophenolate to tacrolimus-azathioprine—a randomised controlled study. . XVIII International Congress of the Transplantation Society; 2000; Rome.

265. Yu L, Wang Y, Fu SJ, et al. Clinical experience with prograf (Tacrolimus, FK 506) in Chinese patients after renal transplantation. Transplantation Proceedings 2000;**32**(7):1709-10.

266. Nichelle L, Canet S, Garrigue V, et al. Arterial hypertension in renal transplant recipients treated with tacrolimus or cyclosporine-Neoral. Transplantation Proceedings 2002;**34**:2824-5.

267. Heering P, Ivens K, Aker S, et al. Distal tubular acidosis induced by FK506. Clinical Transplantation 1998;**12**(5):465-71.

268. Ichimaru N, Takahara S, Kokado Y, et al. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. Atherosclerosis 2001;**158**(2):417-23.

269. Salvadori M. Therapeutic equivalence of mycophenolate sodium versus mycophenolate mofetil in de novo renal transplant recipients. Transplant Proc 2001;**33**(7-8):3245-7.

270. Salvadori M, Holzer H, Civati G, et al. Long-term administration of enteric-coated mycophenolate sodium (EC-MPS; myfortic) is safe in kidney transplant patients. Clinical Nephrology 2006; 66(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/888/CN-00571888/frame.html.

271. Budde K, Curtis J, Knoll G, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. American journal of transplantation 2004; 4(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/927/CN-00480927/frame.html.

272. Budde K, Knoll G, Curtis J, et al. Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. Transplantation Proceedings 2005; 37(2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/586/CN-00521586/frame.html.

273. Budde K, Knoll G, Curtis J, et al. 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 2006;**35**:454-64.

274. Shehata M, Bhandari S, Venkat-Raman G, et al. Effect of conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium on maximum tolerated dose and gastrointestinal symptoms following kidney transplantation. Transplant International 2009; 22(8). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/850/CN-00720850/frame.html.

275. Ortega F, Sánchez-Fructuoso A, Cruzado JM, et al. Gastrointestinal quality of life improvement of renal transplant recipients converted from mycophenolate mofetil to enteric-coated mycophenolate sodium drugs or agents: mycophenolate mofetil and enteric-coated mycophenolate sodium. Transplantation 2011; 92(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/773/CN-00798773/frame.html.

276. Langone A, Doria C, Greenstein S, et al. Does reduction in mycophenolic acid dose compromise efficacy regardless of tacrolimus exposure level? An analysis of prospective data from the Mycophenolic Renal Transplant (MORE) Registry. Clinical Transplantation 2013;**27**(1):15-24.

277. Chan L, Shihab F, Pankewycz O, et al. Mycophenolic Acid (MPA) Dosing: Effect on Efficacy to 4 Years after Kidney Transplantation in the Mycophenolic Acid Observational Renal Transplant (MORE) Study. American Journal of Transplantation 2013;**13**:337-37.

278. Shah T, Vu D, Cho Y, et al. Drug Tolerability and Outcomes in Kidney Transplant Recipients Treated with Two Formulations of Mycophenolic Acid. Journal of Pharmaceutics & Drug Development 2013;**1**(1).

279. Langone AJ, Chan L, Bolin P, et al. Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. Transplantation 2011; 91(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/964/CN-00778964/frame.html.

280. Chan L, Mulgaonkar S, Walker R, et al. Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. Transplantation 2006; 81(9). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/338/CN-00556338/frame.html.

281. Hwang HS, Hyoung BJ, Kim S, et al. Improved gastrointestinal symptoms and quality of life after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in renal transplant patients receiving tacrolimus. Journal of Korean medical science 2010; 25(12). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/264/CN-00780264/frame.html.

282. Tedesco-Silva H, Johnston T, Kim YS, et al. Everolimus-treated renal transplant patients have a lower incidence of CMV and BKV: results from a multicenter, prospective study [abstract: 1659]. American journal of transplantation 2010; 10(Suppl 4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/903/CN-00774903/frame.html.

283. Cibrik D, Silva HT, Vathsala A, et al. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. Transplantation 2013; 95(7). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/288/CN-00877288/frame.html.

284. Takahara S, Uchida K, Yoshimura N, et al. Efficacy and safety of concentration controlled everolimus with reduced dose cyclosporine in japanese adult de-novo renal transplant patients: 12 month results. American Journal of Transplantation 2012;**12**:300.

285. Saito K, Uchida K, Takahara S, et al. Efficacy of everolimus with reduced cyclosporine in japanese de novo renal transplant recipients: 24-month, randomized, multicenter study. American Journal of Transplantation 2013;**13**:314.

286. Paoletti E, Marsano L, Bellino D, et al. Everolimus for regression of left ventricular hypertrophy of renal transplant recipients: A randomized controlled trial. American Journal of Transplantation 2012;**12**:31.

287. Paoletti E, Marsano L, Bellino D, et al. Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. Transplantation 2012; 93(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/251/CN-00881251/frame.html.

288. Favi E, Citterio F, Spagnoletti G, et al. Prospective clinical trial comparing two immunosuppressive regimens, tacrolimus and mycophenolate mofetil versus everolimus and low-dose cyclosporine, in de novo renal transplant recipients: results at 6 months follow-up. Transplantation Proceedings 2009; 41(4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/900/CN-00754900/frame.html.

289. Favi E, Citterio F, Spagnoletti G, et al. A PROSPECTIVE CLINICAL TRIAL COMPARING TACROLIMUS-MMF TO CYCLOSPORINE-EVEROLIMUS IN DE NOVO RENAL TRANSPLANT RECIPIENTS: 2 YEARS RESULTS. Transplant International 2009;**22**:241-41.

290. Favi E, Spagnoletti G, Gargiulo A, et al. The combination of everolimus and low dose cyclosporine allows similar results as the standard tacrolimus and MMF regimen: 3 year results of a prospective clinical trial in renal transplant recipients [abstract no: 1645]. American journal of transplantation 2010; 10(Suppl 4). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/468/CN-00776468/frame.html.

291. Favi E, Spagnoletti G, Silvestrini N, et al. Thymoglobulin plus basiliximab vs basiliximab as induction therapy in deceased donor kidney transplant recipients treated with tacrolimus and mycophenolate mofetil: 1-year results of a prospective clinical trial. American Journal of Transplantation 2013;**13**:426.

292. Gonzalez F, Espinoza M, Herrera P, et al. Everolimus versus azathioprine in a cyclosporine and ketoconazole based immunosuppressive therapy in kidney transplantation: 1-year follow-up of a comparative clinical trial [abstract no: P187]. Transplant international 2007; 20(Suppl 2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/558/CN-00740558/frame.html.

293. Miserlis G, Papanikolaou V, Vergoulas G, et al. Efficacy and safety of everolimus with low dose cyclosporine A compared with mycophenolate mofetil and full dose cyclosporine A

in de novo renal transplant recipients [abstract no: 1641]. Transplantation 2008; 86(Suppl 2). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/580/CN-00740580/frame.html.

294. Watarai Y, Yamamoto T, Tsujita M, et al. Efficacy and Safety of Everolimus Based Immunosuppression on De Novo Kidney Transplantation with 4 Years Follow-up, Especially in Protocol Biopsy Findings and Donor Specific Antibody Production. Transplant International 2013;**26**:197-97.

295. Loriga G, Ciccarese M, Pala PG, et al. De Novo Everolimus-Based Therapy in Renal Transplant Recipients: Effect on Proteinuria and Renal Prognosis. Transplantation Proceedings 2010;**42**:1297-302.

296. Dantal J, Vitko S, Margreiter R, et al. Everolimus (certican (TM), RAD) is associated with a reduced incidence of CMV infection following renal transplantation. [abstract]. American journal of transplantation 2002; 2(Suppl 3). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/492/CN-00415492/frame.html.

297. Oppenheimer F, Oyen O, Viljoen H, et al. 36-month results of an international study with everolimus for the prevention of allograft rejection in de novo kidney transplant recipients [abstract]. American journal of transplantation 2003; 3(Suppl 5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/927/CN-00446927/frame.html.

298. Novartis C. RAD001/Everolimus: A 12 month, multi-center, randomized, open-label non-inferiority study comparing the safety and efficacy of concentration-controlled Everolimus with low dose tacrolimus to CellCeptÒ (mycophenolate mofetil) with standard dose tacrolimus in de novo renal transplant recipients.: Novartis, 2014.

299. Tedesco H, Felipe C, Sandes T, et al. A prospective randomized trial aimed to reduce the incidence of cytomegalovirus (CMV) infection in kidney transplant recipients. Transplantation 2012;**94**:4.

300. Tedesco H, Felipe C, Wang L, et al. A prospective randomized trial aimed to reduce the incidence of cytomegalovirus (CMV) infection in kidney transplant (KT) recipients. American Journal of Transplantation 2013;**13**:56.

301. Favi E, Silvestrini N, Pedroso J, et al. Extended-release tacrolimus plus everolimus vs extended-release tacrolimus plus micophenolate mofetil in primary deceased donor kidney transplant recipients: 1-year results of an open label, randomized phase 2 clinical trial. American Journal of Transplantation 2013;**13**:316.

302. Kamar N, Allard J, Ribes D, et al. Assessment of glomerular and tubular functions in renal transplant patients receiving cyclosporine A in combination with either sirolimus or everolimus. Clinical Nephrology 2005;**63**:80-6.

303. Rostaing L, Tran Van T, Cointault O, et al. Assessment of Renal Function in DeNovo Renal Transplant Patients Receiving Either Sirolimus or Everolimus in Addition to Cyclosporine A. Journal of the American Society of Nephrology 2001;**12**:A4785.

304. Evers S, Goossens M, de Vet H, et al. Criteria list for assessment of methodologial quality of economic evaluations: Concensus on health economic criteria. International Journal of Technology Assessment in Health Care 2005;**21**:240-45.

305. Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics 2006;**24**:355-71.

306. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 2004;**8**:iii-iiv.

307. Abecassis MM, Seifeldin R, Riordan ME. Patient outcomes and economics of once-daily tacrolimus in renal transplant patients: results of a modeling analysis. Transplantation proceedings 2008;**40(5):1443-1445**.

308. Chilcott J B ARLHM, et al. The economics of renal transplantation with basiliximab (simulect) in preventing acute rejection in renal transplantation. 15 2002:486.

309. Craig AM, McKechnie T, McKenna M, et al. A cost-effectiveness analysis of tacrolimus versus cyclosporine microemulsion following kidney transplantation. Transplantation Proceedings 2002;**34**:1646-48.

310. Crompton JA, Somerville T, Smith L, et al. Lack of economic benefit with basiliximab induction in living related donor adult renal transplant recipients. Pharmacotherapy 2003;**23**:443-50.

311. Emparan C. Economic evaluation of new immunosuppressive drugs in renal transplantation. Expert Review of Clinical Immunology 2006;**2**:183-86.

312. Emparan C, Wolters H, Laukotter M, et al. Cost-effectiveness analysis of basixilimab induction and calcineurin-sparing protocols in "old to old" programs using Markov models. Transplantation Proceedings 2003;**35**:1324-25.

313. Juergensen JS, Arns W, Hass B. Cost-effectiveness of immunosuppressive regimens in renal transplant recipients in Germany: a model approach. European Journal of Health Economics 2010;**11**:15-25.

314. McEwan P, Baboolal K, Conway P, et al. Evaluation of the cost-effectiveness of sirolimus versus cyclosporin for immunosuppression after renal transplantation in the United Kingdom (Structured abstract). Clinical Therapeutics 2005; 27(11). http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22006006258/frame.html.

315. McEwan P, Dixon S, Baboolal K, et al. Evaluation of the cost effectiveness of sirolimus versus tacrolimus for immunosuppression following renal transplantation in the UK (Structured abstract). Pharmacoeconomics 2006; 24(1). http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22006008105/frame.html.

316. Lazzaro C, McKechnie T, McKenna M. Tacrolimus versus cyclosporin in renal transplantation in Italy: cost-minimisation and cost-effectiveness analyses. Journal of Nephrology 2002;**15**:580-8.

317. Walters SJ, Whitfield M, Akehurst RL, et al. Economic implications of the use of basiliximab in addition to triple immunosuppressive therapy in renal allograft recipients: a UK perspective. Pharmacoeconomics 2003;**21**:129-38.

318. Orme ME, Jurewicz WA, Kumar N, et al. The cost effectiveness of tacrolimus versus microemulsified cyclosporin: a 10-year model of renal transplantation outcomes. Pharmacoeconomics 2003;**21**:1263-76.

319. Earnshaw SR, Graham CN, Irish WD, et al. Lifetime cost-effectiveness of calcineurin inhibitor withdrawal after de novo renal transplantation. Journal of the American Society of Nephrology 2008;**19**:1807-16.

320. Muduma G, Odeyemi I, Pollock RF. A UK analysis of the cost of switching renal transplant patients from an immediate-release to a prolonged-release formulation of tacrolimus based on differences in trough concentration variability. Journal of Medical Economics 2014;**17**(7):520-6.

321. Muduma G, Odeyemi I, Smith-Palmer J, et al. Budget impact of switching from an immediate-release to a prolonged-release formulation of tacrolimus in renal transplant recipients in the UK based on differences in adherence. Patient Prefer Adherence 2014;**8**:391-9.

322. Muduma G, Shaw J, Hart WM, et al. Cost utility analysis of immunosuppressive regimens in adult renal transplant recipients in England and Wales. Patient Prefer Adherence 2014;**8**:1537-46.

323. Jurgensen JS, Ikenberg R, Greiner RA, et al. Cost-effectiveness of modern mTOR inhibitor based immunosuppression compared to the standard of care after renal transplantation in Germany. European Journal of Health Economics 2014.

324. Popat R, Syed A, Puliatti C, et al. Outcome and cost analysis of induction immunosuppression with IL2Mab or ATG in DCD kidney transplants. Transplantation 2014;**97**(11):1161-65.

325. Drummond M, O'Brien B, GL. S, et al. *Methods for the economic evaluation of health care programmes.* Oxford: Oxford Medical Publications, 1987.

326. Crompton JA, Sundberg A, Smith L, et al. Economic analysis of basiliximab and mycophenolate mofetil in living-related donor renal transplant program. Pharmacotherapy 2003;**23**:413-13.

327. Emparan C, Wolters H, Laukotte M, et al. The cost-effectiveness of Basiliximab induction in "old-to-old" kidney transplant programs: Bayesian estimation, simulation, and uncertainty analysis. Transplantation Proceedings 2005;**37**:2069-71.

328. Emparan C, Laukotter M, Wolters H, et al. Calcineurin-free protocols with basiliximab induction allow patients included in "old to old" programs achieve standard kidney transplant function. Transplantation Proceedings 2003;**35**:1326-7.

329. Schnitzler M, Johnston K, Axelrod D, et al. Associations of renal function at 1-year after kidney transplantation with subsequent return to dialysis, mortality and healthcare costs. . Transplantation 2011;**91**:1347-56.

330. Levy AR, Briggs AH, Johnston K, et al. Projecting long-term graft and patient survival after transplantation. Value in Health 2014;**17**:254-60.

331. Barnieh L, Yilmaz S, McLaughlin K, et al. The cost of kidney transplant over time. Progress in transplantation (Aliso Viejo, Calif) 2014;**24**(3):257-62.

332. McEwan P, Baboolal K, Conway P, et al. Evaluation of the cost-effectiveness of sirolimus versus cyclosporin for immunosuppression after renal transplantation in the United Kingdom. Clinical Therapeutics 2005;**27**:1834-46.

333. McEwan P, Dixon S, Baboolal K, et al. Evaluation of the cost effectiveness of sirolimus versus tacrolimus for immunosuppression following renal transplantation in the UK. PharmacoEconomics 2006;**24**:67-79.

334. Oberbauer R, Kreis H, Campistol JM, et al. Renal function improves significantly after early cyclosporine withdrawal in sirolimus-treated renal transplant recipients: 3-year results of the Rapamune Maintenance Regimen (RMR) trial [abstract no: F-FC041]. Journal of the American Society of Nephrology : JASN 2003; 14(Nov). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/606/CN-00550606/frame.html.

335. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and metya-analysis of individual patient data. BMJ 2014;**349**:g6679.

336. Neri L, McEwan P, Sennfalt K, et al. Characterizing the relationship between health utility and renal function after kidney transplantation in UK and US: A cross-sectional study. Health and Quality of Life Outcomes 2012;**10**.

337. Organ Donation and Transplantation. Activity Report 2012/2013, 2013.

338. Pruthi R, Steenkamp R, Feest T. UK Renal Registry 16th Annual Report: Chapter 8 Survival and Cause of Death of UK Adult Patients on Renal Replacement Therapy in 2012: National and Centre-specific Analyses. Nephron Clinical Practice 2013;**125**:139-70.

339. Opelz G, Dohler B. Collaborative Transplant Study Report. Influence of time of rejection on long-term graft survival in renal transplantation. Transplantation 2008;**85**(5):661-66.

340. Jurgensen JS, Arns W, Hass B. Cost-effectiveness of immunosuppressive regimens in renal transplant recipients in Germany: a model approach (Structured abstract). European Journal of Health Economics 2010;**11**(1):15-25.

341. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2012;**12**(5):1157-67.

342. Kuypers DR, Peeters PC, Sennesael JJ, et al. Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring. Transplantation 2013;**95**(2):333-40.

343. Wu MJ, Cheng CY, Chen CH, et al. Lower variability of tacrolimus trough concentration after conversion from prograf to advagraf in stable kidney transplant recipients. . Transplantation 2011;**92**(6):648-52.

344. Borra LC RJ, Kal JA, Mathot RA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after

kidney transplantation. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2010;**25**(8):2757-63.

345. Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. American Journal of Transplantation 2003;**3**:178-85.

346. Webster AC, Woodroffe RC, Taylor RS, et al. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: Meta-analysis and meta-regression of randomised trial data. British Medical Journal 2005;**331**:810-14.

347. Tedesco-Silva H, Vitko S, Pascual J, et al. 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. Transplant International 2007; 20(1). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/615/CN-00574615/frame.html.

348. AWMSG. Secretariat Assessment Report – Advice No. 1712 Belatacept (Nulojix®). : Bristol-Myers Squibb, 2012.

349. Gamboa O, Montero C, Mesa L, et al. Cost-effectiveness analysis of the early conversion of tacrolimus to mammalian target of rapamycin inhibitors in patients with renal transplantation. Transplantation Proceedings 2011;**43**:3367-76.

350. Rely K, Alexandre PK, Garcia-Garcia EG, et al. Cost-utility assessment of sirolimus versus tacrolimus for primary prevention of graft rejection in renal transplant recipients in Mexico. Value in Health 2012;**15 (4)**:A156.

351. Niemczyk M, Nowak M, Pilecki T, et al. Economic evaluation of sirolimus-based immunosuppressive regimens in kidney graft recipients. Transplantation Proceedings 2006;**38**:74-7.

352. Earnshaw S R GCNIWDSRSMA. Lifetime cost-effectiveness of calcineurin inhibitor withdrawal after de novo renal transplantation. Journal of the American Society of Nephrology 2008;**19(9):1807-1816**.

353. NHS Blood and Transplant. National Organ Retrieval Service: Service evaluation [available from: http://www.nhsbt.nhs.uk/download/board_papers/sept13/National_Organ_Retrieval_Service_Service_Evaluation.pdf]: NHS Blood and Transplant,, 2013.

354. Butler JA, Peveler RC, Roderick P, et al. Modifiable risk factors for non-adherence to immunosuppressants in renal transplant recipients: A cross-sectional study. Nephrology Dialysis Transplantation 2004;**19**:3144-49.

355. Taylor RS, Elston J. The use of surrogate outcomes in model-based cost-effectiveness analyses: A survey of UK Health Technology Assessment reports. Health Technology Assessment 2009;**13**:iii-40.

356. Webster AC, Lee VW, Chapman JR, et al. Target of rapamycin inhibitors (TOR-I; sirolimus and everolimus) for primary immunosuppression in kidney transplant recipients. Cochrane database of systematic reviews (Online) 2006:CD004290.

357. Lee AJ, Morgan CL, Conway P, et al. Characterisation and comparison of health-related quality of life for patients with renal failure. Current Medical Research and Opinion 2005;**21**:1777-83.

358. Tedesco-Silva H, Garcia VD, Contieri FL, et al. Comparison of the safety and efficacy of cyclosporine minimization versus cyclosporine elimination in de novo renal allograft patients receiving sirolimus. Transplantation proceedings 2010; 42(5). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/678/CN-00761678/frame.html.

359. Tedesco-Silva H, Kim YS, Johnston T, et al. Concentration-controlled everolimus with reduced cyclosporine concentration in de novo renal transplant recipients: Efficacy results at 24 months. American Journal of Transplantation 2011;**11**:46.

360. Dean PG, Larson TS, Rea DJ, et al. The effects of calcineurin inhibitor avoidance on renal function and graft histology after kidney transplantation: a prospective, randomized comparison of tacrolimus and sirolimus [abstract no:259]. Transplantation 2004; 78(2 Suppl). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/154/CN-00509154/frame.html.

361. National Institute for Health and Clinical Excellence. Organ donation for transplantation. Costing report. Implementing NICE guidance. In: NICE, ed. London, UK, 2011.

362. Neri L, Dukes J, Brennan DC, et al. Impaired renal function is associated with worse self-reported outcomes after kidney transplantation. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2011;**20**:1689-98.

363. Levy A, Johnston K, Kalsekar A, et al. Modeled long term projections of clinical outcomes from BENEFIT and BENEFIT-EXT. American Journal of Transplantation 2012;**12**:406-07.

364. Goring SM, Levy AR, Ghement I, et al. A network meta-analysis of the efficacy of belatacept, cyclosporine and tacrolimus for immunosuppression therapy in adult renal transplant recipients. Current Medical Research and Opinion 2014;**30**:1473-87.

365. Baboolal K, McEwan P, Sondhi S, et al. The cost of renal dialysis in a UK setting—a multicentre study. Nephrology Dialysis Transplantation 2008;**23**(6):1982-89.

366. Beaudet A, Palmer JL, Timlin L, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. Journal of Medical Economics 2011;**14**(3):357-66.

367. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;**35**(11):1095-108.

368. Dukes JL, Seelam S, Lentine KL, et al. Health-related quality of life in kidney transplant patients with diabetes. Clinical Transplantation 2013;**27**:E554-E62.

369. Cole EH, Johnston O, Rose CL, et al. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. Clinical Journal of the American Society of Nephrology 2008;**3**(3):814-21.

370. National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal. London: National Institute for Health and Care Excellence, 2013.

371. Pruthi R, Casula A, MacPhee I. UK Renal Registry 16th Annual Report: Chapter 3 Demographic and biochemistry profile of kidney transplant recipients in the UK in 2012: National and centre-specific analyses. Nephron Clinical Practice 2013;**125**:55-80.

372. Kaltenthaler E, Tappenden P, Paisley S, et al. Technical Support Document 13: Identifying and Reviewing Evidence to Inform the Conceptualisation and population of Cost-Effectiveness Models. In: National Institute for HCEDS, Unit, ed. London: NICE, 2011.

373. Bond M, Pitt M, Akoh J, et al. The effectiveness and cost-effectiveness of methods of storing donated kidneys from deceased donors: A systematic review and economic model. Health Technology Assessment 2009;**13**:xi-180.

374. Ansell D, Feest T, Williams A, et al. UK Renal Registry Report 2005: 8th Annual Report of the Renal Association. Bristol: UK Renal Registry, 2005.

375. Johnston O, Rose CL, Gill JS, et al. Risks and benefits of preemptive second kidney transplantation. Transplantation 2013;**95**(5):705-10.

376. Opelz G, Doehler B, Collaborative Transplant S. Influence of Immunosuppressive Regimens on Graft Survival and Secondary Outcomes After Kidney Transplantation. Transplantation 2009;**87**:795-802.

377. Hariharan S, McBride MA, Cherikh WS, et al. Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney International 2002;**62**(1):311-8.

378. Kasiske BL, Andany MA, Danielson B. A thirty percent chronic decline in inverse serum creatinine is an excellent predictor of late renal allograft failure. American Journal of Kidney Diseases 2002;**39**(4):762-8.

379. Meier-Kriesche HU, Baliga R, Kaplan B. Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. Transplantation 2003;**75**(8):1291-5.

380. Salvadori M, Rosati A, Bock A, et al. Estimated one-year glomerular filtration rate is the best predictor of long-term graft function following renal transplant. Transplantation 2006;**81**(2):202-6.

381. UK Transplant Registry. Statistical methodology and risk-adjustment for survival rate estimation. Secondary Statistical methodology and risk-adjustment for survival rate estimation 2011. http://www.odt.nhs.uk/uk-transplant-registry/centre-specific-reports/kidney/pdf/Statistical_methodology_and_risk_adjustment.pdf.

382. Opelz G, Dohler B. Association of HLA mismatch with death with a functioning graft after kidney transplantation: a collaborative transplant study report. American Journal of Transplantation 2012;**12**(11):3031-8.

383. Opelz G, Dohler B. Association between steroid dosage and death with a functioning graft after kidney transplantation. American Journal of Transplantation 2013;**13**(8):2096-105.

384. Webb L, Casula A, Tomson C, et al. Survival after Renal Transplant Failure: A Uk Renal Registry Analysis. Nephrology Dialysis Transplantation 2012;**27**(Suppl. 2):ii312.

385. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. American Journal of Transplantation 2003;**3**:590-98.

386. Vanrenterghem Y, Ponticelli C, Morales JM, et al. Prevalence and management of anemia in renal transplant recipients: a European survey. Am J Transplant 2003;**3**(7):835-45.

387. Fuggle SV, Allen JE, Johnson RJ, et al. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. Transplantation 2010;**89**(6):694-701.

388. Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet 2010;**376**(9749):1303-11.

389. *Health survey for England 2012*. London: The Health and Social Care Information Centre, 2013.

390. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2010;**13**(5):509-18.

391. Liem YS, Bosch JL, Myriam Hunink MG. Preference-based quality of life of patients on renal replacement therapy: A systematic review and meta-analysis. Value in Health 2008;**11**:733-41.

392. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;**43**(3):203-20.

393. Johnson JA, Luo N, Shaw JW, et al. Valuations of EQ-5D health states: are the United States and United Kingdom different? Medical Care 2005;**43**(3):221-8.

394. Currie CJ, Morgan CL, Dixon S, et al. The financial costs of hospital care for people with diabetes who have single and multiple macrovascular complications. Diabetes research and clinical practice 2005;**67**(2):144-51.

395. Currie CJ, McEwan P, Peters JR, et al. The routine collation of health outcomes data from hospital treated subjects in the Health Outcomes Data Repository (HODaR): descriptive analysis from the first 20,000 subjects. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2005;**8**(5):581-90.

396. Wyld M, Morton RL, Hayen A, et al. A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Chronic Kidney Disease Treatments. PLoS Medicine 2012;**9**.

397. Curtis L. *Unit costs of health and social care 2014*. Cantebury: Personal Social Sciences Research Unit, 2014.

398. Moore J. Kidney transplant protocol. Exeter: Royal Devon and Exeter NHS Foundation Trust, 2012.

399. Harvala H, Stewart C, Muller K, et al. High risk of cytomegalovirus infection following solid organ transplantation despite prophylactic therapy. Journal of Medical Virology 2013;**85**(5):893-8.

400. Ling C, Chamberlain G. Preliminary report: PORTRAIT database study - Cardiff. Cardiff: Cardiff Research Consortium, 2011.

401. Cavallo R, Elia M, Gruosso V, et al. Molecular epidemiology of Epstein-Barr virus in adult kidney transplant recipients. Transplant Proc 2010;**42**(7):2527-30.

402. Riella LV, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. Am J Transplant 2012;**12**(8):1975-82.

403. Department of Health. Reference costs guidance 2013-14 [available from https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2013-to-2014]. In: Department of Health, ed. England: Department of Health, 2014.

404. Commercial Medicines Unit. eMit national database (2014/06). Drugs and pharmaceutical electronic market information (eMit): Department of Health, 2014.

405. Joint Formulary Committee. *British National Formulary. 68 ed*. London: BMJ Group and Pharmaceutical Press, 2014.

406. Department of Health. NHS Reference Costs 2013 to 14 [available from https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014]. London: Department of Health, 2014.

407. NHS England. NHS standard contract for adult kidney transplant service: Schedule 2 - the services; A. Service specifications: NHS England,, 2013.

408. Welsh Renal Clinical Network. Immunosuppression following renal transplantation. Caerphilly: Welsh Health Specialised Services Committee, 2012.

409. Ling C, Pandit P, Bennett H. Belatacept micro-costing model - UK. Cardiff: Cardiff Research Consortium, 2011.

410. Hex N, Bartlett C, Wright D, et al. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. Diabetic Medicine 2012;**29**(7):855-62.

411. Davies MJ, Chubb BD, Smith IC, et al. Cost-utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus. Diabetic Medicine 2012;**29**(3):313-20.

412. Gillies CL, Lambert PC, Abrams KR, et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. BMJ 2008;**336**(7654):1180-5.

413. Currie CJ, Gale EA, Poole CD. Estimation of primary care treatment costs and treatment efficacy for people with Type 1 and Type 2 diabetes in the United Kingdom from 1997 to 2007*. Diabetic Medicine 2010;**27**(8):938-48.

414. Alva ML, Gray A, Mihaylova B, et al. The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). Diabetic medicine : a journal of the British Diabetic Association 2014.

415. NHS Kidney Care. Developing robust reference costs for kidney transplants - Update: NHS Kidney Care,, 2011.

416. National Casemix Office. HRG4+ Reference Costs Code to Group [available from: http://www.hscic.gov.uk/casemix/costing]: Health and Social Care Information Centre, 2014.

417. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;**64**(2):163-71.

418. Davis S. Assessing technologies that are not cost-effective at a zero price. Sheffield, UK: NICE Decision Support Unit, 2014.

419. Tedesco Silva H, Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. American Journal of Transplantation 2010; 10(6). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/614/CN-00762614/frame.html.

420. Ekberg H, Tedesco-Silva H, Demirbas A, et al. 2-year results of the symphony study: Comparing standard immunosuppression against low-dose cyclosporine, tacrolimus or sirolimus associated with MMF, daclizumab and corticosteroids in de-novo renal transplantation. Transplant International 2007;**20**:25-25.

421. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). American Journal of Transplantation 2010;**10**:535-46.

Appendix 1 Literature searching strategies

Clinical effectiveness

The following search strategies were used to identify studies of intervention effectiveness for this appraisal. They were first run on April 14th 2014 and the same strategy was used on November 18th 2014 to update the literature base: this most recent search is recorded below. The effectiveness searches take 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 RCTs or controlled trials). The search was not limited by language and it was not limited to human only studies because such a limit would have blocked retrieval of includable studies for Rabbit ATG (line 8 of the Medline search). The effectiveness searches were combined with the systematic review searches in our update searches.

Search Annex

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Tuesday, November 18th 2014

Searcher: Chris Checked by: Simon/ Jenny

Hits: 73

Search Strategy:

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	81142
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34392
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41464
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36554
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46102
6	1 or 2 or 3 or 4 or 5	114277
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor	1063

	antibody").ti,ab,kw,ot.	
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.	6382
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.	17331
10	Tacrolimus/	13055
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	219
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28176
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	21975
14	Sirolimus/	14369
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3088
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	74259
17	6 and 16	9593
18	Randomized Controlled Trial.pt.	400000
19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	850201
20	clinical trial.pt.	501246
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	348859
22	18 or 19 or 20 or 21	1324400
23	(systematic adj3 review$).ti,ab,kw,ot.	65381
24	22 or 23	1361806
25	17 and 24	2456
26	limit 25 to yr="2014 -Current"	73

Notes: N/A

File: N/A

Database: Embase

Host: OVID

Data Parameters: 1974 to 2014 November 17

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 259

Search Strategy:

#	Searches	Results
1	kidney transplantation/	97441
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	50853
3	(Renal adj3 transplant$).ti,ab,kw,ot.	55991
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	51947
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	65675
6	1 or 2 or 3 or 4 or 5	153480
7	basiliximab/	6681
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2311
9	thymocyte antibody/	20236
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.	8854
11	tacrolimus/	53638
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.	26290
13	belatacept/	989
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	547
15	mycophenolic acid/	9985
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	35917

17	rapamycin/	36443
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	28739
19	everolimus/	14356
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	6988
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	148218
22	6 and 21	25662
23	randomized controlled trial/	355008
24	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	1028637
25	("controlled trial$" or "clinical trial$").ti,ab,ot.	428701
26	23 or 24 or 25	1300553
27	(systematic adj3 review$).ti,ab,kw,ot.	77376
28	26 or 27	1343995
29	22 and 28	3537
30	limit 29 to yr="2014 -Current"	259

Notes: N/A

File: N/A

Database: Cochrane CDSR, DARE & CENTRAL

Host: Wiley

Data Parameters: Issue 11 of 12, November 2014, Issue 4 of 4, Oct 2014, Issue 10 of 12, October 2014

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 64 (CDSR 10; DARE 3; CENTRAL 51)

ID Search Hits

#1 MeSH descriptor: [Kidney Transplantation] this term only 3311

#2 (Kidney* near/3 transplant*) 5789

#3 (Renal near/3 transplant*) 4385

#4 ((kidney or renal) near/3 (recipient* or dono* or donation* or replac*)) 3706

#5 ((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)) 4956

#6 #1 or #2 or #3 or #4 or #5 8481 7509

#7 (Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody") 486

#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*) 346

#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") 2463

#10 MeSH descriptor: [Tacrolimus] this term only 1180

#11 (Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818") 58

#12 ("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil) 3315

#13 (Sirolimus or Rapamune or Rapamycin or "ay 22-989") 2034

#14 MeSH descriptor: [Sirolimus] this term only 1067

#15 (Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD") 724

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 7002

#17 #6 and #16 Publication Year from 2014 67

Notes: N/A

File: N/A

Database: Web of Science

Host: ISI Thompson Reuters

Data Parameters: 1900-2014

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 2290

1. TOPIC: ((Kidney* near/3 transplant*))
2. TOPIC: ((Renal near/3 transplant*))
3. TOPIC: (((kidney or renal) near/3 (recipient* or dono* or donation* or replac*)))
4. TOPIC: (((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)))
5. #4 OR #3 OR #2 OR #1
6. TOPIC: ((Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody"))
7. 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*))
8. 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"))
9. TOPIC: ((Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818"))
10. TOPIC: (("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil))
11. TOPIC: ((Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD"))
12. #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6
13. #13 AND #5 (Refined by: PUBLICATION YEARS: (2005 OR 2009 OR 2011 OR 2007 OR 2010 OR 2006 OR 2008 OR 2013 OR 2012 OR 2014))
14. TOPIC: (((random* or rct* or "controlled trial*" or "clinical trial*")))
15. #16 AND #15

Notes: auto-suggest was turned off.

File: N/A

Database: HMIC

Host: OVID

Data Parameters: 1979 to September 2014

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 0

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	120
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	83
3	(Renal adj3 transplant$).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	313
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.	10
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	32
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$).ti,ab,ot.	10838
20	clinical trial.pt.	0
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	5592
22	18 or 19 or 20 or 21	12088
23	(systematic adj3 review$).ti,ab,kw,ot.	3692
24	22 or 23	14553
25	17 and 24	2
26	limit 25 to yr="2014 -Current"	0

Notes: N/A

File: N/ATrials registries

The following search strategies were used in Clinical Trials.Gov and the ISRCTN Registry, Controlled Trials. These were hand-searched on 19.10.2014 via: https://clinicaltrials.gov/ and http://www.controlled-trials.com/ respectively.

(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)

Web Searches

The following web-sites were hand-searched:

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	https://www.csnscn.ca/
Kidney Foundation of Canada	www.kidney.ca/

Australian and New Zealand Society of Nephrology
https://www.nephrology.edu.au/

Kidney Health Australia www.kidney.org.au/

Kidney Society Auckland www.kidneysociety.co.nz/

On-going trials

The following terms were used to search the ClinicalTrials.gov and Controlled Trials (ISRCTN) trial registers for the interventions:

(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

The following search strategies were used to identify studies reporting cost or economic data. They were first run on April 8th 2014 and the same strategy was used on November 18th 2014 to update the literature base. 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 not limited by language and it was not limited to human only studies because such a limit would have blocked retrieval of includable studies for Rabbit ATG (line 8 of the Medline search). Searching was date limited 2002-current in line with the previous assessment.

Database: MEDLINE
Host: OVID
Data Parameters: 1946 to Present
Date Searched: Tuesday, November 18th 2014
Searcher: Chris
Hits: 27
Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	81142
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34392
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41464
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36554
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46102
6	1 or 2 or 3 or 4 or 5	114277
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1063
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.	6382
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.	17331
10	Tacrolimus/	13055

11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	219
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28176
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	21975
14	Sirolimus/	14369
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3088
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	74259
17	6 and 16	9593
18	Economics/	27421
19	exp Economics, Pharmaceutical/	2601
20	exp Economics, Medical/	13982
21	exp Economics, Hospital/	20161
22	(pharmacoeconomic* or socioeconomics or economic$).ti,ab,kw.	183564
23	ec.fs.	349785
24	exp "Costs and Cost Analysis"/	189530
25	(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.	530644
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	896638
27	17 and 26	440
28	limit 27 to yr="2014 -Current"	27

Notes: N/A

File: N/A

Database: Embase

Host: OVID

Data Parameters: 1974 to 2014 November 17

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 131

Search Strategy:

#	Searches	Results
1	kidney transplantation/	97441
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	50853
3	(Renal adj3 transplant$).ti,ab,kw,ot.	55991
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	51947
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	65675
6	1 or 2 or 3 or 4 or 5	153480
7	basiliximab/	6681
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2311
9	thymocyte antibody/	20236
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.	8854
11	tacrolimus/	53638
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.	26290
13	belatacept/	989
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	547
15	mycophenolic acid/	9985
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	35917
17	rapamycin/	36443
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	28739
19	everolimus/	14356
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	6988

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	148218
22	6 and 21	25662
23	exp Economics/	220356
24	models, economic/	104606
25	exp health economics/	630542
26	exp "Costs and Cost Analysis"/	260530
27	Cost of illness/	14509
28	resource allocation/	15619
29	pe.fs.	61812
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.	665827
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1288868
32	22 and 31	1464
33	limit 32 to yr="2014 -Current"	131

Notes: N/A

File: N/A

Database: Cochrane NHS EEDS

Host: Wiley

Data Parameters: Issue 4 of 4, October 2014

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 29

ID Search Hits

#1 MeSH descriptor: [Kidney Transplantation] this term only 3274

#2 (Kidney* near/3 transplant*) 5590

#3 (Renal near/3 transplant*) 4265

#4 ((kidney or renal) near/3 (recipient* or dono* or donation* or replac*)) 3480

#5 ((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal)) 4701

#6 #1 or #2 or #3 or #4 or #5 8481

#7 (Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody") 457

#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*) 330

#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") 2328

#10 MeSH descriptor: [Tacrolimus] this term only 1168

#11 (Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818") 52

#12 ("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil) 3143

#13 (Sirolimus or Rapamune or Rapamycin or "ay 22-989") 1881

#14 MeSH descriptor: [Sirolimus] this term only 1037

#15 (Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD") 602

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 6587

#17 #6 and #16 Publication Date from 2005 to 2014 1273

Notes: N/A

File: N/A

Database: Web of Science

Host: ISI Thompson Reuters

Data Parameters: 1900-2014

Date Searched: Tuesday, November 18th 2014

Searcher: Chris

Hits: 40

lines 1-13 of the WOS Effectiveness search was used combined with.

TOPIC: ((pharmacoeconomic* or socioeconomics or economic* or pric* or cost* or cba or cea or cua or "health utilit*" or "value for money”))

Notes: N/A
File: N/A

Database: Econlit
Host: EBSCO Host
Data Parameters: 1886-2014
Date Searched: Tuesday, November 18th 2014
Searcher: Chris
Hits: 0

(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: Tuesday, November 18th 2014
Searcher: Chris
Hits: 3

(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

Searches for utility data

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	333

	or shortform twenty of short form twenty).ti,ab,kw.	
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 SearchHits

#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

Study	Rationale
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(17-18): 1095-100.	Population
Abramowicz, D.: Carmen Rial, M.: Vitko, S.: Castillo, D.: Manas, D.: Lao, M.: *et al* (2005) Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. *Journal of the American Society of Nephrology* 16: 2234-2240.	Population
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
Agha, I.: Brennan, D. (2002) BK virus and current immunosuppressive therapy. *Graft* 5: S65.	Study Design
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(6): 568-73.	Intervention
Albano, L.: Alamartine, E.: Toupance, O.: Moulin, B.: Merville, P.: Rerolle, J. P.: *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. *Annals of Transplantation* 17: 58-67.	Population
Alberú, J.: Pascoe, M. D.: Campistol, J. M.: Schena, F. P.: Rial Mdel, C.: Polinsky, 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. *Transplantation* 92, 303-310.	Population

Alloway, R.: Steinberg, S.: Khalil, K.: Gourishankar, S.: Miller, J.: Norman, D.: *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. *Transplantation Proceedings* 37, 867-870.	Study Design
Andrassy, J.: Hoffmann, V. S.: Rentsch, M.: Stangl, M.: Habicht, A.: Meiser, B.: *et al* (2012) Is cytomegalovirus prophylaxis dispensable in patients receiving an mtor inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation* 94(12): 1208-1217.	Population
Andres, A.: Delgado-Arranz, M.: Morales, E.: Dipalma, T.: Polanco, N.: Gutierrez-Solis, E.: *et al* (2010) Extended-release tacrolimus therapy in de novo kidney transplant recipients: Single-center experience. *Transplantation Proceedings* 42(8): 3034-3037.	Study Design
Araki, M.: Flechner, S. M.: Ismail, H. R.: Flechner, L. M.: Zhou, L. M.: Derweesh, I. H.: *et al* (2006) Posttransplant diabetes mellitus in kidney transplant recipients receiving calcineurin or mTOR inhibitor drugs. *Transplantation* 81(3): 335-341.	Study Design
Arns, W.: Breuer, S.: Choudhury, S.: Taccard, G.: Lee, J.: Binder, V.: *et al* (2005) Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clinical Transplantation* 19: 199-206.	Outcome
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(7): 965-979.	Study Design
Artz, M. A.: Boots, J. M.: Ligtenberg, G.: Roodnat, J. I.: Christiaans, M. H.: Vos, P. F.: *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*(6): 937-945.	Population
Artz, M. A.: Boots, J. M.: Ligtenberg, G.: Roodnat, J. I.: Christiaans, M. H.: Hené, R. J.: *et al* (2002) Randomized conversion from cyclosporine to tacrolimus in renal transplant patients: improved lipid profile and unchanged plasma homocysteine levels. *Transplantation Proceedings* 34(5): 1793-4.	Population

Artz, M. A.: Boots, J. M.: Ligtenberg, G.: Roodnat, J. I.: Christiaans, M. H.: Vos, P. F.: *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(7): 1880-8.	Population
Åsberg, A.: Apeland, T.: Reisaeter, A. V.: Foss, A.: Leivestad, T.: Heldal, K.: *et al* (2013) Long-term outcomes after cyclosporine or mycophenolate withdrawal in kidney transplantation - results from an aborted trial. *Clinical Transplantation* 27: E151-156	Population
Baas, M. C.: Gerdes, V. E. A.: Berge, I. J. M.: Heutinck, K. M.: Florquin, S.: Meijers, J. C. M.: *et al* (2013) Treatment with everolimus is associated with a procoagulant state. *Thrombosis research* 132: 307-311.	Outcome
Baczkowska, T.: Perkowska-Ptasińska, A.: Sadowska, A.: Lewandowski, Z.: Nowacka-Cieciura, E.: *et al* (2005) Cieciura, T. Serum TGF-beta1 correlates with chronic histopathological lesions in protocol biopsies of kidney allograft recipients. *Transplantation Proceedings* 37: 773-775.	Intervention
Bakker, R. C.: Hollander, A. A.: Mallat, M. J.: 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(3):1027-34.	Intervention
Bataille, S.: Moal, V.: Gaudart, J.: Indreies, M.: Purgus, R.: Dussol, B.: *et al* (2010) Cytomegalovirus risk factors in renal transplantation with modern immunosuppression. *Transplant Infectious Disease* 12: 480-488.	Outcome
Bemelman,F.J. de Maar,E.F. Press, R.R. van Kan H.J. ten Berge, I.J., Homan van der Heide, J.J., de Fijter, H.W. (2009) Minimization of Maintenance Immunosuppression Early After Renal Transplantation: An Interim Analysis. *Clinical and Translational Research* 88: 421-428	
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. *Pediatric Transplantation* 14: 909-918.	No Data

Birnbaum, L. M.: Lipman, M.: Paraskevas, S.: Chaudhury, P.: Tchervenkov, J.: Baran, D.: *et al* (2009) Management of chronic allograft nephropathy: A systematic review. *Clinical Journal of the American Society of Nephrology* 4(4): 860-865.	Outcome
Brennan, D. C.: Agha, I.: Bohl, D. L.: Schnitzler, M. A.: Hardinger, K. L.: Lockwood, M.: *et al* (2005) Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *American Journal of Transplantation* 5: 582-594.	Duplicate
Budde, K.: Glander, P.: Diekmann, F.: Dragun, D.: Waiser, J.: Fritsche, L.: *et al* (2004) Enteric-coated mycophenolate sodium: safe conversion from mycophenolate mofetil in maintenance renal transplant recipients. *Transplantation Proceedings* 36(2 Suppl): 524S-527S.	Population
Budde, K.: Curtis, J.: Knoll, G.: Chan, L.: Neumayer, H. H.: Seifu, Y.: *et al* (2004) Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *American Journal of Transplantation* 4(2): 237-43.	Population
Budde, K.: Knoll, G.: Curtis, J.: Chan, L.: Pohanka, E.: Gentil, M.: *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(2): 103-111.	Study Design
Budde, K.: Knoll, G.: Curtis, J.: Chan, L.: Pohanka, E.: Gentil, M.: *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). *Nieren- und Hochdruckkrankheiten* 35(10): 454-464.	Language
Budde, K.: Knoll, G.: Curtis, J.: Kahana, L.: Pohanka, E.: Seifu, Y.: *et al* (2005) Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. *Transplantation Proceedings* 37: 912-915.	Study Design
Bunnapradist, S.: Ciechanowski, K.: West-Thielke, P.: Mulgaonkar, S.: Rostaing, L.: Vasudev, B.: *et al* (2013) Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT	Population

trial. *American Journal of Transplantation* 13: 760-769.	
Busque, S.: Cantarovich, M.: Mulgaonkar, S.: Gaston, R.: Gaber, A. O.: Mayo, P. R.: *et al* (2011) The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *American Journal of Transplantation* 11: 2675-2684.	Outcome
Burke, G. W. (2011) Randomized trial of 2 antibody induction steroid avoidance protocols accompanied by maintenance therapy with Prograf and Myfortic. clinicaltrials.gov/ct2/show/NCT01172418	Comparator
Cabello, M.: García, P.: González-Molina, M.: Díez de los Rios, M. J.: García-Sáiz, M.: Gutiérrez, C.: *et al* (2010) Pharmacokinetics of once- versus twice-daily tacrolimus formulations in kidney transplant patients receiving expanded criteria deceased donor organs: a single-center, randomized study. *Transplantation Proceedings* 42: 3038-3040.	Population
Cabello, M.: García, P.: González-Molina, M.: Díez de los Rios, M. J.: García-Sáiz, M.: Gutiérrez, C.: *et al* (2010) Pharmacokinetics of once- versus twice-daily tacrolimus formulations in kidney transplant patients receiving expanded criteria deceased donor organs: a single-center, randomized study. *Transplantation Proceedings* 42, 3038-3040.	Study Design
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. *American Journal of Transplantation* 12: 1146-1156.	Population
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. *Nephrology, dialysis, transplantation* 28: 462-465.	Population
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. *Transplantation Proceedings* 41: 4138-4146.	Population
Chadban, S. J.: Eris, J. M.: Kanellis, J.: Pilmore, H.: Lee, P. C.: Lim, S. K.: *et al* (2014) A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of	Language

care in de novo kidney transplant recipients. *Transplant International* 27(3): 302-311.	
Chan, L.: Greenstein, S.: Hardy, M. A.: Hartmann, E.: Bunnapradist, S.: Cibrik, D.: *et al* (2008) Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. Transplantation 85: 821-826.	Comparator
Chhabra, D.: Alvarado, A.: Dalal, P.: Leventhal, J.: Wang, C.: Sustento-Reodica, N.: *et al* (2013) Impact of calcineurin-inhibitor conversion to mTOR inhibitor on renal allograft function in a prednisone-free regimen. *American Journal of Transplantation* 13: 2902-2911.	Population
Chisholm, M. A.: Middleton, M. D. (2006) Modified-release tacrolimus. *Annals of Pharmacotherapy* 40(2): 270-275.	Study Design
Ciancio, G.: Miller, J.: Gonwa, T. A. (2005) Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 80(2 Suppl): S191-200.	Study Design
Citterio, F.: Scatà, 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(5): 1685-6.	Population
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. *Transplantation* 83: 1041-1047.	Population
Cruzado, J. M.: Bestard, O.: Riera, L.: Torras, J.: Gil-Vernet, S.: Seron, D.: *et al* (2007) Immunosuppression for dual kidney transplantation with marginal organs: The old is better yet. *American Journal of Transplantation* 7(3): 639-644.	Study Design
Dantal, J.: Berthoux, F.: Moal, M. C.: Rostaing, L.: Legendre, C.: Genin, R.: *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*	Duplicate

25(1): 138.	
Dean, P. G.: Lund, W. J.: Larson, T. S.: Prieto, M.: Nyberg, S. L.: Ishitani, M. B.:*et al* (2004) Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation* 77(10): 1555-61.	Outcome
Diekmann, F.: Gutierrez-Dalmau, A.: Lopez, S.: Cofan, F.: Esforzado, N.: Ricart, M. J.: *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(8): 2316-2321.	Population
Dudley, C.: Pohanka, E.: Riad, H.: Dedochova, J.: Wijngaard, P.: Sutter, C.: *et al* (2005) Mycophenolate mofetil substitution for cyclosporine a in renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. *Transplantation* 79: 466-475.	Population
Durlik, M.: Paczek, L.: Rutkowski, B.: Lewandowska, D.: Debska-Slizien, A.: Chamienia, A.: *et al* (2010) The efficacy and safety of ciclosporin (Equoral (R)) capsules after renal transplantation: A muiticentre, open-label, phase IV clinical trial. *Annals of Transplantation* 15(3): 51-59.	Study Design
Ekberg, H.: Grinyó, J.: Nashan, B.: Vanrenterghem, Y.: Vincenti, F.: Voulgari, A.: *et al* (2007) Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. *American Journal of Transplantation* 7: 560-570.	Comparator
Ekberg, H.: Tedesco-Silva, H.: Demirbas, A.: Vítko, S.: Nashan, B.: Gürkan, A.: *et al* (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. *New England Journal of Medicine* 357: 2562-2575.	Intervention
El-Agroudy, A. E.: El-Dahshan, K. F.: Wafa, E. W.: Sheashaa, H. A.: Gad, Z. A.: Ismail, A. M.: *et al* (2009) Safe conversion of mycophenolate mofetil to azathioprine in kidney transplant recipients with sirolimus-based immunosuppression. *Nephrology* 14: 255-261.	Population
El-Sabrout, R.: Delaney, V.: Qadir, M.: Butt, F.: Hanson, P.: Butt, K. M. (2003) Sirolimus in combination with tacrolimus or mycophenolate mofetil for minimizing acute rejection risk in	Study Design

renal transplant recipients - A single center experience. *Transplantation Proceedings* 35(S3): 89S-94S.	
Facundo, C.: Diaz, J. M.: Guirado, L.: Duran, F.: Herreros, M. A.: Diaz, M.: *et al* (2002) Results of a triple induction regime with tacrolimus, mycophenolate mofetil, and prednisone in renal transplantation. *Transplantation Proceedings* 34(1): 98.	Study Design
Favi, E.: Citterio, F.: Spagnoletti, G.: Gargiulo, A.: Delreno, F.: Romagnoli, J.: *et al* (2009) Prospective clinical trial comparing two immunosuppressive regimens, tacrolimus and mycophenolate mofetil versus everolimus and low-dose cyclosporine, in de novo renal transplant recipients: results at 6 months follow-up. *Transplantation Proceedings* 41, 1152-1155.	Study Design
Favi, E.: Spagnoletti, G.: Salerno, M. P.: Pedroso, J. A.: Romagnoli, J.: Citterio, F. (2013) Tacrolimus plus mycophenolate mofetil vs. cyclosporine plus everolimus in deceased donor kidney transplant recipients: Three-yr results of a single-center prospective clinical trial. *Clinical Transplantation* 27, E359-e367.	Study Design
Ferguson, R.: Grinyó, J.: Vincenti, F.: Kaufman, D. B.: Woodle, E. S.: Marder, B. A.: *et al* (2011) Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *American Journal of Transplantation* 11: 66-76.	Population
Ferrer, F.: Machado, S.: Alves, R.: Macario, F.: Bastos, C.: Roseiro, A.: *et al* (2010) Induction With Basiliximab in Renal Transplantation. *Transplantation Proceedings* 42(2): 467-470.	Study Design
Filipe, R.: Mota, A.: Alves, R.: Bastos, C.: Macario, F.: Figueiredo, A.: *et al* (2009) Kidney Transplantation With Corticosteroid-Free Maintenance Immunosuppression: A Single Center Analysis of Graft and Patient Survivals. *Transplantation Proceedings* 41(3): 843-845.	Study Design
Filler, G.: Webb, N. J.: Milford, D. V.: Watson, A. R.: Gellermann, J.: Tyden, G.: *et al* (2005) Four-year data after pediatric renal transplantation: a randomized trial of tacrolimus vs. cyclosporin microemulsion. *Pediatric Transplantation* 9: 498-503.	Outcome
Flechner S. M.: Goldfarb, D.: Modlin, C.: Feng, J.: Krishnamurthi, V.: Mastroianni, B.: *et al* (2002) Kidney	Population

transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. *Transplantation* 74(8): 1070-6.	
Flechner, S.: Friend, P.: Campistol, J.: Weir, M.: Diekmann, F.: Russ, G. (2009) De novo immunosuppression with mammalian target of rapamycin inhibitors and posttransplantation malignancy in focus. *Transplantation Proceedings* 41(6 Suppl): S42-44.	Study Design
Friend, P. J. (2011) Thymoglobulin induction and steroid-free immunosuppression in kidney transplantation from deceased donors after cardiac death - an open label randomised controlled trial to evaluate the role of thymoglobulin as induction immunosuppression in kidney transplants from deceased donors after cardiac death. clinicaltrials.gov/ct2/show/NCT01239563	No Data
Frimat, L.: Cassuto-Viguier, E.: Provot, F.: Rostaing, L.: Charpentier, B.: Akposso, K.: *et al* (2010) Long-Term Impact of Cyclosporin Reduction with MMF Treatment in Chronic Allograft Dysfunction: REFERENECE Study 3-Year Follow Up. *Journal of transplantation* [online].	Population
Frimat, L.: Cassuto-Viguier, E.: Charpentier, B.: Noël, C.: Provôt, F.: Rostaing, L.: *et al* (2006) Impact of cyclosporine reduction with MMF: a randomized trial in chronic allograft dysfunction. The 'reference' study. *American Journal of Transplantation* 6: 2725-2734.	Population
Foroncewicz, B.: Mucha, K.: Ciszek, M.: Malkowski, P.: Durlik, M.: Szmidt, J.: *et al* (2013) A comparison between two tacrolimus-based immunosuppression regimens in renal transplant recipients: 7-year follow-up. *Annals of Transplantation* 18(1): 384-392.	Study Design
Gaber, A. O.: Kahan, B. D.: Buren, C.: Schulman, S. L.: Scarola, J.: Neylan, J. F. Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. *Transplantation* 86: 1187-1195.	Population
Garcia, I. (2002) Efficacy and safety of dual versus triple tacrolimus-based therapy in kidney transplantation: Two-year follow-up. *Transplantation Proceedings* 34(5): 1638-9.	Comparator

Gonzalez, F.: Espinoza, M.: Herrera, P.: Rocca, X.: Reynolds, E.: Lorca, E.: *et al* (2010) Everolimus versus azathioprine in a cyclosporine and ketoconazole-based immunosuppressive therapy in kidney transplant: 3-year follow-up of an open-label, prospective, cohort, comparative clinical trial. *Transplantation Proceedings* 42, 270-272.	Study Design
Gelder, T.: Tedesco Silva, H.: Fijter, J. W.: Budde, K.: Kuypers, D.: Arns, W.: *et al* (2010) Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. *Transplantation* 89: 595-599.	Comparator
Gelder, T.: Silva, H. T.: Fijter, H.: Budde, K.: Kuypers, D.: Mamelok, R. D.: *et al* (2011) How delayed graft function impacts exposure to mycophenolic acid in patients after renal transplantation. *Therapeutic Drug Monitoring* 33: 155-164.	Population
Gelder, T.: Silva, H. T.: Fijter, J. W.: Budde, K.: Kuypers, D.: Tyden, G.: *et al* (2008) Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation* 86: 1043-1051.	Comparator
Gonwa, T.: Johnson, C.: Ahsan, N.: Alfrey, E. J.: Halloran, P.: Stegall, M.: *et al* (2003) Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine plus mycophenolate mofetill after cadaveric kidney transplantation: Results at three years. *Transplantation* 75: 2048-2059.	Population
Gonzalez Molina, M.: Morales, J. M.: Marcen, R.: Campistol, J. M.: Oppenheimer, F.: Seron, D.: *et al* (2007) Renal Function in Patients With Cadaveric Kidney Transplants Treated With Tacrolimus or Cyclosporine. *Transplantation Proceedings* 39(7): 2167-2169.	Study Design
Gürkan, A.: Kaçar, S.: Erdoğdu, U.: Varilsüha, C.: Kandemir, G.: Karaca, C.: *et al* (2008) The effect of sirolimus in the development of chronic allograft nephropathy. *Transplantation Proceedings* 40: 114-116.	Population
Grafals, M. (2011) Low dose thymoglobulin as induction agent on prednisone-free regimens of renal transplant recipients. clinicaltrials.gov/ct2/show/NCT01280617	Comparator
Grinyo, J.: Alberu, J.: Contieri, F. L.: Manfro, R. C.: Mondragon, G.: Nainan, G.: *et al* (2012) Improvement in renal	Population

function in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: 2-year results from the long-term extension of a phase II study. *Transplant International* 25: 1059-1064.	
Grushkin, C.: Mahan, J. D.: Mange, K. C.: Hexham, J. M.: Ettenger, R. (2013) De novo therapy with everolimus and reduced-exposure cyclosporine following pediatric kidney transplantation: A prospective, multicenter, 12-month study. *Pediatric Transplantation* 17(3): 237-243.	Population
Grushkin, C.: Mahan, J. D.: Mange, K. C.: Hexham, J. M.: Ettenger, R. (2013) De novo therapy with everolimus and reduced-exposure cyclosporine following pediatric kidney transplantation: A prospective, multicenter, 12-month study. *Pediatric Transplantation* 17(3): 237-243.	Study Design
Hakemi, M.: Shahebrahimi, K.: Ganji, M. R.: Najafi, I.: Broumand, B. (2002) Side effects of mycophenolate mofetil versus azathioprine in iranian renal transplant recipients (single-center experience). *Transplantation Proceedings* 34(6): 2091-2.	Study Design
Han, D. J.: Park, J. B.: Kim, Y. S.: Kim, S. J.: Ha, J.: Kim, H. C.: *et al* (2012) A 39-month follow-up study to evaluate the safety and efficacy in kidney transplant recipients treated with modified-release tacrolimus (FK506E)-based immunosuppression regimen. *Transplantation Proceedings* 44, 115-117.	Study Design
Han, F.: Wu, J.: Huang, H.: Zhang, X.: He, Q.: Wang, Y.:*et al* (2011) Conversion from cyclosporine to sirolimus in chronic renal allograft dysfunction: a 4-year prospective study. *Experimental and Clinical Transplantation* 9: 42-49.	Population
Hazzan, M.: Labalette, M.: Copin, M. C.: Glowacki, F.: Provôt, F.: Pruv, F. R.: *et al* (2005) Predictive factors of acute rejection after early cyclosporine withdrawal in renal transplant recipients who receive mycophenolate mofetil: results from a prospective, randomized trial. *Journal of the American Society of Nephrology* 16: 2509-2516.	Outcome
Heller, T.: Gelder, T.: Budde, K.: Fijter, J. W.: Kuypers, D.: Arns, W.: *et al* (2007) Plasma concentrations of mycophenolic acid acyl glucuronide are not associated with diarrhea in renal transplant recipients. *American Journal of Transplantation* 7:	Outcome

1822-1831.	
Hest, R. M.: Gelder, T.: Vulto, A. G.: Mathot, R. A. (2005) Population pharmacokinetics of mycophenolic acid in renal transplant recipients. *Clinical Pharmacokinetics* 44, 1083-1096.	Study Design
Hirsch, H. H.: Vincenti, F.: Friman, S.: Tuncer, M.: Citterio, F.: Wiecek, A.: *et al* (2013) Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. *American Journal of Transplantation* 13: 136-145.	Outcome
Höcker, B.: Kovarik, J. M.: Daniel, V.: Opelz, G.: Fehrenbach, H.: Holder, M.: *et al* (2008) Pharmacokinetics and immunodynamics of basiliximab in pediatric renal transplant recipients on mycophenolate mofetil comedication. *Transplantation* 86: 1234-1240.	Comparator
Holdaas, H.: Rostaing, L.: Serón, D.: Cole, E.: Chapman, J.: Fellstrøm, B.: *et al* (2011) Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 92: 410-418.	Population
Holdaas, H.: Rostaing, L.: Serón, D.: Cole, E.: Chapman, J.: Fellstrøm, B.: *et al* (2011) Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 92: 410-418.	Duplicate
Hooff, J.: Walt, I.: Kallmeyer, J.: Miller, D.: Dawood, S.: Moosa, M. R.: *et al* (2012) Pharmacokinetics in stable kidney transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. *Therapeutic Drug Monitoring* 34: 46-52.	Study Design
Huang, H. F.: Yao, X.: Chen, Y.: Xie, W. Q.: Shen-Tu, J. Z.: Chen, J. H.: *et al* (2014) Cyclosporine A and tacrolimus combined with enteric-coated mycophenolate sodium influence the plasma mycophenolic acid concentration - a randomised controlled trial in Chinese live related donor kidney transplant recipients. *International Journal of Clinical Practice* Supplement 68(181): 4-9.	Outcome
Iaria, G.: Pisani, F.: Iorio, B.: Lucchesi, C.: De Luca, L.: Ielpo, B. (2006) Long-Term Results of Kidney Transplantation With	Study Design

Cyclosporine- and Everolimus-Based Immunosuppression. *Transplantation Proceedings* 38(4): 1018-1019.	
Ireland, R. (2011) Early switch from calcineurin inhibitors to mTOR inhibitors leads to improved renal graft function. *Nature Reviews Nephrology* 7, 243.	Study Design
Isrctn (2006) A randomised prospective trial of Daclizumab induction followed by Sirolimus in association with Mycophenolate Mofetil and steroids versus standard Cyclosporin based triple therapy for rejection prophylaxis in renal transplantation. controlled-trials.com/ISRCTN74336394	No Data
Isrctn (2004) A Prospective Randomised Trial of the use of Cellcept to allow early Tacrolimus Withdrawal in Live Donor Kidney Transplantation. controlled-trials.com/ISRCTN63298320	No Data
Isrctn (2006) Mycophenolate sodium versus Everolimus or Cyclosporine with Allograft Nephropathy as Outcome. controlled-trials.com/ISRCTN69188731	No Data
Jevnikar, A.: Arlen, D.: Barrett, B.: Boucher, A.: Cardella, C.: Cockfield, S. M.: *et al* (2008) Five-year study of tacrolimus as secondary intervention versus continuation of cyclosporine in renal transplant patients at risk for chronic renal allograft failure. *Transplantation* 86: 953-960.	Population
Jose, M. (2007). Calcineurin inhibitors in renal transplantation: adverse effects. *Nephrology* 12: S66-S74.	Study Design
Joss, N.: Rodger, R. S.: McMillan, M. A.: Junor, B. J. (2007) Randomized study comparing cyclosporine with azathioprine one year after renal transplantation - 15-Year outcome data. *Transplantation* 83(5): 582-587.	Population
Jungraithmayr, T. C.: Wiesmayr, S.: Staskewitz, A.: Kirste, G.: Bulla, M.: Fehrenbach, H.: *et al* (2007) Five-year outcome in pediatric patients with mycophenolate mofetil-based renal transplantation. *Transplantation* 83, 900-905.	Study Design
Jurewicz, W. A. (2003) Tacrolimus versus cyclosporin immunosuppression: long-term outcome in renal transplantation. *Nephrology, Dialysis, Transplantation* 18(Suppl 1): i7-11.	Population

Kahan, B. D. (2003) Two-year results of multicenter phase III trials on the effect of the addition of sirolimus to cyclosporine-based immunosuppressive regimens in renal transplantation. *Transplantation Proceedings* 35(3 Suppl):37S-51S.	Population
Kamar, N.: Allard, J.: Ribes, D.: Durand, D.: Ader, J. L.: Rostaing, L. (2005) Assessment of glomerular and tubular functions in renal transplant patients receiving cyclosporine A in combination with either sirolimus or everolimus. *Clinical Nephrology* 63(2): 80-86.	Study Design
Kamar, N.: Rostaing, L.: Cassuto, E.: Villemain, F.: Moal, M. C.: Ladrière, M.: *et al* (2012) A multicenter, randomized trial of increased mycophenolic acid dose using enteric-coated mycophenolate sodium with reduced tacrolimus exposure in maintenance kidney transplant recipients. *Clinical Nephrology* 77: 126-136.	Population
Kandaswamy, R.: Melancon, J. K.: Dunn, T.: Tan, M.: Casingal, V.: Humar, A.: *et al* (2005) A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients--an interim analysis. *American Journal of Transplantation* 5: 1529-1536.	Population
Ke-Pu, L.: Xiao-Min, Y.: Shuai-Jun, M.: Zhi-Bin, L.: Geng, Z.: Jian-Lin, Y. (2011) Effects of tacrolimus and cyclosporine A on inflammatory cytokines and blood lipid after renal transplantation. *Journal of Clinical Rehabilitative Tissue Engineering Research* 15(31): 5769-5772.	Language
Khwaja, K.: Asolati, M.: Harmon, J.: Melancon, J. K.: Dunn, T.: Gillingham, K.: *et al* (2004) Outcome at 3 years with a prednisone-free maintenance regimen: A single-center experience with 349 kidney transplant recipients. *American Journal of Transplantation* 4(6): 980-7.	Study Design
Kihm, L. P.: Hinkel, U. P.: Michael, K.: Sommerer, C.: Seckinger, J.: Morath, C.: *et al* (2009) Contrast enhanced sonography shows superior microvascular renal allograft perfusion in patients switched from cyclosporine A to everolimus. *Transplantation* 88: 261-265.	Population
Koch, M.: Becker, T.: Lueck, R.: Neipp, M.: Klempnauer, J.: Nashan, B. (2009) Basiliximab induction therapy in kidney transplantation: Benefits for long term allograft function after 10	Study Design

years? *Biologics: Targets and Therapy* 3: 51-56.	
Khosroshahi, H. T.: Tubbs, R. S.: Shoja, M. M.: Ghafari, A.: Noshad, H.: Ardalan, M. R. (2008) Effect of prophylaxis with low-dose anti-thymocyte globulin on prevention of acute kidney allograft rejection. *Transplantation Proceedings* 40: 137-139.	Population
Kovac, D.: Kotnik, V.: Kandus, A. (2005) Basiliximab and mycophenolate mofetil in combination with low-dose cyclosporine and methylprednisolone effectively prevent acute rejection in kidney transplant recipients. *Transplantation Proceedings* 37(10): 4230-4234.	Study Design
Krämer, B. K.: Böger, C.: Krüger, B.: Marienhagen, J.: Pietrzyk, M.: Obed, A.: *et al* (2005) Cardiovascular risk estimates and risk factors in renal transplant recipients. *Transplantation Proceedings* 37: 1868-1870.	Outcome
Krämer, B. K.: Klinger, M.: Vítko: Glyda, M.: Midtvedt, K.: Stefoni, S.: *et al* (2012) Tacrolimus-based, steroid-free regimens in renal transplantation: 3-year follow-up of the ATLAS trial. *Transplantation* 94: 492-498.	Comparator
Kreis, H. (2007). Worse renal transplant outcomes with sirolimus-mycophenolate than with calcineurin inhibitor regimens. *Nature Clinical Practice Nephrology* 3(8): 424-425.	Study Design
Kwon, O.: Cho, J. H.: Choi, J. Y.: Park, S. H.: Kim, Y. L.: Kim, H. K.: *et al* (2013) Long-term Outcome of Azathioprine Versus Mycophenolate Mofetil in Cyclosporine-Based Immunosuppression in Kidney Transplantation: 10 Years of Experience at a Single Center. *Transplantation Proceedings* 45(4): 1487-1490.	Study Design
Kumar, A.: Zaman, W.: Chaurasia, D.: Gupta, A.: Sharma, R. K.: Gulati, S. (2002) Prospective randomized trial to evaluate the efficacy of single low dose ATG induction in renal transplant recipient with spousal kidney. *Indian Journal of Urology* 19: 58-62.	Study Design
Krämer, B. K.: Zülke, C.: Kammerl, M. C.: Schmidt, C.: Hengstenberg, C.: Fischereder, M.: *et al* (2003) Cardiovascular risk factors and estimated risk for CAD in a randomized trial comparing calcineurin inhibitors in renal transplantation. *American Journal of Transplantation* 3(8):982-7.	Outcome

Krischock, L.: Marks, S. D. (2010) Induction therapy: Why, when, and which agent? *Pediatric Transplantation* 14(3): 298-313.	Study Design
Langone, A. J.: Chan, L.: Bolin, P.: Cooper, M. (2011) Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. *Transplantation* 91: 470-478.	Population
Lezaic, V. D.: Marinkovic, J.: Ristic, S.: Dokic, Z. M.: Basta Jovanovic, G.: Radivojevic, D. M.: *et al* (2005) Conversion of azathioprine to mycophenolate mofetil and chronic graft failure progression. *Transplantation Proceedings* 37: 734-736.	Population
Lin, C. C.: Chuang, F. R.: Lee, C. H.: Wang, C. C.: Chen, Y. S.: Liu, Y. W.: *et al* (2005) The renal-sparing efficacy of basiliximab in adult living donor liver transplantation. *Liver Transplantation* 11, 1258-1264.	Study Design
Liu, Y.: Yang, M. S.: Yuan, J. Y. (2013) Immunosuppressant utilization and cardiovascular complications among Chinese patients after kidney transplantation: A systematic review and analysis. *International Urology and Nephrology* 45(3): 885-892.	Study Design
Liu, B.: Lin, Z. B.: Ming, C. S.: Zhang, W. J.: Chen, Z. S.: Sha, B. (2003) Randomized trial of tacrolimus in combination with mycophenolate mofetil versus cyclosporine with mycophenolate mofetil in cadaveric renal transplant recipients with delayed graft function. *Transplantation proceedings* 35: 87-88.	Study Design
Liu, M.: Zhang, W.: Gu, M.: Yin, C.: Zhang, W. Y.: Lv, Q.: *et al* (2007) Protective effects of sirolimus by attenuating connective tissue growth factor expression in human chronic allograft nephropathy. *Transplantation Proceedings* 39: 1410-1415.	Outcome
Liu, Y.: Zhou, P.: Han, M.: Xue, C. B.: Hu, X. P.: Li, C. (2010) Basiliximab or Antithymocyte Globulin for Induction Therapy in Kidney Transplantation: A Meta-analysis. *Transplantation Proceedings* 42(5): 1667-1670.	Study Design
Ljuca, F.: Imamovic, S.: Mesic, D.: Hasukic, S. H.: Omerovic, S.: Bazardzanovic, M. (2009) Micophenolat Mofetil versus Azathioprine: effects on renal graft function in early posttransplant period. *Bosnian journal of basic medical*	Study Design

sciences 9(2): 156-160.	
Lou, H. X.: Vathsala, A. (2004) Conversion from mycophenolate mofetil to azathioprine in high-risk renal allograft recipients on cyclosporine-based immunosuppression. *Transplantation Proceedings* 36(7): 2090-1.	Population
Loriga, G.: Ciccarese, M.: Pala, P. G.: Satta, R. P.: Fanelli, V.: Manca, M. L.: *et al* (2010) De Novo Everolimus-Based Therapy in Renal Transplant Recipients: Effect on Proteinuria and Renal Prognosis. *Transplantation Proceedings* 42(4): 1297-1302.	Study Design
Loriga, G.: Ciccarese, M.: Pala, P. G.: Satta, R. P.: Fanelli, V.: Manca, M. L. De Novo Everolimus-Based Therapy in Renal Transplant Recipients: Effect on Proteinuria and Renal Prognosis. *Transplantation Proceedings* 42(4): 1297-1302.	Population
Luan, F. L.: Zhang, H.: Schaubel, D. E.: Miles, C. D.: Cibrik, D.: Norman, S.: *et al* (2008) Comparative risk of impaired glucose metabolism associated with cyclosporine versus tacrolimus in the late posttransplant period. *American Journal of Transplantation* 8(9): 1871-1877.	Study Design
Luan, F. L.: Zhang, H.: Schaubel, D. E.: Miles, C. D.: Cibrik, D.: Norman, S.: *et al* (2008) Comparative risk of impaired glucose metabolism associated with cyclosporine versus tacrolimus in the late posttransplant period. *American Journal of Transplantation* 8(9): 1871-1877.	Outcome
Maiorano, A.: Stallone, G.: Schena, A.: Infante, B.: Pontrelli, P.: Schena, F. P.: *et al* (2006) Sirolimus interferes with iron homeostasis in renal transplant recipients. *Transplantation* 82: 908-912.	Population
Martínez-Castelao, A.: Sarrias, X.: Bestard, O.: Gil-Vernet, S.: Serón, D.: Cruzado, J. M.: *et al* (2005) Arterial elasticity measurement in renal transplant patients under anticalcineurin immunosuppression. *Transplantation Proceedings* 37: 3788-3790.	Population
Martínez-Castelao, A.: Sarrias, X.: Bestard, O.: Gil-Vernet, S.: Serón, D.: Cruzado, J. M.: *et al* (2005) Arterial elasticity measurement in renal transplant patients under anticalcineurin immunosuppression. *Transplantation Proceedings* 37, 3788-	Study Design

3790.	
Mathew, T.: Kreis, H.: Friend, P. (2004). Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies*. *Clinical transplantation* 18(4): 446-449.	Study Design
Meier, M.: Nitschke, M.: Weidtmann, B.: Jabs, W. J.: Wong, W.: Suefke, S.: *et al* (2006) Slowing the progression of chronic allograft nephropathy by conversion from cyclosporine to tacrolimus: a randomized controlled trial. *Transplantation* 81, 1035-1040.	Study Design
Meier, M.: Nitschke, M.: Weidtmann, B.: Jabs, W. J.: Wong, W.: Suefke, S.: *et al* (2006) Slowing the progression of chronic allograft nephropathy by conversion from cyclosporine to tacrolimus: a randomized controlled trial. *Transplantation* 81: 1035-1040.	Language
Meier-Kriesche, H. U.: Davies, N. M.: Grinyo, J.: Heading, R.: Mamelok, R.: Wijngaard, P.: *et al* (2005) Mycophenolate sodium does not reduce the incidence of GI adverse events compared with mycophenolate mofetil. *American Journal of Transplantation* 5(5): 1164-1164.	Study Design
Metcalfe, M. S.: Jain, S.: Waller, J. R.: Saunders, R. N.: Bicknell, G. R.: Nicholson, M. L. (2002) A randomized trial of mycophenolate mofetil versus azathioprine as calcineurin inhibitor sparing agents in the treatment of chronic allograft nephropathy. *Transplantation Proceedings* 34(5): 1812-4.	Population
Monaco, A. P.: Morris P. J. (2011). Everolimus and Long-Term Outcomes in Renal Transplantation: Seeking an Optimal Strategy for Immunosuppression. *Transplantation* 92(3): S1-S2.	Study Design
Montagnino, G.: Sandrini, S.: Casciani, C.: Schena, F. P.: Carmellini, M.: Civati, G.: *et al* (2005) A randomized trial of steroid avoidance in renal transplant patients treated with everolimus and cyclosporine. *Transplantation Proceedings* 37: 788-790.	Comparator
Moore, R. (2008). New-onset diabetes after renal transplantation: Comparing ciclosporin and tacrolimus. *Nature Clinical Practice Nephrology* 4(1): 20-21.	Comparator

Moore, R. (2008). New-onset diabetes after renal transplantation: Comparing ciclosporin and tacrolimus. *Nature Clinical Practice Nephrology* 4(1): 20-21.	Study Design
Morales, J. M.: Campistol, J. M.: Kreis, H.: Mourad, G.: Eris, J.: Schena, F. P.: *et al* (2005) Sirolimus-based therapy with or without cyclosporine: long-term follow-up in renal transplant patients. *Transplantation Proceedings* 37, 693-696.	Study Design
Morales, J. M.: Campistol, J. M.: Kreis, H.: Mourad, G.: Eris, J.: Schena, F. P.: *et al* (2005) Sirolimus-based therapy with or without cyclosporine: long-term follow-up in renal transplant patients. *Transplantation Proceedings* 37: 693-696.	Language
Morales, J. M.: Hartmann, A.: Walker, R.: Arns, W.: Senatorski, G.: Grinyo, J. M.: *et al* (2009) Similar Lipid Profile But Improved Long-Term Outcomes With Sirolimus After Cyclosporine Withdrawal Compared to Sirolimus With Continuous Cyclosporine. *Transplantation Proceedings* 41: 2339-2344.	Outcome
Moscarelli, L.: Caroti, L.: Antognoli, G.: Zanazzi, M.: Di Maria, L.: Carta, P.: *et al* (2013) Everolimus leads to a lower risk of BKV viremia than mycophenolic acid in de novo renal transplantation patients: a single-center experience. *Clinical Transplantation* 27(4): 546-554.	Study Design
Mulay, A. V.: Hussain, N.: Fergusson, D.: Knoll, G. A. (2005) Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: A systematic review of randomized trials. *American Journal of Transplantation* 5(7): 1748-1756.	No Data
Nashan, B.: Ivens, K.: Suwelack, B.: Arns, W.: Abbud, F. M. (2004) Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant patients: preliminary results from the myfortic prospective multicenter study. *Transplantation Proceedings* 36(2 Suppl): 521S-523S.	Population
Nct (2002) Phase II/III, open-label, randomized, controlled, multiple-dose study of efficacy and safety of BMS-224818 as part of a quadruple drug regimen in first renal transplant recipients. clinicaltrials.gov/show/NCT00035555	No Data
Nct (2004) A Phase III, Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Prograf (Tacrolimus)/MMF, Modified Release (MR)	No Data

Tacrolimus/MMF and Neoral (Cyclosporine)/MMF in de Novo Kidney Transplant Recipients. clinicaltrials.gov/show/NCT00064701	
Nct (2004) A Multi-centre, Randomized, Open-label, Study to Compare Conversion From Calcineurin Inhibitors to Rapamune Versus Standard Therapy in Established Renal Allograft Recipients on Maintenance Therapy With Mild to Moderate Renal Insufficiency. clinicaltrials.gov/ct2/show/NCT00273871	No Data
Nct (2002) A Randomized, Open-label, Comparative Evaluation of Conversion From Calcineurin Inhibitors to Sirolimus Versus Continued Use of Calcineurin Inhibitors in Renal Allograft Recipients. clinicaltrials.gov/ct2/show/NCT00038948	No Data
Nichelle, L.: Canet, S.: Garrigue, V.: Chong, G.: Mourad, G. (2002) Arterial hypertension in renal transplant recipients treated with tacrolimus or cyclosporine-neoral. *Transplantation proceedings* 34(7): 2824-2825.	Intervention
Novoa, P. A.: Grinyó, J. M.: Ramos, F. J.: Errasti, P.: Franco, A.: Aldana, G.: *et al* (2011) De novo use of everolimus with elimination or minimization of cyclosporine in renal transplant recipients. *Transplantation Proceedings* 43: 3331-3339.	Comparator
Oberbauer, R. (2005). Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: A systematic review of randomized trials. *American Journal of Transplantation* 5(12): 3023.	Study Design
Oberbauer, R. (2005). Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: A systematic review of randomized trials. *American Journal of Transplantation* 5(12): 3023.	Outcome
Oberbauer, R.: Hutchison, B.: Eris, J.: Arias, M.: Claesson, K.: Mota, A.: *et al* (2003) Health-related quality-of-life outcomes of sirolimus-treated kidney transplant patients after elimination of cyclosporine A: results of a 2-year randomized clinical trial. *Transplantation* 75(8): 1277-85.	Comparator
Oppenheimer, F.: Rebollo, P.: Grinyo, J. M.: Ortega, F.: Sanchez-Plumed, J.: Gonzalez-Molina, M.: *et al* (2009) Health-related quality of life of patients receiving low-toxicity immunosuppressive regimens: a substudy of the Symphony	Intervention

Study. *Transplantation* 87: 1210-1213.	
Ortega, F.: Sánchez-Fructuoso, A.: Cruzado, J. M.: Gómez: Alamillo, J. C.: Alarcón, A.: Pallardó, L.: *et al* (2011) Gastrointestinal quality of life improvement of renal transplant recipients converted from mycophenolate mofetil to enteric-coated mycophenolate sodium drugs or agents: mycophenolate mofetil and enteric-coated mycophenolate sodium. *Transplantation* 92: 426-432.	Outcome
Ozdemir, B. H.: Ozdemir, A. A.: Erdal, R.: Ozdemir, F. N.: Haberal, M. (2011) Rapamycin Prevents Interstitial Fibrosis in Renal Allografts through Decreasing Angiogenesis and Inflammation. *Transplantation Proceedings* 43(2): 524-526.	Study Design
Painter, P. L.: Topp, K. S.: Krasnoff, J. B.: Adey, D.: Strasner, A.: Tomlanovich, S.: *et al* (2003) Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. Kidney International 63(6): 2309-16.	Comparator
Parrott, N. R.: Hammad, A. Q.: Watson, C. J.: Lodge, J. P.: Andrews, C. D. (2005) Multicenter, randomized study of the effectiveness of basiliximab in avoiding addition of steroids to cyclosporine a monotherapy in renal transplant recipients. *Transplantation* 79: 344-348.	Comparator
Pascual, J.: Segoloni, G.: Gonzalez Molina, M.: del Castillo, D.: Capdevila, L.: Arias, M.: *et al* (2003) Comparison between a two-drug regimen with tacrolimus and steroids and a triple one with azathioprine in kidney transplantation: results of a European trial with 3-year follow up. *Transplantation Proceedings* 35(5): 1701-3.	Population
Pascual, J.: Galeano, C.: Royuela, A.: Zamora, J. (2010) A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation* 90(4): 343-349.	Comparator
Pavlakis, M. (2006) Mycophenolate mofetil versus sirolimus as an adjunct to calcineurin inhibition after renal transplantation. Nature clinical practice. *Nephrology* 2: 558-559.	Outcome
Pavlakis, M. (2006) Mycophenolate mofetil versus sirolimus as an adjunct to calcineurin inhibition after renal transplantation. Nature clinical practice. *Nephrology* 2, 558-559.	Study Design

Pescovitz, M. D.: Vincenti, F.: Hart, M.: Melton, L.: Whelchel, J.: Mulgaonkar, S.:*et al* (2007) Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *British Journal of Clinical Pharmacology* 64: 758-771.	Intervention
Picard, N. (2010) Does Tacrolimus, in Comparison With Sirolimus, Increase Mycophenolic Acid Exposure in Kidney Transplant Recipients? *Clinical Pharmacology & Therapeutics* 87(6): 650-651.	Study Design
Pliszczynski, J.: Kahan, B. D. (2011). Better actual 10-year renal transplant outcomes of 80% reduced cyclosporine exposure with sirolimus base therapy compared with full cyclosporine exposure without or with concomittant sirolimus treatment. *Transplantation Proceedings* 43(10): 3657-3668.	Population
Pliszczynski, J.: Kahan, B. D. (2011) Better actual 10-year renal transplant outcomes of 80% reduced cyclosporine exposure with sirolimus base therapy compared with full cyclosporine exposure without or with concomittant sirolimus treatment. *Transplantation Proceedings* 43(10): 3657-3668.	Study Design
Ponticelli, C.: Salvadori, M.: Scolari, M. P.: Citterio, F.: Rigotti, P.: Veneziano, A.: *et al* (2011) Everolimus and minimization of cyclosporine in renal transplantation: 24-month follow-up of the EVEREST study. *Transplantation* 91: e72-73.	Comparator
Prokopenko, E.: Scherbakova, E.: Vatazin, A.: Pasov, S.: Budnikova, N.: Agafonova, S. (2005) Does mycophenolate mofetil increase the incidence of infections in renal transplant recipients? *Drugs Under Experimental & Clinical Research* 31(5-6): 199-205.	Study Design
Renner, F. C.: Dietrich, H.: Bulut, N.: Celik, D.: Freitag, E.: Gaertner, N.: *et al* (2013) The risk of polyomavirus-associated graft nephropathy is increased by a combined suppression of CD8 and CD4 cell-dependent immune effects. *Transplantation Proceedings* 45: 1608-1610.	No Data
Riegersperger, M.: Plischke, M.: Steiner, S.: Seidinger, D.: Sengoelge, G.: Winkelmayer, W. C.: *et al* (2013) Effect of conversion from ciclosporin to tacrolimus on endothelial progenitor cells in stable long-term kidney transplant recipients. *Transplantation* 95: 1338-1345.	Population

Rostaing, L.: Massari, P.: Garcia, V. D.: Mancilla-Urrea, E.: Nainan, G.: Carmen Rial, M.: *et al* (2011) Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. *Clinical Journal of the American Society of Nephrology* 6: 430-439.	Population
Ruggenenti, P.: Codreanu, I.: Cravedi, P.: Perna, A.: Gotti, E.: Remuzzi, G. (2006) Basiliximab combined with low-dose rabbit anti-human thymocyte globulin: a possible further step toward effective and minimally toxic T cell-targeted therapy in kidney transplantation. *Clinical Journal of the American Society of Nephrology* 1: 546-554.	Comparator
Ruiz, J. C.: Alonso, A.: Arias, M.: Campistol, J. M.: Gonzalez Molina, M.: Gonzalez Posada, J. M.: *et al* (2006) Conversion to sirolimus. *Nefrologia* 26: 52-63.	Study Design
Russ, G.: Segoloni, G.: Oberbauer, R.: Legendre, C.: Mota, A.: Eris, J.: *et al* (2005) Superior outcomes in renal transplantation after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function. *Transplantation* 80: 1204-1211.	Comparator
Rush, D. N.: Cockfield, S. M.: Nickerson, P. W.: Arlen, D. J.: Boucher, A.: Busque, S.: *et al* (2009) Factors associated with progression of interstitial fibrosis in renal transplant patients receiving tacrolimus and mycophenolate mofetil. *Transplantation* 88, 897-903.	Study Design
Samadzadeh, B.: Alemi, M.: Heidarnejadiyan, J.: Torkamanasadi, F. (2012) Prophylactic effect of mycophenolate mofetil on early outcomes of living donor kidney transplantation. *Iranian Journal of Kidney Diseases* 6: 63-68.	Population
Sanchez-Fructuoso, A. I. (2008). Everolimus: An update on the mechanism of action, pharmacokinetics and recent clinical trials. *Expert Opinion on Drug Metabolism and Toxicology* 4(6): 807-819.	Comparator
Sanchez-Fructuoso, A. I. (2008). Everolimus: An update on the mechanism of action, pharmacokinetics and recent clinical trials. *Expert Opinion on Drug Metabolism and Toxicology* 4(6): 807-819.	Study Design

Schena, F. P.: Pascoe, M. D.: Alberu, J.: Carmen Rial, M.: Oberbauer, R.: Brennan, D. C.: *et al* (2009) Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 87: 233-242.	Population
Sellares, J.: Moreso, F.: Carlos Ruiz, J.: Seron, D. (2011) Mean Glomerular Volume After Renal Transplantation in Patients Receiving Sirolimus and Cyclosporine A Compared With Elimination of Cyclosporine A at 3 Months. *Transplantation* 91(1): E5-E6.	Comparator
Shamseddin, M. K.: Gupta, A. (2011). Sirolimus: not so sparing in the Spare-the-Nephron trial. *Kidney International* 79(12): 1379-1379.	Language
Shihab, F. S.: Waid, T. H.: Conti, D. J.: Yang, H.: Holman, M. J.: Mulloy, L. C.: *et al* (2008) Conversion from cyclosporine to tacrolimus in patients at risk for chronic renal allograft failure: 60-month results of the CRAF Study. *Transplantation* 85: 1261-1269.	Population
Silva, H. T.: Yang, H. C.: Abouljoud, M.: Kuo, P. C.: Wisemandle, K.: Bhattacharya, P.:*et al* (2007) One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *American Journal of Transplantation* 7: 595-608.	Population
Silva, H. T.: Yang, H. C.: Meier-Kriesche, H. U.: Croy, R.: Holman, J.: Fitzsimmons, W. E.: *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(6): 636-641.	Population
Solà, R.: Díaz, J. M.: Guirado, L.: Sainz, Z.: Gich, I.: Picazo, M.: García, R.: *et al* (2003) Tacrolimus in induction immunosuppressive treatment in renal transplantation: comparison with cyclosporine. *Transplantation Proceedings* 35(5): 1699-700.	Study Design
Sollinger, H. (2004) Enteric-coated mycophenolate sodium: therapeutic equivalence to mycophenolate mofetil in de novo renal transplant patients. *Transplantation Proceedings* 36(2 Suppl): 517S-520S.	Study Design

Sollinger, H. (2004) Enteric-coated mycophenolate sodium: therapeutic equivalence to mycophenolate mofetil in de novo renal transplant patients. *Transplantation Proceedings* 36(S2): 517S-520S.	Comparator
Stallone, G.: Infante, B.: Schena, A.: Battaglia, M.: Ditonno, P.: Loverre, A.: *et al* (2005) Rapamycin for treatment of chronic allograft nephropathy in renal transplant patients. *Journal of the American Society of Nephrology* 16: 3755-3762.	Population
Stoves, J.: Newstead, C. G.: Baczkowski, A. J.: Owens, G.: Paraoan, M.: Hammad, A. Q. (2004) A randomized controlled trial of immunosuppression conversion for the treatment of chronic allograft nephropathy. *Nephrology, Dialysis, Transplantation* 19(8): 2113-20.	Population
Su, V. C. H.: Greanya, E. D.: Ensom, M. H. H. (2011) Impact of mycophenolate mofetil dose reduction on allograft outcomes in kidney transplant recipients on tacrolimus-based regimens: A systematic review. *Annals of Pharmacotherapy* 45(2): 248-257.	Study Design
Sun, C. S.: Hao, J. W.: Sun, J. (2002). A comparison between the therapeutic effects of mycophenolate mofetil and azathioprine in the management of patients after renal transplantation. *Herald Med* 21: 544.	Language
Suszynski, T. M.: Gillingham, K. J.: Rizzari, M. D.: Dunn, T. B.: Payne, W. D.: Chinnakotla, S.: *et al* (2013) Prospective randomized trial of maintenance immunosuppression with rapid discontinuation of prednisone in adult kidney transplantation. *American Journal of Transplantation* 13: 961-970.	Population
Suwelack, B.:, Gerhardt, U.: Kobelt, V.: Hillebrand, U.: Matzkies, F.: Hohage, H. (2002) Design and preliminary results of a randomized study on the conversion of treatment with calcineurin inhibitors to mycophenolate mofetil in chronic renal graft failure: effect, on serum cholesterol levels. *Transplantation Proceedings* 34(5): 1803-5.	Study Design
Takahashi, K.: Uchida, K.: Yoshimura, N.: Takahara, S.: Teraoka, S.: Teshima, R.: *et al* (2013) Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. *Transplantation Research* 2: 14.	Intervention

Tan, J.: Yang, S.: Wu, W. (2005) Basiliximab (Simulect) reduces acute rejection among sensitized kidney allograft recipients. *Transplantation Proceedings* 37, 903-905.	Comparator
Tedesco, H. (2011) Efficacy and safety of induction strategies combined with low tacrolimus exposure in kidney transplant recipients receiving everolimus or sodium mycophenolate. clinicaltrials.gov/ct2/show/NCT01354301	No Data
Tedesco-Silva, H.: Vitko, S.: Pascual, J.: Eris, J.: Magee, J. C.: Whelchel, J.: *et al* (2007) 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. *Transplant International* 20: 27-36.	Comparator
Trompeter, R.: Filler, G.: Webb, N. J.: Watson, A. R.: Milford, D. V.: Tyden, G.: *et al* (2002) Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. *Pediatric Nephrology* 17(3): 141-9.	No Data
Turconi, A.: Rilo, L. R.: Goldberg, J.: de Boccardo, G.: Garsd, A.: Otero, A. (2005) Open-label, multicenter study on the safety, tolerability, and efficacy of Simulect in pediatric renal transplant recipients receiving triple therapy with cyclosporin, mycophenolate, and corticosteroids. *Transplantation Proceedings* 37(2): 672-674.	No Data
Turconi, A.: Rilo, L. R.: Goldberg, J.: de Boccardo, G.: Garsd, A.: Otero, A. (2005) Open-label, multicenter study on the safety, tolerability, and efficacy of Simulect in pediatric renal transplant recipients receiving triple therapy with cyclosporin, mycophenolate, and corticosteroids. *Transplantation Proceedings* 37(2): 672-674.	Study Design
Urbizu, J. M.: Amenabar, J. J.: Gomez-Ullate, P.: Zarraga, S.: Lampreabe, I. (2002) Immunosuppression using tacrolimus/mycophenolate versus neoral/mycophenolate following kidney transplantation: A single-center experience. *Transplantation Proceedings* 34(1): 87-8.	Study Design
Vacher-Coponat, H.: Brunet, C.: Moal, V.: Loundou, A.: Bonnet, E.: Lyonnet, L.: *et al* (2006) Tacrolimus/mycophenolate killer lymphocyte recon kidney transplant mofetil improved natural titution one year after by reference to cyclosporine/azathioprine. *Transplantation* 82(4): 558-566.	Outcome

van Hooff, JP.: Squifflet, J. P.: Wlodarczyk, Z.: Vanrenterghem, Y.: Paczek, L. (2003) A prospective randomized multicenter study of tacrolimus in combination with sirolimus in renal-transplant recipients. *Transplantation* 75(12): 1934-9.	Comparator
Vester, U.: Kranz, B.: Wehr, S.: Boger, R.: Hoyer, P. F. (2002) Everolimus (Certican) in combination with neoral in pediatric renal transplant recipients: interim analysis after 3 months. *Transplantation Proceedings* 34(6): 2209-10.	Study Design
Vincenti, F.: Jensik, S. C.: Filo, R. S.: Miller, J.: Pirsch, J. (2002) A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years.[Erratum appears in Transplantation 2002 Apr 27;73(8):1370] *Transplantation* 73: 775-782.	Population
Vincenti, F.: Rostaing, L. (2005) Rationale and design of the DIRECT study: a comparative assessment of the hyperglycemic effects of tacrolimus and cyclosporine following renal transplantation. *Contemporary clinical trials* 26: 17-24.	No Data
Vincenti, F.: Tuncer, M.: Castagneto, M.: Klinger, M.: Friman, S.: Scheuermann, E. H.: *et al* (2005) Prospective, multicenter, randomized trial to compare incidence of new-onset diabetes mellitus and glucose metabolism in patients receiving cyclosporine microemulsion versus tacrolimus after de novo kidney transplantation. *Transplantation Proceedings* 37, 1001-1004.	Study Design
Vincenti, F.: Tuncer, M.: Castagneto, M.: Klinger, M.: Friman, S.: Scheuermann, E. H.: *et al* (2005) Prospective, multicenter, randomized trial to compare incidence of new-onset diabetes mellitus and glucose metabolism in patients receiving cyclosporine microemulsion versus tacrolimus after de novo kidney transplantation. *Transplantation Proceedings* 37: 1001-1004.	Duplicate
Vitko, S.: Klinger, M.: Salmela, K.: Wlodarczyk, Z.: Tyden, G.: Senatorski, G.: *et al* (2005) Corticosteroid-free regimens - Tacrolimus monotherapy after basiliximab administration and tacrolimus/mycophenolate mofetil - in comparison with a standard triple regimen in renal transplantation: Results of the Atlas study. *Transplantation* 80(12): 1734-1741.	Comparator

Waid, T. (2005) Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. *Clinical Transplantation* 19: 573-580.	Intervention
Walker, R. G.: Cottrell, S.: Sharp, K.: Tripodi, R.: Nicholls, K. M.: Fraser, I. *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. *Nephrology* 12: 607-614.	Outcome
Wang, K.: Zhang, H.: Li, Y.: Wei, Q.: Li, H.: Yang, Y.: *et al* (2004) Safety of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplantation Proceedings* 36(7): 2068-70.	Study Design
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(9): 947-953.	Study Design
Wang, K.: Zhang, H.: Li, Y.: Wei, Q.: Li, H.: Yang, Y.: *et al* (2004) Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplantation Proceedings* 36(7): 2071-2.	Study Design
Watorek, E.: Szymczak, M.: Boratynska, M.: Patrzalek, D.: Klinger, M. (2011) Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. *Transplantation Proceedings* 43, 2967-2969.	Study Design
Watorek, E.: Szymczak, M.: Boratynska, M.: Patrzalek, D.: Klinger, M. (2011) Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. *Transplantation Proceedings* 43: 2967-2969.	Comparator
Watson, C. J.: Firth, J.: Williams, P. F.: Bradley, J. R.: Pritchard, N.: Chaudhry, A.: *et al* (2005) A randomized controlled trial of late conversion from CNI-based to sirolimus-based immunosuppression following renal transplantation. *American Journal of Transplantation* 5: 2496-2503.	Population
Wissing, K. M.: Fomegne, G.: Broeders, N.: Ghisdal, L.: Hoang, A. D.: Mikhalski, D.: *et al* (2008) HLA mismatches remain risk factors for acute kidney allograft rejection in patients receiving quadruple immunosuppression with anti-	Study Design

interleukin-2 receptor antibodies. *Transplantation* 85(3): 411-416.	
Wlodarczyk, Z.: Ostrowski, M.: Mourad, M.: Krämer, B. K.: Abramowicz, D.: Oppenheimer, F.: *et al* (2012) Tacrolimus pharmacokinetics of once- versus twice-daily formulations in de novo kidney transplantation: a substudy of a randomized phase III trial. *Therapeutic Drug Monitoring* 34: 143-147.	Population
Yao, G.: Albon, E.: Adi, Y.: Milford, D.: Bayliss, S.: Ready, A.: *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(49): iii-65.	Comparator
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(6): 468-471.	Language

Appendix 4 Quality assessment

Induction therapies

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Bingyi 2003	Unclear	NR	NR	Unclear[a]	NR	Unclear[a]	Unclear	Inadequate	NR	Inadequate
Kahan 1999	Unclear	NR	Adequate	Adequate	NR	Adequate	Unclear	Adequate	Adequate	Unclear[b]
Lawen 2003	Unclear	NR	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate	Adequate
Nashan 1997	Adequate	Unclear	Unclear	Adequate	NR	Adequate	Unclear	Adequate	Adequate	Inadequate
Ponticelli 2001, 2001	Unclear	NR	Adequate	Adequate	NR	Adequate	Unclear	Adequate	Adequate	Unclear[c]
Albano 2013 (OSAKA trial;NCT00717470)[d]	Unclear	Unclear	Unclear	Inadequate	NR	Inadequate	Unclear	Unclear[e]	Inadequate	Adequate
Sheashaa 2003 (Sheashaa 2005, 2008 and 2011)	Unclear	Adequate	Adequate	Inadequate	NR	NR	Unclear	Unclear[f]	Unclear	Inadequate
Charpentier 2001	Unclear	NR	NR	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Unclear[c]
Samsel 2008	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Sheashaa 2008	Unclear	Adequate	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Charpentier 2003[d]	Unclear	Adequate	Inadequate[g]	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Brennan 2006	Unclear	Unclear	Adequate	Inadequate	Inadequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
Lebranchu 2002	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Mourad 2004	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate

Sollinger 2001	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Unclear[b]
Kyllonen 2007	Adequate	Adequate	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate

[a] described as a placebo-controlled trial but no further mention made of blinding; [b] non-EU population ; [c] lack of clarity regarding key demographic information which may influence applicability; [d] study of both induction and maintenance treatments; [e] numbers do not seem to add up; [f] all participants appear to remain in the study but this is unclear; [g] statistically significant between group difference in participant age

Maintenance therapies

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Schleibner 1995	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Unclear[a]	Adequate	Inadequate
Laskow 1996 + Vincenti 1996	Unclear	Unclear	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Mayer 1997 (Mayer 2002,1999)	Unclear	NR	Inadequate[b]	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
Radermacher 1998	Unclear	NR	Adequate	NR	NR	NR	Unclear	Adequate	Unclear	Inadequate
Jarzembowski 2005	Unclear	NR	Adequate	NR	NR	NR	Unclear	Inadequate	Unclear	Inadequate
Baboolal 2002	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	NR	Unclear	Inadequate
Campos 2002	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Unclear[c]
Margreiter (2002) (Kramer 2005 and Kramer 2008)	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Van Duijnhoven 2002	Unclear	Unclear	Unclear	NR	NR	NR	Unclear	Unclear [a]	Unclear	Inadequate
Waller 2002 (Murphy 2003)	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Unclear[c]
Charpentier 2003[d]	Unclear	Adequate	Inadequate[e]	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Toz 2004	Unclear	NR	Unclear	NR	Adequate	NR	Unclear	Inadequate	NR	Inadequate
Hardinger 2005 (Brennan 2005)	Unclear	NR	Adequate	NR	NR	NR	Unclear	Inadequate	Adequate	Unclear[f]
Sollinger 1995	Unclear	NR	Unclear	Partial[g]	NR	Partial[g]	Unclear	NR	Adequate	Inadequate

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012 has Australien SG results only)	Unclear	NR	Inadequate[h]	Adequate	NR	Adequate	Unclear	NR	Adequate	Inadequate
Sadek 2002	Adequate	Unclear	Adequate	Inadequate	NR	Inadequate	Unclear	Inadequate	Adequate	Adequate
Tuncer 2002	Unclear	NR	Unclear	Inadequate	Inadequate	Inadequate	Unclear	NR	NR	Inadequate
Merville 2004	Unclear	Unclear	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	Unclear	Unclear	Partial[i]	NR	NR	NR	Unclear	Inadequate	Adequate	Inadequate
Wlodarczyk 2005 (Wlodarczyk 2002)	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Inadequate	Adequate	Inadequate
Vacher-Coponat 2012	Adequate	Adequate	Unclear	Inadequate	Adequate	Inadequate	Unclear	Inadequate	Adequate	Inadequate
Zadrazil 2012	Unclear	NR	Adequate	NR	NR	NR	Unclear	Adequate	Adequate	Unclear[c]
Hernandez 2007	Adequate	Adequate	Partial[i]	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Rowshani 2006	Adequate	NR	Unclear	Inadequate	Adequate	Inadequate	Unclear	Inadequate	Unclear	Unclear[c]
Ulsh (1999)/Yang 1999	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	NR	Adequate	Unclear[f]
Weimer 2006 (Weimer 2005)	Unclear	NR	Adequate	NR	NR	NR	Unclear	Adequate	Adequate	Unclear[c]
Wlodarczyk 2009	Unclear	Adequate	Partial[i]	Inadequate	Inadequate	Inadequate	Unclear	Adequate	Inadequate	Unclear[c]
Kramer 2010 (NCT00189839)	Unclear	Adequate	Adequate	Partial[j]	Adequate	Partial[j]	Unclear	Adequate	Inadequate	Adequate
Tsuchiya 2013	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Oh 2014	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Unclear[f]
Albano 2013: (NCT00717470) OSAKA Trial[d]	Unclear	Unclear	Unclear	Inadequate	NR	Inadequate	Unclear	Unclear[k]	Inadequate	Adequate
Ciancio 2008 / (Ciancio 2011 (3016), R01DK25243-25)	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Unclear[f]
Salvadori 2004	Adequate	NR	Adequate	Adequate	Adequate	Adequate	Unclear	Adequate	Adequate	Adequate
Vincenti 2005 (Vincenti 2010)	Unclear	Unclear	Adequate	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Adequate
BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	Unclear	Unclear	Unclear	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	Unclear	Unclear	Unclear	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
Ferguson 2011	Adequate	Unclear	Unclear	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Unclear[f]
Lorber 2005	Unclear	NR	Adequate	Partial[g]	Partial[g]	Partial[g]	Unclear	Inadequate	Adequate	Unclear[f]
ATLAS Vitko 2005 (Vitko 2004 & 2005b)	Adequate	Adequate	Unclear	Partial[g]	Partial[g]	Partial[g]	Unclear	Adequate	Adequate	Inadequate
Takahashi 2013	Adequate	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Chadban 2013 (SOCRATES)	Unclear	Adequate	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Tedesco Silva 2010	Unclear	Unclear	Unclear	Inadequate	Adequate	Inadequate	Unclear	Adequate	Adequate	Unclear[c]
Bertoni 2011	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	Adequate	Unclear	Unclear	Inadequate	Inadequate	Inadequate	Unclear	Adequate	Inadequate	Adequate
Mjornstedt 2012 (NCT00634920)	Adequate	Adequate	Partial[i]	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Adequate
Barsoum 2007	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Unclear[f]
Stallone 2003	Unclear	NR	Adequate	NR	NR	NR	Unclear	Inadequate	Unclear	Inadequate
Anil Kumar 2005	Adequate	NR	Inadequate[l]	NR	Adequate	NR	Unclear	Inadequate	Adequate	Unclear[f]
Mendez 2005 / (Gonwa 2003)	Unclear	NR	Inadequate[m]	Inadequate	NR	Inadequate	Unclear	Adequate	Unclear	Unclear[f]
Sampaio 2008	Adequate	NR	Inadequate[m]	NR	NR	NR	Unclear	Adequate	Unclear	Inadequate
Gelens 2006	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Unclear[c]
Gallon 2006 (Chhabra 2012)	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Van Gurp 2010	Unclear	Adequate	Unclear	NR	NR	NR	Unclear	Adequate	Inadequate	Adequate
Flechner 2002 (Flechner 2004, 2007)	Adequate	NR	Unclear	NR	Adequate	NR	Unclear	Adequate	Adequate	Unclear[f]
Noris 2007/ (Ruggenenti 2007)	Unclear	NR	Unclear	NR	Adequate	NR	Unclear	Inadequate	Adequate	Inadequate
Lebranchu 2009 / (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	Partial[n]	Unclear	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Büchler 2007 (Lebranchu 2012, Joannides 2010)	Adequate	NR	Adequate	Inadequate	Inadequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
Soleimani 2013	Unclear	NR	Partial[i]	NR	NR	NR	Unclear	Inadequate	Inadequate	Unclear[c]
Durrbach 2008 : (0468E1 – 100969)	Unclear	Unclear	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Kreis (2000) - Identified from Campistol 2005	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Unclear	Inadequate
Guba 2010	Unclear	Adequate	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Martinez-Mier 2006	Unclear	NR	Adequate	NR	NR	NR	Unclear	NR	Adequate	Inadequate
Nafar 2012 : (IRCT138804333049N7)	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Adequate	NR	Inadequate
Larson 2006 (Stegall 2003)	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Inadequate
Schaefer 2006	Unclear	NR	Inadequate[o]	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Unclear[c]
Heilman 2011 (Heilman, 2012; NCT00170053)	Adequate	NR	Adequate	Inadequate	Inadequate	Inadequate	Unclear	Adequate	Adequate	Inadequate
Welberry Smith 2008	Unclear	NR	Unclear	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Inadequate
Silva 2013 (NCT01802268)	Adequate	NR	Adequate	NR	NR	NR	Unclear	Adequate	Inadequate	Unclear[f]
Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	Unclear	NR	Adequate	NR	NR	NR	Unclear	Adequate	Adequate	Inadequate
Charpentier 2003 (Groth 1999)	Adequate	Unclear	Inadequate[m]	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Inadequate
Chen 2008	Unclear	Unclear	Adequate	NR	NR	NR	Unclear	Inadequate	Adequate	Unclear[f]
Vitko 2006	Unclear	Unclear	Unclear	Inadequate	NR	Inadequate	Unclear	Inadequate	Unclear	Inadequate
Flechner 2011 / (the ORION study, NCT00266123)	Unclear	NR	Partial[i]	Inadequate	NR	Inadequate	Unclear	Adequate	Inadequate	Adequate
Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	Unclear	NR	Adequate	Inadequate	NR	Inadequate	Unclear	Adequate	Adequate	Adequate

Study, year	Random allocation	Allocation concealment	Baseline similarity	Care providers blinded	Outcome assessors blinded	Patients blinded	All a priori outcomes reported	Complete data reported	ITT	Limitations to applicability
Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	Adequate	Unclear	Inadequate[p]	NR	NR	NR	Unclear	Inadequate	NR	Unclear[f]

[a] all participants appear to remain in the study but this is unclear; [b] statistically significant between group difference in age and PRA grade; [c] lack of clarity regarding key demographic information which may influence applicability; [d] study of both induction and maintenance treatments; [e] statistically significant between group difference in number of previous transplants and PRA grade; [f] non-EU population; [g] blinding occurred until 12 months; [h] statistically significant between group difference in PRA grade; [i] statistically significant sex difference between groups; [j] blinding occurred until 24 weeks; [k] numbers do not seem to add up; [l] statistically significant between group difference in proportion of organs from ECD donors; [m] statistically significant between group difference in participant age; [n] minimisation including a random element; [o] statistically significant between group difference in HLA mismatches; [p] statistically significant between group difference in age and pre-transplant diabetes

Appendix 5 Study characteristics

Induction

Study (multiple publications)	Previous MTA	n	Maintenance used	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (CrCl)	Serum Creatinine	Adverse events
BAS vs placebo (5 studies)											
Bingyi 2003	✓ [b]	12	**CsA +AZA + CCS**			1yr	1yr			6m, 1yr	1yr
Kahan 1999	✓	346	**CsA + CCS**	1 yr	1yr	1yr		1yr	1yr		1yr
Lawen 2003	✓[a]	123	**CsA + MMF + CCS**	6m, 1yr	6m, 1yr	6m, 1yr	6m[c] , 1yr	6m	1yr[d]		6m
Nashan 1997	✓	380	**CsA + CCS**			6m		6m	6m, 1yr		1yr
Ponticelli 2001, (2001)	✓	340	**CsA + Aza+ CCS.**	6m	6m	6m	6m[c]		1m, 3m, 6m 1 yr	1m, 3m, 6m, 1yr	6m
BAS vs no induction (2 studies)											
Albano 2013 (OSAKA trial;NCT00717470)	×	1251	**CsA + MMF + CCS**	6m	6m	6m	6m	6m	6m		6m
Sheashaa 2003 (Sheashaa 2005, 2008 & 2011)	✓[b]	100	**CSA +AZA+ CCS**	1yr, 3yr, 5yr, 7yr, 10yr	1yr [c], 3yr, 5yr, 7yr, 10yr	1yr, 3yr, 5yr, 7yr, 10yr			1yr, 3yr, 5yr, 7yr, 10yr	1yr , 3yr, 5yr, 7yr, 10yr	3yr, 5yr, 7yr, 10yr
ATG vs no induction (4 studies)											
Charpentier 2001	×	309	**TAC + AZA + CCS**	1yr	1yr	1yr			1yr[e]	1yr	1yr
Samsel 2008	×	79	**CsA + MMF (converted to AZA) + CCS**	1yr, 2yr, 3yr, 4yr, 5yr	1yr, 2yr, 3yr, 4yr, 5yr	1yr	1yr		1yr[d]	6m, 1yr, 2yr, 3yr, 4yr, 5yr	5yr
Sheashaa 2008	×	80	**CNI + prolif + CCSen.**	5yr	5yr	1yr, 5yr		1yr	1yr[e], 5yr[e]		5yr
Charpentier 2003	×	555	**TAC + AZA + CCS**	6m	6m	6m		6m		6m	6m

Study (multiple publications)	Previous MTA	n	Maintenance used	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (CrCl)	Serum Creatinine	Adverse events
BAS vs ATG (4 studies)											
Brennan 2006	×	278	**CsA + MMF + CCS**	1yr	1yr	1yr			1yr[d]	1yr	1yr
Lebranchu 2002	✓ [a]	100	**CsA + MMF + CCS**	6m, 1yr	6m, 1yr	6m, 1yr	6m, 1yr	6m, 1yr	6m[d], 1yr[d]	6m, 1yr	6m
Mourad 2004	×	105	**CsA + MMF + CCS**	1yr	1yr	1yr		1yr		1yr	1yr
Sollinger 2001	✓	135	**CsA + MMF + CCS.**	1yr	1yr	6m, 1yr	1yr	1yr			1yr
BAS vs ATG vs no induction (1 studies)											
Kyllonen 2007	×	155	**CsA + AZA + CCS**	1yr, 5yr	1yr, 5yr	1yr	1yr		1yr, 2yr[f], 3yr[f], 4yr[f], 5yr[f]	1yr	1yr, 5yr

Key: Notes:(a) abstract, (b) identified in TA99, (c) Kaplein Meier, (d) DGF, (e) eGFR, (f) CG

Maintenance

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Tac + Aza vs CsA + Aza (13 studies)										
Schleibner 1995	✓	47	6wk	6wk	6wk				6wk	
Laskow 1996 (Vincenti 1996)	×	120	1yr	1yr	42d			42d, 1yr	Day 42, 1yr	
Mayer 1997 (Mayer 2002, 1999)	✓	448	1yr, 5yr	1yr, 5yr	1yr, 4yr				1yr, 4yr	1yr
Radermacher 1998	✓	41			1yr				1yr, 4yr	
Jarzembowski 2005	×	35	1yr	1yr	1yr				1m, 6m, 1yr, 3yr, 5yr	
Baboolal 2002	✓	51		1yr, 2yr	1yr	1yr	1yr	1yr[a]		
Campos 2002	✓	166	1yr	1yr	1yr	1yr				1yr
Margreiter 2002 (Kramer 2005 & Kramer 2008)	✓	560	6m, 1yr, 2yr, 3yr	6m, 1yr, 3yr	6m, 1yr, 2yr, 3yr		6m, 1yr, 2yr	2yr, 3yr	6m, 1yr, 2yr	6m, 2yr
Van Duijnhoven 2002	✓	23			1yr			3m, 6m, 1yr, 2yr, 3yr		
Waller 2002 (Murphy 2003)	✓	102	1yr	1yr				1yr[a]		
Charpentier 2003	×	555	6m	6m	6m		6m			6m
Toz 2004	✓	35								
Hardinger 2005 (Brennan 2005)	×	200	1yr	1yr	1yr		1yr	1yr[a]	6m, 1yr	1yr
CsA + MMF low vs CsA + AZA vs CsA + MMF (2 studies)										
Sollinger 1995	✓	499	6m	6m	6m		6m		6m	6m

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Tricontinental MMF renal study 1996 (Mathew 1998, Clayton 2012)	✓	497	6m, 1yr, 3yr	6m, 1yr, 3yr	6m		6m		6m, 1yr, 3yr	6m, 3yr
CsA + MMF vs CsA + AZA (4 studies)										
Sadek 2002	✓	477	1yr	1yr	1yr					1yr
Tuncer 2002	✓	76	1yr, 3yr, 5yr						1yr	
Merville 2004	×	71	1yr	1yr	1yr	1yr	1yr	6m, 1yr	6m, 1yr	1yr
Remuzzi 2007 (The MYSS trial, Remuzzi 2004)	×	336	6m, 1yr, 5yr	5yr	6m, 1yr, 5yr			6m[b], 5yr	6m	6m, 1yr, 5yr
TAC + MMF vs CsA + AZA (2 studies)										
Wlodarczyk 2005 (Wlodarczyk 2002)	×	489	6m	6m	3m, 6m			3m[a]	6m	6m
Vacher-Coponat 2012	×	289	1yr, 3yr	1yr, 3yr	1yr		1yr	1yr[b], 3yr		1yr, 3yr
TAC + MMF vs CsA + MMF (4 studies)										
Zadrazil 2012	×	53	1yr	1yr				6m,1yr	6m	
Hernandez 2007	×	240	1yr, 2yr	2yr	2yr		2yr	6m[b], 1yr[b]	1yr	2yr
Rowshani 2006	×	126	1yr	1yr	1yr			1yr		1yr
Yang 1999 (Ulsh 1999)	✓	60	1yr	1yr	1yr	1yr		1yr[a]	1yr	1yr
TAC + AZA vs CsA + AZA vs CsA + MMF (1 study)										
Weimer 2006 (Weimer 2005)	×	81	1yr	1yr	1yr			1yr	1yr	1yr
TAC + MMF vs TAC PR + MMF (4 studies)										

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Wlodarczyk 2009	×	122								
Kramer 2010 (NCT00189839)	×	667	1yr	1yr	6m, 1yr		1yr	1yr[b]	1yr	1yr
Tsuchiya 2013	×	102	1yr	1yr	1yr			1yr		1yr
Oh 2014	×	104	6m	6m	6m			6m		
TAC + MMF vs TAC PR 0.2 + MMF vs TAC PR 0.3 (1 study)										
Albano 2013: (NCT00717470) OSAKA Trial	×	1251	6m	6m	6m		6m	6m		6m
MMF + TAC vs MPS + TAC (1 study)										
Ciancio 2008 / (Ciancio 2011 (3016), R01DK25243-25)	×	150	1yr, 4yr	1yr, 4yr	1yr, 2yr, 4yr		1yr	1m, 3m, 6m,1yr, 2yr, 3yr, 4yr	1m, 3m, 6m, 1yr, 2yr, 3yr, 4yr	1yr, 4yr
MMF + CsA vs MPS + CsA (1 study)										
Salvadori 2004	×	423	6m, 1yr	6m, 1yr	6m, 1yr		6m			6m, 1yr
BEL low+ MMF vs BEL high + MMF vs CsA + MMF (3 studies)										
Vincenti 2005 (Vincenti 2010)	×	218	1yr	1yr	6m, 1yr		6m, 1yr, 5yr	1yr		1yr, 5yr
BENEFIT (Vincenti 2010, Larsen 2010, Vincenti 2012, Rostaing 2013)	×	686	1yr, 2yr, 3yr, 5yr	1yr, 2yr, 3yr, 5yr	1yr, 2yr, 3yr, 4yr, 5yr		1yr	1yr, 2yr, 3yr, 5yr		1yr, 2yr, 3yr, 5yr
BENEFIT EXT (Durrbach 2010 Medina Pestana 2012, Charpentier 2013 Larsen 2010)	×	578	1yr, 2yr, 3yr, 5yr	1yr, 2yr, 3yr, 5yr	1yr, 2yr, 3yr, 5yr		1yr, 5yr	1yr, 2yr, 3yr, 5yr		1yr, 2yr, 3yr, 5yr
BEL+MMF vs BEL+SIR vs TAC+MMF (1 study)										
Ferguson 2011	×	89	1yr	1yr	6m, 1yr		6m	1yr		1yr
EVL low + CsA vs EVL high + CsA vs MMF+CsA (3 studies)										

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Lorber 2005	×	583	1yr, 3yr	1yr, 3yr	1yr, 3yr			1yr, 2yr, 3yr	1yr, 3yr	3yr
ATLAS Vitko 2005 (Vitko 2004 & 2005b)	×	588	6m, 1yr, 3yr	6m, 1yr, 3yr	6m, 1yr, 3yr			1yr, 2yr, 3yr	1yr, 2yr, 3yr	1yr, 3yr
Takahashi 2013	×	122	1yr	1yr	1yr		1yr	1yr		1yr
EVL vs CsA vs MPS (1 study)										
Bemelman 2009	×	81								
EVL vs EVL +CsA vs CsA + MPS (1 study)										
Chadban 2013 (SOCRATES)	×	126	1yr	1yr	1yr		1yr	1yr		1yr
EVL low + CsA vs EVL high + CsA vs MPA + CsA (1 study)										
Tedesco Silva 2010	×	783	1yr	1yr	1yr		1yr	1yr	1yr	1yr
EVL + CsA vs MPS + CsA (1 study)										
Bertoni 2011	×	106	1yr	1yr	1yr			1yr[b]		
EVL + MPS vs CsA + MPS (2 studies)										
Budde 2011 (Budde 2012 , Liefeldt 2012, NCT00154310)	×	300								
Mjornstedt 2012 (NCT00634920)	×	202	1yr	1yr	1yr		1yr	1yr	1yr	1yr
SRL + CsA vs MMF + CsA (2 studies)										
Barsoum 2007	×	113	2yr	2yr	2yr			1yr, 2yr		2yr
Stallone 2003	×	90	1yr	1yr				6m, 1yr[b]	1yr	

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
SRL + TAC vs MMF + TAC (6 studies)										
Anil Kumar 2005	×	150	1yr, 2yr	1yr				1yr	1yr	1yr
Mendez 2005 / (Gonwa 2003)	×	361	6m, 1yr	6m, 1yr	6m, 1yr			6m[b], 1yr	6m, 1yr	6m, 1yr
Sampaio 2008	×	100	1yr	1yr	1yr	1yr	1yr	1yr	1yr	1yr
Gelens 2006	×	54								
Gallon 2006 (Chhabra 2012)	×	83	3yr, 8.5yr	3yr, 8.5yr				1yr[b], 3yr[b], 8.5yr		3yr
Van Gurp 2010	×	634	6m	6m	6m		6m	6m[b]		6m
SRL + MMF vs CsA + MMF (10 studies)										
Flechner 2002 (Flechner 2004, 2007)	×	61	1yr, 2yr, 5yr	1yr, 2yr, 5yr	1yr, 2yr, 5yr	1yr, 5yr	1yr, 5yr	1m, 3m, 6m, 1yr, 2yr, 5yr	1m, 3m, 6m, 1yr, 2yr, 5yr	1yr,2yr, 5yr
Noris 2007 (Ruggenenti 2007)	×	21	1yr, 2yr	1yr, 2yr				1yr, 2yr	1yr, 2yr	2yr
Lebranchu 2009 (Servais 2009, Lebranchu 2011, Joannides 2011, 2004-002987-62)	×	192	1yr, 4yr	1yr, 4yr	1yr, 4yr			6m[a], 1yr[b], 4yr	6m, 1yr	1yr, 4yr
Büchler 2007 (Lebranchu 2012, Joannides 2010)	×	145	1yr, 5yr	1yr, 5yr	1yr, 5yr	1yr	1yr	1yr[b], 5yr	5yr	1yr, 5yr
Soleimani 2013	×	88							1m, 1yr, 3yr, 4yr, 5yr	
Durrbach 2008 : (0468E1 – 100969)	×	69	6m	6m	6m	6m		6m[b]	6m	6m
Kreis (2000) - Identified from Campistol 2005	×	78	1yr	1yr	1yr		1yr	1yr[b]	6m, 1yr	1yr
Guba 2010	×	140	1yr	1yr	1yr			1yr	1yr	1yr
Martinez-Mier 2006	×	41	1yr	1yr	1yr			6m, 1yr	6m, 1yr	

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Nafar 2012 : (IRCT138804333049N7)	×	100	1yr, 2yr, 3yr, 4yr	1yr, 2yr, 3yr, 4yr	1yr			1yr, 2yr, 3yr, 4yr	1yr, 2yr, 3yr, 4yr	
TAC + MMF vs SRL + MMF (4 studies)										
Larson 2006 (Stegall 2003)	×	162	1yr	1yr				1yr , 2yr[b]		
Schaefer 2006	×	80	1yr	1yr	1yr				1yr	
Heilman 2011 (Heilman, 2012; NCT00170053)	×	122	1yr, 2yr	1yr, 2yr	1yr			1yr[b], 2yr	1yr	2yr
Welberry Smith 2008	×	51	1yr	1yr	1yr		1yr	1yr	1yr	
TAC + MPS vs SRL + MPS (1 study)										
Silva 2013 (NCT01802268)	×	204	2yr	2yr	2yr		2yr	2yr	2yr	
TAC + SRL vs MMF + SRL (1 study)										
Hamdy 2005 (Hamdy 2005, Hamdy 2008, Hamdy 2010)	×	132	1yr, 2yr, 3yr, 4yr, 5yr	2yr, 3yr, 4yr, 5yr	1yr, 3yr			1yr, 2yr, 3yr, 4yr	2yr	2yr, 4yr
SRL + AZA vs CsA + AZA (1 study)										
Charpentier 2003 (Groth 1999)	✓	83	1yr	1yr	6m		6m	6m , 1yr	6m, 1yr	1yr
TAC + SRL vs CsA + SRL (1 study)										
Chen 2008	×	41	1yr	1yr	1yr		1yr	6m , 1yr[b]		1yr
SRL low + TAC vs SRL high + TAC vs MMF + TAC (1 study)										
Vitko 2006	×	977	6m		6m		6m	6m	6m	6m
SRL + TAC vs SRL + MMF vs MMF + TAC (1 study)										

Study (multiple publications)	Previous MTA	n	Patients survival	Graft survival	BPAR	Time to BPAR	Severity of BPAR	Graft Function (eGFR)	Serum Creatinine	Adverse Events
Flechner 2011 / (the ORION study, NCT00266123)	×	450	1yr, 2yr	2yr	1yr, 2yr		1yr, 2yr	1yr[b], 2yr		2yr
MMF + CsA vs MMF + low CsA vs MMF + low TAC vs MMF low SRL (1 study)										
Grinyo 2009, (Ekberg 2009, Demirbas 2009, Ekberg 2010, Frei 2010, Claes 2012)	×	1529	1yr	1yr	6m, 1yr	1yr	1yr	1yr[b], 2yr, 3yr		1yr, 3yr
TAC + MMF vs TAC + SRL vs CsA + MMF vs CsA + SRL (1 study)										
Anil Kumar 2008 / (Kumar 2006, Anil Kumar 2005; CRG110600009)	×	200	5yr	1yr, 2yr, 3yr, 4yr, 5yr	1yr			1yr[b], 2yr, 3yr, 4yr, 5yr	1yr, 2yr, 3yr, 4yr, 5yr	1yr, 5yr

Key: Notes:a DGF, b eGFR and DGF

Appendix 6 Network Meta-Analysis

WinBUGS code

Fixed effects binomial likelihood with logit link

```
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)      # vague priors for all trial baselines
    for (k in 1:na[i])  {       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
       or[c,k] <- exp(d[k] - d[c])
       lor[c,k] <- (d[k]-d[c])
      }
}


# ranking
```

```
for (k in 1:nt) {

   rk[k] <- rank(d[],k)                          # assumes events are “bad”

   best[k] <- equals(rk[k],1)                    #calculate probability that treat k
is best

}

}
```

Random effects binomial likelihood with logit link

```
model{                              # *** PROGRAM STARTS

for(i in 1:ns){                     # LOOP THROUGH STUDIES

    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm

    delta[i,1] <- 0             # treatment effect is zero for control arm

    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines

    for (k in 1:na[i]) {             # LOOP THROUGH ARMS

        r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood

        logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor

        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators

#Deviance contribution

        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))

            +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}

#  summed residual deviance contribution for this trial

    resdev[i] <- sum(dev[i,1:na[i]])

    for (k in 2:na[i]) {             # LOOP THROUGH ARMS

# trial-specific LOR distributions

        delta[i,k] ~ dnorm(md[i,k],taud[i,k])

# mean of LOR distributions (with multi-arm trial correction)

        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]

# precision of LOR distributions (with multi-arm trial correction)

        taud[i,k] <- tau *2*(k-1)/k

# adjustment for multi-arm RCTs

        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])

# cumulative adjustment for multi-arm trials
```

```
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])           # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
       or[c,k] <- exp(d[k] - d[c])
       lor[c,k] <- (d[k]-d[c])
      }
}

# ranking
for (k in 1:nt) {
   rk[k] <- rank(d[],k)                          # assumes events are “bad”
   best[k] <- equals(rk[k],1)                   #calculate probability that treat k
is best
}

}
```

Fixed effects normal likelihood and identify link

```
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     #   LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
    for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
        var[i,k] <- pow(se[i,k],2)  # calculate variances
        prec[i,k] <- 1/var[i,k]     # set precisions
```

```
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
        theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
for (c in 1:nt-1){
       for (k in 2:nt) {
              IC[c,k] <- d[k] - d[c]
       }
       }
# ranking
for (k in 1:nt) {
     rk[k] <- nt + 1- rank(d[],k)
   best[k] <- equals(rk[k],1)
       }
       }
```

Random effects normal likelihood and identify link

```
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     #   LOOP THROUGH STUDIES
    w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0             # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)           # vague priors for all trial baselines
    for (k in 1:na[i]) {             #  LOOP THROUGH ARMS
```

```
        var[i,k] <- pow(se[i,k],2)   # calculate variances
        prec[i,k] <- 1/var[i,k]      # set precisions
        y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
        theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
        dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
      }
#  summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
    for (k in 2:na[i]) {             # LOOP THROUGH ARMS
# trial-specific LOR distributions
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])            #Total Residual Deviance
d[1]<-0       # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
for (c in 1:nt-1){
       for (k in 2:nt) {
              IC[c,k] <- d[k] - d[c]
       }
```

```
       }
# ranking
for (k in 1:nt) {
     rk[k] <- nt + 1- rank(d[],k)
       best[k] <- equals(rk[k],1)
       }
}
```

Induction therapy results

Graft Loss

Results of random effects model and consistency analyses

As there are direct data for 3 comparisons and 3 treatments, but a 3-arm trial, there are no inconsistency degrees of freedom (ICDF) for this network. Comparing the DIC between the consistency and inconsistency models (Table 226) suggests that the consistency models provide a slightly better fit to the data for both the fixed and random effects models. Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably.

Table 226. Comparison of fixed and random effects consistency and inconsistency models for induction therapy on graft loss

	Fixed effects model		**Random effects model**	
	Consistency model	**Inconsistency model**	**Consistency model**	**Inconsistency model**
OR[BAS vs placebo/no treatment]	0.84 (0.59, 1.21)	0.81 (0.55, 1.19)	0.84 (0.55, 1.30)	0.81 (0.49, 1.29)
OR[ATG vs placebo/no treatment]	0.78 (0.45, 1.34)	0.89 (0.43, 1.95)	0.78 (0.42, 1.43)	0.90 (0.40, 2.03)
OR[ATG vs BAS]	0.92 (0.53, 1.59)	0.80 (0.38, 1.66)	0.93 (0.51, 1.69)	0.80 (0.40, 1.80)
Estimate of between-study heterogeneity			0.15 (0.01, 0.63)	0.16 (0.01, 0.70)
Total residual deviance	19.56	20.26	20.44	21.16
Relative number of model parameters	14.63	15.60	15.71	16.66
DIC	34.19	35.86	36.15	37.82

Mortality

Results of random effects model and consistency analyses

As there are direct data for 3 comparisons and 3 treatments, but a 3-arm trial, there are no inconsistency degrees of freedom (ICDF) for this network. Comparing the DIC between the consistency and inconsistency models suggests that the consistency models provide a better fit to the data for both the fixed and random effects models. Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 227).

Table 227. Comparison of fixed and random effects consistency and inconsistency models for induction therapy on mortality

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
OR[BAS vs placebo/no treatment]	0.89 (0.49, 1.62)	0.91 (0.47, 1.74)	0.82 (0.28, 1.77)	0.81 (0.19, 1.99)
OR[ATG vs placebo/no treatment]	0.68 (0.28, 1.39)	0.59 (0.17, 1.79)	0.56 (0.14, 0.14)	0.51 (0.07, 2.01)
OR[ATG vs BAS]	0.72 (0.34, 1.47)	0.74 (0.29, 1.79)	0.68 (0.23, 1.73)	0.68 (0.15, 2.32)
Estimate of between-study heterogeneity			0.39 (0.02, 1.74)	0.46 (0.02, 2.20)
Total residual deviance	25.08	26.12	24.66	25.53
Relative number of model parameters	13.35	14.28	15.41	16.49
DIC	38.43	40.40	40.07	42.02

BPAR

Results of random effects model and consistency analyses

As there are direct data for 3 comparisons and 3 treatments, but a 3-arm trial, there are no inconsistency degrees of freedom (ICDF) for this network. Comparing the DIC between the consistency and inconsistency models suggests that the consistency models provide a better fit to the data for both the fixed and random effects models. Furthermore, the posterior

median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 228).

Table 228. Comparison of fixed and random effects consistency and inconsistency models for induction therapy on BPAR

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
OR[BAS vs placebo/no treatment]	0.50 (0.40, 0.62)	0.51 (0.40, 0.64)	0.50 (0.37, 0.64)	0.50 (0.37, 0.71)
OR[ATG vs placebo/no treatment]	0.35 (0.25, 0.49)	0.34 (0.22, 0.53)	0.35 (0.24, 0.51)	0.33 (0.19, 0.55)
OR[ATG vs BAS]	0.70 (0.51, 0.97)	0.73 (0.47, 1.12)	0.71 (0.49, 1.04)	0.75 (0.46, 1.26)
Estimate of between-study heterogeneity			0.12 (0.01, 0.46)	0.13 (0.01, 0.52)
Total residual deviance	21.00	21.96	21.08	21.83
Relative number of model parameters	14.01	15.00	15.84	16.96
DIC	35.01	36.96	36.92	38.79

Graft Function

Results of random effects model and consistency analyses

As there are direct data for 3 comparisons and 3 treatments, the inconsistency degrees of freedom (ICDF) for this network is 1. Comparing the DIC between the consistency and inconsistency models suggests very little difference between the models, however the mean effect for ATG from the direct evidence (the inconsistency model) is much larger than that when both direct and indirect evidence are used (the consistency model): 3.44 (-2.49, 9.36) vs 0.75 (-3.99, 5.48) from the fixed effects model. Nevertheless the 95% CrIs overlap considerably (see Table 229).

Table 229. Comparison of fixed and random effects consistency and inconsistency models for induction therapy on CRC-GRF

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
BASvs placebo/no induction	2.62 (0.13, 5.08)	2.11 (-0.46, 4.67)	2.60 (-1.00, 6.19)	2.00 (-1.79, 5.64)
ATG vs placebo/no induction	0.75 (-3.99, 5.48)	3.44 (-2.49, 9.36)	0.54 (-5.82, 6.65)	3.41 (-4.50, 11.36)
ATG vs BAS	-1.86 (-6.72, 3.00)	-6.05 (-13.46, 1.34)	-2.03 (-8.53, 4.19)	-6.04 (-15.13, 3.05)
Estimate of between-study heterogeneity			2.27 (0.12, 4.80)	2.14 (0.11, 4.78)
Total residual deviance	14.28	13.11	12.38	11.95
Relative number of model parameters	7.98	8.99	9.85	10.41
DIC	22.26	22.10	22.23	22.36

Maintenance therapy results

Graft Loss

Fixed effects model results

Table 230. ORs (for Intervention vs Comparator treatment) for the outcome graft loss from a fixed effects network meta-analysis (Posterior median (95%CrI))

	Comparator treatment										
Intervention trtment	CYC + AZA	TAC + AZA	MMF + CYC	TAC + MMF	BEL + SIR	BEL + MMF	EVL + CYC	SRL + TAC	SRL + CYC	SRL + MMF	SRL + AZA
TAC + AZA	1.01 (0.71, 1.44)										
MMF + CYC	0.83 (0.53, 1.29)	0.83 (0.47, 1.44)									
TAC + MMF	0.73 (0.41, 1.27)	0.72 (0.37, 1.40)	0.87 (0.56, 1.36)								
BEL + SIR	1.46 (0.19, 10.34)	1.45 (0.18, 10.58)	1.75 (0.23, 11.93)	2.01 (0.27, 13.62)							
BEL + MMF	0.67 (0.33, 1.35)	0.66 (0.30, 1.45)	0.80 (0.46, 1.39)	0.92 (0.45, 1.84)	0.46 (0.07, 3.37)						
EVL + CYC	0.76 (0.41, 1.43)	0.76 (0.37, 1.55)	0.92 (0.58, 1.44)	1.05 (0.56, 1.97)	0.52 (0.07, 4.09)	1.15 (0.56, 2.35)					
SRL + TAC	1.26 (0.58, 2.72)	1.25 (0.54, 2.91)	1.52 (0.77, 2.97)	1.73 (0.97, 3.14)	0.87 (0.12, 6.90)	1.90 (0.80, 4.52)	1.65 (0.74, 3.71)				
SRL + CYC	0.59 (0.14, 2.12)	0.59 (0.13, 2.21)	0.71 (0.17, 2.39)	0.82 (0.20, 2.72)	0.40 (0.04, 4.09)	0.88 (0.20, 3.38)	0.77 (0.18, 2.83)	0.47 (0.11, 1.61)			
SRL + MMF	1.24 (0.69, 2.23)	1.23 (0.62, 2.42)	1.49 (0.98, 2.28)	1.71 (1.10, 2.67)	0.85 (0.12, 6.46)	1.86 (0.93, 3.74)	1.62 (0.88, 3.02)	0.98 (0.50, 1.91)	2.09 (0.61, 8.77)		
SRL + AZA	0.25	0.25	0.30	0.35	0.17	0.38	0.33	0.20	0.42	0.20	

	(0.01, 2.47)	(0.01, 2.54)	(0.01, 3.12)	(0.01, 3.66)	(0.01, 3.77)	(0.01, 4.19)	(0.01, 3.53)	(0.01, 2.25)	(0.01, 6.49)	(0.01, 2.17)	
EVL	0.10 (0.01, 1.96)	0.10 (0.01, 2.00)	0.13 (0.01, 2.27)	0.14 (0.01, 2.72)	0.07 (0.01, 2.55)	0.16 (0.01, 3.03)	0.14 (0.01, 2.50)	0.08 (0.01, 1.64)	0.17 (0.01, 4.52)	0.08 (0.01, 1.58)	0.41 (0.01, 36.99)

Consistency analysis results

There are direct data for 18 comparisons and 12 treatments in the network, however 4 independent loops are informed by multi-arm trials only and so the inconsistency degrees of freedom (ICDF), reflecting the number of independent loops in the network is 18 – (12 - 1) – 4 = 3. Comparing the DIC between the consistency and inconsistency models suggests there is little difference between the random effects models (154.4 vs 153.6). Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 231).

Table 231. Comparison of fixed and random effects consistency and inconsistency models for maintenance therapy on graft loss

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
TAC+AZA vs CYC+AZA	1.01 (0.71, 1.44)	1.00 (0.71, 1.43)	1.13 (0.67, 2.15)	1.11 (0.65, 2.11)
MMF+CYC vs CYC+AZA	0.83 (0.53, 1.29)	0.69 (0.42, 1.10)	0.76 (0.35, 1.44)	0.59 (0.24, 1.24)
TAC+MMF vs CYC+AZA	0.73 (0.41, 1.27)	1.79 (0.64, 5.51)	0.69 (0.28, 1.55)	1.79 (0.40, 8.47)
SRL+AZA vs CYC+AZA	0.25 (0.01, 2.47)	0.25 (0.01, 2047)	0.25 (0.01, 3.10)	0.25 (0.01, 3.17)
TAC+MMF vs MMF+CYC	0.87 (0.56, 1.35)	0.85 (0.50, 1.42)	0.92 (0.48, 1.77)	1.14 (0.51, 3.11)
BEL+MMF vs MMF+CYC	0.80 (0.45, 1.39)	0.73 (0.41, 1.30)	0.82 (0.35, 1.97)	0.70 (0.27, 1.71)
EVL+CYC vs MMF+CYC	0.92 (0.59, 1.44)	0.92 (0.59, 1.44)	0.84 (0.39, 1.63)	0.84 (0.38, 1.64)
SRL+TAC vs MMF+CYC	1.52 (0.77, 2.97)	0.55 (0.11, 2.03)	0.57 (0.64, 3.93)	0.76 (0.11, 5.21)
SRL+CYC vs MMF+CYC	0.71 (0.17, 2.39)	0.55 (0.13, 1.85)	0.73 (0.15, 3.10)	0.69 (0.13, 3.73)
SRL+MMF vs MMF+CYC	1.49 (0.98, 2.28)	1.42 (0.91, 2.23)	1.40 (0.72, 2.58)	1.13 (0.49, 2.23)
EVL vs CYC+AZA	0.13 (0.01, 2.27)	0.13 (0.01, 2.28)	0.13 (0.01, 2.67)	0.12 (0.01, 2.69)

BEL+SIR vs TAC+MMF	2.01 (0.27, 13.63)	11.82 (0.59, 5642.03)	2.05 (0.22, 18.01)	12.33 (0.48, 6727.78)
BEL+MMF vs TAC+MMF	0.92 (0.45, 1.84)	9.13 (0.46, 4429.31)	0.89 (0.32, 2.53)	9.55 (0.38, 5014.05)
SRL+TAC vs TAC+MMF	1.73 (0.97, 3.14)	2.48 (1.22, 5.31)	1.71 (0.80, 3.69)	2.59 (1.05, 6.95)
SRL+MMF vs TAC+MMF	1.71 (1.10, 2.67)	2.34 (0.95, 5.97)	1.52 (0.74, 2.91)	2.43 (0.78, 8.17)
Total residual deviance	107.6	103.8	93.64	90.14
Relative number of model parameters	49.868	53.499	60.791	63.518
DIC	157.498	157.299	154.431	153.658

Mortality

Fixed effects model results

Table 232. ORs (for Intervention vs Comparator treatment) for the outcome mortality from a fixed effects network meta-analysis (Posterior median (95%CrI))

	Comparator treatment											
Intervention trtment	CYC + AZA	TAC + AZA	MMF + CYC	TAC + MMF	BEL + SIR	BEL + MMF	EVL + MPS	EVL + CYC	SRL + TAC	SRL + CYC	SRL + MMF	SRL + AZA
TAC + AZA	1.40 (0.80, 2.55)											
MMF + CYC	0.95 (0.49, 1.85)	0.67 (0.28, 1.62)										
TAC + MMF	1.53 (0.68, 3.48)	1.08 (0.40, 2.96)	1.61 (0.92, 2.88)									
BEL + SIR	0.32 (0.01, 8.29)	0.22 (0.01, 6.20)	0.34 (0.01, 8.25)	0.21 (0.01, 4.96)								
BEL + MMF	0.47 (0.16, 1.30)	0.33 (0.10, 1.07)	0.50 (0.22, 1.07)	0.31 (0.12, 0.78)	1.48 (0.06, 746.80)							
EVL + MPS	0.93 (0.09, 9.81)	0.66 (0.06, 7.43)	0.98 (0.10, 9.46)	0.61 (0.06, 6.29)	3.15 (0.06, 2029)	1.97 (0.18, 21.70)						
EVL + CYC	1.41 (0.57, 3.46)	1.00 (0.34, 2.91)	1.48 (0.82, 2.73)	0.92 (0.40, 2.11)	4.43 (0.17, 2261)	2.98 (1.13, 8.21)	1.51 (0.15, 16.00)					
SRL + TAC	1.39 (0.53, 3.66)	0.99 (0.32, 3.04)	1.47 (0.69, 3.13)	0.91 (0.50, 1.64)	4.35 (0.17, 2178)	2.95 (1.02, 8.84)	1.50 (0.14, 16.46)	0.99 (0.37, 2.59)				
SRL +	0.62	0.44	0.66	0.41	2.00	1.32	0.67	0.44	0.45			

CYC	(0.14, 2.48)	(0.09, 1.98)	(0.17, 2.25)	(0.10, 1.43)	(0.06, 1052)	(0.29, 5.75)	(0.05, 8.92)	(0.10, 1.73)	(0.11, 1.68)			
SRL + MMF	1.74 (0.75, 4.12)	1.24 (0.44, 3.46)	1.84 (1.04, 3.33)	1.14 (0.67, 1.95)	5.45 (0.22, 2730)	3.70 (1.44, 9.99)	1.88 (0.18, 19.72)	1.24 (0.54, 2.87)	1.25 (0.62, 2.57)	2.79 (0.77, 11.44)		
SRL + AZA	0.19 (0.01, 6.02)	0.14 (0.01, 4.51)	0.20 (0.01, 6.82)	0.13 (0.01, 4.39)	0.62 (0.01, 641.3)	0.41 (0.01, 15.10)	0.19 (0.01, 13.93)	0.14 (0.01, 4.87)	0.14 (0.01, 5.03)	0.30 (0.01, 13.27)	0.11 (0.01, 3.86)	
EVL	0.24 (0.01, 6.09)	0.17 (0.01, 4.58)	0.26 (0.01, 5.99)	0.16 (0.01, 3.89)	0.75 (0.01, 729.2)	0.51 (0.01, 13.38)	0.24 (0.01, 13.20)	0.17 (0.01, 4.02)	0.17 (0.01, 4.53)	0.38 (0.01, 12.10)	0.14 (0.01, 3.46)	1.23 (0.01, 1232)

Consistency analysis results

There are direct data for 20 comparisons and 13 treatments in the network, however 4 independent loops are informed by multi-arm trials only and so the inconsistency degrees of freedom (ICDF), reflecting the number of independent loops in the network is 20 – (13 - 1) – 4 = 4. Comparing the DIC between the consistency and inconsistency models suggests that the consistency model provides a better fit to the data (139.5 vs 143.9). Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 233).

Table 233. Comparison of fixed and random effects consistency and inconsistency models for maintenance therapy on mortality

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
TAC+AZA vs CYC+AZA	1.40 (0.80, 2.54)	1.40 (0.80, 2.55)	1.38 (0.74, 2.60)	1.38 (0.73, 2.61)
MMF+CYC vs CYC+AZA	0.95 (0.49, 1.85)	0.89 (0.43, 1.83)	1.06 (0.45, 1.95)	0.88 (0.40, 1.93)
TAC+MMF vs CYC+AZA	1.53 (0.68, 3.48)	2.26 (0.40, 18.76)	1.53 (0.63, 3.71)	2.32 (0.38, 6.89)
SRL+AZA vs CYC+AZA	0.19 (0.01, 6.02)	0.20 (0.1, 5.98)	0.20 (0.01, 6.03)	0.20 (0.01, 6.60)
TAC+MMF vs MMF+CYC	1.61 (0.92, 2.88)	1.84 (0.95, 3.57)	1.61 (0.89, 3.00)	1.89 (0.93, 735.09)
BEL+MMF vs MMF+CYC	0.50 (0.22, 1.07)	0.42 (0.17, 0.93)	0.50 (0.21, 1.11)	0.41 (0.16, 0.98)
EVL+MPS vs MMF+CYC	0.98 (0.10, 9.46)	0.98 (0.10, 9.62)	1.00 (0.09, 10.08)	0.98 (0.10, 10.43)
EVL+CYC vs MMF+CYC	1.48 (0.82, 2.73)	1.48 (0.82, 2.73)	1.48 (0.77, 2.83)	1.46 (0.76, 2.87)
SRL+TAC vs MMF+CYC	1.47 (0.69, 3.13)	0.77 (0.10, 3.71)	1.46 (0.65, 3.23)	0.82 (0.10, 4.48)
SRL+CYC vs MMF+CYC	0.66 (0.17, 2.25)	0.63 (0.17, 2.17)	0.66 (0.17, 2.37)	0.65 (0.16, 2.41)
SRL+MMF vs	1.83 (1.04, 3.33)	1.88 (0.99, 3.63)	1.81 (0.98, 3.42)	1.84 (0.90, 3.82)

MMF+CYC				
EVL vs MMF+CYC	0.26 (0.01, 5.99)	0.26 (0.01, 6.05)	0.27 (0.01, 5.96)	0.24 (0.01, 6.00)
BEL+SIR vs TAC+MMF	0.21 (0.01, 4.96)	1.15 (0.01, 740.26)	0.21 (0.01, 5.21)	1.17 (0.01, 753.70)
BEL+MMF vs TAC+MMF	0.31 (0.12, 0.78)	4.85 (0.16, 2421.16)	0.31 (0.11, 0.83)	4.94 (0.16, 2457.75)
SRL+TAC vs TAC+MMF	0.91 (0.50, 1.64)	0.95 (0.47, 1.88)	0.91 (0.48, 1.70)	0.94 (0.44, 1.94)
SRL+MMF vs TAC+MMF	1.14 (0.67, 1.95)	1.54 (0.63, 3.79)	1.13 (0.62, 2.01)	1.53 (0.58, 4.06)
Total residual deviance	85.74	85.85	85.17	85.32
Relative number of model parameters	51.958	56.274	54.343	58.586
DIC	137.698	142.124	139.513	143.906

BPAR

Fixed effects model results

Table 234. ORs (for Intervention vs Comparator treatment) for the outcome BPAR from a fixed effects network meta-analysis (Posterior median (95%CrI))

	Comparator treatment											
Intervention trtment	CYC + AZA	TAC + AZA	MMF + CYC	TAC + MMF	BEL + SIR	BEL + MMF	EVL + MPS	EVL + CYC	SRL + TAC	SRL + CYC	SRL + MMF	SRL + AZA
TAC + AZA	0.55 (0.41, 0.73)											
MMF + CYC	0.47 (0.34, 0.66)	0.86 (0.55, 1.34)										
TAC + MMF	0.43 (0.29, 0.63)	0.78 (0.48, 1.28)	0.90 (0.70, 1.17)									
BEL + SIR	0.18 (0.01, 1.39)	0.32 (0.01, 2.60)	0.38 (0.01, 2.85)	0.41 (0.01, 3.16)								
BEL + MMF	0.83 (0.50, 1.39)	1.52 (0.84, 2.73)	1.75 (1.20, 2.59)	1.94 (1.23, 3.07)	4.67 (0.62, 137.00)							
EVL + MPS	1.48 (0.65, 3.54)	2.70 (1.13, 6.77)	3.12 (1.48, 7.01)	3.45 (1.56, 8.05)	8.48 (0.94, 266.2)	1.78 (0.77, 4.3)						
EVL + CYC	0.46 (0.30, 0.70)	0.84 (0.50, 1.40)	0.97 (0.76, 1.25)	1.07 (0.75, 1.54)	2.59 (0.33, 77.35)	0.55 (0.35, 0.87)	0.31 (0.13, 0.68)					
SRL + TAC	0.39 (0.21, 0.70)	0.70 (0.36, 1.37)	0.82 (0.49, 1.36)	0.90 (0.55, 1.46)	2.18 (0.27, 66.47)	0.46 (0.24, 0.88)	0.26 (0.10, 0.65)	0.84 (0.47, 1.48)				

SRL + CYC	0.28 (0.08, 0.81)	0.50 (0.14, 1.54)	0.58 (0.18, 1.63)	0.64 (0.19, 1.79)	1.56 (0.15, 51.73)	0.33 (0.09, 0.99)	0.18 (0.04, 0.67)	0.60 (0.18, 1.73)	0.71 (0.21, 2.04)			
SRL + MMF	0.32 (0.21, 0.48)	0.59 (0.36, 0.97)	0.68 (0.53, 0.87)	0.75 (0.57, 0.99)	1.82 (0.24, 54.07)	0.39 (0.25, 0.61)	0.22 (0.09, 0.48)	0.70 (0.49, 1.00)	0.84 (0.50, 1.40)	1.17 (0.41, 3.92)		
SRL + AZA	1.15 (0.47, 2.81)	2.10 (0.82, 5.38)	2.44 (0.94, 6.33)	2.69 (1.02, 7.14)	6.61 (0.68, 213.7)	1.39 (0.50, 3.86)	0.78 (0.22, 2.62)	2.51 (0.94, 6.73)	2.99 (1.02, 8.74)	4.22 (1.03, 19.13)	3.57 (1.34, 9.52)	
EVL	1.26 (0.49, 3.35)	2.30 (0.86, 6.36)	2.66 (1.10, 6.67)	2.94 (1.17, 7.65)	7.25 (0.76, 231.7)	1.52 (0.58, 4.09)	0.85 (0.26, 2.78)	2.74 (1.12, 6.92)	3.27 (1.17, 9.35)	4.61 (1.17, 20.58)	3.90 (1.55, 10.09)	1.09 (0.30, 4.10)

Consistency analysis

There are direct data for 21 comparisons and 13 treatments in the network, however 3 independent loops are informed by multi-arm trials only and so the inconsistency degrees of freedom (ICDF), reflecting the number of independent loops in the network is 21 – (13 - 1) – 3 = 6. Comparing the DIC between the consistency and inconsistency random effects models suggests the consistency model has a slightly better fit to the data (156.3 vs 159.7). Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 235).

Table 235. Comparison of fixed and random effects consistency and inconsistency models for maintenance therapy on BPAR

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
TAC+AZA vs CYC+AZA	0.55 (0.41, 0.74)	0.55 (0.41, 0.73)	0.58 (0.36, 0.93)	0.58 (0.35, 0.94)
MMF+CYC vs CYC+AZA	0.47 (0.34, 0.66)	0.49 (0.34, 0.71)	0.47 (0.25, 0.88)	0.49 (0.24, 1.01)
TAC+MMF vs CYC+AZA	0.43 (0.29, 0.64)	0.34 (0.14, 0.78)	0.40 (0.19, 0.79)	0.34 (0.10, 1.14)
SRL+AZA vs CYC+AZA	1.15 (0.47, 2.81)	1.15 (0.47, 2.82)	1.16 (0.34, 3.96)	1.15 (0.33, 4.00)
TAC+MMF vs MMF+CYC	0.91 (0.70, 1.17)	0.99 (0.75, 1.31)	0.85 (0.52, 1.35)	0.79 (0.41, 1.43)
BEL+MMF vs MMF+CYC	1.75 (1.20, 2.59)	1.68 (1.15, 2.50)	1.71 (0.91, 3.20)	1.56 (0.79, 3.01)
EVL+MPS vs MMF+CYC	3.12 (1.48, 7.01)	3.13 (1.49, 7.02)	3.14 (1.01, 10.09)	3.15 (1.00, 10.19)
EVL+CYC vs MMF+CYC	0.97 (0.76, 1.25)	0.97 (0.76, 1.25)	0.97 (0.61, 1.54)	0.97 (0.60, 1.56)
SRL+TAC vs MMF+CYC	0.81 (0.49, 1.36)	0.19 (0.02, 0.75)	0.82 (0.40, 1.64)	0.16 (0.02, 0.89)
SRL+CYC vs MMF+CYC	0.58 (0.18, 1.63)	0.43 (0.11, 1.29)	0.59 (0.15, 2.03)	0.50 (0.08, 1.62)
SRL+MMF vs	0.68 (0.53, 0.87)	0.69 (0.54, 0.34)	0.92 (0.62, 1.44)	1.05 (0.67, 1.74)

MMF+CYC				
EVL + MMF+CYC	2.66 (1.10, 6.67)	2.66 (1.09, 6.67)	2.67 (0.82, 8.77)	2.79 (0.79, 10.27)
BEL+SIR vs TAC+MMF	0.41 (0.01, 3.16)	1.15 (0.03, 44.21)	0.43 (0.01, 4.08)	1.16 (0.03, 50.80)
BEL+MMF vs TAC+MMF	1.94 (1.23, 3.07)	6.96 (0.88, 196.37)	2.02 (0.01, 4.37)	7.08 (0.73, 227.01)
SRL+TAC vs TAC+MMF	0.90 (0.55, 1.46)	1.21 (0. 63, 2.32)	0.96 (0.51, 1.80)	1.22 (0.54, 2.78)
SRL+MMF vs TAC+MMF	0.75 (0.57, 0.99)	1.07 (0.45, 2.55)	1.09 (0.67, 1.89)	1.14 (0.41, 3.20)
SRL+CYC vs SRL+TAC	0.71 (0.21, 2.04)	1.05 (0.03, 42.95)	0.72 (0.18, 2.52)	1.05 (0.02, 46.43)
SRL+MMF vs SRL+TAC	0.84 (0.50, 1.40)	0.68 (0.25, 1.75)	1.113 (0.57, 2.38)	0.68 (0.18, 2.43)
Total residual deviance	117	115.9	88.44	87.91
Relative number of model parameters	53.843	59.588	67.828	71.836
DIC	170.843	175.488	156.268	159.746

Graft Function

Fixed effects model results

Table 236. Mean differences (for Intervention vs Comparator treatment) for the outcome Graft Function from a fixed effects network meta-analysis (Posterior median (95%CrI))

	Comparator treatment										
Intervention trtment	CYC + AZA	TAC + AZA	MMF + CYC	TAC + MMF	BEL + SIR	BEL + MMF	EVL + MPS	EVL + CYC	SRL + TAC	SRL + CYC	SRL + MMF
TAC + AZA	12.54 (11.17, 13.90)										
MMF + CYC	4.34 (3.12, 5.57)	-8.19 (-9.73, -6.66)									
TAC + MMF	5.37 (5.07, 5.68)	-7.17 (-8.56, -5.77)	1.03 (-0.21, 2.27)								
BEL + SIR	12.68 (0.02, 25.32)	0.14 (-12.57, 12.87)	8.34 (-4.35, 21.04)	7.31 (-5.34, 19.96)							
BEL + MMF	13.02 (9.95, 16.10)	0.49 (-2.73, 3.70)	8.68 (5.83, 11.53)	7.65 (4.58, 10.73)	0.34 (-12.49, 13.21)						
EVL + MPS	3.08 (-3.18, 9.33)	-9.45 (-15.79, -3.14)	-1.26 (-7.41, 4.86)	-2.30 (-8.56, 3.97)	-9.59 (-23.69, 4.49)	-9.94 (-16.75, -3.18)					
EVL + CYC	6.01 (3.30, 8.73)	-6.53 (-9.41, -3.66)	1.67 (-0.76, 4.09)	0.64 (-2.09, 3.36)	-6.67 (-19.60, 6.24)	-7.01 (-10.77, -3.25)	2.93 (-3.65, 9.52)				
SRL + TAC	1.12 (-1.79, 4.02)	-11.42 (-14.57, -	-3.22 (-6.16, -	-4.25 (-7.16, -	-11.56 (-24.52,	-11.90 (-15.98, -	-1.97 (-8.76, 4.85)	-4.89 (-8.69, -			

		8.28)	0.30)	1.35)	1.40)	7.83)		1.08)			
SRL + CYC	-1.39 (-4.53, 1.77)	-13.93 (-17.27, -10.59)	-5.73 (-8.82, -2.64)	-6.76 (-9.90, -3.61)	-14.07 (-27.08, -1.05)	-14.42 (-18.6, -10.21)	-4.47 (-11.34, 2.41)	-7.40 (-11.32, -3.49)	-2.51 (-4.93, -0.09)		
SRL + MMF	1.94 (0.01, 3.87)	-10.60 (-12.84, -8.36)	-2.40 (-4.28, -0.52)	-3.43 (-5.36, -1.50)	-10.74 (-23.53, 2.05)	-11.08 (-14.50, -7.69)	-1.14 (-7.54, 5.27)	-4.07 (-7.15, -1.01)	0.82 (-2.29, 3.94)	3.33 (-0.04, 6.69)	
SRL + AZA	10.80 (8.40, 13.20)	-1.74 (-4.50, 1.02)	6.45 (3.76, 9.15)	5.43 (3.01, 7.85)	-1.87 (-14.78, 11.02)	-2.22 (-6.12, 1.67)	7.73 (1.03, 14.44)	4.79 (1.17, 8.42)	9.69 (5.90, 13.45)	12.20 (8.22, 16.14)	8.86 (5.78, 11.94)

Consistency analysis results

There are direct data for 18 comparisons and 12 treatments in the network, however 2 independent loops are informed by multi-arm trials only and so the inconsistency degrees of freedom (ICDF), reflecting the number of independent loops in the network is 18 – (12 - 1) – 2 = 5. Comparing the DIC between the consistency and inconsistency random effects models suggests the consistency model has a slightly better fit to the data (147.8 vs 150.0). Furthermore, the posterior median estimates are similar between the consistency and inconsistency models and the 95% CrIs overlap considerably (see Table 237).

Table 237. Comparison of fixed and random effects consistency and inconsistency models for maintenance therapy on CRC-GRF

	Fixed effects model		Random effects model	
	Consistency model	Inconsistency model	Consistency model	Inconsistency model
TAC+AZA vs CYC+AZA	12.54 (11.17, 13.9) 12.54; 0.70	13.09 (11.7, 14.48) 13.09; 0.71	9.31 (4.32, 14.28) 9.30; 2.54	9.78 (4.65, 14.87) 9.77; 2.61
MMF+CYC vs CYC+AZA	4.34 (3.12, 5.57) 4.34; 0.63	6.00 (4.53, 7.47) 6.00; 0.75	1.61 (-4.16, 7.41) 1.61; 2.95	3.60 (-3.88, 11.09) 3.59; 3.82
TAC+MMF vs CYC+AZA	5.37 (5.07, 5.68) 5.37; 0.16	5.30 (4.99, 5.61) 5.30; 0.16	6.53 (0.38, 12.68) 6.53; 3.14	5.29 (-4.13, 14.71) 5.29; 4.80
SRL+AZA vs CYC+AZA	10.80 (8.40, 13.20) 10.80; 1.22	10.80 (8.40, 13.20) 10.80; 1.22	10.78 (1.07, 20.44) 10.78; 4.94	10.77 (1.10, 20.48) 10.77; 4.94
TAC+MMF vs MMF+CYC	1.03 (-0.21, 2.27) 1.03; 0.63	5.20 (2.56, 7.84) 5.20; 1.35	4.92 (0.87, 8.98) 4.92; 2.07	4.98 (-0.75, 10.70) 4.98; 2.92
BEL+MMF vs MMF+CYC	8.68 (5.83, 11.53) 8.68; 1.45	8.52 (5.55, 11.48) 8.52; 1.51	8.94 (3.13, 14.79) 8.94; 2.98	7.83 (1.48, 14.18) 7.83; 3.24
EVL+MPS vs MMF+CYC	-1.26 (-7.41, 4.86) -1.27; 3.13	-1.26 (-7.41, 4.87) -1.26; 3.13	-1.27 (-12.45, 9.93) -1.27; 5.71	-1.25 (-12.49, 9.91) -1.26; 5.72
EVL+CYC vs MMF+CYC	1.67 (-0.76, 4.09) 1.67; 1.24	1.67 (-0.75, 4.09) 1.67; 1.24	3.26 (-1.82, 8.34) 3.25; 2.59	3.25 (-1.82, 8.34) 3.26; 2.60
SRL+CYC vs MMF+CYC	-5.73 (-8.82, -2.64) -5.73; 1.58	1.20 (-3.08, 5.47) 1.20; 2.18	-3.23 (-11.07, 4.64) -3.22; 4.00	1.19 (-9.14, 11.52) 1.20; 5.27
SRL+MMF vs MMF+CYC	-2.40 (-4.28, -0.52) -2.40; 0.96	-2.66 (-4.92, -0.41) -2.67; 1.15	2.24 (-1.55, 6.05) 2.24; 1.94	2.00 (-2.34, 6.39) 2.01; 2.23
BEL+SIR vs TAC+MMF	7.31 (-5.35, 19.96) 7.30; 6.44	7.80 (-5.02, 20.63) 7.80; 6.54	5.79 (-9.53, 21.06) 5.79; 7.80	7.76 (-8.18, 23.79) 7.77; 8.12
BEL+MMF vs	7.65 (4.58, 10.73)	9.58 (-1.03, 20.20)	4.02 (-2.72, 10.73)	9.60 (-4.61, 23.70)

TAC+MMF	7.65; 1.57	9.58; 5.42	4.02; 3.43	9.58; 7.24
SRL+TAC vs TAC+MMF	-4.25 (-7.16, -1.35) -4.26; 1.48	-8.36 (-12.11, -4.60) -8.36; 1.92	-6.88 (-13.01, -0.75) -6.88; 3.12	-9.87 (-17.58, -2.18) -9.87; 3.93
SRL+MMF vs TAC+MMF	-3.43 (-5.36, -1.50) -3.43; 0.98	-2.14 (-5.45, 1.15) -2.15; 1.68	-2.69 (-6.92, 1.57) -2.68; 2.16	-0.61 (-7.01, 5.82) -0.61; 3.27
SRL+CYC vs SRL+TAC	-2.51 (-4.93, -0.09) -2.51; 1.23	-5.24 (-7.92, -2.57) -5.24; 1.37	-1.26 (-8.97, 6.45) -1.26; 3.93	-5.22 (-15.03, 4.55) -5.24; 5.00
SRL+MMF vs SRL+TAC	0.82 (-2.29, 3.94) 0.82; 1.59	4.14 (-5.31, 13.59) 4.14; 4.82	4.20 (-2.02, 10.41) 4.20; 3.17	4.08 (-9.18, 17.46) 4.11; 6.80
Total residual deviance	277.7	245.7	82.75	83.42
Relative number of model parameters	45.987	50.949	65.058	66.594
DIC	323.687	296.649	147.808	150.014

Appendix 7 Adverse events

Adverse events; meta-analyses at 1-year follow-up

Where data permitted, the 1–year follow-up results of individual studies were pooled using meta-analyses; new onset diabetes (NODAT), post-transplant lymphoproliferative disorder (PTLD), malignancy (including PTLD), any infections, and cytomegalovirus (CMV) were considered. The DerSimonian–Laird random effects method was used for pooling. Odd ratio (OR) was used as a measure of treatment effect.

The number of studies included in the individual meta-analyses was between two and eight, therefore we did not investigate publication bias; tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry (Cochrane handbook, 2008).[196] In addition, no corrections for multiple comparisons were executed. Therefore any meta-analyses results presented in this section must be interpreted with caution

Induction regimens

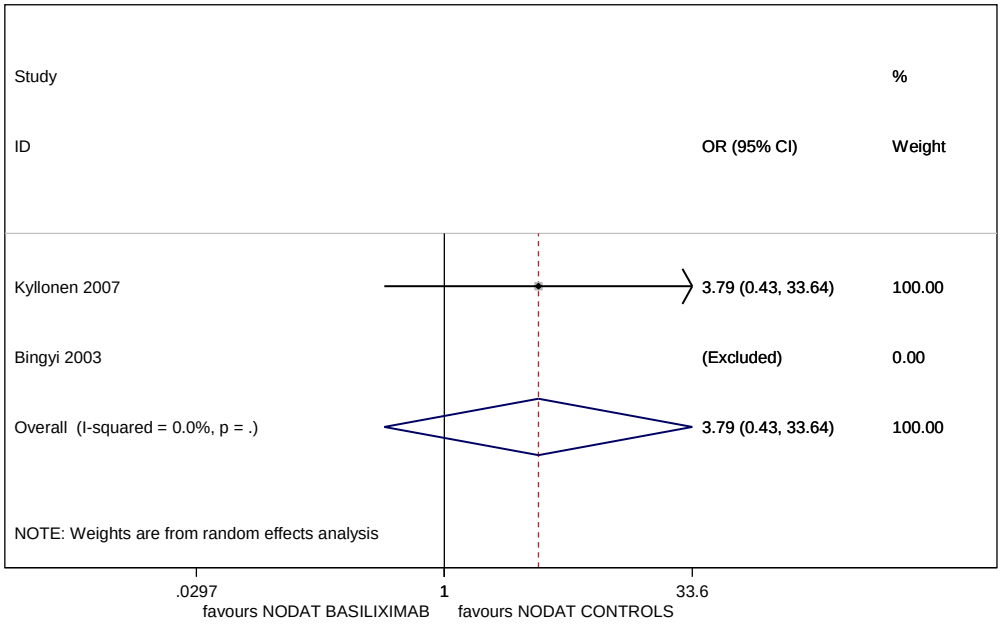
Eleven studies reported some AE at 1–year follow-up: four studies compared Basiliximab with placebo or no induction (Bingyi et al. 2003, Kahan et al. 1999, Nashan et al. 1997, Lawen et al. 2003)[66 67 69 81], four studies compared Basiliximab and rATG (Brennan et al. 2006, Mourad et al. 2004, Lebranchu et al. 2002, Sollinger et al. 2001)[89 90 92 199]; two studies compared rATG with no induction (Charpentier et al .2001, Samsel et al. 2008)[82 84], and one study compared basiliximab, rATG and no induction (Kyllonen et al. 2007)[86].

All AE are summarised in the sections below according to induction therapy used. Similarly to the clinical effectiveness outcomes studies comparing Basiliximab with placebo, and Basiliximab with no induction were combined

Basiliximab versus placebo and no induction

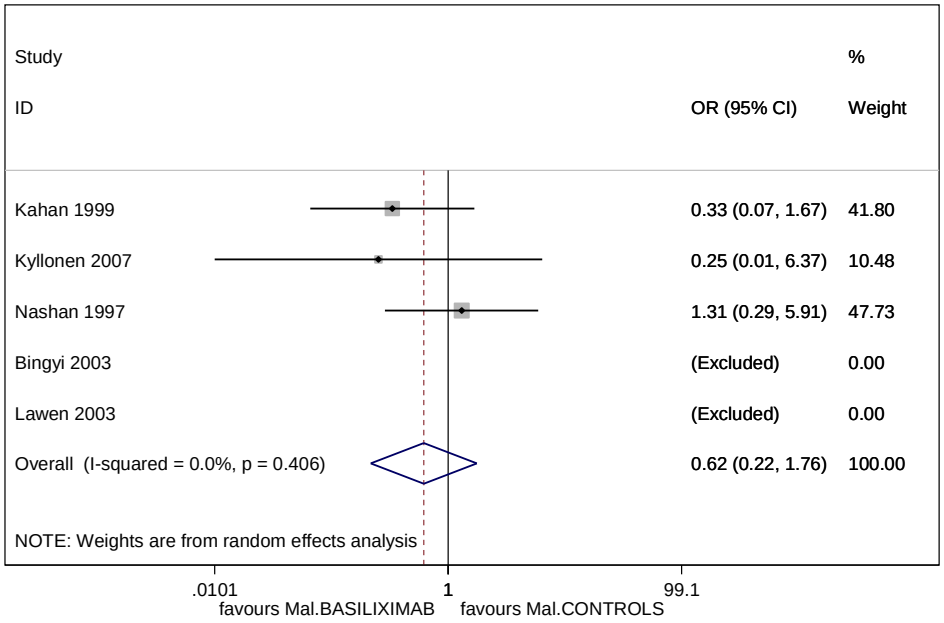
NODAT, PTLD, malignancy, infections and CMV infections were reported in studies comparing Basiliximab versus placebo and Basiliximab versus no induction (results from studies comparing Basiliximab with placebo, and Basiliximab with no induction were combined). No differences between Basiliximab and control arms were identified for any AE. The NODAT (**Figure 121**), malignancy (**Figure 122**) PTLD (**Figure 123**), Infections (**Figure 124**) and CMV results (**Figure 125**) are presented below. In summary, no difference in NODAT, PTLD, malignancy, infections and CMV infections were found between Basiliximab and control arms.

Figure 121 NODAT; Basiliximab versus placebo and no induction



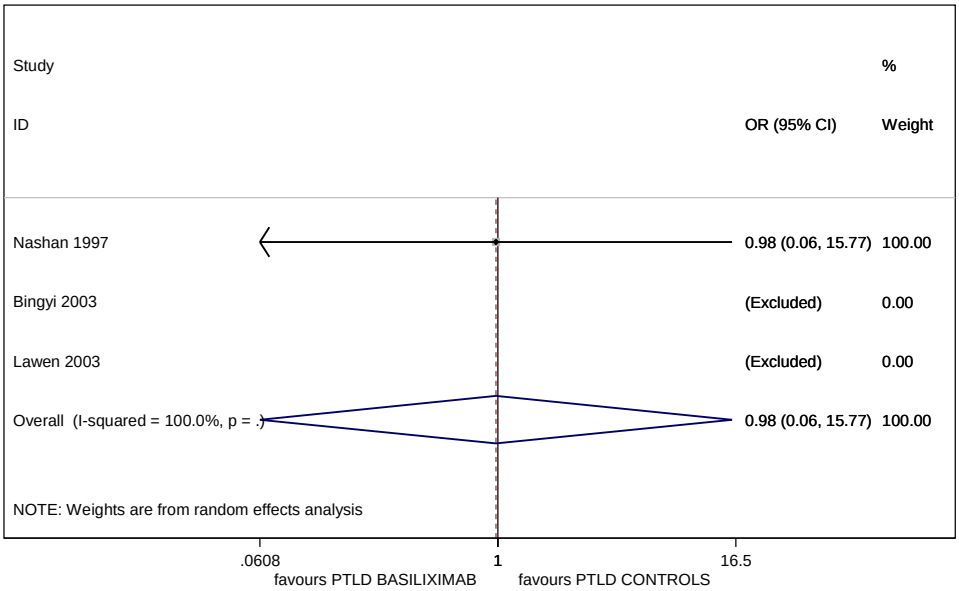
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 122 Malignancy; Basiliximab versus placebo and no induction



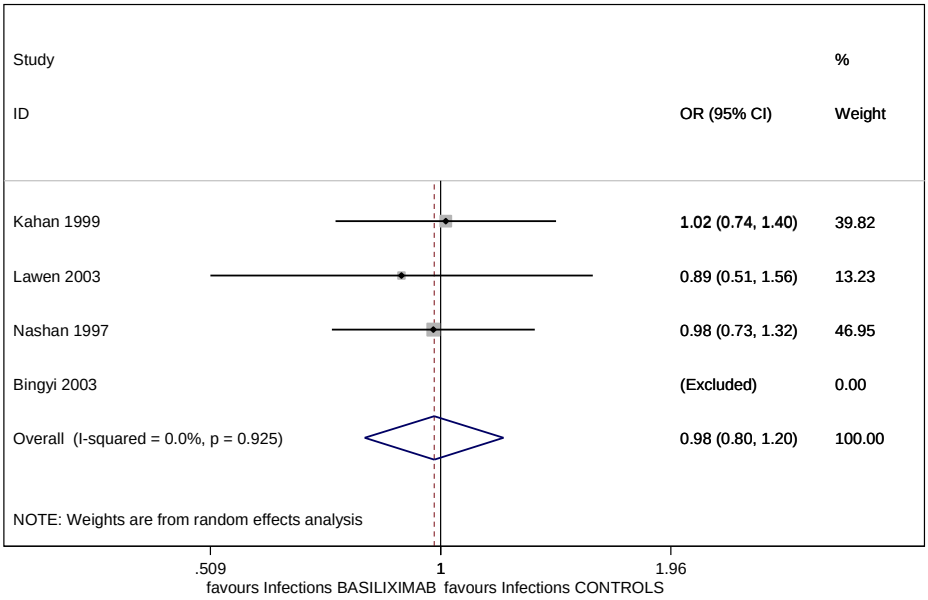
Key: OR, odds ratio; ID, identification; Mal., malignancy. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Figure 123 PTLD; Basiliximab versus placebo and no induction



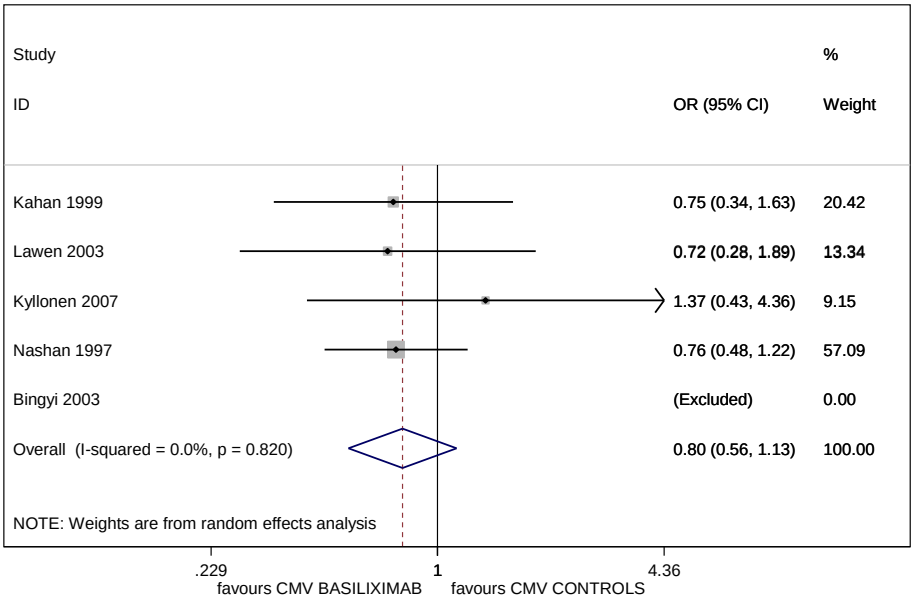
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 124 Infections; Basiliximab versus placebo and no induction



Key: OR, odds ratio; ID, identification. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Figure 125 CMV; Basiliximab versus placebo and no induction



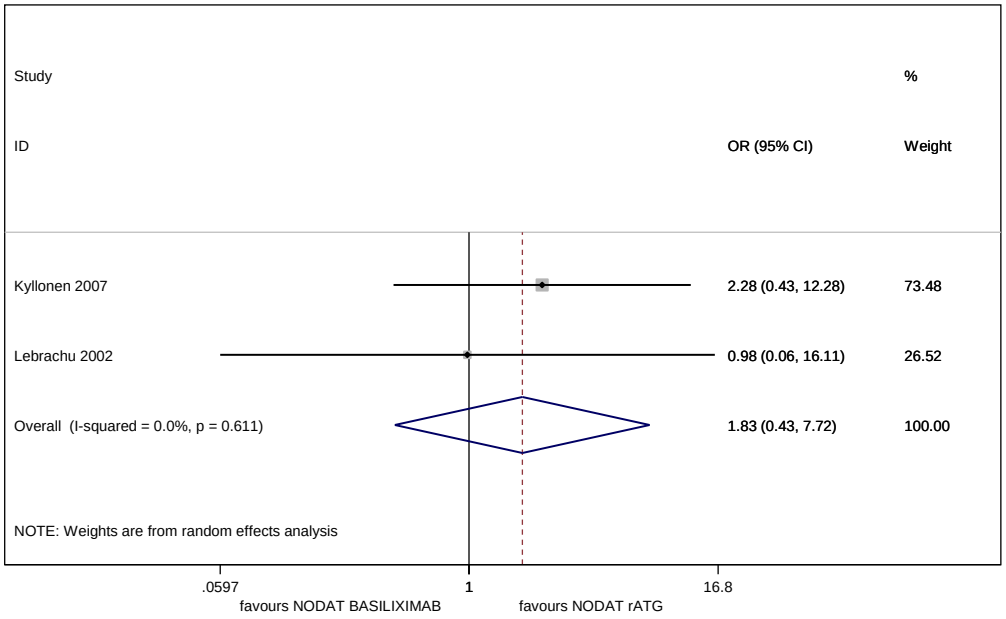
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Basiliximab versus rATG

NODAT, PTLD, malignancy, infections and CMV infections were reported in studies comparing Basiliximab versus rATG. More infections and more CMV infections were reported in rATG compared with Basiliximab in one study (Brennan et al. 2006)[89]. However, less CMV infections were reported in rATG compared with Basiliximab in a different study (Mourad at al.2004)[199]. In addition, these differences were not reported in the three-arm study comparing BAS, rATG and no induction (Kyllonen et al. 2007)[86]. The NODAT (**Figure 126**), malignancy (**Figure 127**), PTLD (**Figure 128**), infections (**Figure 129**) and CMV results (**Figure 130**) are presented below.

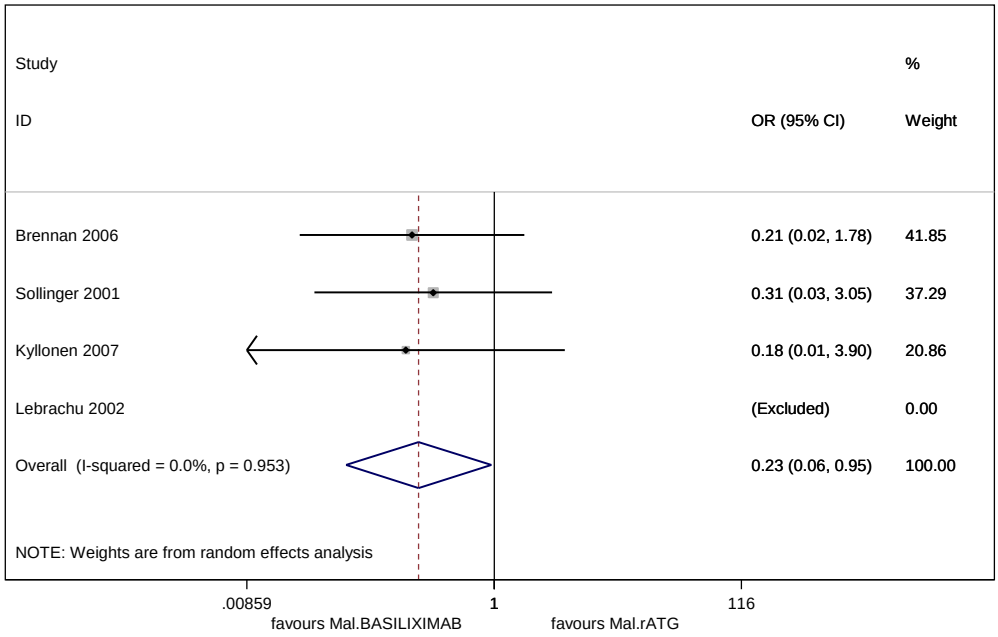
In summary, no difference in NODAT, PTLD, malignancy and infections were found between the two induction regimens, rATG and BAS. Some evidence suggested more CMV infections in rATG regimens compared with BAS regimens (Mourad at al.2004)[199]. However this finding was contradicted by results of the three-arm study comparing BAS, rATG and no induction (Kyllonen et al. 2007).[86]

Figure 126 NODAT; Basiliximab versus rATG



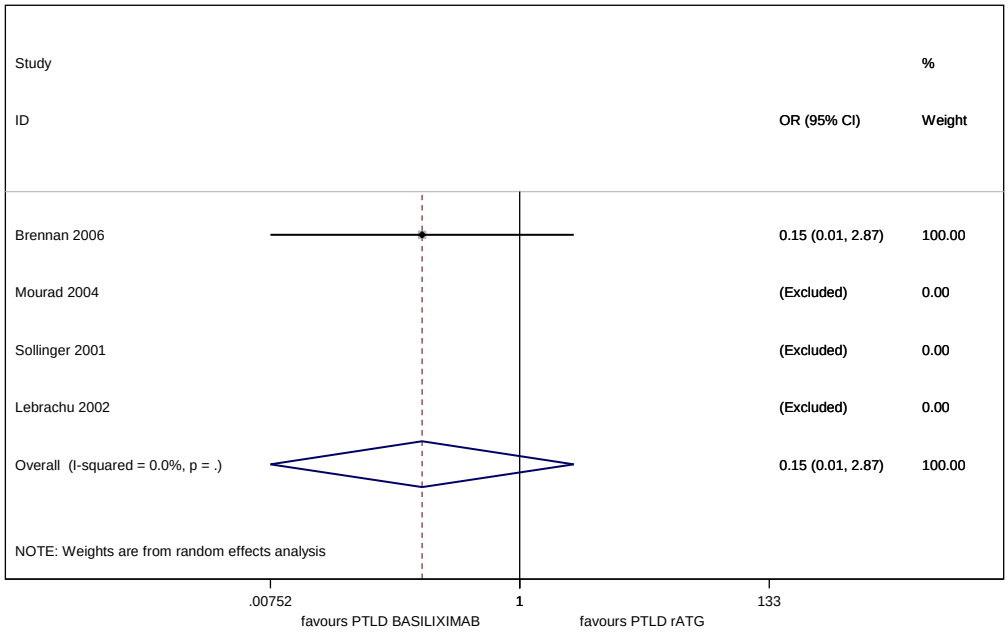
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; rATG, Rabbit antithymocyte globulin. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data the estimate of between-study variance Tau-squared was 0.000.

Figure 127 Malignancy; Basiliximab versus rATG



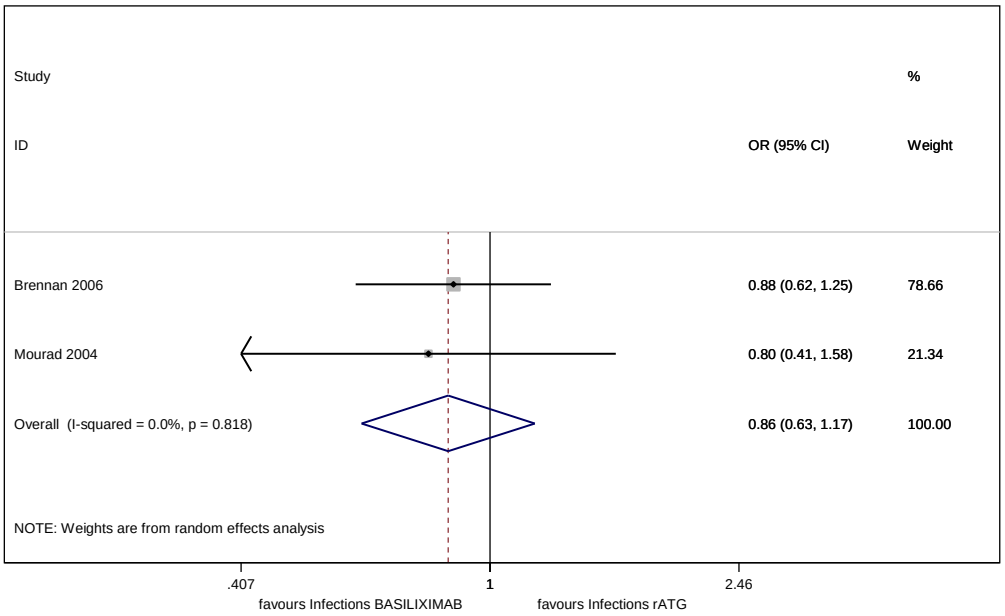
Key: OR, odds ratio; ID, identification; Mal., malignancy. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Figure 128 PTLD; Basiliximab versus rATG



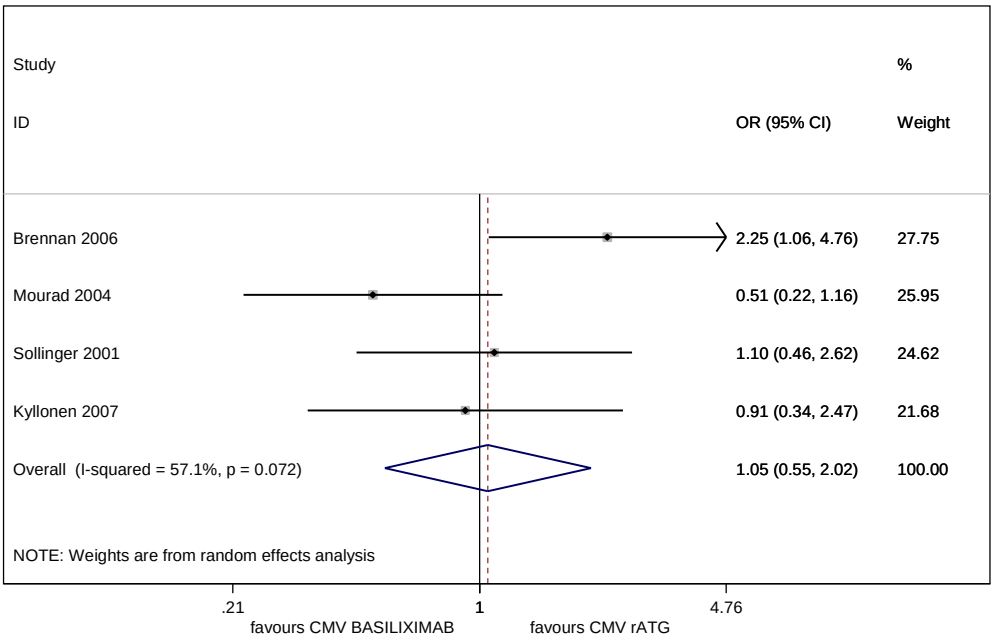
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 129 Infections; Basiliximab versus rATG



Key: OR, odds ratio; ID, identification. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 130 CMV; Basiliximab versus rATG



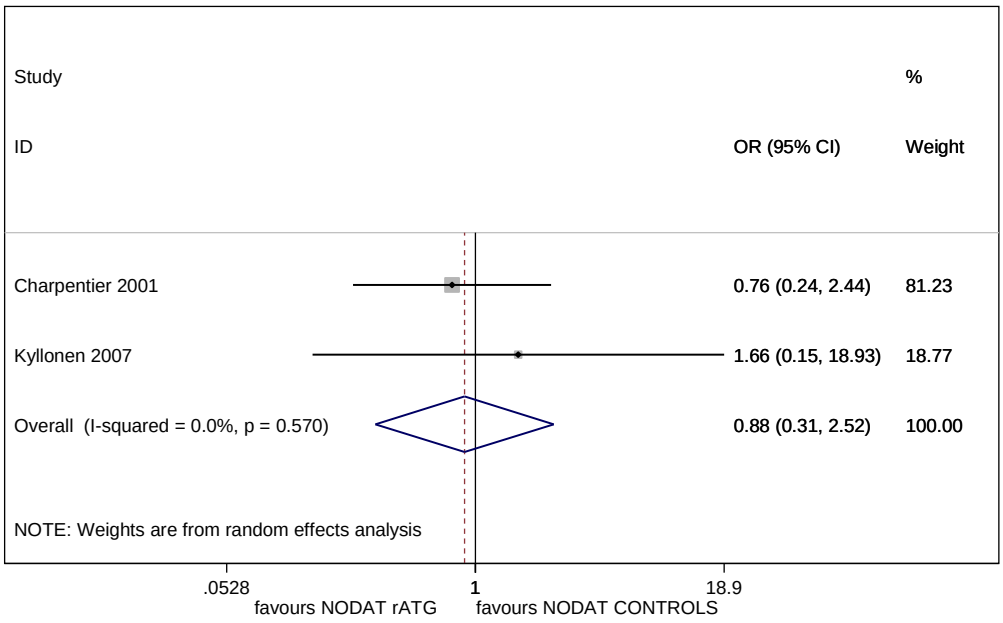
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.251.

rATG versus no induction

NODAT, malignancy, and CMV were reported in studies comparing rATG versus no induction. More CMV infections were reported in the rATG arm compared with controls in one study (Charpentier et al. 2001)[82]; however these differences were not reported in the three-arm study comparing BAS, rATG and no induction (Kyllonen et al. 2007) [86]. The NODAT (**Figure 131**), malignancy (**Figure 132**) and CMV results (**Figure 133**) are presented below.

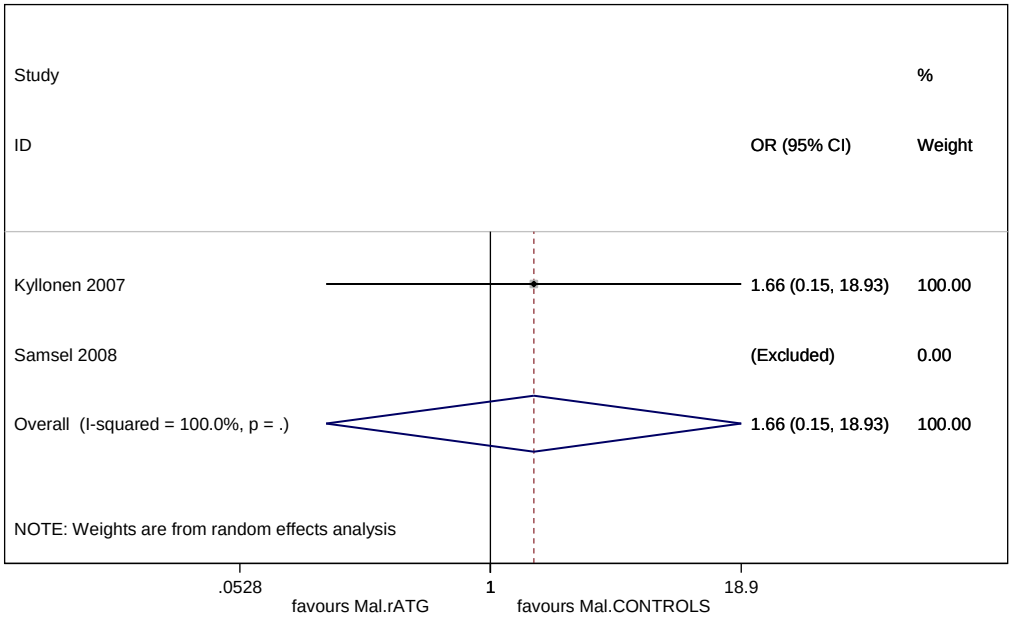
In summary, no difference in NODAT, PTLD, malignancy and infections were found between rATG and no induction regimens at 1–year follow-up. Some evidence suggested more CMV infections in rATG regimens compared with no induction (Charpentier et al. 2001)[82], however this finding was contradicted by results of the three-arm comparing BAS, rATG and no induction (Kyllonen et al. 2007).[86]

Figure 131 NODAT; rATG versus no induction



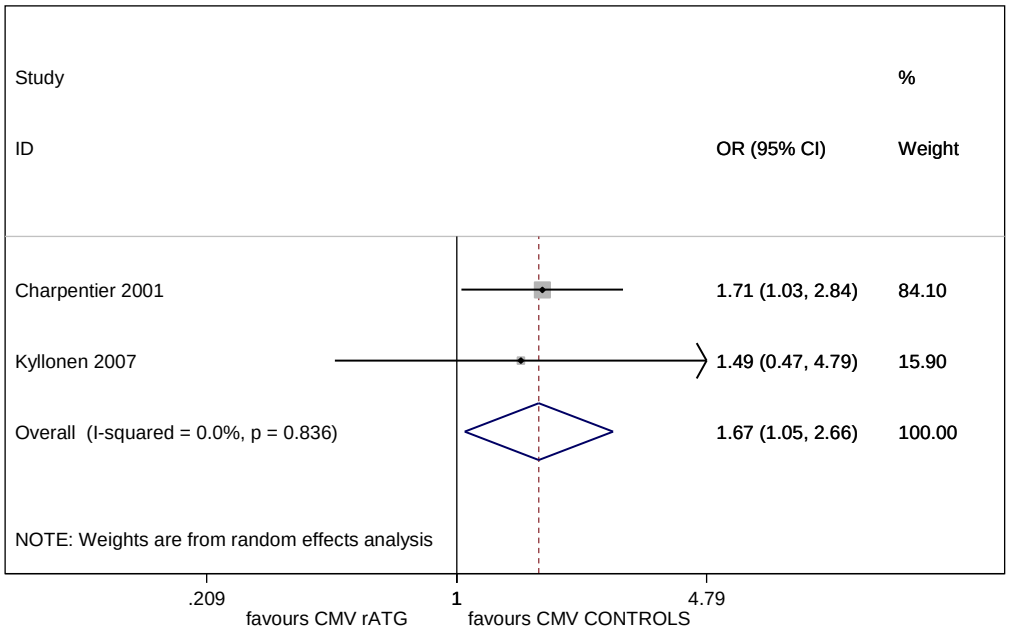
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; rATG, Rabbit antithymocyte globulin. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 132 Malignancy; rATG versus no induction



Key: OR, odds ratio; ID, identification; Mal., malignancy. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 133 CMV; rATG versus no induction



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Maintenance regimens

Thirty nine studies (of the 76 maintenance studies) reported some AE at 1–year follow-up. Twenty nine studies reported NODAT, 22 studies reported malignancy, nine studies reported PTLD, 15 studies reported infections and 28 studies reported CMV infections. For consistency, point estimates and confidence intervals for the odd ratio reported in the studies were calculated using Stata and corresponding p-values were reported.

All studies were polled irrespective of concomitant treatments used in the individual studies. For example, to compare CSA and TAC therapies, results of a study comparing a triple regimen of CSA +AZA+CCS with a triple regimen of TAC+AZA+CCS were pooled with results of a study comparing the following two regimens BAS+CCS+MMF+S and BAS+ CSA +MMF+CCS; studies were pooled irrespective of induction and concomitant therapies used in the studies, as long as the same therapies were used in the two comparative arms.

Ferguson et al. 2011 compared three regimens BEL+MMF and TAC+MMF and BEL+SIR, however only BEL+MMF and TAC+MMF results were used in meta-analyses.[138] Similarly, a one study by Chadban et al. 2013 compared EVL+CSA and MPS+CSA and EVL, however only results of EVL+CSA and MPS+CSA arms were used in meta-analyses [144] Finally, SYMPHONY trial compared low CSA+MMF, low TAC +MMF, SRL+MMF, and CSA+MMF, however only results of low CSA+MMF, low TAC +MMF and SRL+MMF were used in meta-analyses. [420] In addition, one study reported AE at 1-year follow-up, but the study did not use comparable concomitant rtherapies and therefore the results of this study could not be included in meta-analyses (Vacher-Coponat et al. 2012).[119]

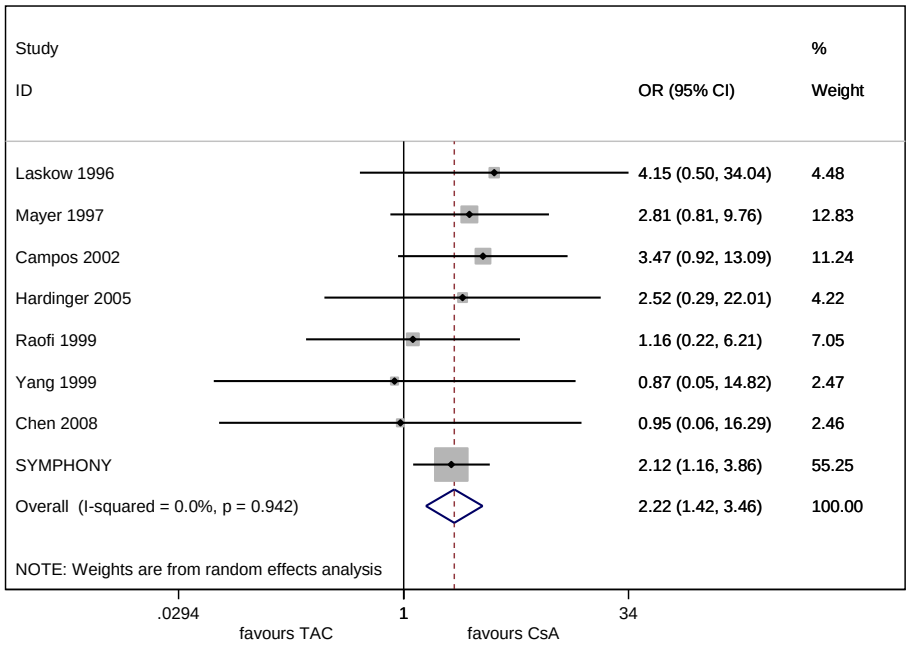
Tacrolimus versus Cyclosporine

Ten studies comparing TAC with CSA reported AE; six studies used TAC + AZA + CS and CSA+ AZA + CS regimens (Laskow et al. 1996, Mayer et al. 1997, Raofi et al. 199 [Jarzembowski et al. 200], Campos et al. 2002, Hardinger et al. 2005, Baboolal at al. 2002), two studies compared TAC+MMF+CCS and CSA+MMF+CCS regimens (Yang et al. 1999,Weimer at al 2006), one study compared TAC+SRL+CCS and CSA+SRL+CCS regimens (Chen et al. 2008) and one study comparing four regimens

also compared low TAC +MMF+CCS and low CSA+MMF +CCS regimens (SYMPHONY)[420].

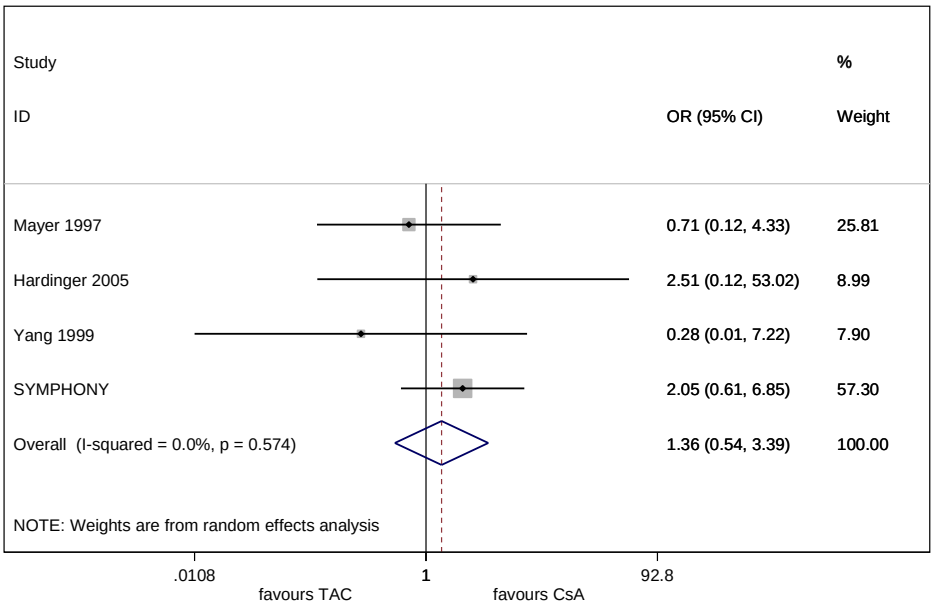
The meta-analyses suggested more cases of NODAT in TAC regimens compared with CSA (**Figure 134**), no difference for malignancy (**Figure 135**), no difference for infections (**Figure 136**) and no difference for CMV infections (**Figure 137**). Three studies reported no PTLD cases in both arms. [108 245 420] In summary, no difference in PTLD, malignancy, infections and CMV infection were found between TAC and CSA regimens at 1–year -follow-up. The meta-analysis (including 8 studies) suggested more cases of NODAT in TAC regimens compared with CSA.

Figure 134 NODAT; Tacrolimus versus Cyclosporine



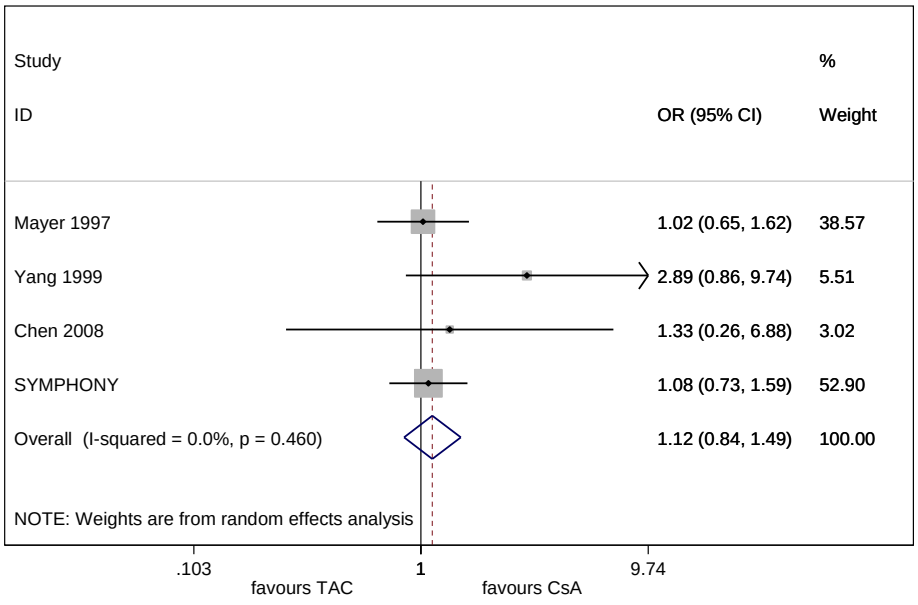
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 135 Malignancy; Tacrolimus versus Cyclosporine



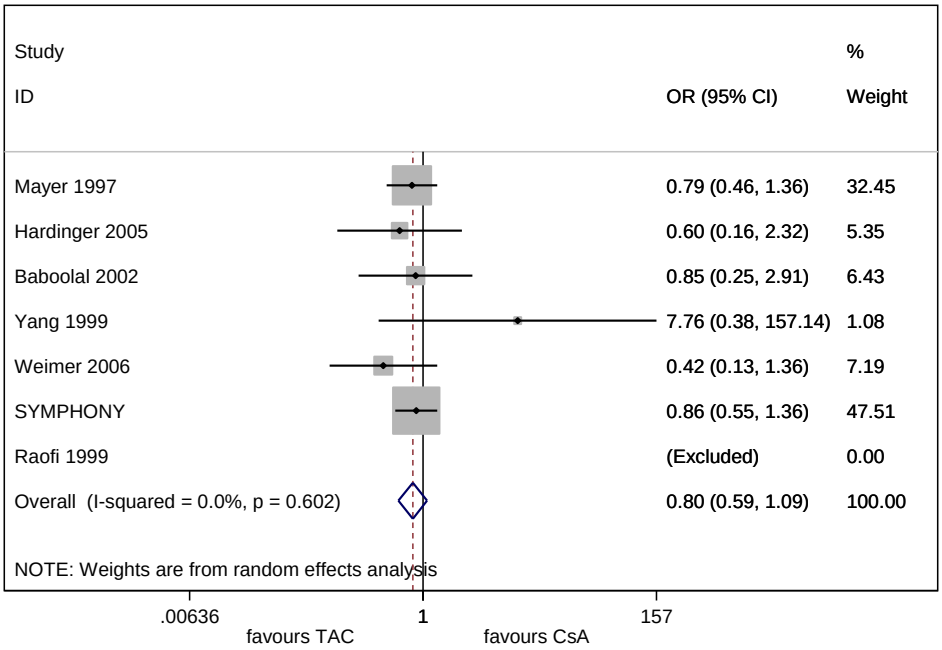
Key: OR, odds ratio; ID, identification; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 136 Infections; Tacrolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; TAC, Tacrolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; ; the estimate of between-study variance Tau-squared was 0.000.

Figure 137 CMV; Tacrolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; TAC, Tacrolimus; CSA, cyclosporine.
Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Mycophenolate Mofetil versus Cyclosporine

One three-arm study comparing MMF with CSA reported AE; this study used the following regimens MMF+AZA+CCS and CSA+AZA+CCS (Sadek et al. 2002)[113]. No difference was found between the two arms for infections, OR= 0.86 (95% CI 0.54-1.37). No other AE were reported in this study.

In summary, no difference in infections and CMV infection was found between MMF and CSA regimens at 1–year -follow-up. However, only one study reported infection.

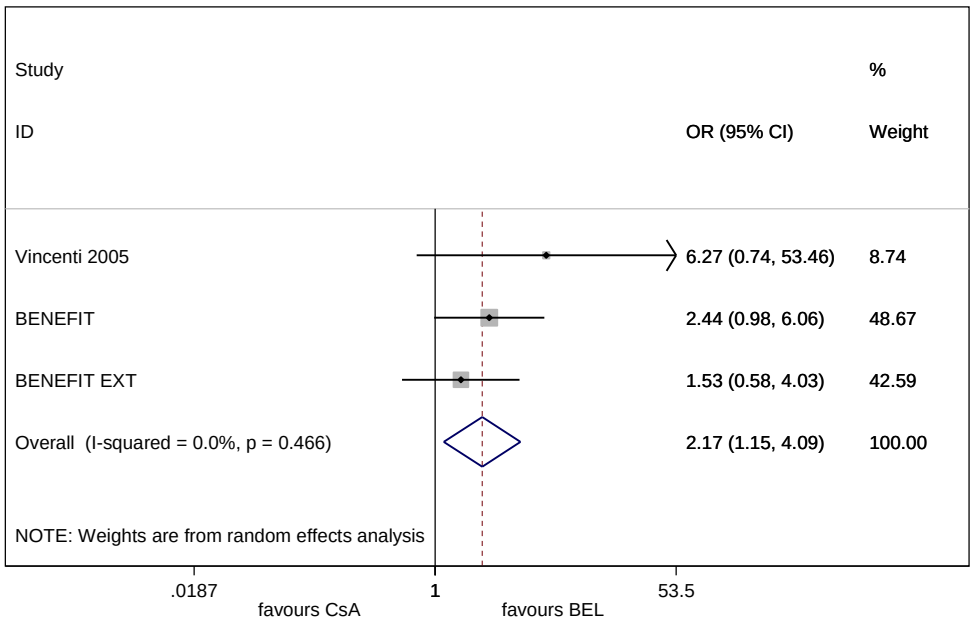
Belatacept versus Cyclosporine

Three studies comparing BEL with CSA reported AE; three studies used BEL+MMF+CCS and CSA+MMF+CCS regimens (Vincenti et al.2005, BENEFIT, BENEFIT-EXT)[71 135 421]. Two studies BENEFIT, BENEFIT-EXT)[135 421] had two BEL

regimes, using low and high BEL doses. Only the results of the low BEL arms (closer to the licence dose) were used in the analyses.

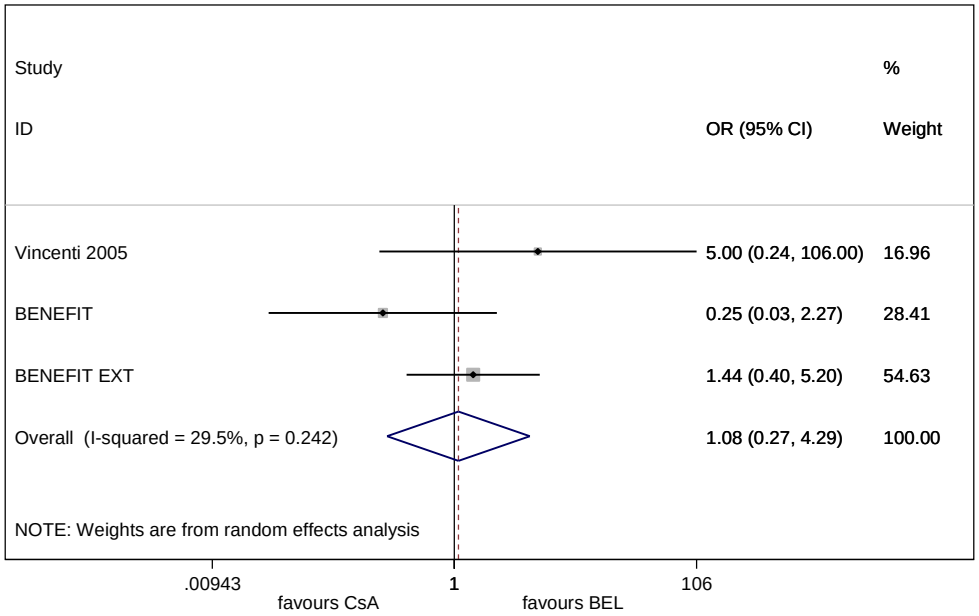
The meta-analyses suggested more cases of NODAT in CSA regimens compared with BEL regimens (**Figure 138**), no difference for malignancy (**Figure 139**), no difference for PTLD (**Figure 140**), no difference for infections (**Figure 141**) and CMV infections (**Figure 142**) between BEL and CSA regimens were identified. In summary, no difference in malignancy, PTLD, infections, and CMV infection were found between BEL and CSA regimens at 1–year -follow-up. The meta-analysis (including 3 studies) suggested more cases of NODAT in CSA regimens compared with BEL regimens.

Figure 138 NODAT; Belatacept versus Cyclosporine



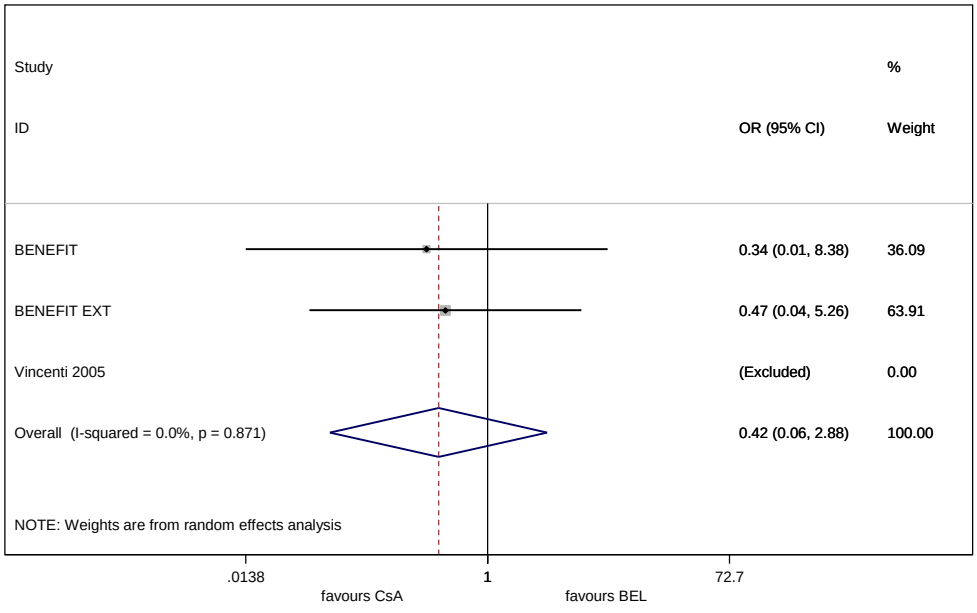
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 139 Malignancy; Belatacept versus Cyclosporine



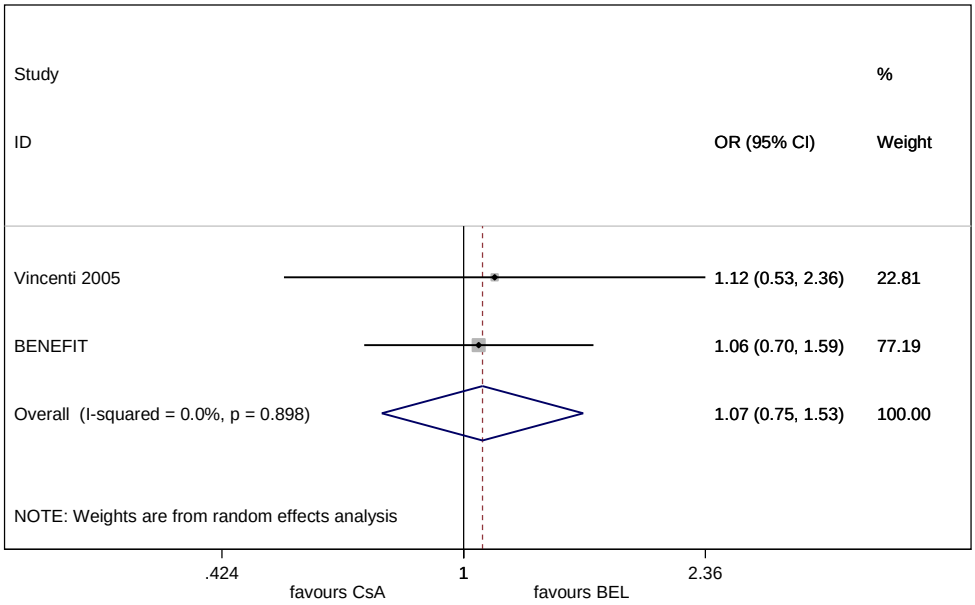
Key: OR, odds ratio; ID, identification; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.472.

Figure 140 PTLD; Belatacept versus Cyclosporine



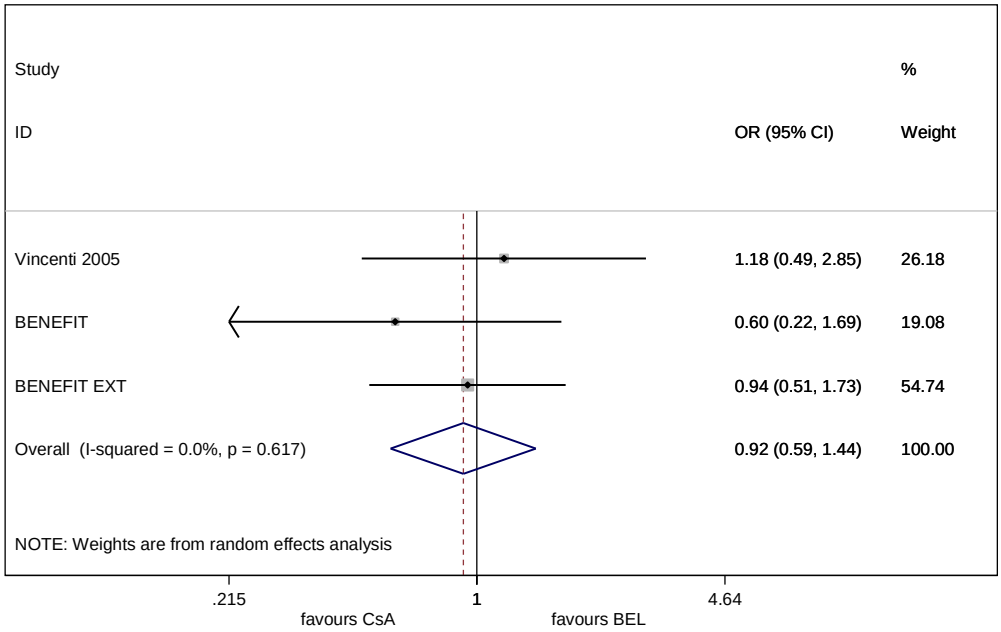
Key: OR, odds ratio; ID, identification PTLD, post-transplant lymphoproliferative disorder; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 141 Infections; Belatacept versus Cyclosporine



Key: OR, odds ratio; ID, identification; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 142 CMV; Belatacept versus Cyclosporine



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; BEL, Belatacept; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Everolimus versus Cyclosporine

One study comparing EVL with CSA reported AE; this study used the following regimens EVL+MPS+CCS and CSA+MPS+CCS (Mjornstedt et al. 2012)[150]. No difference was found between the two arms for malignancy, OR= 1.02 (95% CI 0.14-7.39), for infections, OR= 0.79 (95% CI 0.45-1.38) and for CMV infections, OR= 1.54 (95% CI 0.63-3.79). PTLD and NODAT were not reported in this study.

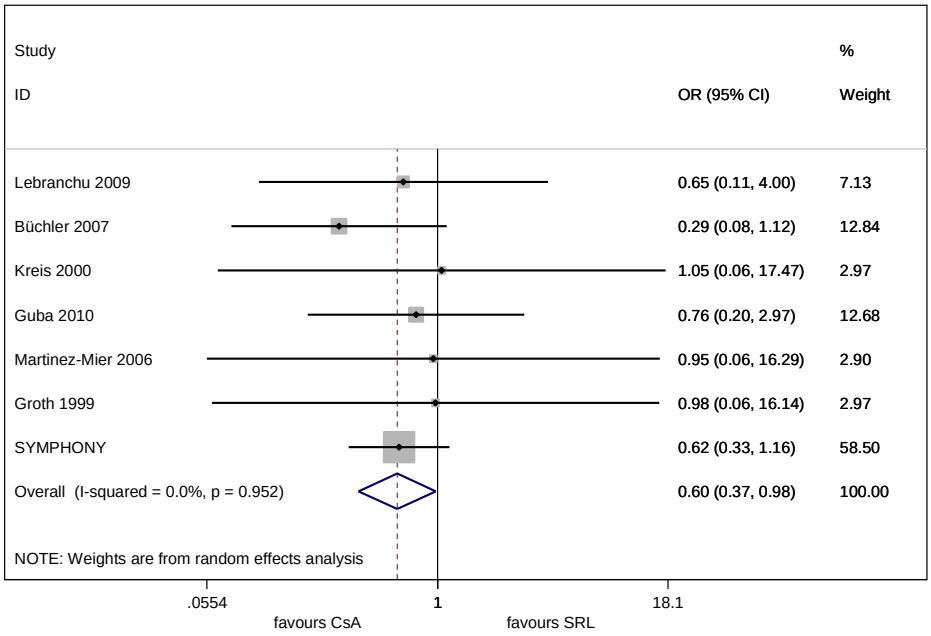
In summary, no difference in malignancy, infections and CMV infection were found between EVL and CSA regimens at 1–year -follow-up. However, only one study reported malignancy, infections and CMV infection.

Sirolimus versus Cyclosporine

Eight studies comparing SRL with CSA reported AE; six studies used SRL+MMF+CCS and CSA+MMF+CCS regimens (Lebranchu et al. 2009, Büchler et al. 2007, Kreis et al. 2000, Guba et al. 2010, Martinez-Mier et al. 2006 and Flechner et al. 2002)[163 167 173 174 205 206], one study used SRL+AZA+CCS and CSA+AZA+CCS regimens (Groth et al. 1999[Charpentier 2003])[185], and one study comparing four regimens also compared SRL+MMF+CCS and CSA+MMF+CCS regimens (SYMPHONY)[420].

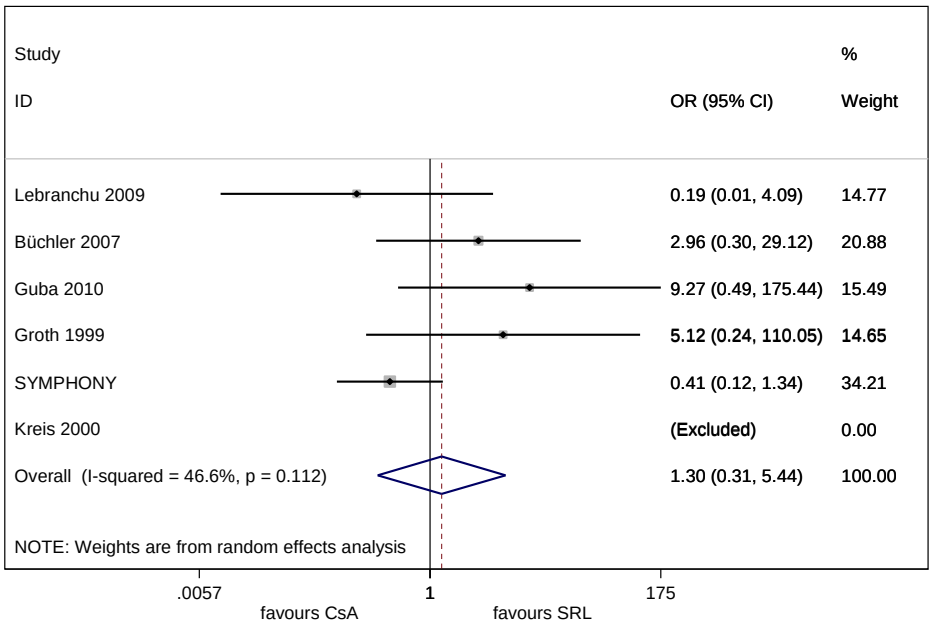
The meta-analyses suggested more cases of NODAT in CSA regimens compared with SRL (**Figure 143**), no difference in malignancy (**Figure 144**), no difference in PTLD (**Figure 145**), no difference for infections (**Figure 146**) and more cases of no difference for infections CMV in CSA compared with SRL regimen (**Figure 147**). In summary, no difference in malignancy, PTLD, infections, and CMV infection were found between SRL and CSA regimens at 1–year -follow-up. The meta-analysis (including 7 studies) suggested more cases of NODAT in CSA regimens compared with SRL.

Figure 143 NODAT; Sirolimus versus Cyclosporine



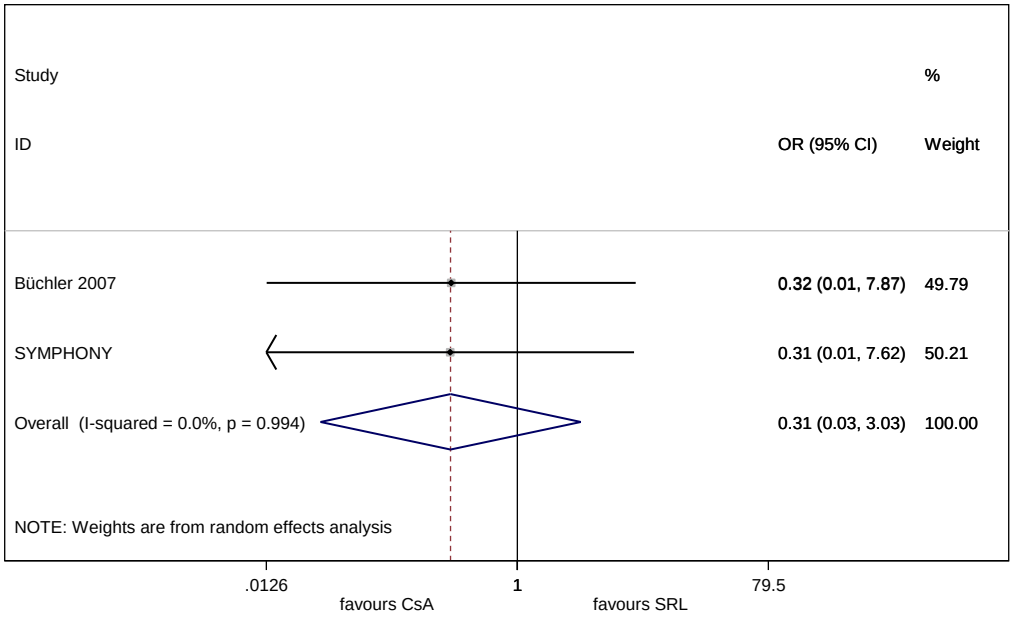
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 144 Malignancy; Sirolimus versus Cyclosporine



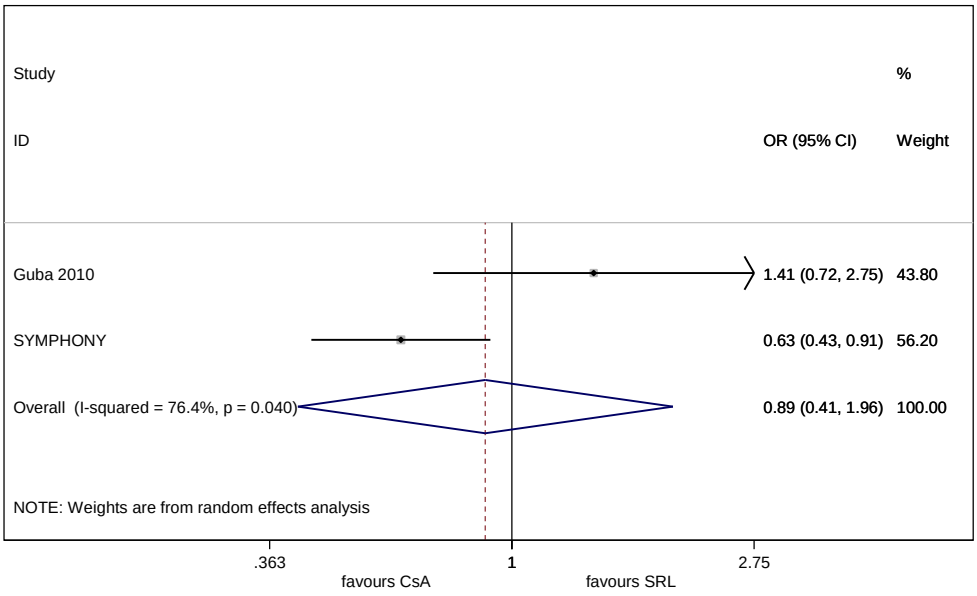
Key: OR, odds ratio; ID, identification; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis; the estimate of between-study variance Tau-squared was 0.000.

Figure 145 PTLD; Sirolimus versus Cyclosporine



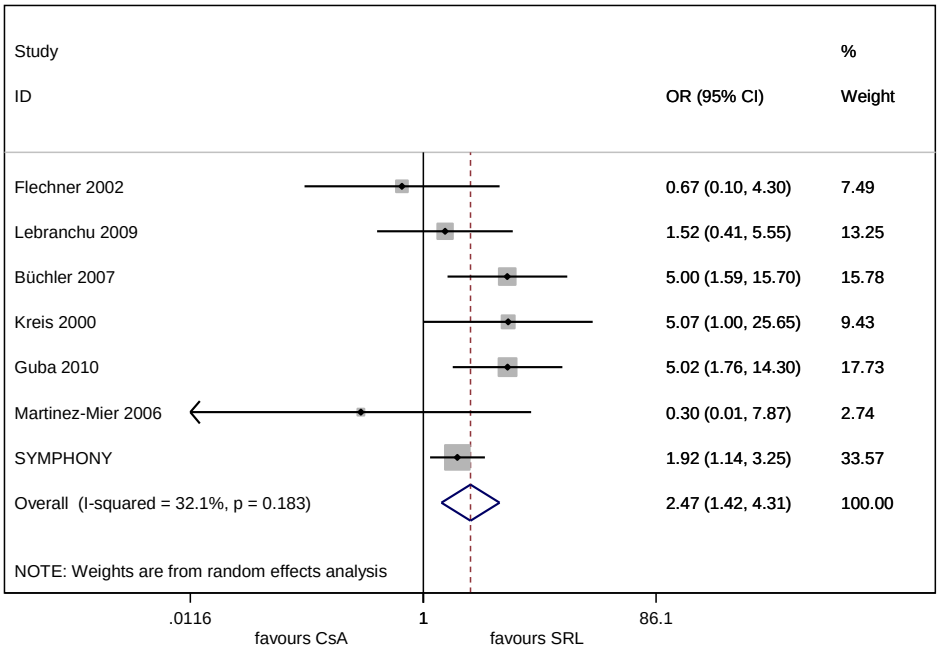
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder; SRL, sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 146 Infections; Sirolimus versus Cyclosporine



Key: OR, odds ratio; ID, identification; SRL, Sirolimus; CSA, cyclosporine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.248.

Figure 147 CMV; Sirolimus versus Cyclosporine



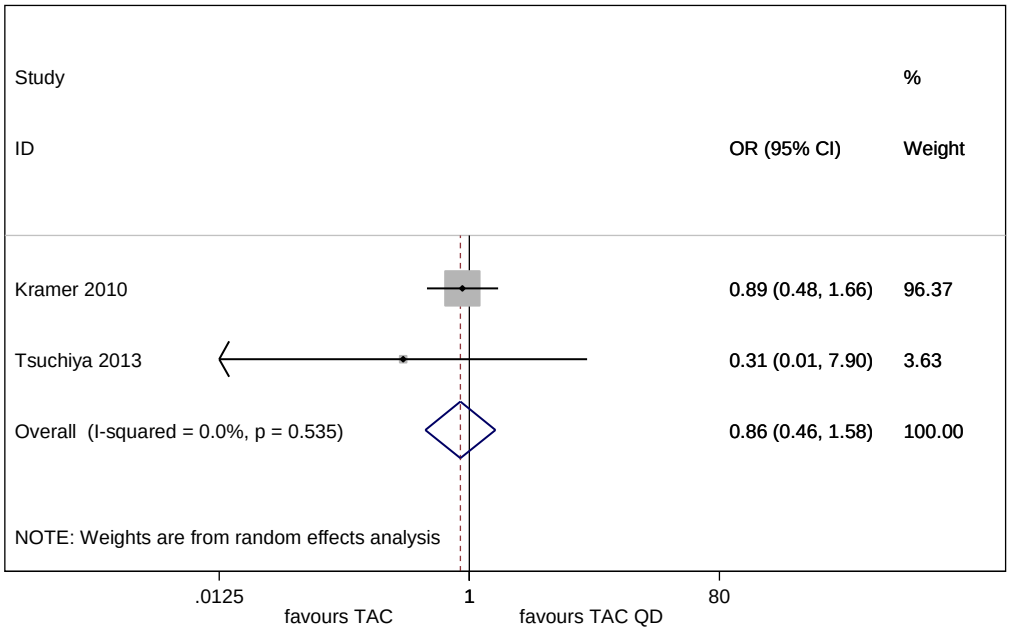
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; SRL, Sirolimus; CSA, cyclosporine.
Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Tacrolimus (short release) versus Prolong Release Tacrolimus

Two studies comparing TAC with TAC-PR reported AE; both studies used TAC+MMF+CCS and TAC PR+MMF+CCS regimens (Kramer et al. 2010 and Tsuchiya et al. 2013)[72 128].

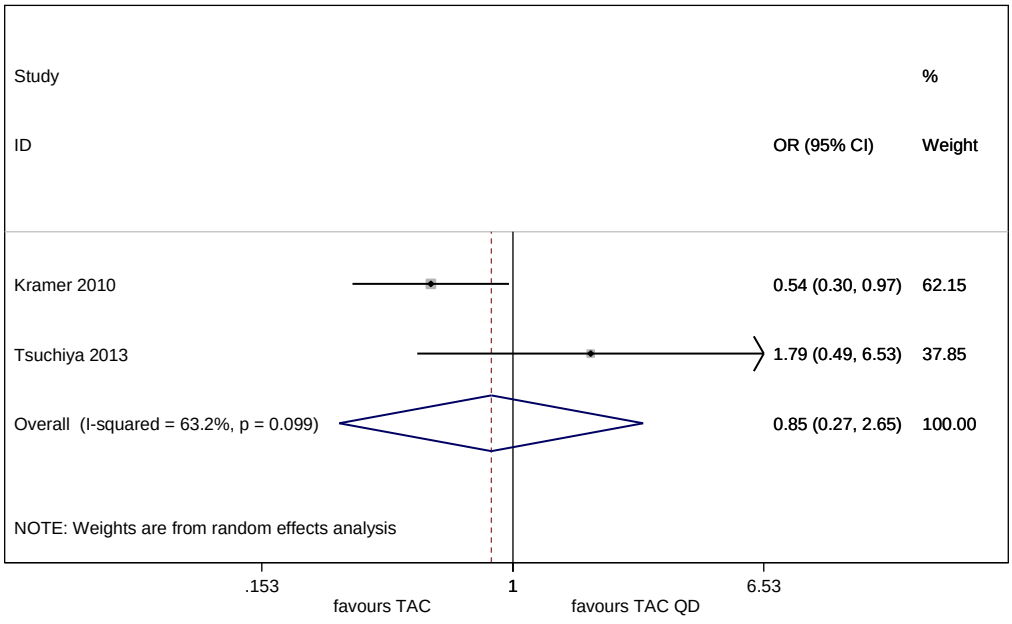
The meta-analyses suggested no differences for NODAT (**Figure 148**) and no differences for CMV (**Figure 149**). In addition, no difference was found between the two arms for malignancy, OR=1.32 (95% CI 0.45-3.85). No results for PTLD were reported. In summary, no difference in NODATs and CMV infection were found between TAC and TAC-PR regimens at 1–year -follow-up. However, only two studies reported NODATs and CMV infection.

Figure 148 NODAT; Tacrolimus versus Prolong Release Tacrolimus



Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; TAC QD, Tacrolimus Prolong Release. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 149 CMV; Tacrolimus versus Prolong Release Tacrolimus



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; TAC, Tacrolimus; TAC QD, Prolong Release Tacrolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.452.

Mycophenolate Mofetil versus Tacrolimus

One study comparing MMF with TAC reported AE; this study used the following regimens MMF+SRL+CCS and TAC+SRL+CCS (Hamdy et al. 2005)[181]. No difference was found between the two arms for NODAT, OR= 1.59 (95% CI 0.71-3.59). No other AE were reported in this study.

In summary, no difference in NODAT was found between MMF and TAC regimens at 1–year -follow-up. However, only one study reported NODAT.

Belatacept versus Tacrolimus

One three-arm study comparing BEL with TAC reported AE; this study used the following regimens BEL+MMF+CCS and TAC+MMF+CCS (Fergusson et al. 2011).[138] No difference was found between the two arms for NODAT, OR= 3.41 (95% CI 0.13-86.87), for malignancy, OR= 3.41 (95% CI 0.13-86.87), and for CMV infections, OR= 2.29 (95% CI 0.20-26.58). PTLD and infections were not reported in this study.

In summary, no difference in NODAT, malignancy, infections and CMV infection were found between BEL and TAC regimens at 1–year -follow-up. However, only one study reported NODAT, malignancy, infections and CMV infection.

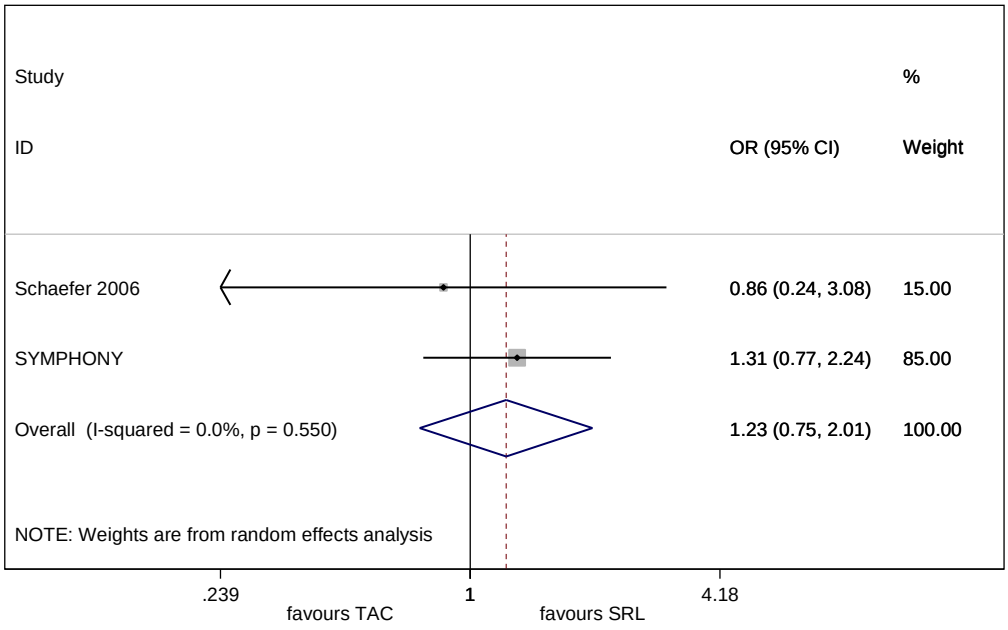
Sirolimus versus Tacrolimus

Two studies comparing SRL with TAC reported AE; one study used SRL+MMF+CCS and TAC+MMF+CCS regimens (Schaefer et al. 2006)[78], and one study comparing four regimens also compared SRL+MMF+CCS and TAC+MMF+CCS regimens (SYMPHONY)[420].

The meta-analysis suggested no difference for NODAT (**Figure 150**). However publication bias was not explored and the number of pooled studies is small, therefore the result must be interpreted with caution. No difference was found between the two

arms for malignancy, OR= 0.83 (95% CI 0.32-2.19), for PTLD, OR= 0.31 (95% CI 0.01-7.72), for infections, OR=0.68 (95% CI 0.47-0.98), and for CMV infections, OR= 1.66 (95% CI 0.97-2.84). In summary, no difference in NODAT, PTLD, malignancy, infections and CMV infection was found between SRL and TAC regimens at 1–year - follow-up. However, only two studies reported NODATs, and only one study reported PTLD, malignancy, infections and CMV infection.

Figure 150 NODAT; Sirolimus versus Tacrolimus



Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; TAC, Tacrolimus; SRL, Sirolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

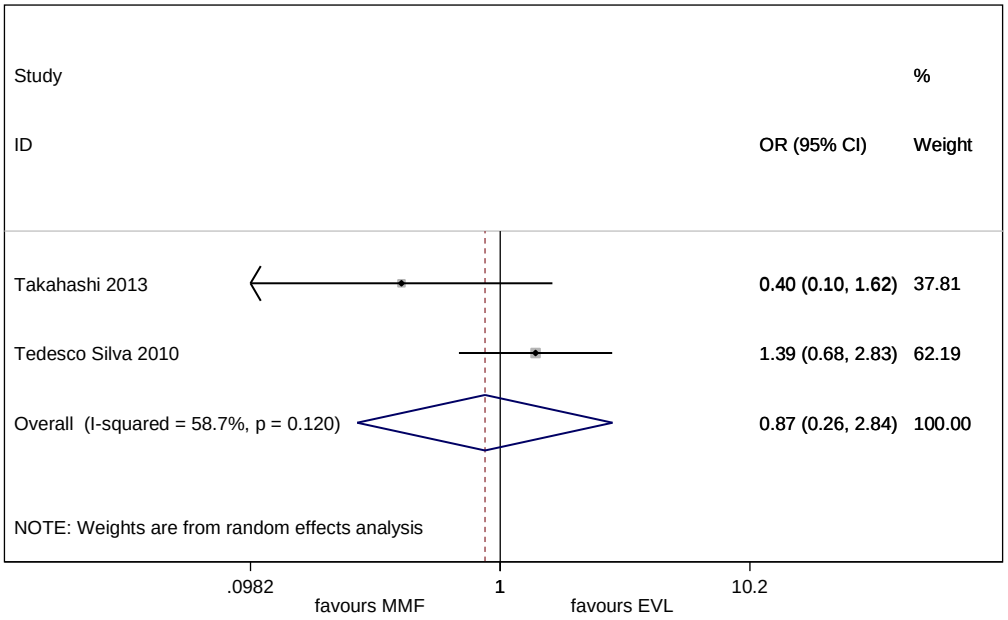
Everolimus versus Mycophenolate Mofetil

Three studies comparing EVL with MMF reported AE; all studies used EVL+CSA+CCS and MMF+CSA+CCS regimens (Vitko et al. 2005, Tedesco Silva et al. 2010 and Takahashi et al. 2013)[142 143 145]. Tedesco Silva et al. 2010[145] reported using MPA; it was assumed that MMF was used.

The meta-analyses suggested no differences for NODAT (**Figure 151** and infections (**Figure 152**), conversely a significant difference was found for CMV infections (**Figure**

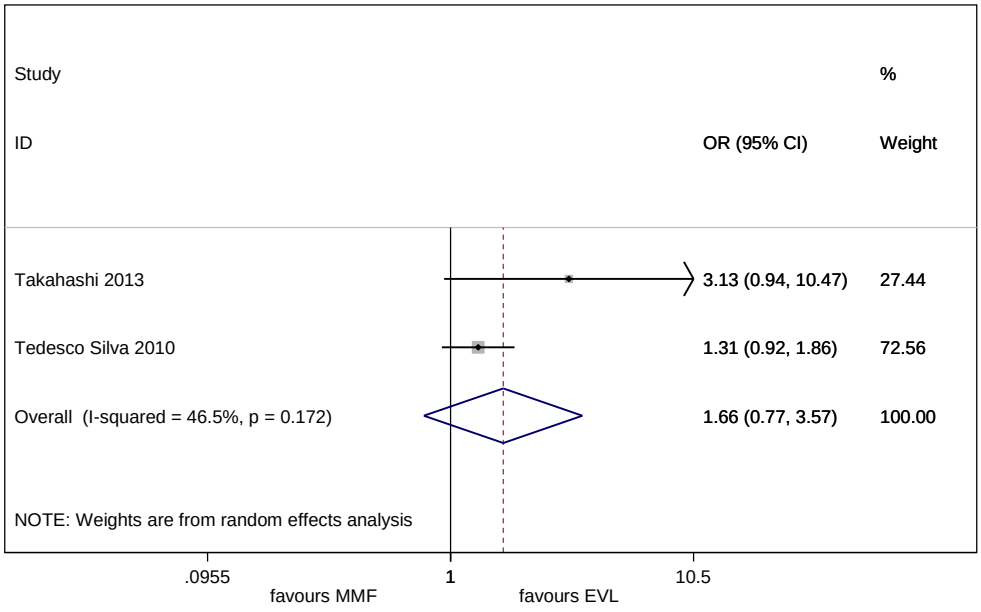
153); more CMV infections were found in MMF compared with EVL. No difference was found between the two arms for malignancy OR= 0.19 (95% CI 0.01-4.12). PTLD was not reported in these studies. In summary, no difference in NODAT, PTLD, malignancy and infection were found between EVL and MMF regimens at 1–year - follow-up. The meta-analysis (including 3 studies) suggested more cases of CMV infections in MMF regimens compared with EVL.

Figure 151 NODAT; Everolimus versus Mycophenolate mofetil



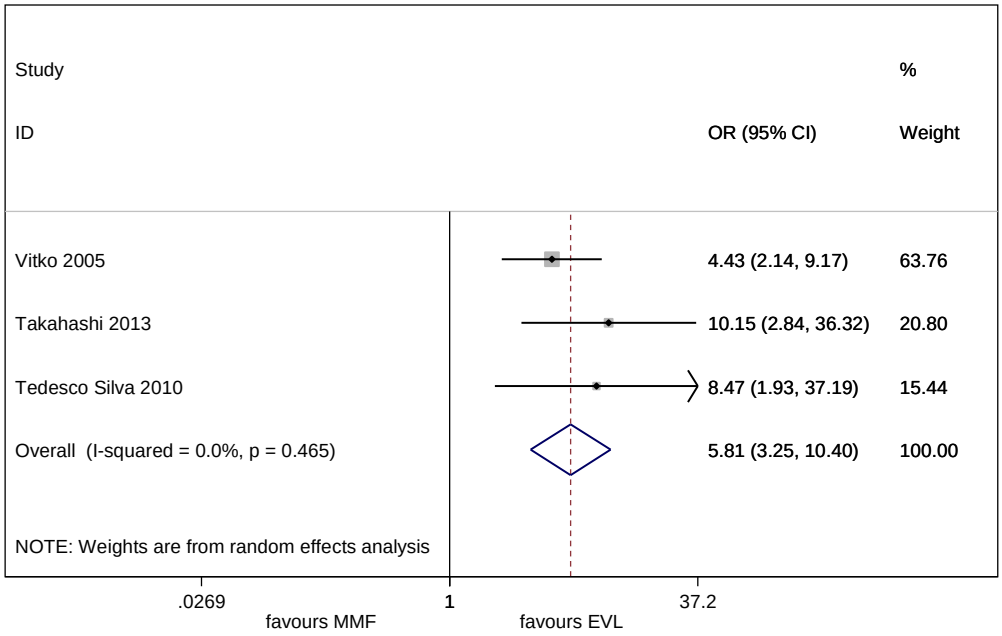
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.456.

Figure 152 Infection; Everolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; ; the estimate of between-study variance Tau-squared was 0.178.

Figure 153 CMV; Everolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; EVL, Everolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

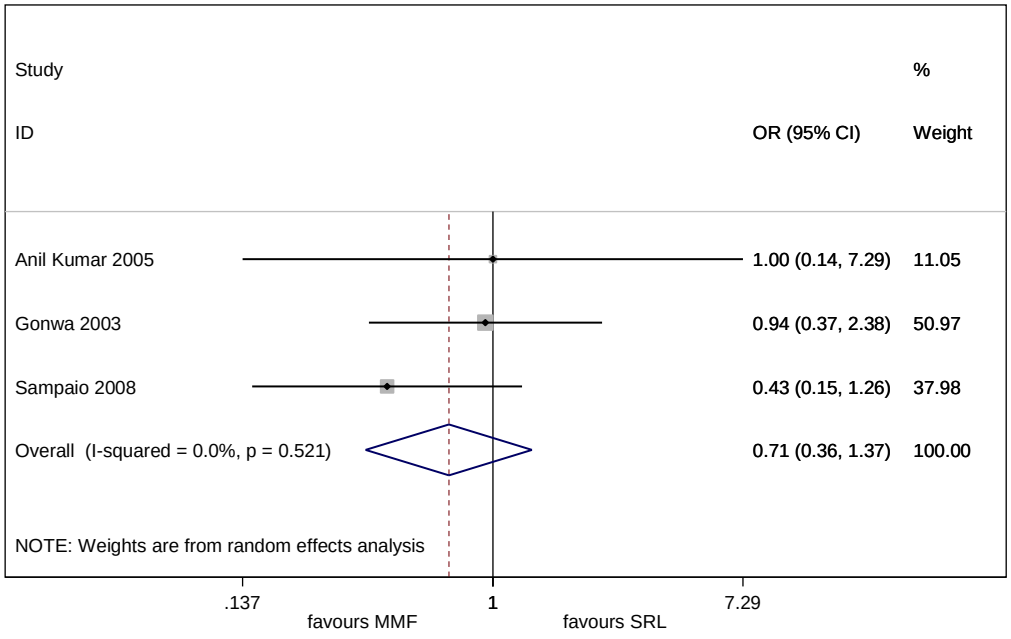
Sirolimus versus Mycophenolate Mofetil

Three studies comparing SRL with MMF reported AE; all studies used SRL+TAC+CCS and MMF+TAC+CCS regimens (Mendez et al. 2005, Anil Kumar et al. 2005 and Sampaio et al. 2008).[153 154 156]

The meta-analyses suggested no differences for NODAT (**Figure 154**), malignancy (**Figure 155**), and PTLD (**Figure 156**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms for CMV infections OR= 1.00 (95% CI 0.30-3.34). Infections were not reported in these studies.

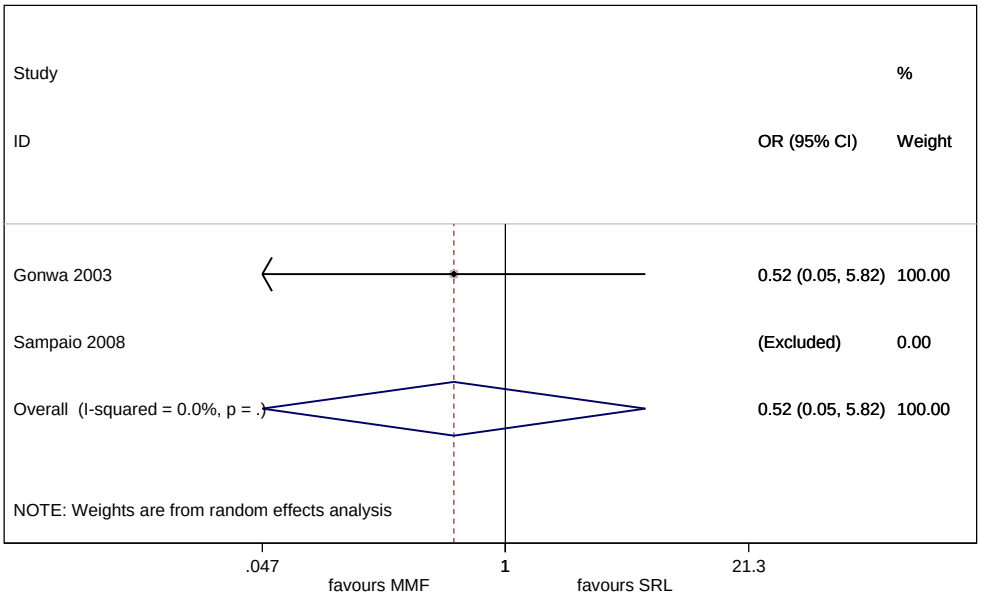
In summary, no difference in NODAT, PTLD, malignancy, and CMV infection were found between SRL and MMF regimens at 1–year -follow-up. However, only three studies reported NODAT and PTLD; two studies reported malignancy; and only one study reported CMV infections.

Figure 154 NODAT; Sirolimus versus Mycophenolate mofetil



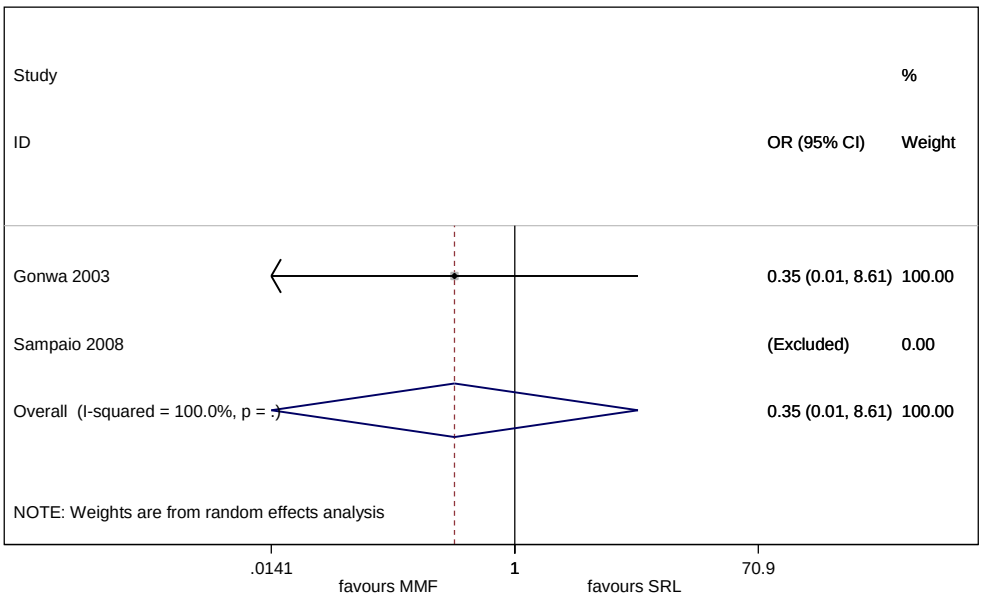
Key: OR, odds ratio; ID, identification; NODAT, new onset diabetes; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Figure 155 Malignancy; Sirolimus versus Mycophenolate mofetil



Key: OR, odds ratio; ID, identification; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 156 PTLD; Sirolimus versus Mycophenolate mofetil



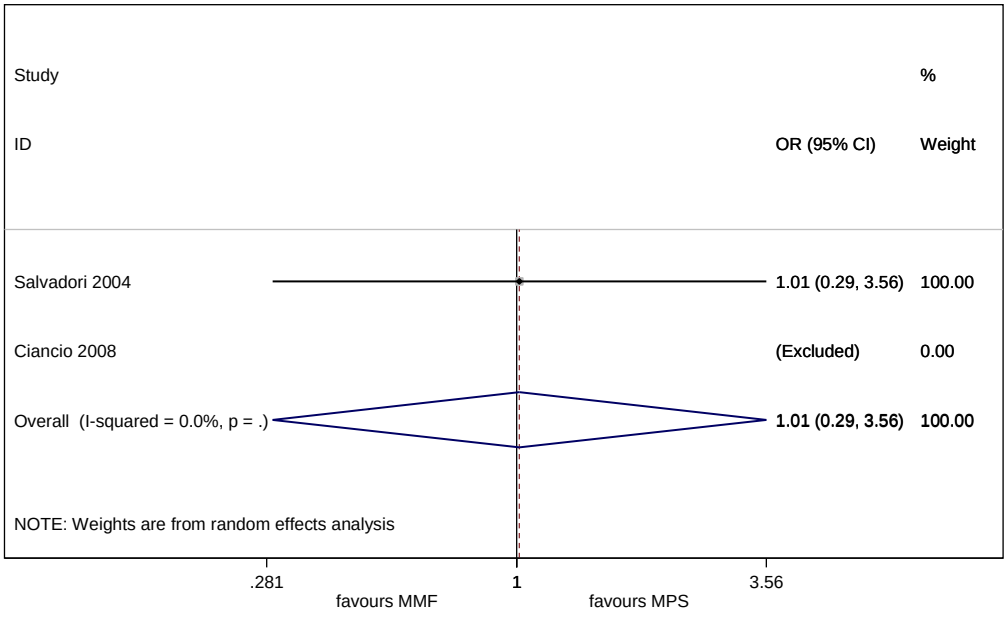
Key: OR, odds ratio; ID, identification; PTLD, post-transplant lymphoproliferative disorder; SRL, Sirolimus; MMF, Mycophenolate mofetil. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data.

Mycophenolate Mofetil versus Mycophenolate Sodium

Two studies comparing MMF with MPS reported AE; one study used MMF+TAC+CCS and MPS+TAC+CCS regimens (Cianco et al. 2008)[130] and one study used MMF+CSA+CCS and MPS+CSA+CCS regimens (Salvadori et al. 2004).[132]

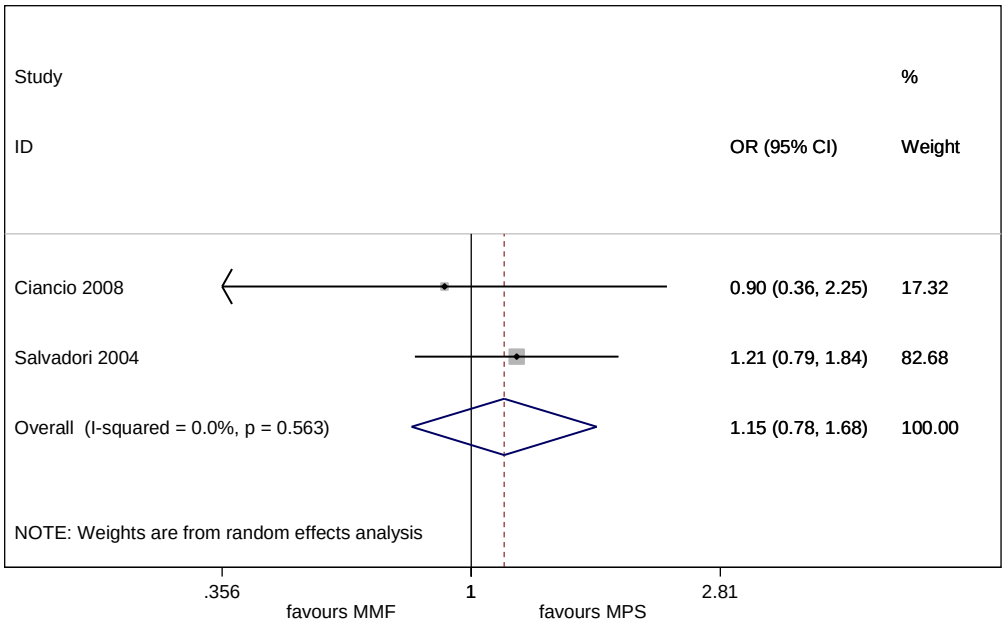
The meta-analyses suggested no differences for malignancy (**Figure 157**) and infections (**Figure 158**) and CMV infections (**Figure 159**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms for NODAT, OR= 1.06 (95% CI 0.33-3.37). In summary, no difference in NODAT, malignancy, infections and CMV infections were found between MMF and MPS regimens at 1–year -follow-up. However, only two studies reported malignancy, infections and CMV infections, and only one study reported NODAT.

Figure 157 Malignancy; Mycophenolate mofetil versus Mycophenolate sodium



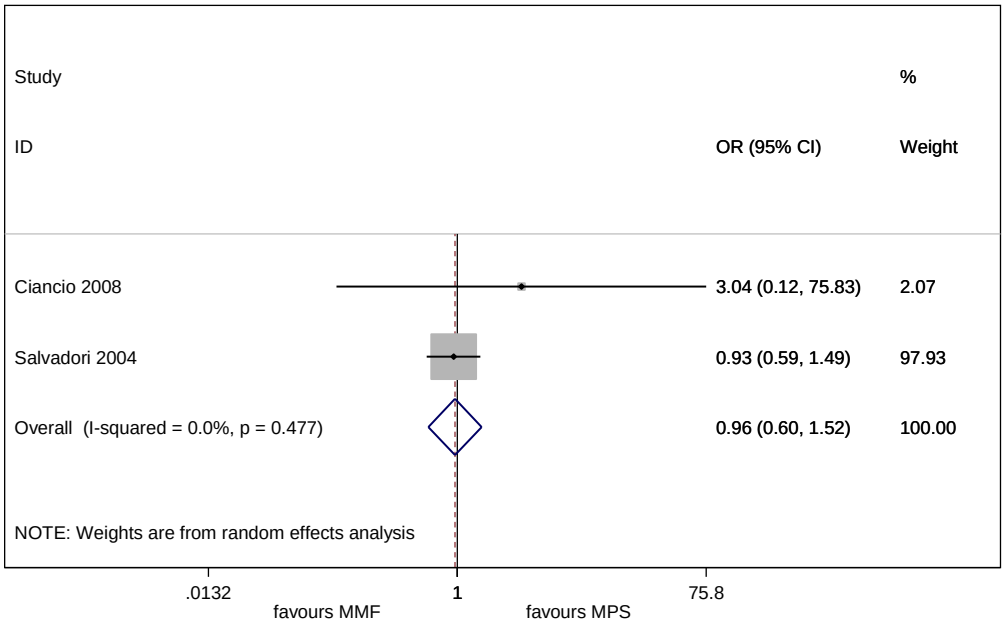
Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium.
Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; studies with no events in both arms were excluded from the analysis.

Figure 158 Infections; Mycophenolate mofetil versus Mycophenolate sodium



Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; ; the estimate of between-study variance Tau-squared was 0.000.

Figure 159 CMV: Mycophenolate mofetil versus Mycophenolate sodium



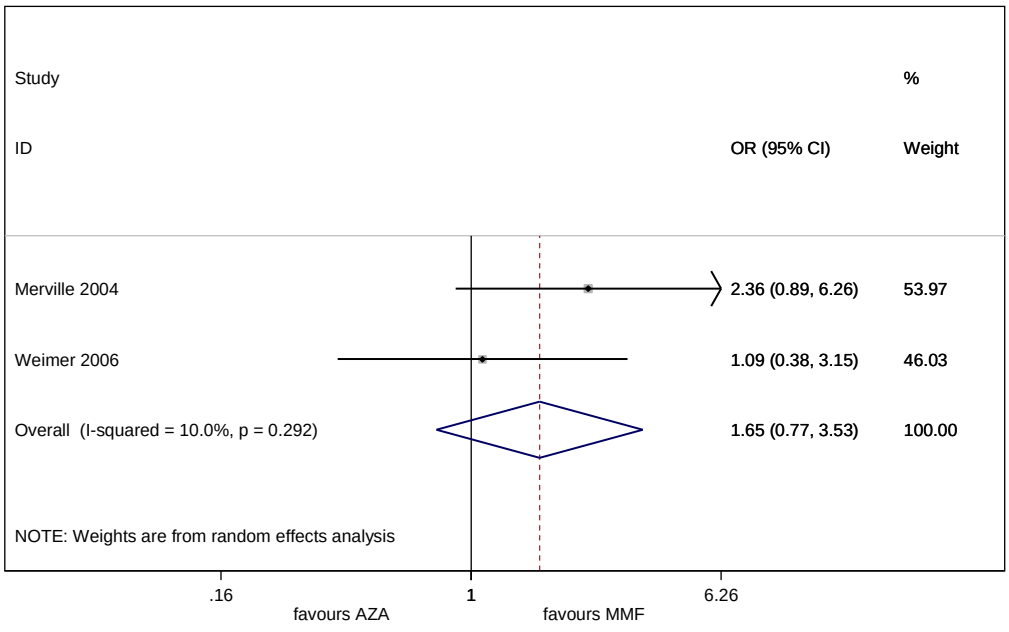
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; MMF, Mycophenolate mofetil; MPS, Mycophenolate sodium. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Mycophenolate Mofetil versus Azathioprine

Three studies comparing MMF with AZA reported AE; one study used MMF+CSA+CCS and AZA+CSA+CCS regimens (Merville et al. 2004)[114] and two three-arm studies also used MMF+CSA+CCS and AZA+CSA+CCS regimens (Sadek et al. 2002 and Weimer et al. 2006).[113 125]

The meta-analyses suggested no differences for CMV infections (**Figure 160**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms for infections, OR= 1.60 (95% CI 0.98-2.60). NODAT, malignancy, and PTLD were not reported in these studies. In summary, no difference in infections and CMV infection were found between MMF and AZA regimens at 1–year -follow-up. However, only three studies reported CMV infection, and only one study reported infections.

Figure 160 CMV; Mycophenolate mofetil versus Azathioprine



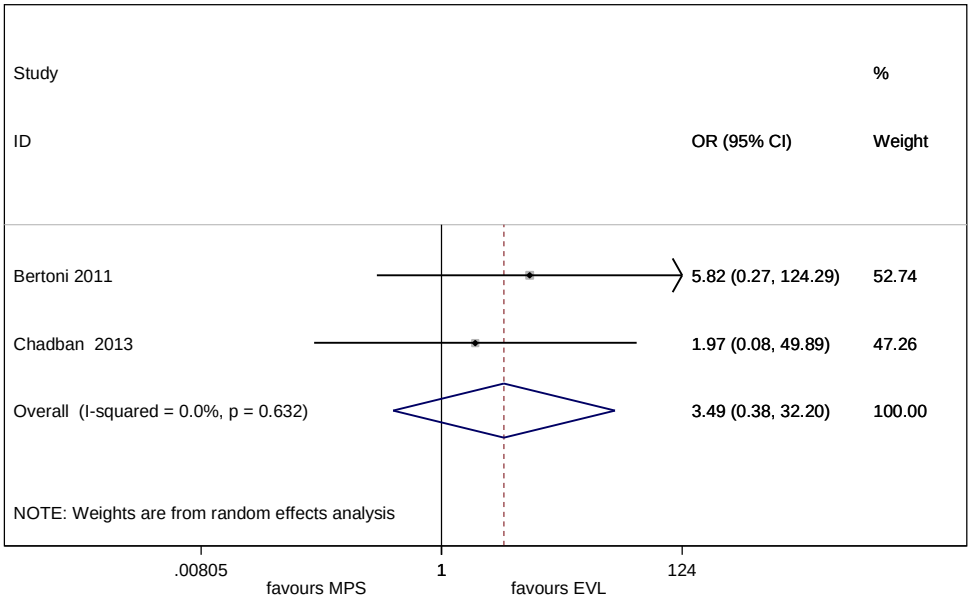
Key: OR, odds ratio; ID, identification; CMV, cytomegalovirus; MMF, Mycophenolate mofetil; AZA, Azathioprine. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.030.

Everolimus versus Mycophenolate Sodium

Two studies comparing EVL with MPS reported AE; one study used EVL+CSA+CCS and MPS+CSA+CCS regimens (Bertoni et al. 2011)[146] and one three-arm study also used EVL+CSA+CCS and MPS+CSA+CCS regimens (Chadban et al. 2013).[144]

The meta-analyses suggested no differences for malignancy (**Figure 161**). However publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution. No difference was found between the two arms for NODAT, OR= 0.45 (95% CI 0.17-1.19), infections, OR= 0.57 (95% CI 0.22-1.51), and CMV infections, OR= 0.29 (95% CI 0.05-1.69). PTLD was not reported in the two studies. In summary, no difference in NODAT, malignancy, infections and CMV infections were found between EVL and MPS regimens at 1–year -follow-up. However, only two studies reported malignancy, and only one study reported NODAT, infections and CMV infections.

Figure 161 Malignancy; Everolimus versus Mycophenolate sodium



Key: OR, odds ratio; ID, identification; MMF, Mycophenolate mofetil; EVL, Everolimus. Note: DerSimonian & Laird random effects meta-analysis with 1–year follow-up data; the estimate of between-study variance Tau-squared was 0.000.

Summary

Induction regimens

No difference in NODAT, PTLD, malignancy and infections were found between the two induction regimens, rATG and BAS when compared with each other or with no induction (and/or placebo) regimens at 1–year follow-up. Some evidence suggested more CMV infections in rATG regimens compared with BAS regimens(Mourad at al.2004)[199], and in rATG regimens compared with no induction (Charpentier et al. 2001)[82]; was identified. However this finding was contradicted by results of the three-arm comparing BAS, rATG and no induction (Kyllonen et al. 2007).[86] However, publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution.

Maintenance regimens

The meta-analyses of AE at 1–year follow-up suggested significant differences in AE for the following regimens. The meta-analysis comparing TAC and CSA regimens (including 8 studies) suggested more cases of NODAT in TAC regimens compared with CSA regimens. The meta-analyses comparing BEL with CSA regimens (including 3 studies). suggested more cases of NODAT in CSA regimens compared with BEL regimens (including 3 studies). The meta-analyses comparing SRL and CSA regimens (including 7 studies) suggested more cases of NODAT in CSA regimens compared with SRL. The meta-analysis comparing MMF and EVL (including 3 studies) suggested more cases of CMV infections in MMF regimens compared with EVL. However, publication bias was not explored and the number of pooled studies is small, therefore all results must be interpreted with caution.

Appendix 8 Ongoing trials

Ongoing studies; identified trials

N	Study ID	Sponsor/ Collaborators	Trial name	Sample size	Status
1	NCT01780844	Astellas Pharma Global Development, Inc., Kyowa Hakko Kirin Company, Limited	A Study to Assess the Efficacy and Safety of ASKP1240 in de Novo Kidney Transplant Recipients	149	Active, not recruiting
2	NCT01817322	Samsung Medical Center	Kidney Graft Function Under the Immunosuppression Strategies (MyLowCsA)	140	Active not recruiting
3	NCT01354301	Hospital do Rim e Hipertensão	Efficacy and Safety of Induction Strategies Combined With Low Tacrolimus Exposure in Kidney Transplant Recipients Receiving Everolimus or Sodium Mycophenolate	300	Active not recruiting
4	NCT00494741	Mario Negri Institute for Pharmacological Research, Agenzia Italiana del Farmaco	MMF vs. AZA for Kidney Transplantation (ATHENA)	224	Active not recruiting
5	NCT00782821	University of Cincinnati Millennium Pharmaceuticals, Inc. , Genzyme, a Sanofi Company	Randomized Trial of Induction Therapies in High Immunological Risk Kidney Transplant Recipients	40	Active not recruiting
6	NCT00693446	Nantes University Hospital	A Study To Compare Sirolimus Versus Tacrolimus In De Novo Simultaneous Pancreas- Kidney Allograft Recipients Receiving An Induction Therapy With Antithymocyte Globulin Plus Mycophenolate Mofetil Plus Corticosteroids	118	Active not recruiting
7	NCT01114529	Novartis Pharmaceuticals	Efficacy, Safety and Evolution of Cardiovascular Parameters in Renal Transplant Recipients (ELEVATE)	717	Active not recruiting
8	NCT00256750	Bristol-Myers Squibb	Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression (BENEFIT)	660	Active not recruiting
9	NCT00114777	Bristol-Myers Squibb	Study of Belatacept in Subjects Who Are Undergoing a Renal Transplant (BENEFIT-EXT)	600	Active not recruiting
10	NCT00514514	Novartis Pharmaceuticals	Study Investigating a Standard Regimen in de Novo Kidney Transplant Patients Versus a Calcineurin Inhibitor (CNI)-Free Regimen and a CNI-low Dose Regimen	450	Active not recruiting
11	NCT00533442	University of Miami Astellas Pharma Inc	Rapamycin Versus Mycophenolate Mofetil in Kidney-Pancreas Recipients	190	Active not recruiting
12	NCT01005706	Medical University of South Carolina, Pfizer (formerly Wyeth)	Sirolimus Conversions in African-American Renal Transplant Recipients	40	Active not recruiting

13	NCT01878786	Matthew Cooper	A Pilot Study Comparing the Safety and Efficacy of Everolimus With Other Medicines in Recipients of ECD/DCD Kidneys (Evered)	50	Active not recruiting
14	NCT01187953	Veloxis Pharmaceuticals	Double-Blind,Double-Dummy,Effic/Safety,LCP-Tacro™ Vs Prograf®,Prevention Rejection,De Novo Adult Kidney Tx (LCPTacro3002)	540	Active not recruiting
15	NCT01053221	University of Wisconsin, Madison	Mycophenolic Acid Monotherapy in Recipients of HLA-identical Living-Related Transplantation	30	Active not recruiting
16	NCT01062555	University of Minnesota - Clinical and Translational Science Institute Roche Pharma AG, Pfizer (formerly Wyeth), Genzyme, a Sanofi Company	Calcineurin Inhibitor Sparing After Kidney Transplantation (CNI-Sparing)	600	Active not recruiting
17	NCT01239563	University of Oxford, Oxford University Hospitals NHS Trust Genzyme, a Sanofi Company	Thymoglobulin Induction in Kidney Transplant Recipients (TIKT)	40	Not yet recruiting
18	NCT01837043	Nair, Vinay, D.O., Mount Sinai School of Medicine, Bristol-Myers Squibb	Early Conversion From CNI to Belatacept in Renal Transplant Recipients With Delayed and Slow Graft Function	90	Not yet recruiting
19	NCT02137239	Bristol-Myers Squibb	Evaluation of Acute Rejection Rates in de Novo Renal Transplant Recipients Following Thymoglobulin Induction, CNI-free, Nulojix (Belatacept)-Based Immunosuppression	240	Not yet recruiting
20	NCT01875224	University of Arizona Bristol-Myers Squibb	Comparison of NODAT in Kidney Transplant Patients Receiving Belatacept Versus Standard Immunosuppression	32	Not yet recruiting
21	NCT01822483	Irmandade Santa Casa de Misericórdia de Porto Alegre, Novartis	A Prospective Study to Investigate Mycophenolic Acid (MPA) Exposure Through Area Under the Curve (AUC) in Renal Transplants Recipients Treated With Mycophenolate Mofetil (MMF) and After Conversion to Mycophenolate Sodium (EC-MPS) (AUC-MPA)	100	Not yet recruiting
22	NCT02058875	University of Saskatchewan Novartis Pharmaceuticals Canada Inc.	Cardiovascular Risk Following Conversion to Full Dose Myfortic® and Neoral® Two-hour Post Level Monitoring (COBACAM)	100	Not yet recruiting
23	NCT01895049	Helio Tedesco Silva Junior, Novartis, Sanofi	Comparison Between Two Tacrolimus-based Immunosuppressant Regimens and Induction With Thymoglobulin in Kidney Transplants From Deceased Donors With Expanded Criteria	200	Not yet recruiting
24	NCT02056938	Nantes University Hospital	ATG Versus Basiliximab in Kidney Transplant Displaying Low Immunological Risk But High Susceptibility to DGF (PREDICT-DGF)	460	Recruiting
25	NCT01856257	National Institute of Allergy and Infectious Diseases (NIAID), Clinical Trials in Organ Transplantation	Safety and Efficacy of a Steroid-free, Calcineurin Inhibitor-free, Belatacept-based Immunosuppressive Regimen	180	Recruiting

26	NCT01560572	University Medical Centre Groningen, Leiden University Medical Center, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	Steroid Free Immunosuppression or Calcineurin Inhibitor Minimization After Basiliximab Induction Therapy in Kidney Transplantation: Comparison With a Standard Quadruple Immunosuppressive Regimen (Allegro)	300	Recruiting
27	NCT00903188	University Hospital, Antwerp, Novartis Pharmaceuticals Erasme University Hospital, University Hospital, Ghent University Hospital of Liege, Universitair Ziekenhuis Brussel	Calcineurin Inhibitor (CNI) Versus Steroid Cessation in Renal Transplantation (CISTCERT)	152	Recruiting
28	NCT01950819	Novartis Pharmaceuticals	Advancing Renal TRANSplant eFficacy and Safety Outcomes With an eveRolimus-based regiMen (TRANSFORM)	2040	Recruiting
29	NCT01649427	Novartis Pharmaceuticals	Comparison of a Tacrolimus Hexal® Based Regimen Versus a Prograf® Based Regimen in de Novo Renal Transplant Recipients (Spartacus)	326	Recruiting
30	NCT02083991	Vastra Gotaland Region	Trial of Steroid Avoidance and Low-dose CNI by ATG-induction in Renal Transplantation (SAILOR)	200	Recruiting
31	NCT01680861	Gaetano Ciancio	Tacrolimus/Everolimus Versus Tacrolimus/Enteric-Coated Mycophenolate Sodium	50	Recruiting
32	NCT01265537	University of British Columbia, Astellas Pharma Canada, Inc.	A Pilot Study Comparing the Use of Low-target Versus Conventional Target Advagraf (Astellas)	30	Recruiting
33	NCT01663805	MARIO ABBUD FILHO	Effects of the Use of "de Novo" Everolimus in Renal Tranplant Population	80	Recruiting
34	NCT01541176	Nantes University Hospital	Impact of the Absence of Steroids on the Evolution of Renal Function and on the Progression of Graft Fibrosis, Quantified by Numerical Method, in Patients With Renal Transplant (Astronef)	186	Recruiting
35	NCT01656135	University of Regensburg , European Commission	Reference Group Trial for The ONE Study	60	Recruiting
36	NCT02102854	The Methodist Hospital System	Single Dose rATG for Renal Allograft Rejection	30	Recruiting
37	NCT00906204	Wright State University Sanofi, University of Arizona Wake Forest School of Medicine, University of Nebraska, The Methodist Hospital System	Safety Trial of Single Versus Multiple Dose Thymoglobulin Induction in Kidney Transplantation (STAT)	165	Recruiting
38	NCT01729494	University of Cincinnati	Belatacept Early Steroid Withdrawal Trial	315	Recruiting
39	NCT02152345	Columbia University	Belatacept Compared to Tacrolimus in Deceased Donor Renal Transplant Recipients	100	Recruiting
40	NCT01653847	Northwestern University, Novartis	Impact of Two Prednisone-free Maintenance Immunosuppressive Regimens With Reduced Dose FK506+Everolimus vs. Standard Dose Tacrolimus (FK506)+ Mycophenolate Mofetil (MMF) on Subpopulation of T and B Cells, Renal	88	Recruiting

			Allograft Function and Gene Expression Profiles in Renal Allograft Biopsies at 12 Months Post-transplant. Prospective Single Center Study in Recipients of Renal Transplant Allograft		
41	NCT01631058	University of Sao Paulo General Hospital	Immunosuppression in Renal Transplantation in The Elderly: Time to Rethink. - nEverOld Study	90	Recruiting
42	NCT00866879	Northwestern University, Pfizer (formerly Wyeth)	Randomized Conversion of Calcineurin-Inhibitors in Renal Allograft Recipients	275	Recruiting
43	NCT02062892	University of Colorado, Denver, Novartis Pharmaceuticals	Differentiating Everolimus Versus Sirolimus in Combination With Calcineurin Inhibitors in Kidney Transplant Patients (DESIRE)	150	Recruiting
44	NCT00896012	University at Buffalo, Novartis, University of Washington	Kidney Biopsy Controlled Trial of Calcineurin Inhibitor Withdrawal	120	Recruiting (invitation)
45	NCT01860183	Clinical Hospital Merkur, University Medical Centre Ljubljana, Clinical Hospital Centre Osijek, University Hospital Rijeka	Effect of 3g Versus 2 g MMF in Combination With Tacrolimus on Progression of Renal Allograft Interstitial Fibrosis	80	Recruiting
46	NCT01820572	Bristol-Myers Squibb	A Study in Maintenance Kidney Transplant Recipients Following Conversion to Nulojix® (Belatacept)-Based	600	Recruiting
47	NCT02213068	Lorenzo Gallon Bristol-Myers Squibb	Belatacept 3 Month Post Transplant Conversion Study	51	Recruiting
48	NCT01790594	National Institute of Allergy and Infectious Diseases (NIAID) Clinical Trials in Organ Transplantation	Optimization of NULOJIX® (Belatacept) Usage as a Means of Minimizing CNI Exposure in Simultaneous Pancreas and Kidney Transplantation	60	Recruiting
49	NCT01921218	Andrew B Adams, MD, PhD, Bristol-Myers Squibb	Belatacept Therapy for the Failing Renal Allograft (IM103-133)	72	Recruiting
50	NCT02134288	Von Visger, Jon, MD Bristol-Myers Squibb	Belatacept for Renal Transplant Recipients With Delayed Graft Function	40	Recruiting
51	NCT01595984	Centre Hospitalier Universitaire, Amiens Novartis	Comparison of Efficacy and Safety of Treatment With a Calcineurin Inhibitor (CNI)Versus a CNI-free Treatment in Renal Transplantation (CIME)	134	Recruiting
52	NCT02221583	University of Cincinnati, Astellas Pharma Inc	Pharmacokinetics of Immunosuppressants in Renal Transplant Candidates Who Have Undergone Laparoscopic Sleeve Gastrectomy	24	Recruiting
53	NCT01935128	University of Toledo Health Science Campus, Novartis Pharmaceuticals	Calcineurin-inhibitor Elimination/Reduction Randomized to Everolimus/Myfortic® vs Everolimus/Reduced Tacrolimus in Renal Transplant Recipients Following Campath® Induction	50	Recruiting
54	NCT01169701	Novartis	24 Months Follow-up, Two Arm Study to Compare the Cardiovascular Profile in a Regimen With Everolimus + Mycophenolic Acid (MPA) Versus (vs.) a Regimen of CNI+MPA in Maintenance	80	Recruiting

			Renal Transplant Recipients (EVITA)		
55	NCT01544491	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
56	NCT01842269	Chong Kun Dang Pharmaceutical	Evaluate the Efficacy and Safety of My-Rept® Tablet Versus My-Rept® Capsule in Combination With Tacrolimus in Kidney Transplant Patients (My-Rept®_KT_P4)	156	Recruiting
57	NCT01410448	Novartis Pharmaceuticals	Everolimus in de Novo Kidney Transplant Recipients (NEVERWOUND)	396	Recruiting
58	NCT02036554	Seoul St. Mary's Hospital, Novartis	Evaluate Efficacy Study of Combination Therapy of Everolimus and Low Dose Tacrolimus in Renal Allograft Recipients (PROTECT)	234	Recruiting
59	NCT02077556	National Taiwan University Hospital	Effect of Everolimus on the Pharmacokinetics of Tacrolimus in Renal Transplant Patients	70	Recruiting
60	NCT01843348	Novartis Pharmaceuticals	12 Month Athena Study: Everolimus vs. Standard Regimen in de Novo Kidney Transplant Patients (ATHENA)	612	Recruiting
61	NCT02096107	Medical University of South Carolina Novartis	Novartis Everolimus Transition	60	Recruiting
62	NCT01680952	Yonsei University	Study to Evaluate the Safety and Efficacy of Extended Release Tacrolimus (Advagraf®) + Sirolimus (Rapamune®), Versus Extended Release Tacrolimus (Advagraf®) + Mycophenolate Mofetil in Kidney Transplant Patients	60	Recruiting
63	NCT01801280	Klemens Budde Novartis Pharmaceuticals	Influence of Pantoprazole to the Bioavailability of Myfortic® and CellCept®	24	Recruiting
64	NCT01612299	University of Kentucky	Effects of Zortress® + Tacrolimus vs. Standard Immunosuppression on Progression of Coronary Artery Calcifications and Bone Disease in de Novo Renal Transplant Recipients	60	Recruiting
65	NCT02208791	University of Sao Paulo General Hospital	Effects of the Quadruple Immunosuppression on Peripheral Blood Lymphocytes and Development of Anti-HLA Antibodies in Kidney Transplant	45	Recruiting
66	NCT02084446	Ronaldo de Matos Esmeraldo, MD, Novartis Pharmaceuticals	Everolimus + Very Low Tacrolimus vs Enteric-coated Mycophenolate Sodium + Low Tacrolimus in de Novo Renal Transplant	120	Recruiting
67	NCT01276834	Dianet Dialysis Centers, UMC Utrecht	Comparison of Immunosuppression on Progression of Arteriosclerosis in Renal Transplantation (NOCTX-2)	80	Recruiting

68	NCT01976390	Dr.Ronald Pelletier, Novartis	Comparing Everolimus and Sirolimus in Renal Transplant Recipients	60	Recruiting
69	ISRCTN88894088 NCT01120028	University of Oxford	Campath, Calcineurin inhibitor reduction and Chronic allograft nephropathy	800	Recruiting
70	NCT00724022	University Hospital Freiburg, Roche Pharma AG, Astellas Pharma GmbH, Genzyme, a Sanofi Company	Phase IV Study to Evaluate Calcineurin Inhibitor Reduced, Steroid Free Immunosuppression After Renal Transplantation (Harmony)	600	Unknown
71	NCT01550445(a)	Ajou University School of Medicine	Steroid Withdrawal Immunosuppression After Renal Transplantation	30	Unknown
72	NCT00302497	McGill University Health Center	EXTEND Protocol for Transplanted Patient to Evaluate Kidney Function	50	Unknown
73	NCT00199667	University Hospital, Limoges, Hoffmann-La Roche	Concentration Controlled Versus Fixed Dose of MMF in Kidney Transplant Recipients	137	Unknown
74	NCT00556933	University of Nebraska, Genzyme, a Sanofi Company	Improved Induction and Maintenance Immunosuppression in Kidney Transplantation	180	Unknown
75	NCT00807144	Hammersmith Hospitals NHS Trust	Standard Versus Prolonged-release Tacrolimus Monotherapy After Alemtuzumab Induction in Kidney Transplantation	100	Unknown
76	NCT00296296	Stanford University	Immunosuppression Impact on the Metabolic Control of First Kidney Transplant Recipients With Pre-Existing Type 2 Diabetes (DM)	40	Unknown
77	NCT01239472	Andre Barreto Pereira, Novartis	Cytokines Evaluation in Early Calcineurin Inhibitors Withdrawn on Renal Transplant	30	Unknown
78	NCT00707759	Maria Angela Delucchi Bicocchi, University of Chile, Fondo Nacional de Desarrollo Científico y Tecnológico, Chile	Steroid Withdrawal in Pediatric Renal Transplant Immunosuppression: Impact on Growth, Bone Metabolism and Acute Rejection	70	Unknown
79	NCT01334333	University of British Columbia, Simon Fraser University, Astellas Pharma Canada, Inc.	Comparison of Medication Adherence Between Once and Twice Daily Tacrolimus in Stable Renal Transplant Recipients	100	Unknown
80	NCT01399242	Hospital Universitário São José	Efficacy of Certican® in Combination With Myfortic® in Renal (HUSJ1)	40	Unknown
81	NCT00737659	Rabin Medical Center	CellCept® Dose Adjustment Versus Fixed Dose (Standard Care) in Renal Transplant Recipients (MMF)	138	Unknown
82	NCT00309218	Klinik für Kinder- und Jugendmedizin Hoffmann-La Roche	Steroid Withdrawal in Pediatric Renal Transplant Recipients Under Cyclosporine (CyA) and Mycophenolate Mofetil (MMF)	40	Unknown
83	NCT00166712	Northwestern University Northwestern Memorial Hospital	A Trial of Two Steroid-Free Approaches Toward Mycophenolate Mofetil-Based Monotherapy Immunosuppression	40	Unknown
84	NCT00733733	Radboud University Erasmus Medical Center, Maastricht University, Leiden	Anti-T-Lymphocyte Globulin (ATG) in Renal Transplantation of Kidneys With a Non-Heart-	180	Unknown

		University Medical Center, UMC Utrecht, University Medical Centre Groningen, Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	Beating (NHB) Donor		
85	NCT01159080	Asan Medical Center Seoul National University Hospital, Samsung Medical Center	Treatment of the optImuM Dose of calcineUrin Inhibitor and Mycophenolate Sodium in Kidney Recipients (OPTIMUM)	350	Unknown
86	NCT01014234	IRCCS Policlinico S. Matteo	Rapamycin and Regulatory T Cells in Kidney Transplantation	56	Unknown
87	NCT00223678	Vanderbilt University	Mycophenolate Mofetil and Rapamycin as Secondary Intervention vs. Continuation of Calcineurin Inhibitors in Patients at Risk for Chronic Renal Allograft Failure	30	Unknown
88	NCT01455649	Deise de Boni Monteiro de Carvalho	Study to Evaluate the Safety and Efficacy of Switching Calcineurin Inhibitor to Everolimus After Kidney Transplantation in Adults	30	Unknown
89	NCT00166829	National Taiwan University Hospital	The Effect of Sirolimus on the Pharmacokinetics of Tacrolimus	40	Unknown
90	NCT00541814	University Hospital Birmingham, Novartis	Calcineurin Inhibitor Minimisation in Renal Transplant Recipients With Stable Allograft Function (CNIM-SRT)	90	Unknown
	ISRCTN60081949				
91	NCT01640743	IRCCS Policlinico S. Matteo	Effect of Different Therapeutic Strategies on Regulatory T Cells in Kidney Transplantation (EVERTWIST)	58	Unknown
92	NCT00290069	Sociedad Andaluza de Trasplantes de Organos y Tejidos	Renal Function Optimization With Mycophenolate Mofetil (MMF) Immunosuppressor Regimes (ALHAMBRA)	94	Unknown
93	NCT00252655	Wayne State University	Use of Sirolimus vs. Tacrolimus For African-American Renal Transplant Recipients	40	Unknown
94	NCT00141804	University Hospital Muenster, Proverum GmbH, KKS Netzwerk, Fujisawa GmbH	Efficacy and Safety of Sirolimus in Combination With Tacrolimus	190	Unknown
95	NCT00166816	National Taiwan University Hospital	The Pharmacokinetics of Sirolimus When Combined With Cyclosporine or Tacrolimus in Renal Transplant Patients	40	Unknown
96	NCT01436305	National Institute of Allergy and Infectious Diseases (NIAID)	Optimization of NULOJIX® (Belatacept) Usage As A Means of Avoiding Calcineurin Inhibitor (CNI) and Steroids in Renal Transplantation	19	Suspended
97	NCT01244659	EMS	A Randomized Study Assess the Safety and Efficacy of Tacrolimus vs Prograf® in Renal Transplantation Treatment	60	Suspended
98	NCT00729768	Genentech	A Study to Evaluate Efalizumab Compared with Cyclsporine as an Immunosuppressant Regimen in	200	Withdrawn

			De Novo Renal Transplantation		
99	NCT01149993	Georgetown University, Novartis	Attenuating Ischemia Reperfusion Injury After Living Donor Renal Transplantation	0	Withdrawn
100	NCT01038505	University of Miami, Pfizer (formerly Wyeth)	Comparison of Tacrolimus and Myfortic Versus Tacrolimus and Sirolimus	0	Withdrawn
101	NCT00956293	Novartis Pharmaceuticals	Study to Evaluate the Efficacy, Safety and Tolerability of Everolimus in de Novo Renal Transplant Recipients Participating in the Eurotransplant Senior Program (Senator)	207	Terminated
102	NCT00284921	Novartis Pharmaceuticals	MYPROMS-ES02: Safety and Efficacy of Basiliximab, Cyclosporine Microemulsion and Enteric-coated Mycophenolate Sodium (EC-MPS) Versus EC-MPS and Steroid Therapy in Kidney Transplant Recipients Who Are Hepatitis C Positive	60	Terminated
103	NCT00928811	Drexel University College of Medicine, Novartis	Study to Evaluate the Safety of Chronic Administration of Simulect to Subjects Receiving a First Kidney Transplant	5	Terminated
104	NCT00137345(a)	Pfizer (formerly Wyeth)	Study Comparing Sirolimus With Cyclosporine in a Calcineurin Inhibitor (CNI)-Free Regimen in Kidney Transplant Recipients	500	Terminated
105	NCT01387659	The University of Texas, Galveston, Novartis Pharmaceuticals	Evaluate Tolerability of Myfortic®/Simulect® and Tacrolimus Without Steroids in Three Patient Populations	4	Terminated
106	NCT00522548	University of Pennsylvania, Novartis Pharmaceuticals	Study of Gastrointestinal Side Effects in African American Kidney Transplant Recipients Treated With CellCept or Myfortic	37	Terminated
107	NCT00235781	Washington University School of Medicine	Single Dose Thymoglobulin for Induction in Adult Renal Allograft Recipients	90	Terminated
108	NCT00332839	Novartis Pharmaceuticals	Comparison of CNI-based Regimen Versus CNI-free Regimen in Kidney Transplant Recipients.	93	Terminated
109	NCT00217152	Mayo Clinic, Roche Pharma AG	A Kidney Transplant Study to Look at the Effects of Taking Fixed Doses of CellCept Versus Taking Doses of CellCept Based on the Concentration of CellCept in the Blood When Taking Full or Reduced Dose Calcineurin Inhibitors	12	Terminated
110	NCT01324934	Neovii Biotech, Eurotrials, Scientific Consultants, Recerca Clínica S.L., PsyConsult	Efficacy and Safety of ATG-Fresenius Following a Renal Transplantation, Without Corticosteroids	40	Terminated
111	NCT00596947	University of Pennsylvania	Prednisone Withdrawal Versus Prednisone Maintenance After Kidney Transplant	18	Terminated
112	NCT00311311	Pfizer	Study Comparing Effect On Carotid Atherosclerosis Following Conversion From	72	Terminated

			Tacrolimus To Sirolimus Post-Transplant In Kidney Transplant Patients		
113	NCT00434590	Novartis Pharmaceuticals	Efficacy and Tolerability of Full Dose Enteric-coated Mycophenolate Sodium, in Addition to Cyclosporine for Microemulsion Reduced Dose, in Maintenance Renal Transplant Recipients	10	Terminated
114	NCT00148252	University of Oslo School of Pharmacy	Lowering Total Immunosuppressive Load in Renal Transplant Recipients More Than 12 Months Posttransplant	298	Terminated
115	NCT00204230	University Hospital Muenster, Hoffmann-La Roche	MMF and Calcineurin Inhibitor Withdrawal in CAN	86	Terminated
116	NCT01609673	Helady Pinheiro, MD, PhD, Novartis	Study of Everolimus in de Novo Renal Transplant Recipients	1	Terminated
117	NCT01213394	Ramesh Prasad Hoffmann-La Roche	Mycophenolate Mofetil for Reducing Cardiovascular Risk in Renal Transplant Recipients (MMCR)	2	Terminated
118	NCT00991510	Teva Pharmaceutical Industries, Parexel	Comparative Bioavailability of Myfenax® and CellCept® in Kidney Transplant Patients	43	Terminated
119	NCT00658333	Novartis Pharmaceuticals	A Study Designed to Compare the Tolerability of an Increased Dose of Enteric-coated Mycophenolate Acid (MPA) in Renal Transplant Patients Whose Dose of Mycophenolate Mofetil (MMF) Was Reduced Due to Gastrointestinal Symptoms	30	Terminated
120	NCT00133172	Astellas Pharma Inc Astellas Pharma Canada, Inc.	Effect of Rapid Steroid Withdrawal on Subclinical Markers of Rejection	85	Terminated
121	NCT00752479	Mario Negri Institute for Pharmacological Research	Mesenchymal Stem Cells Under Basiliximab/Low Dose RATG to Induce Renal Transplant Tolerance	4	Terminated
122	NCT00928811	Drexel University College of Medicine Novartis	Study to Evaluate the Safety of Chronic Administration of Simulect to Subjects Receiving a First Kidney Transplant	5	Terminated
123	NCT00452361	Pfizer (formerly Wyeth)	Study Evaluating of Calcineurin Inhibitors Versus Sirolimus in Renal Allograft Recipient	31	Terminated
124	NCT00658320	Novartis	Concentration Controlled Everolimus With Reduced Dose Cyclosporine Versus Mycophenolate Mofetil With Standard Dose Cyclosporine in de Novo Renal Transplant Adult Recipients Treated With Basiliximab and Corticosteroids	122	Completed
125	NCT00113269	Astellas Pharma Inc	Safety/Efficacy of Induction Agents With Tacrolimus, MMF, and Rapid Steroid Withdrawal in Renal Transplant Recipients (INTAC)	501	Completed
126	NCT00235300	Genzyme, a Sanofi Company	An Open-label, Prospective, Randomized, Multi-center, Phase II Comparative Trial of	240	Completed

			Thymoglobulin Versus Simulect for the Prevention of Delayed Graft Function and Acute Allograft Rejection in Renal Allograft Recipients.		
127	NCT00965094	Novartis Pharmaceuticals	Efficacy and Safety of Everolimus+EC-MPS After Early CNI Elimination vs EC-MPS +Tacrolimus in Renal Transplant Recipients	36	Completed
128	NCT00154284	Novartis	Everolimus in a Cyclosporine Microemulsion-free Regimen Compared to a Low-dose Cyclosporine Microemulsion Regimen, in de Novo Kidney Transplant Patients (CERTES02)	114	Completed
129	NCT01079143	Novartis Pharmaceuticals	Progression of Renal Interstitial Fibrosis / Tubular Atrophy (IF/TA) According to Epithelial-mesenchymal Transition (EMT) and Immunosuppressive Regimen (Everolimus Based Versus CNI Based) in de Novo Renal Transplant Recipients (CERTITEM)	194	Completed
130	NCT00251004	Novartis	Efficacy and Safety Study of Everolimus Plus Reduced Cyclosporine Versus Mycophenolic Acid Plus Cyclosporine in Kidney Transplant Recipients	833	Completed
131	NCT00543569	Astellas Pharma Inc	A Study to Assess the Safety and Efficacy of Alefacept in Kidney Transplant Recipients	323	Completed
132	NCT01304836	Astellas Pharma Inc	A Study Looking at Diabetes in Kidney Transplant Recipients Receiving Immunosuppressive Regimen With or Without Steroids (ADVANCE)	1166	Completed
133	NCT00369161	Novartis	A Twelve-month, Multicenter, Open-label, Randomized Study of the Safety, Tolerability and Efficacy of Everolimus With Basiliximab, Corticosteroids and Two Different Exposure Levels of Tacrolimus in de Novo Renal Transplant Recipients	228	Completed
134	NCT00284947	Novartis	Safety and Efficacy of Basiliximab in Calcineurin Inhibitor Intolerant Long-term Kidney Transplant Recipients Treated With Mycophenolic Acid and Steroids	7	Completed
135	NCT00239031	Novartis	Study of Enteric-Coated Mycophenolate Sodium (EC-MPS) Plus Reduced-dose Cyclosporine Microemulsion (CsA-ME) Compared to EC-MPS Plus Standard Dose CsA-ME in Eldery de Novo Renal Transplant Recipients Treated With Basiliximab and Short-term Steroids	117	Completed
136	NCT00492869	Novartis Pharmaceuticals	Efficacy and Safety of AEB071 Versus Tacrolimus in Combination With Mycophenolate Acid Sodium, Basiliximab and Steroids in Preventing Acute Rejection After Kidney Transplantation	124	Completed

137	NCT01596062	Novartis Pharmaceuticals	Pharmacodynamics, Efficacy and Safety of Basiliximab 40 or 80 mg in Combination With Ciclosporine Microemulsion or Everolimus, in Adult Low Risk de Novo Renal Transplant Recipients (IDEALE Study)	16	Completed
138	NCT00154232	Novartis Pharmaceuticals	Study to Evaluate the Combination of Enteric-coated Mycophenolate Sodium (EC-MPS), Basiliximab, and C2-monitored Cyclosporine in de Novo Renal Transplant Recipients at Potential High Risk of Delayed Graft Function (DGF)	46	Completed
139	NCT00634920	Novartis Pharmaceuticals	Evaluation of Early Conversion to Everolimus From Cyclosporine in de Novo Renal Transplant Recipients	204	Completed
140	NCT00717470	Astellas Pharma Inc	A Study in Kidney Transplant Subjects to Investigate the Optimal Suppression of Immunity to Help Prevent Kidney Rejection (OSAKA)	1252	Completed
141	NCT00170833	Novartis	Safety, Tolerability and Efficacy of Everolimus With Lower Versus Higher Levels of Tacrolimus in de Novo Renal Transplant Patients	80	Completed
142	NCT00308425	Novartis	Safety and Efficacy of Enteric-coated Mycophenolate Sodium (EC-MPS) Plus Valsartan in Patients With Kidney Transplants (MYTHOS)	119	Completed
143	NCT00610961	University of Florida, Novartis Pharmaceuticals	Induction Related BK Viremia in Renal Transplant Patients	60	Completed
144	NCT00842699	Brigham and Women's Hospital, Genzyme, a Sanofi Company	Characterization of Immunological Profile of Renal Transplant Patients Undergoing Induction Treatment With Thymoglobulin vs. IL-2 Receptor Antagonist Basiliximab	40	Completed
145	NCT00229138	Novartis Pharmaceuticals	Efficacy and Safety of Enteric-Coated Mycophenolate Sodium (EC-MPS) in Kidney Transplant Recipients	291	Completed
146	NCT00101738	Novartis Pharmaceuticals	Freedom Study: Myfortic in Kidney Transplant Patients	342	Completed
147	NCT00820911	Novartis Pharmaceuticals	Efficacy and Safety of AEB071 Versus Cyclosporine in de Novo Renal Transplant Recipients	175	Completed
148	NCT00167947	Pfizer (formerly Wyeth)	Study Evaluating Sirolimus in Kidney Transplant Recipients.	150	Completed
149	NCT00504543	Novartis Pharmaceuticals	Efficacy, Safety and Tolerability of AEB071 Versus Cyclosporine in the Novo Renal Transplant Recipients	311	Completed
150	NCT00403416	Novartis Pharmaceuticals	Efficacy and Safety of AEB071 Plus Tacrolimus (Converted to Mycophenolic Acid After 3 Months), in Renal Transplant Patients	215	Completed

151	NCT00531440	Novartis Pharmaceuticals	This is a 2-year Follow-up Study to Evaluate the Long-term Effects in Patients Who Completed the Study CRAD001A2307.	256	Completed
152	NCT00106639	Pfizer	A 6-Month Study Of CP-690,550 Versus Tacrolimus In Kidney Transplant Patients	61	Completed
153	NCT01336296	University of Cincinnati, Novartis Pharmaceuticals	Evaluate Effects and Safety of Pre-load Myfortic® in Transplant Patients	61	Completed
154	NCT00552201	Centre Hospitalier Universitaire, Amiens, Roche Pharma AG, Astellas Pharma Inc	TACrolimus in Renal Transplantation: Individualization by Pharmacogenetic	280	Completed
155	NCT01028092	University Hospital, Brest,Novartis, Roche Pharma AG, Genzyme, a Sanofi Company, Ministry of Health, France	mTor-inhibitor (EVERolimus) Based Immunosuppressive Strategies for CNI Minimisation in OLD for Old Renal Transplantation (EVEROLD)	327	Completed
156	NCT01435291	Centre Hospitalier Universitaire de Nice	AADAPT - Analysis of Advagraf Dose Adaptation Post Transplantation	45	Completed
157	NCT00771875	University of Cincinnati	Randomized Trial for Mixed Acute Rejection	30	Completed
158	NCT00261820	Pfizer (formerly Wyeth)	Study Comparing Two Immunosuppressive Regimens in De Novo Renal Allograft Recipients	160	Completed
159	NCT00771745	University of Cincinnati, Genzyme, a Sanofi Company	Prospective Pilot Study of Pre-Transplant Thymoglobulin Administration in Living Donor Renal Transplant Recipients	11	Completed
160	NCT00076570	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	Combination Drug Therapy Followed by Single Drug Steroid Free Therapy to Prevent Organ Rejection in Kidney Transplantation	31	Completed
161	NCT00089947	Genzyme, a Sanofi Company	A Study to Evaluate the Effect of Thymoglobulin and Reduced Doses of Steroids to Prevent Renal Transplant Rejection	150	Completed
162	NCT00007787	National Institute of Allergy and Infectious Diseases (NIAID)	Antibody and Delayed Cyclosporine Versus Initial Cyclosporine Alone in Patients Receiving Kidney Transplants	350	Completed
163	NCT00284934	Novartis	Enteric-coated Mycophenolate Sodium (EC-MPS) With Reduced-dose Tacrolimus Versus EC-MPS With Standard-dose Tacrolimus in Stable Kidney Transplant Recipients (OLYMPE)	94	Completed
164	NCT00266123	Pfizer (formerly Wyeth)	Study Comparing Two Sirolimus Regimens vs. Tacrolimus and Mycophenolate Mofetil Regimen in Kidney Transplant Recipients	420	Completed
165	NCT00765661	Veloxis Pharmaceuticals, CTI Clinical Trial and Consulting Services, Aptuit Inc.	Pharmacokinetics of LCP-Tacro(TM) Once Daily And Prograf® Twice A Day in Adult De Novo Kidney Transplant Patients	63	Completed
166	NCT01363752	Astellas Pharma Inc	A Study Looking at Kidney Function in Kidney Transplant Recipients Who Are Taking Anti-rejection Medication Including Tacrolimus and With	853	Completed

			or Without Sirolimus. (ADHERE)		
167	NCT00297765	Astellas Pharma Inc	Optimizing Prograf® Therapy in Renal Transplant Patients (OPTIMA)	323	Completed
168	NCT00213590	University Hospital, Rouen	Renal Function Evaluation After Reduction of Cyclosporine A Dose in Renal Transplant Patients (DICAM)	208	Completed
169	NCT00273871	Pfizer (formerly Wyeth)	Study Comparing Conversion From Calcineurin Inhibitors to Rapamune Versus Standard Therapy in Established Renal Allograft Recipients	190	Completed
170	NCT00369382	Pfizer (formerly Wyeth)	Study Of The Safety And Efficacy Of Conversion From A CNI To Sirolimus In Renally-Impaired Heart Transplant Recipients	121	Completed
171	NCT00717379	Astellas Pharma Inc	Study of Tacrolimus Immunosuppressive Therapy After Kidney Transplantation	50	Completed
172	NCT00496483	Veloxis Pharmaceuticals, CTI Clinical Trial and Consulting Services	Pharmacokinetics of LCP-Tacro in Stable Kidney Transplant Patients	60	Completed
173	NCT01802268	Helio Tedesco Silva Junior, Pfizer	Planned Conversion From TAC to SRL-based Regimen in de Novo Kidney Transplant Recipients	320	Completed
174	NCT00296309	Astellas Pharma Inc, Astellas Pharma Europe B.V.	Comparing Efficacy & Safety of Tacrolimus & MMF With/Without Induction in the Elderly Following Kidney Transplantation.	267	Completed
175	NCT00402168	Bristol-Myers Squibb	A Study of BMS-224818 (Belatacept) in Patients Who Have Undergone a Kidney Transplant and Are Currently on Stable Cyclosporine or Tacrolimus Regimen With or Without Corticosteroids	171	Completed
176	NCT00035555	Bristol-Myers Squibb	Study Comparing the Safety and Efficacy of Belatacept With That of Cyclosporine in Patients With a Transplanted Kidney	230	Completed
177	NCT00455013	Bristol-Myers Squibb	A Phase II Study of Belatacept (BMS-224818) With a Steroid-free Regimen in Subjects Undergoing Kidney Transplantation	93	Completed
178	NCT00183248	University of Miami Immune Tolerance Network (ITN)	Using Donor Stem Cells and Alemtuzumab to Prevent Organ Rejection in Kidney Transplant Patients	9	Completed
179	NCT00284934	Novartis	Enteric-coated Mycophenolate Sodium (EC-MPS) With Reduced-dose Tacrolimus Versus EC-MPS With Standard-dose Tacrolimus in Stable Kidney Transplant Recipients (OLYMPE)	94	Completed
180	NCT00369278	Novartis Pharmaceuticals	Intensified vs. Standard Dose Therapy With Mycophenolate Sodium Plus Cyclosporin Microemulsion and Corticosteroid Combination in Patients With de Novo Renal Transplant Patients	128	Completed

181	NCT00419926	Novartis	Evaluation of the Therapeutic Benefit of an Initial Intensified Dosing Regimen of Mycophenolate Sodium Versus a Standard Regimen in Renal Transplant Patients	313	Completed
182	NCT00812123	University Hospital, Basel, Switzerland, Pfizer (formerly Wyeth)	Calcineurin Free Immunosuppression in Renal Transplant Recipients	127	Completed
183	NCT00154310	Novartis	Efficacy and Safety of Everolimus With Enteric-Coated Mycophenolate Sodium (EC-MPS) in a Cyclosporine Microemulsion-free Regimen Compared to Standard Therapy in de Novo Renal Transplant Patients	300	Completed
184	NCT00170846	Novartis Pharmaceuticals	ASCERTAIN: Assessment of Everolimus in Addition to Calcineurin Inhibitor Reduction in the Maintenance of Renal Transplant Recipients	394	Completed
185	NCT00425308	Novartis Pharmaceuticals	Efficacy and Safety of Everolimus in Combination With Cyclosporine Microemulsion Versus Everolimus in Combination With Enteric-coated Mycophenolate Sodium (EC-MPS), in Adult Renal Transplant Patients in Maintenance.	30	Completed
186	NCT01064791	Novartis Pharmaceuticals	Efficacy, Safety, Tolerability, and Pharmacokinetics of Sotrastaurin Combined With Tacrolimus vs. a Mycophenolic Acid-tacrolimus Regimen in Renal Transplant Patients	298	Completed
187	NCT00149903	Novartis Pharmaceuticals	Study of Enteric-coated Mycophenolate Sodium Versus Mycophenolate Mofetil in Adult de Novo Renal Transplant Patients	300	Completed
188	NCT00275535	Mayo Clinic, Pfizer (formerly Wyeth), Genzyme, a Sanofi Company, Roche Pharma AG	The Comparison of Tacrolimus and Sirolimus Immunosuppression Based Drug Regimens in Kidney Transplant Recipients	165	Completed
189	NCT00371826	Novartis Pharmaceuticals	SOCRATES: Steroid or Cyclosporine Removal After Transplantation Using Everolimus	126	Completed
190	NCT00239057	Novartis	Study of Enteric-coated Mycophenolate Sodium Maintenance Therapy in Patients With Renal Transplant Receiving Cyclosporine Microemulsion and Steroids	23	Completed
191	NCT00811915	University Hospital, Rouen	Study to Compare the Safety and Efficacy of Sirolimus (Rapamune) to Tacrolimus (Advagraf) Associated to Mycophenolate Mofetil (CellCept) Between 12 and 36 Months After Kidney Transplantation (EPARGNE)	65	Completed
192	NCT00461825	Poitiers University Hospital	Maintenance Neoral Monotherapy Compared to Bitherapy in Renal Transplantation	207	Completed
193	NCT01742624	Astellas Pharma Korea, Inc.	Study to Evaluate the Safety and Efficacy of Advagraf vs Prograf in Kidney Transplantation Patients 1 Month After the Transplantation	60	Completed

			(AdProCISE)		
194	NCT00200551	Nantes University Hospital	A Study of Mycophenolate Mofetil and Cyclosporin, Without Concomitant Corticosteroids, After a First Renal Transplant	200	Completed
195	NCT00483756Yes	Pfizer	Study of a JAK3 Inhibitor for the Prevention of Acute Rejection in Kidney Transplant Patients	338	Completed
196	NCT00138970	University of Oslo School of Pharmacy	Calcineurin Inhibitor-Free Immunosuppression in Renal Transplant Recipients at Low Immunogenic Risk	70	Completed
197	NCT00912678	University of Luebeck Astellas Pharma GmbH	Minimizing Immunosuppression in Old for Old Kidney Transplantation (ESP-CNI)	90	Completed
198	NCT00533624	University of Miami, Novartis	Myfortic vs. Cellcept in Kidney Transplant Recipients	150	Completed
199	NCT00413920	Novartis	Efficacy and Safety of Enteric-coated Mycophenolate Sodium and Cyclosporine in Combination With and Without Steroids, in Adult Renal Transplant Recipients	222	Completed
200	NCT01025817 CRAD001AUS92	Novartis Pharmaceuticals	Non-inferiority Study of Safety and Efficacy of Everolimus With Low Dose Tacrolimus to Mycophenolate Mofetil With Standard Dose Tacrolimus in Kidney Transplant Recipients	613	Completed
201	NCT00650468	Astellas Pharma Inc	A Study to Compare Early Steroid Withdrawal and Long-Term Steroid Maintenance Therapy in Kidney Transplant Patients	397	Completed
202	NCT00087581	Hoffmann-La Roche	Study of Therapeutic Monitoring of CellCept (Mycophenolate Mofetil) After Kidney Transplantation	717	Completed
203	NCT00374803	University of Cincinnati, Novartis	Study of Myfortic in Combination With Tacrolimus and Thymoglobulin in Early Corticosteroid Withdrawal	45	Completed
204	NCT00693381	Astellas Pharma Inc	Mycophenolate Mofetil (MMF) Discontinuation From a Tacrolimus/MMF/Steroid Triple Regimen After Kidney Transplantation (DISTAMP)	152	Completed
205	NCT00195273	Pfizer (formerly Wyeth)	Study Evaluating Sirolimus in Kidney Transplant Recipients	61	Completed
206	NCT00239083	Novartis	Efficacy and Safety of Enteric-Coated Mycophenolate Sodium (EC-MPS) in Renal Transplant Patients	40	Completed
207	NCT00885820	Astellas Pharma Inc Astellas Pharma Canada, Inc.	Benefit of Early Protocol Biopsy and Treatment of Subclinical Rejection	240	Completed
208	NCT00400647	Novartis	Gastrointestinal and Health-related Quality of Life in Kidney Transplant Patients Treated With Mycophenolate Mofetil	136	Completed

209	NCT00296361	Astellas Pharma Inc	To Compare the Efficacy and Safety of a Therapy of Tacrolimus With Sirolimus or MMF in Kidney Transplantation. (RESTORE)	634	Completed
210	NCT00238992	Novartis Pharmaceuticals	Study of Enteric-coated Mycophenolate Sodium (EC-MPS) With Steroid Withdrawal vs EC-MPS With Standard Steroid Regimen in de Novo Renal Transplant Recipients.	144	Completed
211	NCT00817687	Hoffmann-La Roche	A Study of the Impact of an Early Biopsy in Patients Treated With CellCept (Mycophenolate Mofetil) After Kidney Transplantation	66	Completed
212	NCT00321113	Astellas Pharma Inc	Comparison of Two Tacrolimus Based Immunosuppressive Regimens in Recipients Receiving Marginal Donor Kidneys (TIGRE)	142	Completed
213	NCT00064701	Astellas Pharma Inc	Comparative Study of Modified Release (MR) Tacrolimus/Mycophenolate Mofetil (MMF) in de Novo Kidney Transplant Recipients	668	Completed
214	NCT00788567	Hoffmann-La Roche	CLEAR Study - A Study of CellCept (Mycophenolate Mofetil) in Recipients of Kidney Transplants	136	Completed
215	NCT00182559	Medical University of Vienna	The Vienna Prograf and Endothelial Progenitor Cell Study	148	Completed
216	NCT00681213	University of Miami Wyeth-Ayesrst Pharmaceuticals, Roche Laboratories, and Fujusawa Healthcare, Inc.	Tacrolimus/Sirolimus Versus Tacrolimus/Mycophenolate Mofetil (MMF) Versus Neoral/Sirolimus in Adult, Primary Kidney Transplantation	150	Completed
217	NCT00166244(b)	Erasmus Medical Hoffmann-La Roche Center	Fixed Dose MMF vs Concentration Controlled MMF After Renal Transplantation	901	Completed
218	NCT00240955	Novartis	Extension Study of Enteric-coated Mycophenolate Sodium With Short-term or no Steroid Use Compared With Enteric-coated Mycophenolate Sodium With Standard Steroid Therapy in de Novo Kidney Recipients	79	Completed
219	NCT01706471	Yonsei University	Safety and Efficacy of the Early Introduction of Everolimus (Certican®) With Low Dose of Cyclosporine in de Novo Kidney Recipients After 1 Month of Transplantation	60	Completed
220	NCT00400400	Novartis Pharmaceuticals	Enteric-coated Mycophenolate Sodium (EC-MPS) and Mycophenolate Mofetil (MMF) in Renal Transplant Patients With Gastrointestinal (GI) Intolerance	400	Completed
221	NCT00121810	Hoffmann-La Roche	Kidney Spare the Nephron (STN) Study - A Study of CellCept (Mycophenolate Mofetil) and Rapamune (Sirolimus) in Kidney Transplant Recipients	305	Completed

222	NCT00189839	Astellas Pharma Inc	A Study to Evaluate the Safety and Efficacy of FK506E (MR4) in Patients Undergoing Primary Kidney Transplantation	699	Completed
223	NCT02005562	Hoffmann-La Roche	OPERA Study: A Study of Two Dosing Regimens of CellCept (Mycophenolate Mofetil) in Kidney Transplant Patients.	263	Completed
224	NCT00758602	Hoffmann-La Roche	A Study of CellCept (Mycophenolate Mofetil) Combined With Tacrolimus and Corticosteroids in Kidney Transplant Patients.	210	Completed
225	NCT00717678	Astellas Pharma Taiwan, Inc.	A Randomized Study to Assess the Safety and Efficacy of Prograf vs Prograf-XL in de Novo Kidney Transplant Recipients	73	Completed
226	NCT00275522	Mayo Clinic , Pfizer (formerly Wyeth)	The Comparison of Three Different Immunosuppressant Regimens in Kidney Transplant Recipients	16	Completed
227	NCT00337493	Hoffmann-La Roche	Pharmacogenetic Study of CellCept (Mycophenolate Mofetil) in Kidney Transplant Patients.	155	Completed
228	NCT00305396	Vanderbilt University, Genzyme, a Sanofi Company	Calcineurin Inhibitor Avoidance With Thymoglobulin and Sirolimus in Kidney Transplantation	80	Completed
229	NCT00187941	University of Florida Hoffmann-La Roche	MPA PK Monitoring Strategy With MMF/FK Based Immunosuppression	22	Completed
230	NCT01280617	Lahey Clinic Brigham and Women's Hospital	Low Dose Thymoglobin in Renal Transplant Patients	58	Completed
231	NCT00777933	Samsung Medical Center	Randomized Trial of Cyclosporine and Tacrolimus Therapy With Steroid Withdrawal in Living-Donor Renal Transplantation	131	Completed
232	NCT01601821	Pfizer	Open Label Comparative Study Of De Novo Renal Allograft Recipients Receiving CSA + MMF + Corticosteroids Versus CSA + Rapamune + Corticosteroids	245	Completed
233	NCT00585468	University of Utah	Pharmacokinetic Profile of Myfortic (Enteric Coated Mycophenolate Sodium) in a Rapid Steroid Withdrawal Protocol	24	Completed
234	NCT01183247	University Hospital, Basel, Switzerland Novartis	An Open, Single Centre, Randomised, Parallel Group Study to Investigate Three Different Immunosuppressive Regimens (SterFreePlus)	63	Completed
235	NCT00248313	Pfizer (formerly Wyeth)	Study Comparing Cyclosporin Dose Reduction With Cyclosporin Elimination in Kidney Transplant Recipients Taking Sirolimus	470	Completed
236	NCT00170885	Novartis	Everolimus in Combination With Cyclosporine Microemulsion in de Novo Renal Transplant Recipients	NR	Completed

237	NCT00895583	Pfizer	Study Evaluating A Planned Transition From Tacrolimus To Sirolimus In Kidney Transplant Recipients	254	Completed
238	NCT00428064	Pfizer (formerly Wyeth)	Study Evaluating Sirolimus and Cyclosporine in Kidney Transplant Recipients	408	Completed
239	NCT00195429	Pfizer (formerly Wyeth)	A Study Comparing the Withdrawal of Steroids or Tacrolimus in Kidney Transplant Recipients	47	Completed
240	NCT00195468	Pfizer (formerly Wyeth)	Study Comparing Cyclosporine Dose Reduction vs. Cyclosporine Elimination in Kidney Transplant Recipients Taking Sirolimus	280	Completed
241	NCT00306397	University Hospital, Basel, Switzerland	Pilot Study to Investigate a Steroid Free Immunosuppressive Regimen for Renal Transplant Recipients	100	Completed
242	NCT01023815	Novartis	Once-a-day Regimen With Everolimus, Low Dose Cyclosporine and Steroids in Comparison With Steroid Withdrawal or Twice a Day Regimen With Everolimus, Low Dose Cyclosporine and Steroids. (EVIDENCE)	184	Completed
243	NCT00518375	Pfizer (formerly Wyeth)	Study Comparing Graft Function in Renal Allograft Recepients Receiving Reduced or Standard Dose CsA With Sirolimus	250	Completed
244	NCT00309270	Mario Negri Institute for Pharmacological Research	Low Dose Sirolimus or CsA-Based Maintenance Immunosuppression After Induction With Campath-1 in Kidney Transplantation	21	Completed
245	NCT00507793	Pfizer (formerly Wyeth)	Study Evaluating the Efficacy and Safety of Cyclosporine Reduction in Kidney Transplant Recipients Receiving Sirolimus	385	Completed
246	NCT00519116	Pfizer (formerly Wyeth)	Study Comparing Standard Dose and Reduced Dose Tacrolimus With Sirolimus in Renal Transplant Patients	150	Completed
247	NCT00518271	Pfizer (formerly Wyeth)	Study Comparing Standard Dose and Reduced Dose Tacrolimus + Sirolimus + Corticosteroids in Renal Allograft Recipients	120	Completed
248	NCT00254709	Pfizer (formerly Wyeth)	Study Evaluating Two Different Sirolimus-based Immunosuppressive Regimens in Elderly Kidney Transplant Recipients	66	Completed
249	NCT00038948	Pfizer (formerly Wyeth)	Study Comparing Conversion to Sirolimus vs. Continued Use of Calcineurin Inhibitors in Kidney Transplant Recipients	830	Completed
250	NCT00470665	Pfizer (formerly Wyeth)	Study Comparing Sirolimus/Prograf vs Sirolimus/CsA in High-Risk Renal Transplant Recipients	460	Completed
251	ISRCTN87678078	Hospital Universitario de Canarias	Efficacy and security of low toxicity immunosuppressive regimen using basiliximab,	240	Completed

			mycophenolate mofetil, neoral or tacrolimus and corticosteroids versus full doses of neoral, thymoglobulin, azathioprine and corticosteroids		
252	ISRCTN94424606	Leeds Teaching Hospitals NHS Trust (UK)	Steroid Avoidance in Leeds with Alemtuzumab or Mycophenolate Mofetil (MMF) Immunosuppression	120	Completed
253	ISRCTN76390219	University Hospitals of Leicester NHS Trust	A randomised controlled trial comparing the use of sirolimus based biphasic immunosuppression with myfortic to allow early CalciNeurin Inhibitor (CNI) withdrawal in renal transplantation	42	Completed
254	ISRCTN55817881	Leiden University Medical Centre (LUMC)	CAlciNeurin-inhibitor Nephrotoxicity and Efficacy Study	126	Completed
255	ISRCTN74429508	University of Munich - Department of Surgery	A randomized multicenter trial to assess the efficacy of a combined therapy with Sirolimus (Rapamune®), MMF (Cellsept®) and corticosteroids after early elimination of cyclosporin compared to a standard immunosuppression with cyclosporin, MMF and corticosteroids in patients after kidney transplantation	140	Completed
256	ISRCTN69188731	Academic Medical Center (AMC), Renal Transplant Unit (The Netherlands)	Mycophenolate sodium versus Everolimus or Cyclosporine with Allograft Nephropathy as Outcome	255	Completed

Key: ID, identification number; NA, not applicable; N, number of studies; PenTAG, PenTAG systematic review.

Appendix 9 Additional results from the PenTAG economic model

Disaggregated discounted costs

Table 238. Disaggregated discount costs in the PenTAG model (deterministic base case)

Regimen	Induction therapy (1st graft)	Maintenance immunosuppression (first graft)	Acute rejection (1st graft)	Infection prophylaxis (1st graft)	CMV infection (1st graft)	Monitoring (1st graft)	Retransplantation
CSA+MMF	£0	£15,996	£1,020	£764	£315	£16,147	£4,933
TAC+MMF	£0	£14,884	£896	£764	£315	£16,394	£4,435
CSA+AZA	£0	£13,519	£1,695	£759	£315	£15,657	£5,506
TAC+AZA	£0	£13,359	£1,184	£755	£315	£16,141	£4,684
CSA+EVL	£0	£96,455	£996	£766	£107	£18,923	£4,542
TAC+SRL	£0	£34,870	£870	£754	£107	£18,020	£5,347
TAC-PR+MMF	£0	£26,612	£878	£760	£315	£15,814	£5,051
BAS+CSA+MMF	£2,197	£16,654	£584	£767	£315	£16,537	£4,473
BAS+TAC+MMF	£2,197	£15,424	£504	£767	£315	£16,756	£4,027
Bas+CSA+AZA	£2,197	£14,204	£1,070	£763	£315	£16,126	£4,947
Bas+SRL+MMF	£2,197	£35,222	£547	£760	£151	£16,353	£4,458
BAS+BEL+MMF	£2,197	£166,297	£908	£771	£315	£14,488	£3,855
BAS+CSA+MPS	£2,197	£35,795	£813	£770	£315	£16,816	£4,199
rATG+CSA+MMF	£4,274	£16,619	£428	£1,700	£315	£16,544	£4,531
rATG+TAC+MMF	£4,274	£15,420	£368	£1,700	£315	£16,786	£4,090
rATG+CSA+AZA	£4,274	£14,228	£814	£1,692	£315	£16,171	£4,963

Table 238. Disaggregated discount costs in the PenTAG model (deterministic base case) (cont.)

Regimen	Immunosuppression (subsequent grafts)	Monitoring (subsequent grafts)	Dialysis	NODAT	Anaemia	Dyslipidaemia	Graft loss	Total
CSA+MMF	£2,712	£3,722	£49,657	£1,469	£866	£409	£146	£98,157
TAC+MMF	£2,424	£3,327	£44,852	£3,119	£877	£408	£133	£92,827
CSA+AZA	£3,038	£4,169	£54,785	£1,455	£843	£405	£174	£102,320
TAC+AZA	£2,583	£3,544	£46,719	£3,120	£872	£408	£167	£93,851
CSA+EVL	£2,493	£3,422	£46,055	£1,400	£878	£621	£130	£176,788
TAC+SRL	£2,928	£4,018	£52,969	£4,632	£839	£609	£182	£126,147
TAC-PR+MMF	£2,761	£3,789	£50,556	£3,563	£845	£401	£153	£111,499
BAS+CSA+MMF	£2,456	£3,370	£45,390	£1,482	£887	£412	£130	£95,654
BAS+TAC+MMF	£2,199	£3,017	£41,015	£3,147	£897	£411	£118	£90,794
Bas+CSA+AZA	£2,725	£3,739	£49,683	£1,470	£867	£409	£153	£98,667
Bas+SRL+MMF	£2,452	£3,364	£44,877	£2,529	£880	£620	£145	£114,554
BAS+BEL+MMF	£2,120	£2,909	£39,519	£661	£921	£419	£110	£235,490
BAS+CSA+MPS	£2,303	£3,160	£42,844	£1,397	£902	£415	£119	£112,045
rATG+CSA+MMF	£2,484	£3,409	£46,014	£1,484	£886	£413	£128	£99,231
rATG+TAC+MMF	£2,230	£3,061	£41,712	£3,157	£898	£412	£116	£94,538
rATG+CSA+AZA	£2,730	£3,747	£49,917	£1,474	£869	£410	£149	£101,751

Additional outcomes

Table 239. Additional clinical outcomes as calculated by the PenTAG model (deterministic base case)

Regimen	Mean undiscounted	Undiscounted life years with	Undiscounted life years on	Acute rejection	NODAT	Proportion receiving 2nd	Proportion receiving 3rd

	life years (life expectancy)	functioning graft	dialysis			transplant	transplant
CSA+MMF	22.346	18.998	3.349	24.6%	5.0%	23.9%	2.7%
TAC+MMF	22.356	19.323	3.033	21.6%	10.6%	21.5%	2.4%
CSA+AZA	22.050	18.398	3.652	40.9%	5.0%	26.5%	3.0%
TAC+AZA	22.372	19.269	3.103	28.6%	10.6%	22.3%	2.6%
CSA+EVL	22.445	19.319	3.126	24.0%	4.7%	22.2%	2.5%
TAC+SRL	21.829	18.323	3.506	21.0%	16.0%	25.5%	3.0%
TAC-PR+MMF	21.848	18.458	3.389	21.2%	12.3%	24.4%	2.7%
BAS+CSA+MMF	22.636	19.554	3.082	14.1%	5.0%	21.8%	2.4%
BAS+TAC+MMF	22.640	19.850	2.790	12.2%	10.6%	19.6%	2.2%
Bas+CSA+AZA	22.380	19.041	3.339	25.8%	5.0%	23.9%	2.7%
Bas+SRL+MMF	22.448	19.434	3.014	13.2%	8.6%	21.4%	2.4%
BAS+BEL+MMF	23.206	20.502	2.704	21.9%	2.2%	18.8%	2.1%
BAS+CSA+MPS	22.877	19.953	2.923	19.6%	4.7%	20.5%	2.3%
rATG+CSA+MMF	22.645	19.515	3.129	10.3%	5.0%	22.1%	2.4%
rATG+TAC+MMF	22.687	19.843	2.843	8.9%	10.6%	20.0%	2.2%
rATG+CSA+AZA	22.417	19.054	3.362	19.6%	5.0%	24.1%	2.7%

Using Solver instead of flexible regression to match mortality at 12 months

Table 240. Deterministic results when Solver is used instead of flexible regression to match mortality at 12 months

Regimen	Total discounted costs	Total discounted QALYs	Net health benefit	
			£20k/QALY	£30k/QALY
CSA+MMF	£98,164	10.8933	5.9851	7.6212
TAC+MMF	£92,824	10.8590	6.2178	7.7649
CSA+AZA	£102,326	10.7492	5.6329	7.3383
TAC+AZA	£93,846	10.8441	6.1518	7.7159
CSA+EVL	£176,780	10.9371	2.0981	5.0444
TAC+SRL	£126,139	10.5766	4.2697	6.3720
TAC-PR+MMF	£111,508	10.6182	5.0428	6.9012
BAS+CSA+MMF	£95,665	11.0261	6.2428	7.8372
BAS+TAC+MMF	£90,791	10.9875	6.4479	7.9611
Bas+CSA+AZA	£98,677	10.9042	5.9703	7.6149
Bas+SRL+MMF	£114,550	10.9005	5.1730	7.0822
BAS+BEL+MMF	£235,605	11.2998	-0.4804	3.4464
BAS+CSA+MPS	£112,082	11.1417	5.5376	7.4057
rATG+CSA+MMF	£99,258	11.0379	6.0750	7.7293
rATG+TAC+MMF	£94,542	11.0166	6.2895	7.8652
rATG+CSA+AZA	£101,780	10.9287	5.8396	7.5360

Table 241. Regimens on the cost-effectiveness frontier when Solver is used instead of flexible regression to match mortality at 12 months

Regimen	Total discounted costs	Total discounted QALYs	ICER (cost per QALY)	Incremental net health benefit	
				£20k/QALY	£30k/QALY
BAS+TAC+MMF	£90,791	10.9875	—	—	—
BAS+CSA+MMF	£95,665	11.0261	£126,290	-0.2051	-0.1239
BAS+CSA+MPS	£112,082	11.1417	£141,959	-0.9103	-0.5555
BAS+BEL+MMF	£235,605	11.2998	£781,117	-6.9283	-4.5148

Removing disutility for NODAT

Table 242. Cost-effectiveness of induction agents when there is no disutility applied for NODAT

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	£102,320	—	10.7902	—	Dominated	-0.3375	-0.2766
Basiliximab	£98,667	-£3,653	10.9450	+0.1548	—	—	—
Rabbit ATG	£101,751	+£3,084	10.9671	+0.0222	£139,073	-0.1320	-0.0806
With CSA+MMF						*vs. Basiliximab*	
No induction	£98,157	—	10.9345	—	Dominated	-0.2577	-0.2160
Basiliximab	£95,654	-£2,503	11.0671	+0.1326	—	—	—
Rabbit ATG	£99,231	+£3,576	11.0768	+0.0097	£366,822	-0.1691	-0.1095
With TAC+MMF						*vs. Basiliximab*	
No induction	£92,827	—	10.9487	—	Dominated	-0.2309	-0.1971
Basiliximab	£90,794	-£2,033	11.0779	+0.1293	—	—	—
Rabbit ATG	£94,538	+£3,744	11.1063	+0.0283	£132,065	-0.1588	-0.0964

Table 243. Cost-effectiveness of maintenance agents when there is no disutility applied for NODAT

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With MMF						*vs. TAC*	
TAC-PR	£111,499	—	10.7191	—	Dominated	-1.1632	-0.8520
CSA	£98,157	-£13,342	10.9345	+0.2154	Dominated	-0.2806	-0.1918
TAC	£92,827	-£5,330	10.9487	+0.0142	—	—	—
With AZA						*vs. TAC*	
CSA	£102,320	—	10.7902	—	Dominated	-0.5673	-0.4262
TAC	£93,851	-£8,469	10.9340	+0.1438	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£114,554	—	10.9733	—	Dominated	-1.2926	-0.8966
CSA	£95,654	-£18,900	11.0671	+0.0938	Dominated	-0.2539	-0.1729
TAC	£90,794	-£4,860	11.0779	+0.0109	—	—	—
BEL	£235,490	+£144,696	11.3130	+0.2350	£615,616	-6.9997	-4.5882
With rATG+MMF						*vs. TAC*	
CSA	£99,231	—	11.0768	—	Dominated	-0.2641	-0.1859
TAC	£94,538	-£4,693	11.1063	+0.0295	—	—	—

Table 243. Cost-effectiveness of maintenance agents when there is no disutility applied for NODAT (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	£102,320	—	10.7902	—	Dominated	-0.3525	-0.2831
MMF	£98,157	-£4,163	10.9345	+0.1443	—	—	—
EVL	£176,788	+£78,631	10.9776	+0.0431	£1,823,831	-3.8884	-2.5779
With TAC						*vs. MMF*	
SRL	£126,147	—	10.7098	—	Dominated	-1.9049	-1.3496
AZA	£93,851	-£32,296	10.9340	+0.2243	Dominated	-0.0658	-0.0488
MMF	£92,827	-£1,024	10.9487	+0.0146	—	—	—
With BAS+CSA						*vs. MMF*	
AZA	£98,667	—	10.9450	—	Dominated	-0.2728	-0.2225
MMF	£95,654	-£3,013	11.0671	+0.1221	—	—	—
MPS	£112,045	+£16,391	11.1776	+0.1106	£148,253	-0.7090	-0.4358
With rATG+CSA						*vs. MMF*	
AZA	£101,751	—	10.9671	—	Dominated	-0.2357	-0.1937
MMF	£99,231	-£2,521	11.0768	+0.1097	—	—	—

Using 2007–2012 donor type distribution

Table 244. Cost-effectiveness of induction agents when the 2007–2012 donor type distribution is used

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	£100,179	—	10.9263	—	Dominated	-0.3342	-0.2753
Basiliximab	£96,648	-£3,531	11.0839	+0.1576	—	—	—
Rabbit ATG	£99,753	+£3,105	11.1039	+0.0199	£155,740	-0.1353	-0.0836
With CSA+MMF						*vs. Basiliximab*	
No induction	£96,243	—	11.0726	—	Dominated	-0.2538	-0.2140
Basiliximab	£93,856	-£2,387	11.2071	+0.1345	—	—	—
Rabbit ATG	£97,435	+£3,579	11.2147	+0.0075	£474,125	-0.1714	-0.1118
With TAC+MMF						*vs. Basiliximab*	
No induction	£91,013	—	11.0447	—	Dominated	-0.2249	-0.1932
Basiliximab	£89,106	-£1,907	11.1743	+0.1296	—	—	—
Rabbit ATG	£92,834	+£3,728	11.2000	+0.0257	£145,129	-0.1607	-0.0986

Table 245. Cost-effectiveness of maintenance agents when the 2007–2012 donor type distribution is used

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With MMF						*vs. TAC*	
TAC-PR	£110,037	—	10.7984	—	Dominated	-1.1975	-0.8804
TAC	£91,013	-£19,024	11.0447	+0.2463	—	—	—
CSA	£96,243	+£5,229	11.0726	+0.0279	£187,412	-0.2336	-0.1464
With AZA						*vs. TAC*	
CSA	£100,179	—	10.9263	—	Dominated	-0.5242	-0.3847
TAC	£91,810	-£8,369	11.0320	+0.1058	—	—	—
With BAS+MMF						*vs. TAC*	
SRL	£113,361	—	11.0876	—	Dominated	-1.2995	-0.8952
TAC	£89,106	-£24,255	11.1743	+0.0867	—	—	—
CSA	£93,856	+£4,749	11.2071	+0.0328	£144,793	-0.2047	-0.1255
BEL	£238,283	+£144,428	11.4794	+0.2723	£530,399	-7.1537	-4.6675
With rATG+MMF						*vs. TAC*	
TAC	£92,834	—	11.2000	—	—	—	—
CSA	£97,435	+£4,601	11.2147	+0.0147	£313,720	-0.2154	-0.1387

Table 245. Cost-effectiveness of maintenance agents when the 2007–2012 donor type distribution is used (cont.)

Maintenance agent	Discounted costs		Discounted QALYs		ICER	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20k/QALY	£30k/QALY
With CSA						*vs. MMF*	
AZA	£100,179	—	10.9263	—	Dominated	-0.3432	-0.2776
MMF	£96,243	-£3,936	11.0726	+0.1463	—	—	—
EVL	£177,623	+£81,380	11.1217	+0.0491	£1,656,502	-4.0199	-2.6635
With TAC						*vs. MMF*	
SRL	£124,830	—	10.7566	—	Dominated	-1.9790	-1.4154
AZA	£91,810	-£33,020	11.0320	+0.2755	Dominated	-0.0525	-0.0392
MMF	£91,013	-£797	11.0447	+0.0127	—	—	—
With BAS+CSA						*vs. MMF*	
AZA	£96,648	—	11.0839	—	Dominated	-0.2628	-0.2163
MMF	£93,856	-£2,792	11.2071	+0.1232	—	—	—
MPS	£110,894	+£17,038	11.3211	+0.1140	£149,509	-0.7379	-0.4540
With rATG+CSA						*vs. MMF*	
AZA	£99,753	—	11.1039	—	Dominated	-0.2267	-0.1881
MMF	£97,435	-£2,318	11.2147	+0.1108	—	—	—

Appendix 10 Summary of parameters in PenTAG economic model

Parameter	Value	Source	PSA distribution
Study characteristics			
Patient age (years)	50	Pruthi et al. 2013[371]	N/A
Patient weight (kg)			
Mean	70.18	Multiple RCTs	Normal(70.18, 1.118)
SD	14.79	Multiple RCTs	N/A
Proportion male	0.617	UK Transplant Registry standard dataset (2007-2012)	N/A
Donor type (first graft)		UK Transplant Registry standard dataset	
DBD	0.664		N/A
DCD	0.079		N/A
Living-related	0.191		N/A
Living-unrelated	0.066		N/A
Donor type (subsequent graft)		UK Transplant Registry standard dataset	
DBD	0.630		N/A
DCD	0.083		N/A
Living-related	0.198		N/A
Living-unrelated	0.089		N/A
Surrogate relationships			
Graft survival (censored for DWFG)			
Acute rejection	1.60	Cole et al. 2008[369]	Log-Normal(0.47, 0.037)
NODAT	1.12	Cole et al. 2008[369]	Log-Normal(0.113, 0.061)
eGFR		Levy et al. 2014[330]	Multivariate Log-Normal
45-60 ml/min/1.73 m²	1.409		
30-45 ml/min/1.73 m²	2.406		
15-30 ml/min/1.73 m²	5.801		

Parameter	Value	Source	PSA distribution
Death with functioning graft			
NODAT	1.41	Cole et al. 2008[369]	Log-Normal(0.344, 0.061)
Sex - female	0.865	UK Transplant Registry standard dataset	Log-Normal(-0.145, 0.036)
Donor type (vs. DBD)		UK Transplant Registry standard dataset	
DCD	1.083		Log-Normal(0.08, 0.061)
Living-related	0.551		Log-Normal(-0.595, 0.071)
Living-unrelated	0.703		Log-Normal(-0.353, 0.081)
Age		UK Transplant Registry standard dataset	
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		N/A
51-60	2.140		Log-Normal(0.761, 0.059)
61-70	4.128		Log-Normal(1.418, 0.053)
71-75	7.583		Log-Normal(2.026, 0.072)
76-80	8.576		Log-Normal(2.149, 0.089)
81-85	13.751		Log-Normal(2.621, 0.144)
86-90	23.552		Log-Normal(3.159, 0.362)
Effectiveness estimates			
Mortality within 12 months [ln(Odds ratio)]			
Induction agents (vs. no induction)		Network meta-analysis	Multivariate Normal
Basiliximab	-0.117		
Rabbit ATG	-0.461		
Maintenance agents (vs. CSA+AZA)		Network meta-analysis	Multivariate Normal
TAC+AZA	0.323		
CSA+MPA	-0.057		

Parameter	Value	Source	PSA distribution
TAC+MPA	0.422		
BEL+MPA	-0.763		
CSA+EVL	0.333		
TAC+SRL	0.325		
SRL+MPA	0.542		
Head-to-head			
MPS vs. MMF	-0.435	Random-effects meta-analysis of Ciancio 2008[130] and Salvadori 2001[269]	Normal(-0.435, 1.231)
TAC-PR vs. TAC	0.245	Krämer 2010[72]	Normal(0.245, 0.481)
Graft loss within 12 months [ln(Odds ratio)]			
Induction agents (vs. no induction)		Network meta-analysis	Multivariate Normal
Basiliximab	-0.171		
Rabbit ATG	-0.253		
Maintenance agents (vs. CSA+AZA)		Network meta-analysis	Multivariate Normal
TAC+AZA	0.135		
CSA+MPA	-0.297		
TAC+MPA	-0.379		
BEL+MPA	-0.492		
CSA+EVL	-0.484		
TAC+SRL	0.159		
SRL+MPA	0.032		
Head-to-head			
MPS vs. MMF	-0.148	Fixed-effects meta-analysis of Ciancio 2008[130] and Salvadori 2001[269]	Normal(-0.148, 0.524)
TAC-PR vs. TAC	0.183	Krämer 2010[72]	Normal(0.183, 0.29)
Biopsy-proven acute rejection within 12 months [ln(Odds ratio)]			

Parameter	Value	Source	PSA distribution
Induction agents (vs. no induction)		Network meta-analysis	Multivariate Normal
Basiliximab	-0.688		
Rabbit ATG	-1.041		
Maintenance agents (vs. CSA+AZA)		Network meta-analysis	Multivariate Normal
TAC+AZA	-0.548		
CSA+MPA	-0.752		
TAC+MPA	-0.921		
BEL+MPA	-0.216		
CSA+EVL	-0.784		
TAC+SRL	-0.957		
SRL+MPA	-0.828		
Head-to-head			
MPS vs. MMF	0.396	Random-effects meta-analysis of Ciancio 2008[130] and Salvadori 2001[269]	Normal(0.396, 0.678)
TAC-PR vs. TAC	-0.025	Random-effects meta-analysis of Krämer 2010[72] and Tsuchiya 2013[128]	Normal(-0.025, 0.383)
Graft function (eGFR) at 12 months [Mean difference (ml/min/1.73 m²)]			
Induction agents (vs. no induction)		Network meta-analysis	Multivariate Normal
Basiliximab	2.615		
Rabbit ATG	0.752		
Maintenance agents (vs. CSA+AZA)		Network meta-analysis	Multivariate Normal
TAC+AZA	9.304		
CSA+MPA	1.609		
TAC+MPA	6.531		
BEL+MPA	10.550		

Parameter	Value	Source	PSA distribution
CSA+EVL	4.863		
TAC+SRL	-0.352		
SRL+MPA	3.846		
Head-to-head			
MPS vs. MMF	3.900	Ciancio 2008[130]	Normal(0.396, 0.678)
TAC-PR vs. TAC	-0.211	Fixed-effects meta-analysis of Krämer 2010[72] and Tsuchiya 2013[128]	Normal(-0.025, 0.383)
Baseline effectiveness (BAS+TAC+MMF)			
Graft loss within 12 months	0.035	UK Transplant Registry standard dataset	N/A
Biopsy-proven acute rejection within 12 months	0.122	Rowshani 2006[122] and Tsuchiya 2013[128]	Beta(14, 101)
Graft function (eGFR) at 12 months (ml/min/1.73 m²)		Pruthi et al. 2013[371]	
Mean	53.4		N/A
SD	18.5		N/A
Adverse events			
NODAT within 12 months			
Baseline (BAS+TAC+MMF)	0.106		
Maintenance agents (vs. TAC) [ln(Odds ratio)]		Network meta-analysis	Multivariate Normal
TAC-PR	0.169		
CSA	-0.816		
BEL	-1.671		
SRL	-0.234		
Maintenance agents (vs. MMF) [ln(Odds ratio)]		Network meta-analysis	Multivariate Normal
MPS	-0.070		
SRL	0.474		
EVL	-0.052		
Cytomegalovirus infection within 12			

Parameter	Value	Source	PSA distribution
months			
Baseline (BAS+TAC+MMF)	0.107	Multiple RCTs	Logit-Normal(-2.12, 0.94)
mTOR-I use (vs. no use) [ln(Odds ratio)]		Network meta-analysis	Multivariate Normal
As CNI	-0.798		
As antimetabolite	-1.153		
Dyslipidaemia within 12 months			
Baseline (BAS+TAC+MMF)	0.202	Multiple RCTs	Logit-Normal(-1.376, 0.982)
mTOR-I use (vs. no use) [ln(Odds ratio)]	0.557	Fixed-effects meta-analysis	Normal(0.557, 0.101)
Anaemia requiring ESA therapy	0.052	Vanrenterghem et al. 2003[386]	Beta(207, 3762)
Retransplantation			
Probability of pre-emptive retransplantation on loss of 1st graft		Bond et al. 2009[373] and Johnston et al. 2013[375]	
Aged 18-34 years	0.108		Beta(3.46, 28.58)
Aged 35-44 years	0.098		Beta(3.51, 32.31)
Aged 45-54 years	0.076		Beta(3.62, 44.01)
Aged 55-64 years	0.054		Beta(3.73, 65.34)
Aged 65+ years	0.02		Beta(3.9, 191.1)
Rate of retransplantation			
Aged under 65 years (Rate declines linearly from age 65 to 80 years after which no retransplantation)	0.104	UK Transplant Registry standard dataset	Normal(0.104, 0.0023)
Baseline rate of death with functioning graft (subsequent grafts)	0.0078	UK Transplant Registry standard dataset	Log-Normal(-4.965, 0.472)
Baseline rate of graft loss (subsequent grafts)	0.0359	UK Transplant Registry standard dataset	Log-Normal(-3.327, 0.084)
Mortality			
Rate of death on dialysis following		Pruthi et al. 2013[338]	

Parameter	Value	Source	PSA distribution
graft loss (by age [years])			
20-24	0.01		Normal(0.01, 0.0032)
25-29	0.012		Normal(0.018, 0.0042)
30-34	0.009		Normal(0.018, 0.0042)
35-39	0.015		Normal(0.043, 0.0066)
40-44	0.021		Normal(0.089, 0.0094)
45-49	0.027		Normal(0.141, 0.0119)
50-54	0.041		Normal(0.226, 0.015)
55-59	0.053		Normal(0.284, 0.0169)
60-64	0.079		Normal(0.437, 0.0209)
65-69	0.107		Normal(0.553, 0.0235)
70-74	0.149		Normal(0.682, 0.0261)
75-79	0.211		Normal(0.792, 0.0281)
80-84	0.275		Normal(0.652, 0.0255)
85+	0.408		Normal(0.452, 0.0213)
Other natural history parameters			
Probability of primary non-function		UK Transplant Registry standard dataset	
DBD	0.026		Beta(147, 5489)
DCD	0.033		Beta(99, 2858)
Living-related	0.015		Beta(53, 3541)
Living-unrelated	0.012		Beta(27, 2149)
Proportion of NODAT in first 6 months	0.75	Woodward et al. 2003[385]	Beta(75, 25)
Risk stratification for cytomegalovirus infection		Harvala et al. 2013 [399]	Dirichlet(52, 93, 79)
High risk (D+/R-)	0.232		
Intermediate risk (D+/R+ or D-/R+)	0.415		
Low risk (D-/R-)	0.353		

Parameter	Value	Source	PSA distribution
Risk stratification for Epstein-Barr virus infection		Cavallo et al. 2010[401]	
Seropositive donors	0.927		Beta(51, 4)
Seropositive recipients	0.997		Beta(289, 1)
Utilities			
Baseline utility		Health Survey for England 2012[389]	Multivariate Normal
Constant	0.9679812		
Coefficient for Age	-0.001807		
Coefficient for Age²	-9.71E-06		
Coefficient for Sex=Male	0.0232887		
Disutilities		Liem et al. 2008[391]	
Functioning graft	0.053		Gamma(1.179, 0.0453)
Haemodialysis	0.277		Gamma(66.9, 0.0041)
Peritoneal dialysis	0.264		Gamma(35.73, 0.0074)
Resource use			
Induction therapy		Brennan et al. 2006[89]	
Basiliximab (20 mg dose + IV administration)	1.964		Normal(1.964, 0.016)
Rabbit ATG			
Drug acquisition (mg/kg)	6.5		Normal(6.5, 0.126)
IV administration	4.525		Normal(4.525, 0.079)
Maintenance therapy			
TAC (with AZA; mg/kg/day)		Margreiter 2002[103]	
0-1 month	0.225		Log-Normal(-1.497, 0.0998)
1-3 months	0.175		Log-Normal(-1.748, 0.0998)
3-6 months	0.135		Log-Normal(-2.007, 0.0998)
6-12 months	0.11		Log-Normal(-2.212, 0.0998)
12-36 months	0.09		Log-Normal(-2.413, 0.0998)
36+ months	0.08		Log-Normal(-2.531, 0.0998)

Parameter	Value	Source	PSA distribution
TAC (with MMF; mg/kg/day)		Rowshani 2006[122]	
0-2 weeks	0.168		Log-Normal(-1.789, 0.0998)
2-6 weeks	0.176		Log-Normal(-1.742, 0.0998)
6-12 weeks	0.11		Log-Normal(-2.212, 0.0998)
3-6 months	0.104		Log-Normal(-2.268, 0.0998)
6-12 months	0.086		Log-Normal(-2.458, 0.0998)
12+ months	0.08		Log-Normal(-2.531, 0.0998)
TAC (with SRL; mg/kg/day)		Gonwa 2003,[155] Anil Kumar 2008[194]	
0-1 month	0.175		Log-Normal(-1.748, 0.0998)
1-3 months	0.11		Log-Normal(-2.212, 0.0998)
3-6 months	0.104		Log-Normal(-2.268, 0.0998)
6-12 months	0.08		Log-Normal(-2.531, 0.0998)
12+ months	0.07		Log-Normal(-2.664, 0.0998)
TAC-PR (with MMF)			
As TAC plus 0.015 mg/kg/day for first 12 months	0.015	Wlodarczyk 2009,[127] Kramer 2010,[72] Tsuchiya 2013,[128] Oh 2014[129]	Normal(0.015, 0.0075)
CSA (with AZA; mg/kg/day)		Margreiter 2002[103]	
0-1 month	6.375		Log-Normal(1.847, 0.0998)
1-3 months	4.525		Log-Normal(1.505, 0.0998)
3-6 months	3.765		Log-Normal(1.321, 0.0998)
6-12 months	3.375		Log-Normal(1.211, 0.0998)
12-36 months	2.93		Log-Normal(1.07, 0.0998)
36+ months	2.84		Log-Normal(1.039, 0.0998)
CSA (with MMF/MPS; mg/kg/day)		Rowshani 2006[122]	
0-2 weeks	7.62		Log-Normal(2.026, 0.0998)
2-6 weeks	5.72		Log-Normal(1.739, 0.0998)
6-12 weeks	3.06		Log-Normal(1.113, 0.0998)
3-6 months	2.86		Log-Normal(1.046, 0.0998)
6-12 months	2.82		Log-Normal(1.032, 0.0998)

Parameter	Value	Source	PSA distribution
12+ months	2.82		Log-Normal(1.032, 0.0998)
CSA (with EVL; mg/kg/day)		Vitko 2004[141]	
0-12 months	3.9		Log-Normal(1.356, 0.0998)
12+ months	2.1		Log-Normal(0.737, 0.0998)
AZA (with TAC; mg/kg/day)		Laskow 1997[94]	
0-6 months	1.5		Log-Normal(0.4, 0.0998)
6+ months	1.2		Log-Normal(0.177, 0.0998)
AZA (with CSA; mg/kg/day)		Sadek 2002[113] and Vacher-Coponat 2012[119]	
0-6 months	1.5		Log-Normal(0.4, 0.0998)
6-12 months	1.4		Log-Normal(0.331, 0.0998)
12-36 months	1.215		Log-Normal(0.19, 0.0998)
36+ months	1.215		Log-Normal(0.19, 0.0998)
MMF (with TAC; g/day)		SYMPHONY[238]	
0-3 months	2		Log-Normal(0.688, 0.0998)
3-12 months	1.736		Log-Normal(0.547, 0.0998)
12+ months	1.472		Log-Normal(0.382, 0.0998)
MMF (with CSA; g/day)		SYMPHONY[238]	
0-3 months	2		Log-Normal(0.688, 0.0998)
3-12 months	1.836		Log-Normal(0.603, 0.0998)
12+ months	1.672		Log-Normal(0.509, 0.0998)
MMF (with SRL; g/day)		SYMPHONY[238]	
0-3 months	2		Log-Normal(0.688, 0.0998)
3-12 months	1.7335		Log-Normal(0.545, 0.0998)
12+ months	1.467		Log-Normal(0.378, 0.0998)
MMF (with BEL; g/day)		BENEFIT[54]	
Throughout	2		Log-Normal(0.688, 0.0998)
MPS (with CSA; mg/day)			
0-3 months	1440		Log-Normal(7.267, 0.0998)
3-9 months	1211		Log-Normal(7.094, 0.0998)

Parameter	Value	Source	PSA distribution
9+ months	1107		Log-Normal(7.004, 0.0998)
SRL (with TAC; mg/day)		Anil Kumar 2008[194]	
0-12 months	3.7		Log-Normal(1.303, 0.0998)
12-60 months	2.75		Log-Normal(1.007, 0.0998)
60+ months	1.8		Log-Normal(0.583, 0.0998)
SRL (with MMF; mg/day)		Lebranchu 2009[163]	
0-3 months	5.2		Log-Normal(1.644, 0.0998)
3-6 months	4.45		Log-Normal(1.488, 0.0998)
6-9 months	3.5		Log-Normal(1.248, 0.0998)
9-12 months	3.25		Log-Normal(1.174, 0.0998)
12-48 months	2.9		Log-Normal(1.06, 0.0998)
48+ months	2.6		Log-Normal(0.951, 0.0998)
EVL (with CSA; mg/day)		Tedesco Silva 2010[145] and Lorber 2005[139]	
0-3 months	2.937		Log-Normal(1.072, 0.0998)
3-6 months	2.75		Log-Normal(1.007, 0.0998)
6-9 months	2.533		Log-Normal(0.925, 0.0998)
9-12 months	2.6		Log-Normal(0.951, 0.0998)
12-24 months	2.6		Log-Normal(0.951, 0.0998)
24+ months	2		Log-Normal(0.688, 0.0998)
BEL (with MMF)		Dosing schedule	
Drug acquisition (250 mg vials per quarter year)			
0-3 months	16.53		Log-Normal(2.805, 0.02)
3-6 months	7.13		Log-Normal(1.964, 0.02)
6+ months	6.24		Log-Normal(1.83, 0.02)
Drug administration (per quarter year)			
0-3 months	5		Log-Normal(1.609, 0.02)
3-6 months	3		Log-Normal(1.098, 0.02)

Parameter	Value	Source	PSA distribution
6+ months	3.26		Log-Normal(1.182, 0.02)
Prednisolone (mg/day)		SYMPHONY[238]	
Throughout	16.3		Log-Normal(2.786, 0.0998)
Proportion of failed grafts explanted (time since transplantation)		Bond et al. 2009[373]	
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(3.8, 91.2)
Subsequent graft	0.059		
Subsequent retransplantation			
Workup for retransplantation	1.444	NHS Reference Costs 2013-14[406]	Normal(1.444, 0.025)
Living donor costs	0.349	NHS Reference Costs 2013-14[406]	Normal(0.349, 0.012)
Deceased donor costs	0.651	NHS Reference Costs 2013-14[406]	1 - Living donor costs
Maintenance immunosuppression			
Tacrolimus (mg/kg/day)	0.1	Assume somewhat higher than for original graft due to increased risk of rejection	Log-Normal(-2.308, 0.0998)
MMF (g/day)	2	Recommended daily dose	Log-Normal(0.688, 0.0998)
Prednisolone (mg/day)	16.3	SYMPHONY[238]	Log-Normal(2.786, 0.0998)
Infection prophylaxis			
Co-trimoxazole (PCP and UTI prophylaxis)			
Septrin (480 mg tablets in first three months)	90		Log-Normal(4.495, 0.0998)
Valganciclovir (CMV prophylaxis): Valcyte 450 mg tablets			
Full dose 0-3 months (D+/R- or D[+/-]/R+ with rATG)	182.6		N/A
Full dose 3-6 months (D+/R-)	182.6		N/A
Full dose 3-6 months (D[+/-	91.3		Uniform(0, 182.6)

Parameter	Value	Source	PSA distribution
]/R+ with rATG)			
Full dose 6-9 months (D+/R-)	34.8		N/A
Dose adjustment for renal function	0.473		Log-Normal(-0.779, 0.246)
Expected number of acute rejection events per patient experiencing 1+ acute rejection event	1.193	Charpentier et al. 2003[88]	Normal(1.193, 0.102)
Antidiabetic medication: metformin 500 mg tablets per 3 months	273.9		Log-Normal(5.608, 0.0998)
Dyslipidaemia			
Statins		Riella et al. 2012[402]	
Fluvastatin (mg per cycle for affected patient)	2191		Log-Normal(7.662, 0.246)
Pravastatin (mg per cycle for affected patient)	548		Log-Normal(6.276, 0.246)
Simvastatin (mg per cycle for affected patient)	91.3		Log-Normal(4.484, 0.246)
Medical management			
Dietetics outpatient attendance (# per cycle)	0.25		Log-Normal(-1.417, 0.246)
GP appointment (# per cycle)	0.25		Log-Normal(-1.417, 0.246)
Anaemia requiring ESA therapy			
Mean weekly dose (x 1000 IU)	5.832	Vanrenterghem et al. 2003[386]	Normal(5.832, 0.067)
Monitoring			
Clinic (per cycle)			
0-3 months	13.0		Log-Normal(2.567, 0.05)
Thereafter as for blood tests (below)			
Subsequent grafts	3		Log-Normal(1.068, 0.246)
Blood tests		Ling and Chamberlain 2011[400]	

Parameter	Value	Source	PSA distribution
0-1 months	13.07		Normal(13.07, 0.259)
1-2 months	6.75		Normal(6.75, 0.186)
2-3 months	4.95		Normal(4.95, 0.159)
3-6 months	8.99		Normal(8.99, 0.215)
6-12 months	3.97		Normal(7.93, 0.202)
12-24 months	2.69		Normal(10.77, 0.235)
24-36 months	3.5		Normal(14, 0.268)
36+ months	1		Log-Normal(-0.03, 0.246)
Subsequent grafts	3		Log-Normal(1.068, 0.246)
Viral PCR (per cycle)			
0-3 months (CMV)	5.42		Log-Normal(2.538, 0.246)
0-6 months (BKV)	1		Log-Normal(-0.03, 0.246)
6-12 months (BKV)	0.5		Log-Normal(-0.723, 0.246)
0-6 months (EBV)	0.0096		Log-Normal(1.068, 0.246)
6-12 months (EBV)	0.0032		Log-Normal(-0.03, 0.246)
Dialysis			
Proportion receiving haemodialysis by age		UK Renal Registry 16th Annual Report (Figure 2.7)[3]	
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)
Unit costs			
Dialysis		NHS Reference Costs 2013-14[406]	
Haemodialysis			

Parameter	Value	Source	PSA distribution
Access surgery	£1,946.32		Normal(1946.32, 97.81)
Temporary access	£823.25		Normal(823.25, 40.43)
Per quarter	£6,093.11		Normal(6093.11, 163.99)
Peritoneal dialysis			
Access surgery	£1,100.71		Normal(1100.71, 119.76)
Per quarter	£6,000.00		Normal(6000, 183.24)
Induction agents			
Basiliximab			
Simulect (per 20 mg)	£842.38	BNF 68[405]	N/A
Rabbit ATG			
Thymoglobuline (per mg)	£6.35	BNF 68[405]	N/A
Maintenance agents			
Tacrolimus (immediate-release capsules)			
NHS acquisition cost (per mg)	£0.5201	eMit[404]	Mixture model
Ciclosporin (immediate release capsules)			
NHS acquisition cost (per mg)	£0.0165	eMit[404]	Mixture model
Mycophenolate mofetil			
NHS acquisition cost (per g)	£0.3774	eMit[404]	Mixture model
Mycophenolate sodium			
Myfortic (per mg)	£0.0045	BNF 68[405]	N/A
Azathioprine			
NHS acquisition cost (per mg)	£0.0011	eMit[404]	Mixture model
Sirolimus			
Rapamune (per mg)	£2.883	BNF 68[405]	N/A
Everolimus			
Certican (per mg)	£9.90	Novartis submission	N/A
Belatacept			

Parameter	Value	Source	PSA distribution
Nulojix (per 250 mg vial)	£354.52	BNF 68[405]	N/A
Prednisolone			
NHS acquisition cost (per mg)	£0.0033	eMit[404]	Mixture model
Acute rejection (per episode)	£3,557.39	Ling et al. 2011[409]	Log-Normal(8.146, 0.246)
Infection prophylaxis			
Co-trimoxazole (PCP and UTI prophylaxis)			
Septrin (per 480 mg tablet)	£0.155	BNF 68[405]	N/A
Valganciclovir (CMV prophylaxis)			
Valcyte (per 450 mg tablet)	£18.02	BNF 68[405]	N/A
Cytomegalovirus infection	£3,008.91	Ling et al. 2011[409]	Log-Normal(7.979, 0.246)
Anaemia requiring ESA therapy			
Erythropoietin			
Binocrit (per 1000 IU)	£4.33	BNF 68[405]	N/A
NODAT			
Anti-diabetic treatment			
Metformin (per 500 mg tablet)	£0.0054	eMit[404]	Normal(0.0054, 0.00001)
Annual cost of complications		Alva et al. 2014[414]	
Inpatient	£1,388.92		Normal(1388.92, 99.42)
Non-inpatient	£694.92		Normal(694.92, 18.54)
Dyslipidaemia			
Statins			
Fluvastatin (per mg)	£0.0022	eMit[404]	Mixture model
Pravastatin (per mg)	£0.0026	eMit[404]	Mixture model
Simvastatin (per mg)	£0.0003	eMit[404]	Mixture model
Medical management			
Dietetics outpatient attendance	£62.70	NHS Reference Costs 2013-14[406]	Normal(62.7, 2.66)
GP appointment	£50.82	PSSRU Unit Costs 2014[397]	Normal(50.82, 5.08)
Drug administration			

Parameter	Value	Source	PSA distribution
Intravenous infusion			
First infusion	£228.95	NHS Reference Costs 2013-14[406]	Normal(228.95, 15.83)
Subsequent infusions	£325.59	NHS Reference Costs 2013-14[406]	Normal(325.59, 45.79)
Monitoring			
Clinic	£145.27	NHS Reference Costs 2013-14[406]	
Viral PCR		University College London Hospitals NHS Foundation Trust. Provider to provider services: 2013-14 tariff. 2013	
EBV	£46.75		Equal to CMV PCR
CMV	£46.75		Log-Normal(3.815, 0.246)
BKV	£46.75		Equal to CMV PCR
Therapeutic drug monitoring (TDM)		Dept of Medical Biochemistry and Immunology, University Hospital of Wales. Therapeutic drug monitoring test repertoire 2013/2014. 2013	
Ciclosporin TDM	£26.71		Log-Normal(3.255, 0.246)
Tacrolimus TDM	£26.71		Equal
Sirolimus TDM	£26.71		Equal
Everolimus TDM	£26.71		Equal
General tests		NHS Kidney Care 2011[415]	
Full blood count	£5.05		Log-Normal(1.615, 0.0998)
Renal profile	£4.54		Log-Normal(1.509, 0.0998)
Liver profile	£4.64		Log-Normal(1.531, 0.0998)
Explant surgery	£4,965.59	NHS Reference Costs 2013-14[406]	Normal(4965.59, 496.56)
Subsequent retransplantation			
Recipient work-up	£848.72	NHS Reference Costs 2013-14[406]	Normal(848.72, 84.87)
Living donor costs	£8,914.05	NHS Reference Costs 2013-14[406]	Normal(8914.05, 891.41)
Deceased donor costs	£10,142.05	NHS Blood and Transplant 2013[353]	Normal(10142.05, 1014.21)
Transplant surgery	£16,030.35	NHS Reference Costs 2013-14[406]	Normal(16030.35, 1603.04)