HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 61 AUGUST 2016
ISSN 1366-5278

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DOI 10.3310/hta20610

NHS
National Institute for Health Research

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Declared competing interests of authors: We would like to acknowledge that Stephen Marks received grants from Astellas and Novartis for immunosuppressive randomised controlled studies in paediatric renal transplant recipients during the conduct of the study. In addition, Jan Dudley was a member of an expert review panel in January 2008 and developed consensus recommendation on the optimal use of CellCept® (Roche Products) in paediatric renal transplantation and received an honorarium for Roche for this work.

Published August 2016
DOI: 10.3310/hta20610

This report should be referenced as follows:

Haasova M, Snowsill T, Jones-Hughes T, Crathorne L, Cooper C, Varley-Campbell J, *et al*. Immunosuppressive therapy for kidney transplantation in children and adolescents: systematic review and economic evaluation. *Health Technol Assess* 2016;**20**(61).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 09/119/01. The protocol was agreed in July 2014. The assessment report began editorial review in May 2015 and was accepted for publication in October 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

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Abstract

Immunosuppressive therapy for kidney transplantation in children and adolescents: systematic review and economic evaluation

Marcela Haasova,[1]* Tristan Snowsill,[1] Tracey Jones-Hughes,[1] Louise Crathorne,[1] Chris Cooper,[1] Jo Varley-Campbell,[1] Ruben Mujica-Mota,[1] Helen Coelho,[1] Nicola Huxley,[1] Jenny Lowe,[1] Jan Dudley,[2] Stephen Marks,[3] Chris Hyde,[1] Mary Bond[1] and Rob Anderson[1]

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Background: End-stage renal disease is a long-term irreversible decline in kidney function requiring kidney transplantation, haemodialysis or peritoneal dialysis. The preferred option is kidney transplantation followed by induction and maintenance immunosuppressive therapy to reduce the risk of kidney rejection and prolong graft survival.

Objectives: To systematically review and update the evidence for the clinical effectiveness and cost-effectiveness of basiliximab (BAS) (Simulect,® Novartis Pharmaceuticals) and rabbit antihuman thymocyte immunoglobulin (Thymoglobuline,® Sanofi) as induction therapy and immediate-release tacrolimus [Adoport® (Sandoz); Capexion® (Mylan); Modigraf® (Astellas Pharma); Perixis® (Accord Healthcare); Prograf® (Astellas Pharma); Tacni® (Teva); Vivadex® (Dexcel Pharma)], prolonged-release tacrolimus (Advagraf,® Astellas Pharma); belatacept (BEL) (Nulojix,® Bristol-Myers Squibb), mycophenolate mofetil (MMF) [Arzip® (Zentiva), CellCept® (Roche Products), Myfenax® (Teva), generic MMF is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt], mycophenolate sodium, sirolimus (Rapamune,® Pfizer) and everolimus (Certican,® Novartis Pharmaceuticals) as maintenance therapy in children and adolescents undergoing renal transplantation.

Data sources: Clinical effectiveness searches were conducted to 7 January 2015 in MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley Online Library) and Web of Science [via Institute for Scientific Information (ISI)], Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment (HTA) (The Cochrane Library via Wiley Online Library) and Health Management Information Consortium (via Ovid). Cost-effectiveness searches were conducted to 15 January 2015 using a costs or economic literature search filter in MEDLINE (via Ovid), EMBASE (via Ovid), NHS Economic Evaluation Databases (via Wiley Online Library), Web of Science (via ISI), Health Economic Evaluations Database (via Wiley Online Library) and EconLit (via EBSCO*host*).

Review methods: Titles and abstracts were screened according to predefined inclusion criteria, as were full texts of identified studies. Included studies were extracted and quality appraised. Data were meta-analysed when appropriate. A new discrete time state transition economic model (semi-Markov) was developed; graft function, and incidences of acute rejection and new-onset diabetes mellitus were used to extrapolate graft survival. Recipients were assumed to be in one of three health states: functioning graft, graft loss or death.

Results: Three randomised controlled trials (RCTs) and four non-RCTs were included. The RCTs only evaluated BAS and tacrolimus (TAC). No statistically significant differences in key outcomes were found between BAS and placebo/no induction. Statistically significantly higher graft function ($p < 0.01$) and less biopsy-proven acute rejection (odds ratio 0.29, 95% confidence interval 0.15 to 0.57) was found between TAC and ciclosporin (CSA). Only one cost-effectiveness study was identified, which informed NICE guidance TA99. BAS [with TAC and azathioprine (AZA)] was predicted to be cost-effective at £20,000–30,000 per quality-adjusted life year (QALY) versus no induction (BAS was dominant). BAS (with CSA and MMF) was not predicted to be cost-effective at £20,000–30,000 per QALY versus no induction (BAS was dominated). TAC (with AZA) was predicted to be cost-effective at £20,000–30,000 per QALY versus CSA (TAC was dominant). A model based on adult evidence suggests that at a cost-effectiveness threshold of £20,000–30,000 per QALY, BAS and TAC are cost-effective in all considered combinations; MMF was also cost-effective with CSA but not TAC.

Limitations: The RCT evidence is very limited; analyses comparing all interventions need to rely on adult evidence.

Conclusions: TAC is likely to be cost-effective (vs. CSA, in combination with AZA) at £20,000–30,000 per QALY. Analysis based on one RCT found BAS to be dominant, but analysis based on another RCT found BAS to be dominated. BAS plus TAC and AZA was predicted to be cost-effective at £20,000–30,000 per QALY when all regimens were compared using extrapolated adult evidence. High-quality primary effectiveness research is needed. The UK Renal Registry could form the basis for a prospective primary study.

Study registration: This study is registered as PROSPERO CRD42014013544.

Funding: The National Institute for Health Research HTA programme.

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Glossary

Acute rejection Process by which the graft recipient's immune system attempts to destroy the graft, usually within the first 3 months of transplantation.

Cadaveric transplant A transplant kidney removed from someone who has died.

Calcineurin inhibitor Ciclosporin or tacrolimus.

Cytomegalovirus A virus that normally causes only a mild 'flu-like' illness. In people with a kidney transplant, cytomegalovirus can cause a more serious illness, affecting the lungs, liver and blood.

Donation after brain death A donation from people in whom the heart is still beating after brain death has occurred (heart-beating donors). Most, but not all, cadaveric transplants. The extended criteria donor kidneys include donations from heart-beating donors who would not normally meet the criteria for transplantation and are likely to have a lower chance of long-term success.

Donation after circulatory death A donation from people who cannot be diagnosed as brainstem dead but whose death is verified by the absence of a heart beat (non-heart-beating donors).

Donor A person who donates an organ to another person (the recipient).

Glomerular filtration rate Flow rate of filtered fluid through the kidney, measured directly by injecting a harmless chemical (e.g. inulin) into the blood and then measuring how much of the chemical is filtered in a given unit of time.

Graft function A measure of the efficiency of the graft by various markers, for example glomerular filtration rate and serum creatinine levels.

Graft loss Absence of kidney function occurring any time after transplantation requiring chronic dialysis and/or retransplantation (excluding loss caused by death).

Haemodialysis Removal of waste products by passing blood out of the body, through a filtering system (dialyser) and then back to the body.

1-Haplotype identical Human leucocyte antigens are inherited as a set called a 'haplotype' from one or both parents. 1-Haplotype identical is not a 'perfect' human leucocyte antigen match; a 2-haplotype identical is a perfect human leucocyte antigen match.

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. This is also used as an abbreviation for glomerulonephritis.

OKT3 A murine monoclonal antibody muromonab-CD3.

Peritoneal dialysis Removal of waste products using the peritoneum as a filter. Dialysis fluid is pumped into the peritoneal cavity and waste products and excess fluid are moved from the blood into the dialysis fluid, which is then drained from the cavity.

Recipient In the context of transplantation, a person who receives an organ from another person (the donor).

Rejection The process whereby a patient's immune system recognises a transplant kidney as foreign and tries to destroy it. Rejection can be acute or chronic.

Renal replacement therapy Dialysis or kidney transplantation.

List of abbreviations

AE	adverse event
AR	acute rejection
AZA	azathioprine
BAS	basiliximab
BEL	belatacept
BKV	BK virus
BNF	*British National Formulary*
BPAR	biopsy-proven acute rejection
CCS	corticosteroid
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHU9D	Child Health Utility 9 dimensions
CI	confidence interval
CKD	chronic kidney disease
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRD	Centre for Reviews and Dissemination
CSA	ciclosporin
CVD	cardiovascular disease
DAC	daclizumab
DARE	Database of Abstracts of Reviews of Effect
DBD	donation after brain death
DCD	donation after circulatory death
DGF	delayed graft function
DIC	deviance information criterion
DWFG	death with functioning graft
EBV	Epstein–Barr virus
eGFR	estimated glomerular filtration rate
eMIT	electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-Y	European Quality of Life-5 Dimensions Youth version
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EVL	everolimus
GFR	glomerular filtration rate
GP	general practitioner
HEED	Health Economic Evaluations Database
HLA	human leucocyte antigen
HMIC	Health Management Information Consortium
HR	hazard ratio
HRG	Healthcare Resource Group
HRG4	Healthcare Resource Group version 4
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ISI	Institute for Scientific Information
ITT	intention to treat
i.v.	intravenous
KTR	kidney transplant recipient
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPS	mycophenolate sodium
MTC	mixed-treatment comparison
MTOR-I	mammalian/mechanistic target of rapamycin inhibitor
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NHSBT	NHS Blood and Transplant
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence

NODAT	new onset diabetes mellitus after transplantation
OR	odds ratio
PBO	placebo
PCR	polymerase chain reaction
PenTAG	Peninsula Technology Assessment Group
PJP	*Pneumocystis jirovecii* pneumonia
PNF	primary non-function
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PTLD	post-transplant lymphoproliferative disease
QALY	quality-adjusted life-year
r-ATG	rabbit antihuman thymocyte immunoglobulin
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SD	standard deviation
SDS	standard deviation score
SE	standard error
SPC	summary of product characteristics
SRL	sirolimus
TAC	tacrolimus
TAC-IR	immediate-release tacrolimus
TAC-PR	prolonged-release tacrolimus
UTI	urinary tract infection
WMD	weighted mean difference

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Kidney transplantation is the preferred treatment for people with end-stage kidney disease. Without immune-suppressing medications, the transplanted kidney would be rejected or lost. To prevent rejection and loss, a combination of medications to dampen the immune system are used. The aim of this assessment was to evaluate the clinical benefits and cost-effectiveness of nine immune-suppressing drugs in children and adolescents. We searched for relevant studies in major databases, trial registries, systematic reviews and references of included studies. All included studies were assessed for their quality.

The review included three randomised trials and four non-randomised studies. The randomised trials evaluated two drugs [basiliximab (BAS) (Simulect,® Novartis Pharmaceuticals) and tacrolimus (TAC)] and their results were used in cost-effectiveness analyses. No child/adolescent randomised trials were found for the other immune-suppressing drugs. We found statistically significant improvements in transplanted kidney function and proven acute rejection for TAC compared with ciclosporin (CSA) in one trial. The cost-effectiveness analyses suggested that TAC is cost-effective when compared with CSA. BAS was found to be cost-effective in one trial-based analysis but not to be cost-effective in another. An economic model, based on evidence from adults, indicated that only one drug combination (BAS followed by immediate-release TAC and azathioprine) would be cost-effective.

In summary, there is very limited evidence for how effective immune-suppressing drugs are in children and adolescents, and cost-effective analyses comparing all immune-suppressing medications may need to rely on results from studies in adults.

Scientific summary

Background

Chronic kidney disease in childhood leads to lifelong health complications. A long-term progression of irreversible decline in kidney function to end-stage renal disease will require renal replacement therapy (kidney transplant, haemodialysis or peritoneal dialysis) for a child or adolescent to survive. The preferred option is kidney transplantation (transfer of a healthy kidney from a donor to a recipient). Kidneys for transplantation may be obtained via living donation (related or unrelated), donation after brain death or donation after circulatory death. Between April 2013 and March 2014, 125 kidney transplant operations were performed on children and adolescents in the UK.

Following kidney transplantation in children and adolescents, major clinical concerns are acute kidney rejection, graft loss and growth. Acute kidney rejection occurs when the immune system attempts to destroy the graft. Immunosuppressive therapy is then implemented to reduce the risk of kidney rejection and prolong graft survival. Immunosuppression comprises induction and maintenance therapy; induction involves powerful antirejection drugs taken at the time of transplantation, when the risk of rejection is highest, and maintenance drugs are less powerful and are used as both initial and long-term therapy.

Objectives

To review and update the evidence for the clinical effectiveness and cost-effectiveness of basiliximab (BAS) (Simulect,® Novartis Pharmaceuticals) and rabbit antihuman thymocyte immunoglobulin (r-ATG) (Thymoglobuline,® Sanofi) as induction immunosuppressive therapy and immediate-release tacrolimus (TAC-IR) [Adoport® (Sandoz); Capexion® (Mylan); Modigraf® (Astellas Pharma); Perixis® (Accord Healthcare); Prograf® (Astellas Pharma); Tacni® (Teva); Vivadex® (Dexcel Pharma)]; prolonged-release tacrolimus (TAC-PR) (Advagraf,® Astellas Pharma); belatacept (BEL) (Nulojix,® Bristol-Myers Squibb); mycophenolate mofetil (MMF) [Arzip® (Zentiva), CellCept® (Roche Products), Myfenax® (Teva), generic MMF is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt], mycophenolate sodium (MPS) (Myfortic,® Novartis Pharmaceuticals), sirolimus (SRL) (Rapamune,® Pfizer), everolimus (EVL) Certican,® Novartis Pharmaceuticals) as maintenance immunosuppressive therapy in children and adolescents undergoing renal transplantation.

Methods

Clinical effectiveness systematic review

Bibliographic literature searching was conducted on 14 April 2014 (updated 7 January 2015). The searches for individual studies [randomised controlled trials (RCTs) and controlled clinical trials] took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a study design limited to RCTs or controlled trials). Literature searches were not restricted to child or young adult populations, primarily to preserve the sensitivity of the searches. In order to update the previous assessment by Yao *et al.* [Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.* A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. *Health Technol Assess* 2006;**10**(49)] the searches were date limited (2002–current). The following databases were searched: MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley Online Library) and Web of Science [via Institute for Scientific Information (ISI) – including conference proceedings]. In addition, the following trials registries were hand-searched in January 2015:

Current Controlled Trials, ClinicalTrials.gov, Food and Drug Administration website, European Medicines Agency website (European Public Assessment Reports).

Separate searches were undertaken to identify systematic reviews of RCTs and non-randomised controlled studies, run from database inception in MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) (The Cochrane Library via Wiley Online Library) and Health Management Information Consortium (via Ovid). 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).

Records and subsequent full papers were dual screened for inclusion independently by two researchers. Disagreements were resolved by discussion, with involvement of a third reviewer. Data were extracted if appropriate and quality appraisal conducted based on Centre for Reviews and Dissemination (CRD) guidance.

Data were tabulated and discussed in a narrative review and, when data permitted, meta-analysis was conducted. Estimates of overall treatment effect and assessment of heterogeneity were performed using a random-effects model. Odds ratios (ORs) and mean differences were calculated (for binary and continuous data, respectively).

Cost-effectiveness systematic review

Bibliographic literature searching was conducted on 8 April 2014 (updated 15 January 2015) in MEDLINE (via Ovid), EMBASE (via Ovid), NHS Economic Evaluation Database (via Wiley Online Library), Web of Science (via ISI – including conference proceedings), Health Economic Evaluations Database (HEED) (via Wiley Online Library) and EconLit (EBSCO*host*). 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, but was not limited by language or to human-only studies.

Records were dual screened by two reviewers (disagreements resolved by discussion). Studies meeting the criteria for inclusion were assessed by one reviewer using the Evers checklist. Studies were based on decision models were quality assessed using the Philips checklist.

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

Appraisal of company submissions

The appraisal of company submissions focused on their model-based economic analyses. Their systematic reviews were primarily assessed to establish whether or not any includable RCTs were missed by our searches. None were found.

Assessment group 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 one-quarter year was used and transitions were assumed to occur mid-cycle. A time horizon of 50 years was adopted. Costs were included from a NHS and Personal Social Services perspective. Health effects were measured in quality-adjusted life-years (QALYs) and calculated by assuming health state-specific utility decrements from a baseline utility, which was age-dependent and derived from the Health Survey for England (Health and Social Care Information Centre. *Health Survey for England – 2012*. London: Health and Social Care Information Centre; 2013). Costs and QALYs were discounted at 3.5% per annum and costs were inflated as necessary to 2014/15 prices.

Model structure

Kidney transplant recipients were assumed to be in one of three health states at any time: *functioning graft* (not dependent on dialysis), *graft loss* (dialysis dependent) or *death*. In addition to these health states, for each regimen the incidence of acute rejection (AR), cytomegalovirus (CMV) infection, dyslipidaemia and new-onset diabetes mellitus after transplantation (NODAT) were estimated, with corresponding costs (one-off for AR and CMV infection; ongoing for dyslipidaemia and NODAT). NODAT was also associated with a utility decrement. The incidences of AR and NODAT (and graft function after 12 months) were used as surrogate determinants of graft survival and the rate of death with functioning graft (DWFG) (NODAT only).

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

Results

Clinical effectiveness systematic review

Three RCTs are included in the clinical effectiveness systematic review: one new RCT and two RCTs from the previous assessment.

Four non-RCTs are included in our review, all of which were also included in the previous assessment by Yao *et al.* (2006).

Induction therapy

Two RCTs of induction therapy evaluating BAS in children and adolescents were identified in the review. No RCTs were identified that evaluated r-ATG in children and adolescents. No non-RCTs in the child and adolescent population evaluated induction therapies.

We found no significant difference in survival, graft loss, graft function and incidences of biopsy-proven acute rejection (BPAR) and time to BPAR between BAS and placebo (PBO)/no induction.

The results of the current review are similar to the previous HTA (Yao *et al.* 2006).

Maintenance therapy

One RCT of maintenance therapy in children and adolescents was identified, evaluating tacrolimus (TAC) compared with ciclosporin (CSA). No RCTs were identified for the other maintenance treatments.

Three non-RCTs evaluating MMF [compared with azathioprine (AZA)] in children and adolescents were identified. One non-RCT compared TAC + AZA with CSA + MMF. No non-RCTs were identified for the other maintenance treatments.

From the RCTs, we found no significant difference in survival or graft loss between TAC and CSA. However, a significantly higher graft function [mean estimated glomerular filtration rate (eGFR) of 71.5 (standard deviation 22.9) ml/minute/1.73 m^2 in TAC vs. mean eGFR of 53.0 (21.6) ml/minute/1.73 m^2 in CSA, t-test = 4.03; $p < 0.01$ at 4-year follow-up] and less BPAR [OR 0.29, favours TAC, 95% confidence interval (CI) 0.15 to 0.57 at 6-month follow-up] was found in TAC compared with CSA.

The results of the current review for survival, graft function and BPAR are similar to the previous HTA. However, the child and adolescent RCT evidence identified in the previous HTA review concluded that TAC lowered graft loss at 2- and 4-year follow-up. The difference in these results is because we excluded graft loss due to death from all analyses to avoid double counting with another key outcome (mortality) and because death-censored graft survival is a well-established clinical outcome (to which DWFG is intrinsically related). After the removal of graft loss due to death from the analyses, the evidence from the RCT suggested statistically non-significant lower graft loss with TAC compared with CSA (OR 0.41, 95% CI 0.16 to 1.00, and OR 0.43, 95% CI 0.18 to 1.01 at 2 and 4 years' follow-up, respectively).

Adverse events

More infections were found in children treated with BAS than those treated with PBO (OR 2.23, favours PBO; 95% CI 1.03 to 4.68) and Grenda *et al.* (Grenda R, Watson A, Vondrak K, Webb NJ, Beattie J, Fitzpatrick M, *et al.* A prospective, randomized, multicenter trial of TAC-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006;**6**:1666–72) found that toxic nephropathy and abdominal pain was higher with BAS compared with no induction ($p = 0.03$ and $p = 0.02$, respectively). In one RCT, no statistically significant differences were found between TAC and CSA for a range of adverse events. In addition, there were no statistically significant differences identified between MMF and AZA, or between TAC + AZA and CSA + MMF, in the non-randomised evidence.

Cost-effectiveness systematic review

Only one previous cost-effectiveness study of immunosuppressive regimens in children and adolescents was identified. The study evaluated the cost-effectiveness of adding BAS induction to maintenance therapy with TAC or CSA combined with AZA and corticosteroids (CCSs). The study also compared CSA with TAC when given in combination with AZA and CCSs, and, separately, MMF versus AZA as part of the triple therapy containing CSA and CCSs.

The analysis was conducted using a Markov model of a cohort with starting age ranging between 3 and 13 years and a 10-year horizon, and found that BAS induction resulted in higher costs and more QALYs than no induction in both the TAC and CSA containing regimens. TAC was found to have a base-case incremental cost-effectiveness ratio (ICER) (incremental cost per QALY) of £145,000/QALY relative to CSA, while MMF had an ICER of £195,000/QALY relative to AZA when given as part of a CSA-containing triple therapy. The sensitivity analysis showed that these results were subject to a high degree of uncertainty.

Analyses based on randomised controlled trial evidence in children and adolescents

Base-case analysis

Compared with no induction, BAS was predicted to be cost-effective at £20,000–30,000 per QALY when used with TAC and AZA [based on Grenda *et al.* (2006), BAS was dominant], but not when used with CSA and MMF [based on Offner *et al.* (2008), BAS was dominated].

Based on Trompeter *et al.* (Trompeter R, Filler G, Webb NJA, Watson AR, Milford DV, Tyden G, *et al.* Randomized trial of tracolimus versus cyclosporin microemulsion in renal transplantation. *Pediatric Nephrology* 2002;**17**:141–9), TAC (when used with AZA) was predicted to be cost-effective at £20,000–30,000 per QALY versus CSA (TAC was dominant).

Scenario analyses

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

Analyses based on randomised controlled trial evidence in adults

Base case

In the base-case deterministic and probabilistic analyses, BAS, TAC, MMF (only when used with CSA) and AZA (only when used with TAC) were predicted to be cost-effective at £20,000–30,000 per QALY. When all regimens were simultaneously compared, only BAS + TAC + AZA was cost-effective at £20,000–30,000 per QALY.

Scenario analyses

Results were robust to removal of the surrogate relationship between AR and graft survival. When it was assumed that weight would follow the ninth centile for age instead of the median, BAS and TAC were still predicted to be cost-effective at £20,000–30,000 per QALY. However, when used with BAS, MPS was predicted to be cost-effective at £30,000 per QALY (ICER £27,000 per QALY) and MMF was predicted to be cost-effective at £20,000 per QALY.

Limitations

The number of included randomised trials is low (also comparative non-RCTs may have been missed); only RCT evidence evaluating BAS and TAC and non-RCT evidence on the use of TAC and MMF was identified. In addition, no studies reporting on quality of life, adherence, growth or supporting the subgroup analyses specified in the review protocol were identified. Significantly, cost-effectiveness analyses comparing all interventions rely on effectiveness estimates from the adult RCTs (which may or may not generalise to children and adolescents). Finally, some of the newer immunosuppressive drugs, such as EVL and SRL, would normally be given to children and adolescents after an initial maintenance therapy that consists of more conventional drugs. This makes it challenging to compare the clinical effectiveness of such regimens because only children and adolescents who are well maintained on their initial maintenance therapy would be given such drugs.

Conclusions

There is limited high-quality evidence for the effectiveness of immunosuppressive agents in children and adolescents. A RCT comparing TAC with CSA demonstrated that TAC resulted in statistically significant improvements in graft function and AR. No other outcomes in that RCT or the other two included RCTs were statistically significant.

Based on effectiveness estimates from the adult population, BAS and TAC are cost-effective at a threshold of £20,000–30,000 per QALY in all considered combinations, while MMF is cost-effective only if used with CSA. Effectiveness estimates in children and adolescents are only available for BAS and TAC. Based on these, TAC (used with AZA and compared with CSA) is cost-effective at £20,000–30,000 per QALY, whereas cost-effectiveness results for BAS are mixed.

Implications for health care

BAS, TAC, MMF and AZA are all used regularly in the NHS. It is not clear whether or not changes to induction agents used in the NHS would significantly affect costs. However, replacing TAC with TAC-PR, SRL, BEL or CSA would likely result in increased costs.

It is possible that replacing MMF with AZA (when used with TAC) will result in reduced costs, while it is likely that replacing these with SRL, EVL or MPS would increase costs.

Recommendations for research

High-quality primary effectiveness research in children and adolescents is needed. Potentially, the UK Renal Registry could form the basis for a prospective study. This may require collection of some information not currently held, but could include health-related quality of life and growth measurements. In addition, given the perceived importance of adherence to immunosuppression in this population, an objective and practical measure of adherence is needed. Furthermore, a systematic review of non-RCTs is recommended.

Study registration

The protocol for the HTA is available on National Institute for Health and Care Excellence (NICE) website [NICE. PROTOCOL: Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance TA99). London: NICE, 2014]. This study is also registered as PROSPERO CRD42014013544.

Funding

Funding for this study was provided by the HTA programme of the National Institute for Health Research.

Chapter 1 Background

The aim of this assessment is to review and update the evidence of the clinical effectiveness and cost-effectiveness of immunosuppressive regimens for renal transplantation in children and adolescents [a review of National Institute for Health and Care Excellence (NICE) guidance TA99].[1] Two therapy stages are assessed: induction therapy [regimens including basiliximab (BAS) (Simulect,® Novartis Pharmaceuticals) or rabbit antihuman thymocyte immunoglobulin (r-ATG) (Thymoglobuline,® Sanofi)] and maintenance therapy [regimens including immediate-release tacrolimus (TAC-IR) [Adoport® (Sandoz); Capexion® (Mylan), Modigraf® (Astellas Pharma); Perixis® (Accord Healthcare); Prograf® (Astellas Pharma); Tacni® (Teva); Vivadex® (Dexcel Pharma)], prolonged-released tacrolimus (TAC-PR) (Advagraf,® Astellas Pharma), belatacept (BEL) (Nulojix,® Bristol-Myers Squibb), mycophenolate mofetil (MMF) [Arzip® (Zentiva), CellCept® (Roche Products), Myfenax® (Teva), generic MMF is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt], mycophenolate sodium (MPS) (Myfortic,® Novartis Pharmaceuticals), sirolimus (SRL) (Rapamune,® Pfizer) and everolimus (EVL) (Certican,® Novartis Pharmaceuticals), alone or in combination].

The systematic review and economic evaluation developed to support the current NICE guidance TA99 was published by Yao *et al.* in 2006.[2] This assessment incorporated relevant evidence presented in the previous report and report new evidence.

Description of health problem

End-stage renal disease

Chronic kidney disease (CKD) in childhood leads to lifelong health complications, often resulting in the need of a kidney transplant.[3] In 2013, 891 children and adolescents < 18 years of age were receiving treatment at paediatric nephrology centres for end-stage renal disease (ESRD).[4] 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 or primarily a progression from CKD, which describes abnormal kidney function and/or structure. Although 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, owing to improved duration and quality of life with transplantation compared with dialysis.[5]

Transplantation

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

Children and adolescents represent a distinct group of transplant recipients and can differ from adults in several important aspects, including the cause of established renal failure, the complexity of the surgical procedure, the metabolism and pharmacokinetic properties of immunosuppressants, the developing immune system and immune response following organ transplantation, the measures of success of the transplant procedure, the number and the degree of comorbid conditions, the susceptibility to post-transplant complications, and the degree of adherence to treatment.[6,7] The metabolism of many immunosuppressive medications substantially differs in young children compared with adults and drug metabolism changes as children grow and develop.

Following kidney transplantation, major clinical concerns for children and adolescents are acute kidney rejection, graft loss and diminished growth. Acute kidney rejection occurs when the immune response of the graft recipient attempts to destroy the graft as the graft is deemed foreign tissue.[5] Therefore, immunosuppressive therapy is implemented to reduce the risk of kidney rejection and prolong survival of the graft. Prior to renal transplantation, growth retardation in children and adolescents with CKD may already be an issue owing to a combination of inadequate nutritional intake, acidosis, renal osteodystrophy and alterations to the growth hormone insulin-like growth factor.[8] However, post transplant, the steroidal therapy often included in immunosuppression regimens can affect longitudinal growth and calcium/phosphorous metabolism.[9,10]

Aetiology, pathology and prognosis

Aetiology

In children, ESRD is usually due to innate structural abnormalities or genetic causes or is acquired in childhood through glomerulonephritis.[11] *Figure 1* displays the causative diagnoses for children and adolescents (< 16 years old) with primary renal disease in 2013.

Pathology

Table 1 displays the distribution of the UK primary renal diagnosis for end-stage renal failure over time, reported from 1999 to 2003, 2004 to 2008 and 2008 to 2013 in children and adolescents aged < 16 years. Renal dysplasia, which is abnormal tissue development in the kidney, is the primary renal disease diagnosis in approximately one-third of all children and adolescents with ESRD.

When chronic renal failure occurs, children and adolescents may experience malaise, nausea, loss of appetite, change in mental alertness, bone pain, headaches, stunted growth, change in urine outputs, urinary incontinence, pale skin, bad breath, poor muscle tone, tissue swelling and hearing deficit. Treatment of chronic renal failure depends on the degree of kidney function that remains and the age of the child/adolescent. Treatment may include dialysis, kidney transplantation, diet restrictions, diuretic therapy and medications (to help with growth and prevent bone density losses).[12]

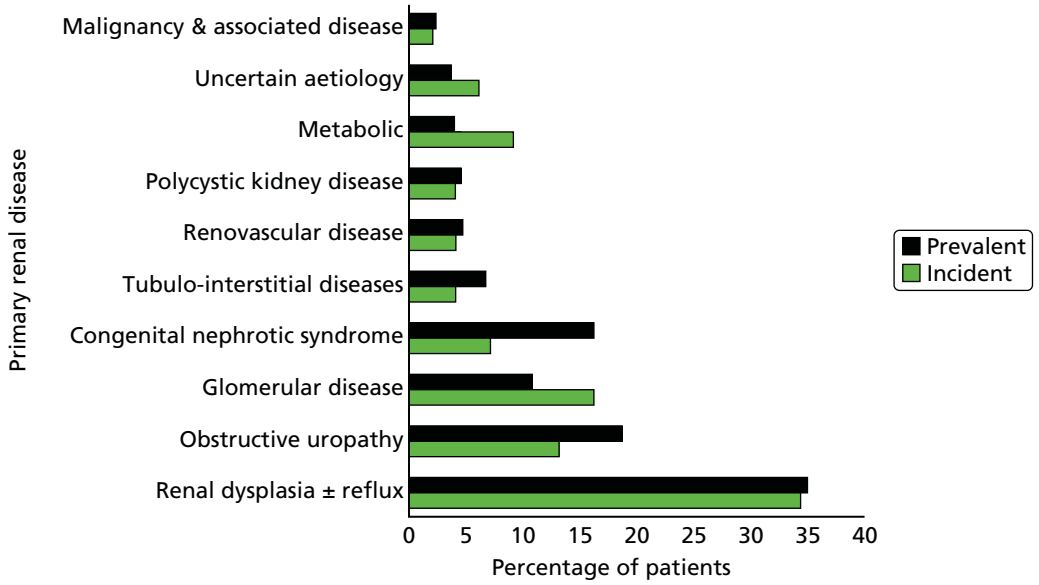

FIGURE 1 Causative diagnoses for children and adolescents; primary renal disease percentage in incident and prevalent children and adolescents with established renal failure patients < 16 years old in 2013. Reproduced with permission from UK Renal Registry 17th Annual Report (figure 4.3, p. 99).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

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

	1999–2003		2004–8		2009–13		1999–2013
Primary renal diagnosis	*n*	%	*n*	%	*n*	%	% change
Renal dysplasia + reflux	157	29.1	191	33.7	182	33.7	4.6
Obstructive uropathy	80	14.8	75	13.3	97	18	3.1
Glomerular disease	130	24.1	112	19.8	83	15.4	–8.7
Tubulointerstitial diseases	42	7.8	46	8.1	41	7.6	–0.2
Congenital nephrotic syndrome	27	5	33	5.8	35	6.5	1.5
Metabolic	29	5.4	25	4.4	31	5.7	0.4
Uncertain aetiology	12	2.2	32	5.7	29	5.4	3.1
Renovascular disease	23	4.3	19	3.4	19	3.5	–0.7
Polycystic kidney disease	16	3	19	3.4	19	3.5	0.6
Malignancy and associated disease	10	1.9	9	1.6	4	0.7	–1.1
Drug nephrotoxicity	14	2.6	5	0.9	0	0	–2.6

Note
Six children in 1999–2003, nine in 2004–8 and 20 in 2009–13 with no primary renal diagnosis recorded are excluded from this table.
Reproduced with permission from UK Renal Registry 17th Annual Report (table. 4.13. p. 102).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

Acute rejection

In patients who survive transplantation, acute rejection (AR) may occur when the immune response of the host attempts to destroy the graft as the graft is identified as foreign tissue.[5] AR is treated by modifying the immunosuppressive regimen (increasing doses or switching treatments). Untreated AR will ultimately result in destruction of the graft; however, high levels of immunosuppression may also increase the risk of other infections and malignancy.[5] AR is primarily measured following a biopsy and graded according to Banff criteria (grades I–III, for which grade III indicates the most severe). The Banff classification[13] is:

- Banff grade I: tubulointerstitial inflammation only.
- Banff grade IA: interstitial inflammation moderate–severe and/or tubulitis moderate.
- Banff grade IB: tubulitis severe.
- Banff grade II: intimal arteritis.
- Banff grade IIA: intimal arteritis mild–moderate.
- Banff grade IIB: intimal arteritis severe.
- Banff grade III: transmural arteritis and/or fibrinoid necrosis.

Although the incidence of AR following a transplant is included in this appraisal, its treatment is outside the scope. In addition to AR affecting the survival of the graft, other reasons which may instigate graft loss include blood clots, narrowing of an artery, fluid retention around the kidney, side effects of other medications and recurrent kidney disease.[14]

It is important to note that failing to stay on the immunosuppression regime prescribed following a kidney transplant will also significantly increase the risk of AR and/or graft loss.[15] If the kidney is lost, ultimately the patient will need to return/start on dialysis, for which the quality of life is reduced and overall costs are higher.[5]

Graft function

Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney. GFR is expressed in terms of volume filtered per unit time [sometimes this is also expressed per average surface area (1.73 m^2)]. There are various methods used to calculate GFR [estimated glomerular filtration rate (eGFR)] from serum creatinine levels, age, sex and ethnic group (e.g. Modification of Diet in Renal Disease, Cockcroft–Gault, and Nankivell). Different methods are used for children and adolescents (e.g. Schwartz and Counahan–Barratt equations). Levels of eGFR represent the level of kidney function and *Table 2* presents the NICE cut-off values for classification of CKD (NICE guidelines CG182).[16] These values apply to children aged > 2 years and up to (and including) adulthood.[17]

Some children and adolescents may experience delayed graft function (DGF) after transplantation and *Figure 2* shows a hypothetical graph to explain the relationship between normally functioning grafts, DGF and primary non-functioning (PNF) grafts. At 7 days post transplant, some of the children and adolescents who need dialysis and whose grafts are therefore classified as DGF will have grafts that never function. When this has been established, these grafts are classified as PNF.

Growth

Normal growth is often affected in children and adolescents with ESRD; short stature is diagnosed if the height standard deviation score (SDS) is < 2.5 of the target height.[19] There are three main factors that may impact post-transplant growth:

- Age at transplantation. Following a transplant, post-transplantation catch-up growth is not uncommon; however, it is unlikely to be sufficient to compensate for the pre-transplant accrued deficit.[20] Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) indicated that children < 6 years of age exhibit catch-up growth whereas children > 6 years at the time of transplantation exhibit limited to no catch-up growth.
- Allograft function. An increase of 1.0 mg/dl in serum creatinine level (indicating a decrease in kidney function) has been associated with a decrease of 0.17 in SDS.[21]
- Corticosteroid (CCS) dose. For example, reducing steroids to every other day[22] and withdrawing or avoiding steroids[23] have been associated with improved growth. Similarly, Grenda *et al.*[24] reported an increase of 0.13 in SDS in a group of primarily pre-pubertal children who withdrew from steroids on day 5 compared with those in whom the dose was tapered to 10 mg/m^2.

TABLE 2 Glomerular filtration rate categories

GFR category	GFR (ml/minute/1.73 m^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	15–29	Severely decreased
5	< 15	Kidney failure

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

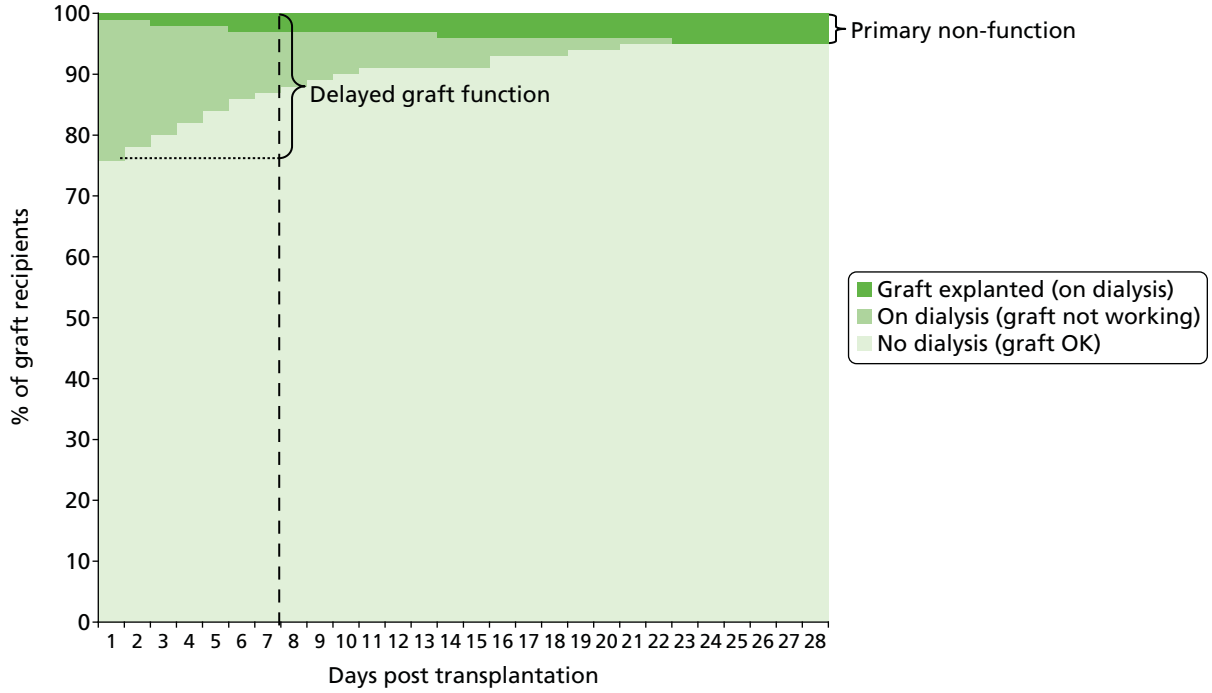

FIGURE 2 Hypothetical graph to explain graft function, DGF and primary non-functioning graft. Reproduced with permission from Bond *et al.*[18] Contains information licensed under the Non-Commercial Government Licence v1.0.

UK data are not available on growth changes following kidney transplant in children and adolescents; however, data from the NAPRTCS are available. The NAPRTCS 2010 annual report indicates that at transplantation, the mean height deficits for all children and adolescents is –1.75 SDS (–1.78 for boys and –1.70 for girls).[25] For children and adolescents who have reached their adult height following kidney transplant ($n = 2867$), the average SDS is –1.40, with 25% having a SDS of –2.2 or worse and 10% are > 3.24 SDS below the population average.[25] In addition, German data reported by Nissel *et al.*,[26] who followed 37 children for a mean duration of 8.5 years to monitor their growth, showed that those children who received their transplant before the start of puberty attained an adult height that was on average 5.2 cm (boys) and 13.0 cm (girls) lower than predicted while those who received their transplant after the onset of puberty had a final adult height that was on average 12.6 cm (both boys and girls) lower than the target.

Prognosis

Data collected for survival rates of children and adolescents < 16 years of age starting RRT between 1999 and 2012 were collected from UK paediatric centres.[4] The median follow-up time was 3.5 years (ranging from 1 day to 15 years). There were a total of 99 deaths reported. *Table 3* shows the survival hazard ratios (HRs) (following adjustment for age at start of RRT, sex and RRT modality) and highlights that children starting RRT at < 2 years of age, compared with 12- to 16-year-olds starting RRT, had a worse survival outcome with a HR of 5.0.

Various factors may influence survival following a kidney transplant. A study of 1189 child/adolescent kidney transplants in England between April 2001 and March 2012 found that 33 children and adolescents did not survive.[27] The most common causes of these 33 deaths were renal ($n = 8$; classified as ESRD, renal dysplasia and disorder of kidney/ureter), infections ($n = 6$) and malignancy ($n = 5$).[27] The age of the recipient was not found to significantly impact patient survival: age 0–1 years (100% survival), age 2–5 years (96% survival), age 6–12 years (97.5% survival) and age 13–18 years (97.4% survival).[27]

TABLE 3 Survival hazard ratio during childhood and adolescence for RRT patients

	Hazard ratio	Confidence interval	*p*-value
Age			
0–< 2 years	5.0	2.8–8.8	< 0.0001
2–< 4 years	2.9	1.4–5.7	0.003
4–< 8 years	2.2	1.3–4	0.006
8–< 12 years	1.4	0.7–2.9	0.400
12–< 16 years	1.0	–	–
Sex			
Female	1.2	0.7–1.9	0.5
Male	1.0	–	–
Modality			
Dialysis	7.1	4.7–10.7	< 0.0001
Transplant	1.0	–	–

Modality, RRT modality.

Note

Survival hazard ratios are adjusted for age at start of RRT, gender and RRT modality; results are presented for children under 16 years of age because data for the 16- to 18-year-old patients were incomplete.

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Important prognostic factors

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

- Age: both the age of the recipient and the age of the donor will influence the survival of the transplant. The number of kidney transplants performed is much lower in infants and small children than in older children. This has been attributed to some centres keeping a child on dialysis until they reach an arbitrary age when they are deemed suitable for a transplant.[28]
- Recipient ethnicity: black patients tend to have worse graft function, shorter graft survival and higher rates of chronic allograft nephropathy than white patients.[29] Racial differences have also been indicated in American children, with poorer outcomes in black children following a kidney transplant than in white or Hispanic children.[30]
- Waiting time to transplant: the longer a person is on dialysis waiting for a kidney transplant, the poorer their outcomes post transplantation.[31]
- Cold ischaemia time: the shorter this time (≤ 20 hours), the better the immediate and long-term outcomes.[32]
- Donor type: receiving a donated kidney from a live donor will probably result in better outcomes than receiving a kidney from a deceased donor.[29] Similarly, receiving a kidney from extended criteria donors (donors who may for example be older, have a history of diabetes mellitus or hypertension or have an increased risk of passing on an infection or malignancy) will have inferior graft survival rates and increased incidences of AR when compared with receiving a standard donated kidney.[33]
- Immunological risk, to include human leucocyte antigen (HLA) and blood group incompatibility: if the number of mismatches from the donor to the recipient are higher, there is an increased likelihood of AR and graft loss.[29]
- Comorbidities, for example diabetes mellitus, cancer and cardiovascular disease (CVD): the higher a patient score on the Charlson Comorbidity Index, the lower the patient and graft survival is likely to be. AR is not significantly correlated to the Charlson Comorbidity Index.[34]

Incidence and/or prevalence

In 2013, 891 children and young people < 18 years of age were receiving treatment for ESRD at UK paediatric nephrology centres, of whom 80.2% had a functioning kidney transplant, 11.7% were receiving haemodialysis and 8.1% were receiving peritoneal dialysis.[4] When comparing RRT data from the most recent 5-year period (2009–13) with the two previous periods (1999–2003 and 2004–8), a sustained increase in the number of younger children (aged 0 to < 8 years when starting RRT) can be seen, while the number of older children (8 to < 16 years when starting RRT) has decreased. Consequently, the total number of children starting RRT has remained relatively constant; 546 children between 1999 and 2003, 575 children between 2004 and 2008, and 560 children between 2008 and 2013.[4]

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

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

One hundred and twenty five kidney transplant operations were performed on children and adolescents in the UK between April 2013 and March 2014.[32] The total number of transplants in children and adolescents and the graft type (living, DBD and DCD) performed each year from 2004 to 2014 are displayed in *Figure 4*. In children and adolescents, most donated kidneys are from living and DBD donors, with very few kidneys being form DCD donors.

Overall survival reported in children and adolescents following kidney transplants from deceased and living donors is similar at both 1- and 5-year follow-up; however, graft survival at 5 years is improved if the donors are living (*Table 5*).[32]

Data on incidence and prevalence of AR in children and adolescents are not available for the UK. However, they are likely to be similar to those reported in the NAPRTCS, which indicates that for transplants occurring between 1987 and 2010, the prevalence in children and adolescents of at least one episode of AR following a kidney transplant is 46% (41% in live donors and 51% in deceased donors).[25]

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

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

F, female; M, male; pmarp, per million age-related population.

Note

Results are presented for children under 16 years old because data for the 16- to 18-year-old patients were incomplete. Reproduced with permission from UK Renal Registry 17th Annual Report (table 4.7, p. 100).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

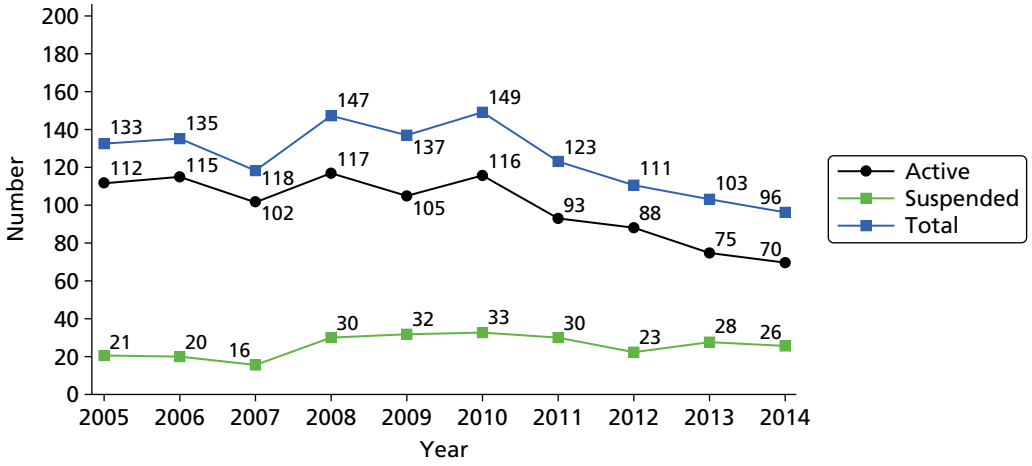

FIGURE 3 Children and adolescents on the kidney-only transplant waiting list at March 2013. Reproduced with permission from NHS Blood and Transplant.[32]

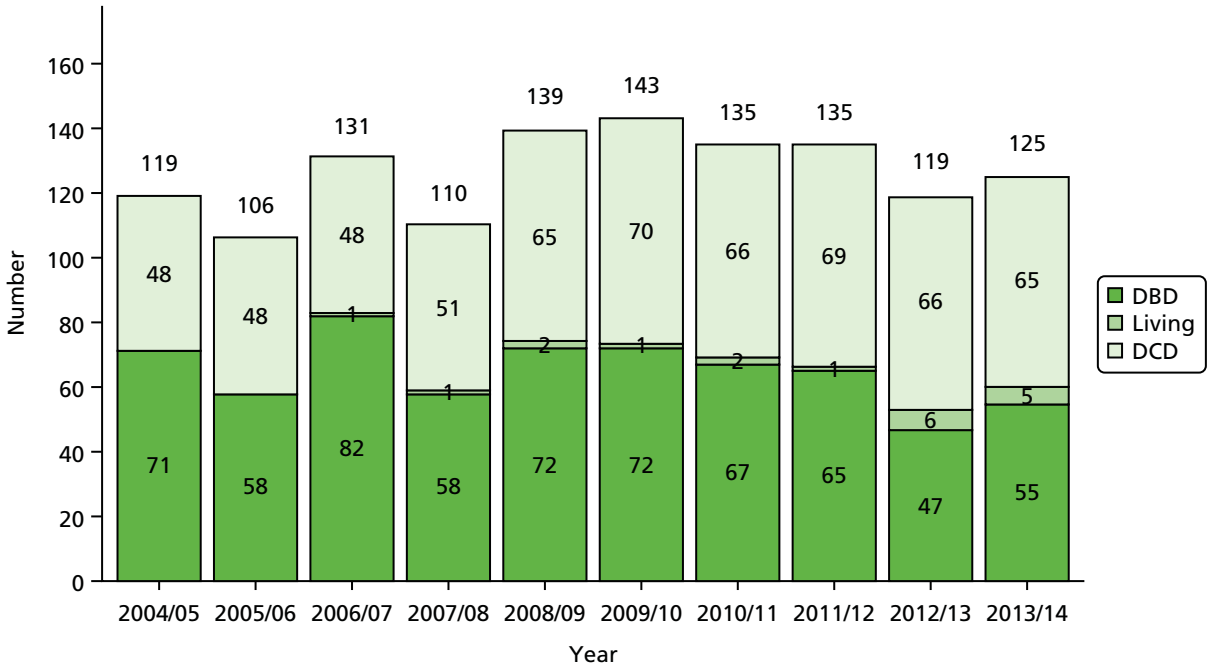

FIGURE 4 Kidney-only transplants in children and adolescents 2004–2014. Reproduced with permission from NHS Blood and Transplant.[32]

TABLE 5 Kidney graft and overall survival in children and adolescents in the UK

	Kidney graft survival		Patient survival	
	1 year,[a] % (95% CI)	5 years,[b] % (95% CI)	1 year,[a] % (95% CI)	5 years,[b] % (95% CI)
Deceased donors	96 (93 to 98)	84 (79 to 88)	99 (97 to 100)	99 (96 to 100)
Living donors	95 (92 to 97)	94 (89 to 96)	99 (97 to 100)	99 (96 to 100)

CI, confidence interval.
a Includes transplants performed between 1 April 2009 and 31 March 2013.
b Includes transplants performed between 1 April 2005 and 31 March 2009.
Data source: NHS Blood and Transplant.[32]

Impact of kidney transplantation

Significance for patients

Living with ESRD may substantially challenge the well-being of children and adolescents. Not only will the disease impact physical health, but mental and social health may also be affected owing to increased hospital visits and the child or adolescent's inability to take part in the same activities as their peers.[35] However, having a kidney transplant will improve the symptoms associated with ESRD and dialysis and reduce the time spent in hospital.[36] The median wait time for a child/adolescent requiring a kidney transplant in the UK is 342 days.[32]

Kidney transplantation requires a lifelong regimen of immunosuppressive medication. Immunosuppressants may produce unpleasant side effects (including possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain).[37] Nevertheless, favourable social and professional outcomes have been observed from a long-term follow-up (15.6 years $\pm$ 3 years) of people who had a kidney transplant as a child (aged 10 years $\pm$ 5 years).[38] Adherence to post-transplant immunosuppressive regimens is important for favourable clinical outcomes in children and adolescents[39] and has been suggested as a core strategy to improve clinical outcomes.[40] In addition, failing to follow treatment may result in an increase in medical costs.[41]

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

The impact on a child/adolescent returning to or starting dialysis (of the psychological burden of graft failure and going back to a previous treatment) is little researched, but necessarily includes the impact of being on dialysis per se: dialysis is time-consuming and may affect education and normal family life and require changes in diet and fluid intake. Common side effects of dialysis (either haemodialysis or peritoneal dialysis) include fatigue, low blood pressure, invasive staphylococcal infections, muscle cramps, itchy skin, peritonitis, hernia and weight gain.[42]

Finally, growth retardation in children and adolescents with ESRD is thought to be a combination of inadequate nutritional intake, acidosis, renal osteodystrophy and alterations to the growth hormone insulin-like growth factor.[8] Ensuring optimal growth or optimisation of final height is a major concern for children and adolescents with ESRD, as short stature may have an impact on social development, self-esteem and quality of life and is associated with an increase in the number of hospitalisations and behavioural and cognitive disorders, and a decrease in the level of education and employment in adulthood.[20,43–45]

Unfortunately, data relating specifically to quality of life are currently available only in the adult population, among whom there are clear quality-of-life improvements from having a functioning kidney transplant compared with being on dialysis.[46–52]

Significance for the NHS

Treatment for ESRD is considered resource-intensive for the NHS because current costs have been estimated to use 1–2% of the total NHS budget to treat 0.05% of the population (both adult and child/adolescent).[53] Based on data from the Department of Health, it is estimated that in 2008/9, the total expenditure on 'renal problems' in England was £1.3B, representing 1.4% of the NHS expenditure.[53] An economic evaluation of treatments for ESRD by de Wit *et al.*[54] showed that transplantation is the most cost-effective form of RRT with increased quality of life and independence for an individual.

There are no apparent reasons why RRT demand may dramatically increase in children and adolescents. However, it is projected that an increasingly overweight population will increase the demand for RRT, with a consequent increase in pressure on services from renal units and other health-care providers dealing with comorbidities. 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.[4]

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: 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 12 weeks in some cases.
- Primary non-function: the graft never works after transplantation.

Long term

- Rejection rates: the percentage of grafts that are rejected by the recipients' bodies; rejection can be acute or chronic.
- Graft survival: the length of time that a graft functions in the recipient.
- Graft function: a measure of the efficiency of the graft by various markers, for example GFR and serum creatinine levels.
- Patient survival: how long the recipient survives.
- Quality of life: how a person's well-being is affected by the transplant.

Current service provision

Management of end-stage kidney disease

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

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

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

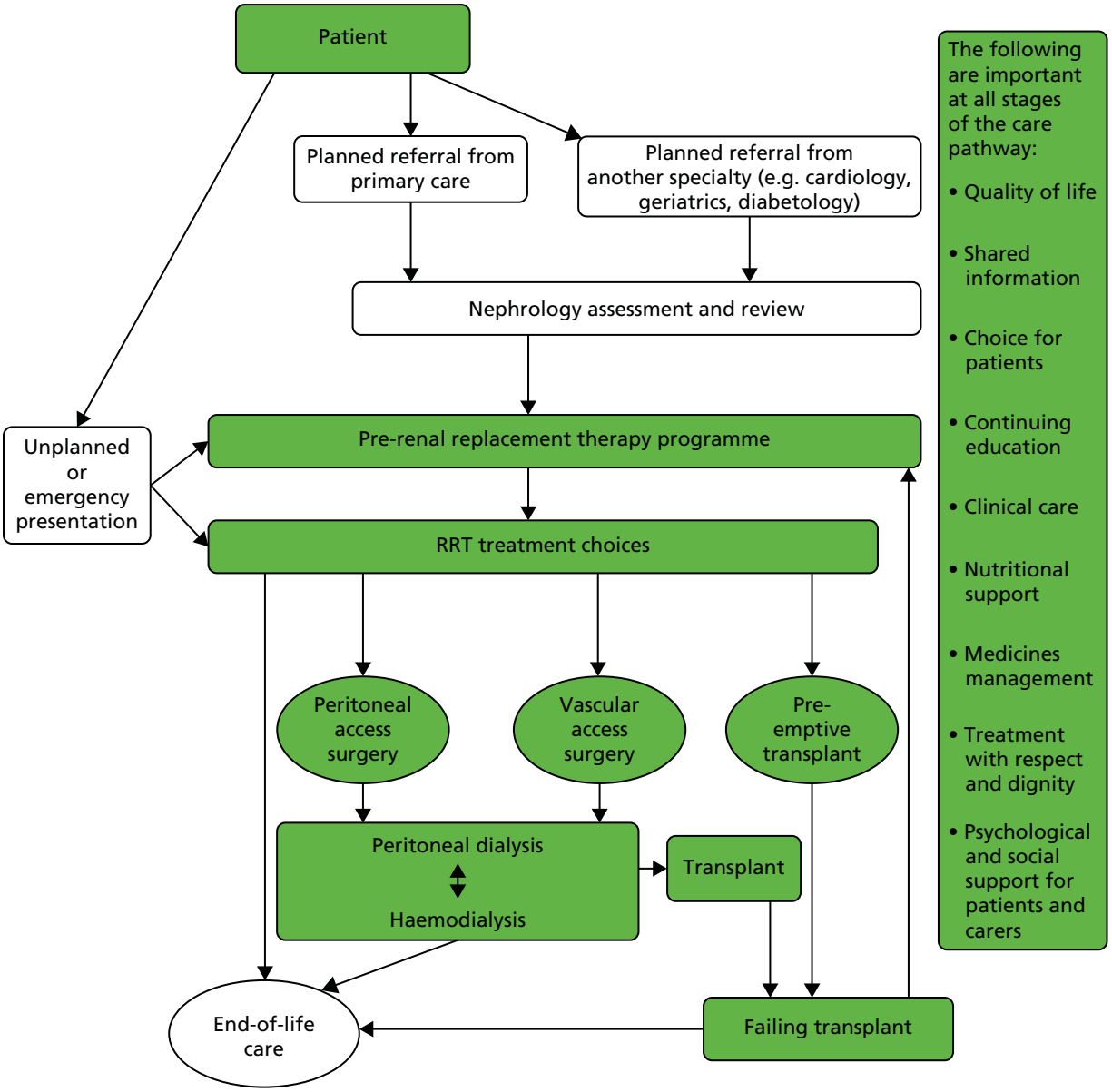

FIGURE 5 The care pathway for RRT. Reproduced with permission from *The National Service Framework for Renal Services. Part One: Dialysis and Transplantation*.[11] © Crown Copyright 2004. Contains public sector information licensed under the Open Government Licence v3.0.

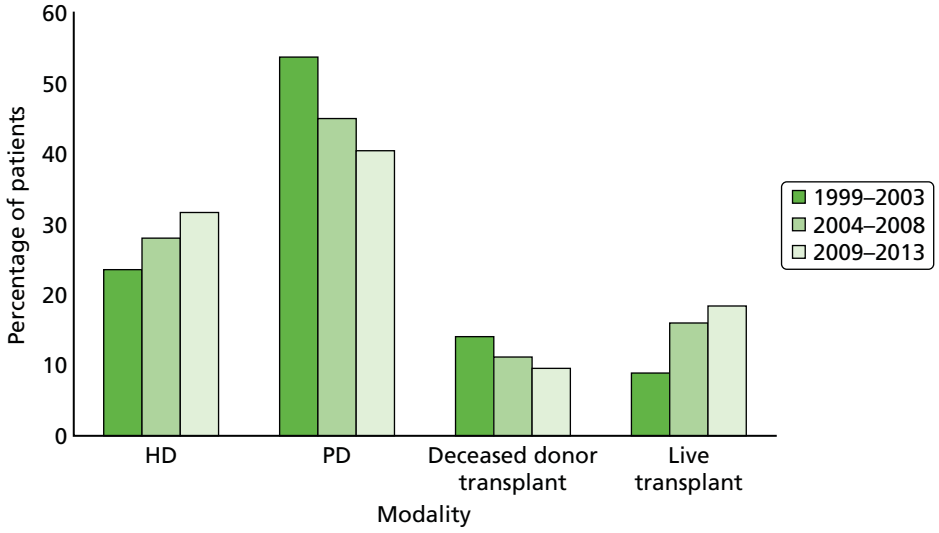

FIGURE 6 Type of treatment at start of RRT for incident children and adolescents < 16 years old by 5-year time period. HD, haemodialysis; PD, peritoneal dialysis. Reproduced with permission from UK Renal Registry 17th Annual Report (figure 4.4. p. 102).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

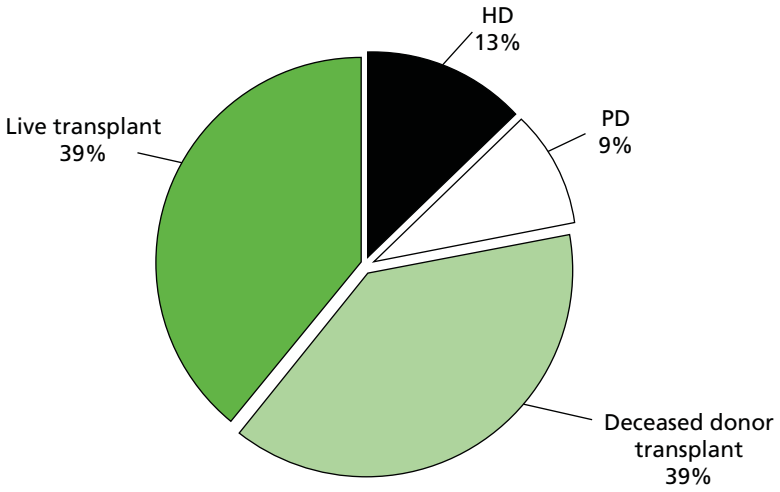

FIGURE 7 Renal replacement therapy treatment used by prevalent children and adolescents < 16 years old in 2013. HD, haemodialysis; PD, peritoneal dialysis. Reproduced with permission from UK Renal Registry 17th Annual Report (figure 4.1. p. 98).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

Management of kidney transplants

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

The first of these is organ procurement, which includes the identification and management of potential donors and assessment of donor suitability. HLAs are carried on cells within the body, enabling the body to distinguish between its 'self' or to recognise 'non-self' that should be attacked. The closer the HLA matching, the less vigorously the body will attack the foreign transplant and, consequently, the chances of graft survival are improved. HLA mismatch refers to the number of mismatches between the donor and the recipient at the A, B and DR loci, with a maximum of two mismatches at each locus.[32] Therefore, a match would have a score of zero and a complete mismatch would have a score of six. However, it should be noted that with the improvements in immunosuppressants, the significance of HLA matching has diminished.[55]

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

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

1. Medical follow-ups to include rejections, nephrotoxicity of calcineurin inhibitors (CNIs) 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 mellitus, liver disease, hypertension, CVD.
4. Ensuring growth is not impeded and maximal 'catch-up' growth is achieved. The 2010 NAPRTCS report suggests that the average final adult height of a renal transplant recipient has increased significantly from –1.93 SDS between 1987 and 1991 to –0.94 SDS between 2002 and 2010.[25]

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

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

Current service cost

The overall cost of CKD to the NHS in England was estimated as £1.45B in 2009–10, with more than half of total estimated expenditure for RRT.[57] The costs of RRT can be divided into costs associated with the transplantation and costs associated with dialysis. Transplantation costs can include the cost of workup for transplantation (assessing recipient suitability), maintaining and co-ordinating 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 AR, and treatment of associated AEs. Should the kidney be lost, the costs of restarting dialysis (dialysis costs, the cost of treatment for AEs attributable to dialysis and the cost of dialysis access surgery) would be incurred.

Data from the *NHS Reference Costs 2013 to 2014* indicated that the cost of kidney transplantation in those < 19 years of age is, on average, £20,576.[58] Paediatric nephrology outpatient clinics are, on average, £249 and the cost of haemodialysis and peritoneal dialysis is, on average, £79,807 and £41,382, respectively.[58]

Variation in services

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

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

- two to three times weekly for the first month after transplantation
- one to two times weekly for months 2 to 3 after transplantation
- every 1 to 2 weeks for months 4 to 6 after transplantation
- every 4 to 6 weeks for months 6 to 12 after transplantation
- once every 3–6 months 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 for the first, second and third years post transplant, respectively, with UK database figures suggesting 39.7, 11.0 and 9.2 visits for the first, second and third years post transplant, respectively.[60]

Service provision (clinic appointments or other services) is likely to increase if AR occurs (possibly requiring hospital admission and escalating treatment) and when there is declining graft function (which might necessitate more regular clinic visits, blood tests and other investigations and changes to treatment regimens). Patients may also present to their general practitioner (GP) or accident and emergency department with AEs 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 dietitian), followed by management as required (e.g. additional prescribing and monitoring).

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

- online access to their results via the 'Renal Patient View' service
- open access to the renal transplant outpatient service
- an established point of contact for enquiries
- access to patient information (which should be available in both written and electronic formats).

Current National Institute for Health and Care Excellence guidance

Current NICE guidance on immunosuppressive therapy for renal transplantation in children and adolescents (NICE technology appraisal guidance, TA99) has the following recommendations for induction and maintenance therapy.[1]

Induction therapy

Basiliximab or daclizumab (DAC), used as part of a ciclosporin (CSA)-based immunosuppressive regimen, is recommended as an option for induction therapy in the prophylaxis of acute organ rejection in children and adolescents undergoing renal transplantation, irrespective of immunological risk. The induction therapy (BAS or DAC) with the lowest acquisition cost should be used, unless it is contraindicated.[1]
The marketing authorisation for DAC has been withdrawn at the request of the manufacturer.

Maintenance therapy

Tacrolimus (TAC) is recommended as an alternative option to CSA when a CNI is indicated as part of an initial or a maintenance immunosuppressive regimen for renal transplantation in children and adolescents. The initial choice of TAC or CSA should be based on the relative importance of their side effect profiles for the individual patient.[1]

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

- there is proven intolerance to CNIs, particularly nephrotoxicity which could lead to risk of chronic allograft dysfunction or
- there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a CNI until the period of high risk has passed.[1]

The use of MMF in CCS reduction or withdrawal strategies for child and adolescent renal transplant recipients is recommended only within the context of randomised clinical trials.[1]

Mycophenolate sodium is currently not recommended for use as part of an immunosuppressive regimen in child or adolescent renal transplant recipients.[1]

Sirolimus is not recommended for children or adolescents undergoing renal transplantation except when proven intolerance to CNIs (including nephrotoxicity) necessitates the complete withdrawal of these treatments.[1]

As a consequence of following this guidance, some medicines may be prescribed outside the terms of their UK marketing authorisation. Health-care professionals prescribing these medicines should ensure that children and adolescents receiving renal transplants and/or their legal guardians are aware of this and that they consent to the use of these medicines in these circumstances.[1]

Description of technology under assessment

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 BAS and r-ATG. The seven interventions considered for maintenance therapy are TAC-IR and TAC-PR, MMF, MPS, BEL, SRL and EVL.

Induction therapy

Basiliximab (Simulect,® Novartis Pharmaceuticals) is a monoclonal antibody which acts as an interleukin 2 receptor antagonist. It has a UK marketing authorisation for prophylaxis of AR in allogeneic renal transplantation in children (aged 1–17 years). The summary of product characteristics (SPC) states it is to be used concomitantly with CSA for microemulsion- and CCS-based immunosuppression, in patients with panel reactive antibodies < 80%, or in a triple maintenance immunosuppressive regimen containing CSA for microemulsion, CCSs and either azathioprine (AZA) or MMF.[7]

Rabbit antihuman thymocyte immunoglobulin is a gamma immunoglobulin. It has a UK marketing authorisation for the prevention of graft rejection in renal transplantation. The SPC states it is usually used in combination with other immunosuppressive drugs. It is administered intravenously. The UK marketing authorisation is not restricted to adults only.[7]

Maintenance therapy

Tacrolimus is a CNI that is available in an immediate-release formulation (Adoport,® Sandoz; Capexion,® Mylan; Modigraf,® Astellas Pharma; Perixis,® Accord Healthcare; Prograf,® Astellas Pharma; Tacni,® Teva; Vivadex,® Dexcel Pharma). All of these formulations of TAC have UK marketing authorisations for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisations include adults and children.[7] TAC (Modigraf®, Astellas Pharma) is available in a granule form which can be suspended in liquid and may be more suitable for those who struggle swallowing pills.

Tacrolimus is also available in a prolonged-release formulation (Advagraf,® Astellas Pharma). It has a UK marketing authorisation for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisation is restricted to adults. The Commission on Human Medicines advises that all oral TAC (including both TAC-IR and TAC-PR) medicines in the UK should be prescribed and dispensed by brand name only.[7]

Belatacept is designed to selectively inhibit CD28-mediated co-stimulation of T-cells. BEL has a UK marketing authorisation for prophylaxis of graft rejection in adults receiving a renal transplant, in combination with CCSs and a mycophenolic acid (MPA; Myfortic,® Novartis Pharmaceuticals). The SPC recommends that an interleukin 2 receptor antagonist for induction therapy is added to this BEL-based regimen. The SPC states that the safety and efficacy of BEL in children and adolescents aged 0–18 years have not yet been established. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[7]

Mycophenolate mofetil is a prodrug of MPA which acts as an antiproliferative agent (Arzip,® Zentiva; CellCept,® Roche Products; Myfenax,® Teva); generic MMF is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt). It has a UK marketing authorisation for use in combination with CSA and CCSs for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. The UK marketing authorisation is not restricted to adults (dosage recommendations for children aged 2–18 years are included in the SPC).[7]

Mycophenolate sodium is an enteric-coated formulation of MPA. This formulation has the same UK marketing authorisation as MMF; however, this is restricted to adults. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[7]

Sirolimus (Rapamune,® Pfizer) is an antiproliferative with a non-calcineurin-inhibiting action. It has a UK marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with CSA and CCSs for 2–3 months. It may be continued as maintenance therapy with CCSs only if CSA can be progressively discontinued. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[7]

Everolimus (Certican,® Novartis Pharmaceuticals) is a proliferation signal inhibitor and is an analogue of SRL. EVL does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation in children and adolescents.[7]

Current usage in the NHS

There is a variation in the use of induction and maintenance therapy in the UK. *Table 6* provides an overview of immunosuppression regimens for low-risk first renal transplants (e.g. blood group and HLA compatible) in the 10 paediatric transplant centres in the UK. Four out of the 10 centres use BAS as a part of induction therapy. Apart from the use of antibody induction, all centres use a single dose of methylprednisolone at the time of transplantation. The table also illustrates the difference in the use of the two proliferative agents (MMF and AZA), the agreement in the use of CNI across all centres (TAC; usually Adoport), and the use of steroids as a part of maintenance therapy. The current NICE guidelines are followed by using TAC + AZA + CCS ± BAS regimens.[1] However, the use of MMF is not limited to proven intolerance to CNIs, or to a very high risk of nephrotoxicity necessitating a temporary minimisation or avoidance of CNI (see *Current National Institute for Health and Care Excellence guidance* for more details).

TABLE 6 The use of immunosuppressive agents in paediatric centres in the UK

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

The TWIST study, A Randomized Trial to Assess the Impact of Early Steroid Withdrawal on Growth in Pediatric Renal Transplantation.

a BAS is used for second and subsequent transplants when the previous transplant was lost as a result of AR.
b 16- to 18-year-old patients follow adult protocol of antibody + TAC + MMF + CCS.
c BAS is used if there are high levels of panel reactive antibodies.
d MMF for second transplantation or post rejection.
e Early CCS withdrawal in certain cases (e.g. risk of diabetes mellitus, etc.).
f BAS for high-risk patients.
g Low thresholds for MMF switching.
h For children who have bony problems (e.g. slipped upper femoral epiphysis) or obesity (e.g. Bardet–Biedl syndrome), BAS with rapid steroid withdrawal is used.

Notes

The TWIST study protocol is based on a European study of an early steroid withdrawal study – the TWIST Study,[24] with two doses of antibody (day zero and day four) and only five doses of steroids (day zero to day four), TAC, and MMF.
Source: Dr Jan Dudley, Bristol Royal Hospital for Children, 2015, personal communication; and Dr Stephen Marks, Great Ormond Street Hospital in London, 2015, personal communication.

Anticipated costs associated with intervention

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

In addition, drug administration costs are also incurred for some maintenance agents. CSA, TAC, SRL and EVL are routinely titrated using therapeutic drug monitoring, which is estimated to cost approximately £26 per test (testing frequency is reduced as patients become stabilised in dosage), and BEL requires intravenous (i.v.) infusion, entailing catheterisation and nursing time. The cost of this is difficult to estimate but estimates range from £154[66] to £320.[11]

TABLE 7 Overview of costs and dose for different immunosuppressive agents

Compound	Unit cost	Recommended dose	Estimated weekly cost for 31.5 kg body weight, surface area 1.1 m^2 (10-year-old male)[a]
AZA	Hospital pharmacy: 0.1 p per mg[b] Community pharmacy: 0.1 p per mg[d]	1–3 mg/kg per day, adjusted according to response[c]	Hospital pharmacy: 22.05 p to 66.15 p Community pharmacy: 22.05 p to 66.15 p
BAS	£75.87 per mg (10-mg vial) and £42.12 per mg (20-mg vial)[c]	Child > 1 year, body weight < 35 kg, 10 mg within 2 hours before transplant surgery and 10 mg 4 days after surgery Child body weight ≥ 35 kg, 20 mg within 2 hours before transplant surgery and 20 mg 4 days after surgery[c]	Cost calculated based on recommended dose: Child < 35 kg: £1517.38 (induction period only) Child ≥ 35 kg: £842.38 (induction period)
BEL	£1.42 per mg[c]	Not licensed for use in children[c] Adult dose 5 mg/kg per 4 weeks	£55.83 (adult, weight-based dose)
CSA	Hospital pharmacy: 1.65 p per mg[b] Community pharmacy: 2.55 p per mg[c]	8–12 mg/kg/day[e]	Hospital pharmacy: £29.10–43.66 Community pharmacy: £44.98–67.47
CCSs	Hospital pharmacy: 0.3 p per mg[b] Community pharmacy: 0.9 p per mg[d]	Methylprednisolone: 10–20 mg/kg or 400–600 mg/m^2 (maximum 1 g) once daily for 3 days[c] Prednisolone: consult local treatment protocols for details.[c] An example: 60 mg/m^2/day during first week, eventually weaned down to < 10 mg/m^2 on alternate days	Hospital pharmacy: £2.83–5.67 Community pharmacy: £8.49–17.01
EVL	£9.90 per mg[f]	Not licensed for use in children[c] Adult dose of 1.5 mg per day[g]	£103.95 (adult non-weight-based dose)
TAC-IR	Hospital pharmacy: 52.0 p per mg[b] Community pharmacy: 118.6 p per mg[c,d]	150 µg/kg twice daily, adjusted according to whole blood concentration	Hospital pharmacy: £34.40 Community pharmacy: £78.45
MMF	Hospital pharmacy: 37.74 p per g[b] Community pharmacy: 40.44 p per g[d]	300 mg/m^2 twice daily (maximum 2 g) if in addition with TAC and CCSs[c] 600 mg/m^2 twice daily (maximum 2 g) if in addition with CSA and CCSs[c]	Hospital pharmacy: £1.74 Community pharmacy: £1.86 Hospital pharmacy: £3.48 Community pharmacy: £3.73
MPS	0.5 p per mg[c]	Not licensed for use in children[c] Adult dose 1440 mg per day[c]	£50.4 (adult non-weight-based dose)
TAC-PR	106.8 p per mg[c]	Not licensed for use in children[c] Adult dose 0.2 mg/kg per day	£47.10 (adult weight-based dose)

TABLE 7 Overview of costs and dose for different immunosuppressive agents (*continued*)

Compound	Unit cost	Recommended dose	Estimated weekly cost for 31.5 kg body weight, surface area 1.1 m^2 (10-year-old male)[a]
r-ATG	£6.35 per mg[c]	Not licensed for use in children[c] 1.5 mg/kg/day administered by intravenous infusion for 7–14 days[h]	£2100.52 (induction period only)
SRL	£2.88 per mg[c,d]	Not licensed for use in children[c] Adult dose 2 mg per day[c]	£40.36 (adult non-weight-based dose)

a Weight to age taken from Astellas' submission and weight to surface area calculated using the Boyd[61] formula (www.ouh.nhs.uk/oxparc/professionals/documents/Body-surfaceareaCCLGChart1.pdf).
b Commercial Medicines Unit electronic market information tool.[62]
c *British National Formulary* volume 68 (January 2015 online update).[63]
d NHS Business Services Authority, NHS Drug Tariff for England and Wales (2015).
e Drugs.com.[64]
f Novartis' submission.
g MHRA SPC.
h Drugs.com.[65]

Note
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 BEL, it assumes that perfect vial sharing is employed (in which one vial may be used by more than one patient to eliminate wastage).

Chapter 2 Definition of the decision problem

Decision problem

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

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

- Basiliximab and r-ATG as an induction therapy, and
- TAC-IR, TAC-PR, MMF, MPS, BEL, SRL, and EVL as a maintenance therapy
- including a review of TA99.

The project was undertaken based on a published scope[7] and in accordance with a protocol.[67]

Interventions

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

The two induction treatments are:

- BAS
- r-ATG.

The seven maintenance treatments are:

- TAC-PR formulation (Advagraf,® Astellas Pharma)
- TAC-IR formulations [Adoport® (Sandoz); Capexion® (Mylan); Modigraf® (Astellas Pharma); Perixis® (Accord Healthcare); Prograf® (Astellas Pharma); Tacni® (Teva); Vivadex® (Dexcel Pharma)]
- BEL MMF
- MPS SRL
- EVL.

These treatments are described in *Chapter 1*, *Summary of Intervention*. Several of the drugs being assessed are used in the NHS outside the terms of their UK marketing authorisation, for example in children and adolescents, or in high-risk people, or in unlicensed drug combinations. Specifically EVL, TAC-PR, BEL, MPS and SRL are not currently licensed for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.

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

Populations including subgroups

The population being assessed are children and adolescents aged 0–18 years (inclusive) undergoing kidney transplantation. Patients receiving multiorgan transplants and those who have received transplants and immunosuppression previously were excluded.

If data allow, the following subgroups were considered:

- different age groups
- level of immunological risk (including HLA compatibility and blood group compatibility)
- people at high risk of rejection within the first 6 months
- people who have had a retransplant within 2 years
- previous AR
- people at high risk of complications from immunosuppression (including new-onset diabetes mellitus).

Relevant comparators

For induction therapy, the treatments are to be compared with each other, as data permit, 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 permit, or with a CNI with or without an antiproliferative agent and/or CCSs.

Outcomes

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

- patient survival
- graft survival
- graft function
- time to and incidence of AR
- severity of AR
- growth
- adverse effects of treatment
- health-related quality of life (HRQoL).

Key issues

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

The viability of the kidney may depend on the type of donor (living related, living unrelated, DBD, DCD or expanded criteria donor), the age of the donor, whether or not they had comorbidities such as diabetes mellitus, and the length of cold ischaemia. Furthermore, the age, sex, ethnicity and health of the recipient, and the length of time the recipient is on dialysis prior to transplantation may affect the outcome of transplantation. These issues have been discussed in more detail in *Chapter 1*, *Important prognostic factors*.

Overall aims and objectives of assessment

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

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

This systematic review was commissioned by NICE to update the previous guidance (TA99).[1] The systematic review and economic evaluation developed to support current NICE guidance TA99, was published by Yao *et al.* in 2006.[2] The differences between the remit of the previous review and the protocol of the current one are discussed in *The previous assessment report*.

There was one departure from the protocol:[67] the age of population eligibility criterion was changed from < 18 years (a common definition of children and adolescents) to ≤ 18 years [the age inclusion criterion applied by the three eligible randomised controlled trial (RCTs)].

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

Identification of studies

Bibliographic literature database searching was conducted on 14 April 2014 and updated on 7 January 2015. The searches for individual effectiveness studies (RCTs and controlled clinical trials) took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND [a study design limit to randomised control trials (RCT) or controlled trials]. In order to update the previous assessment,[2] the searches were date limited (2002–current). These searches were not limited by language or to human-only studies because such a limit may have blocked retrieval of includable studies for R-ATG (line 8 of the MEDLINE search). The following databases were searched: MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley Online Library) and Web of Science [via Institute for Scientific Information (ISI) – including conference proceedings]. In addition, the following trials registries were hand-searched in January 2015: Current Controlled Trials, ClinicalTrials.gov, FDA website, EMA website (European Public Assessment Reports).

Separate searches were undertaken to identify systematic reviews of RCTs and non-randomised studies. These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a pragmatic limit to systematic reviews). The same population and intervention search terms were used as in the individual studies search. A pragmatic, methodological search filter was used to limit by study design. No other limits (e.g. language) were applied to this search. The search was run from database inception in the following databases: MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) (The Cochrane Library via Wiley Online Library) and Health Management Information Consortium (HMIC) (via Ovid).

The search strategies are recorded in *Appendix 1*.

The database search results were exported to, and deduplicated using, EndNote (X5) (Thomson Reuters, CA, USA). Deduplication was also performed manually.

Furthermore, the following websites were searched for background information.

Renal societies (UK)

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

Renal societies (international)

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

Previous Health Technology Assessment review

Studies included in the previous HTA review (Yao *et al.*[2]) were screened using the inclusion criteria for the Peninsula Technology Assessment Group (PenTAG) review (*Inclusion and exclusion criteria*).

Reference lists

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

Ongoing trials

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

Adult randomised controlled trial evidence

In addition, as specified in the review protocol, all child/adolescents RCT and non-RCT evidence included in this review was compared with adult evidence identified from parallel HTA 09/46/01 appraisal.[68] This parallel HTA was conducted by PenTAG to inform the ongoing technology appraisal of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85; NICE appraisal ID 456). The NIHR Evaluation, Trials and Studies Coordinating Centre reference for the adult report is 09/46/01 (www.nice.org.uk/guidance/indevelopment/gid-tag348/documents).

Inclusion and exclusion criteria

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

Study design

The clinical effectiveness review included:

- eligible studies – RCTs in children and adolescents (≤ 18 years), RCTs of adults and children/adolescents in which a subgroup analysis of children and adolescents is reported, and non-randomised controlled studies (comparative quasi-experimental and observational studies were considered)
- search strategy – databases were searched to identify RCTs, systematic reviews of RCTs and systematic reviews of non-randomised controlled studies. Individual non-randomised controlled studies were identified via the bibliographies of systematic reviews (i.e. individual non-randomised controlled studies were not searched for directly).

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

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

Interventions

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

Induction therapy

- Basiliximab.
- Rabbit antihuman thymocyte immunoglobulin.

Maintenance therapy

- TAC-PR formulation.
- TAC-IR formulations.
- Belatacept.
- MMF (generic MMF manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt).
- Mycophenolate sodium.
- Sirolimus.
- Everolimus.

All treatments are described in detail in *Chapter 1*, *Summary of intervention*.

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

Comparator

Studies using the following comparators were included.

Induction therapy

- Regimens without monoclonal or polyclonal antibodies, for example regimens that include methylprednisolone or placebo (PBO).
- Interventions should also be compared with each other.

Maintenance therapy

- A CNI with or without an antiproliferative agent and/or CCSs.
- Interventions should also be compared with each other.

In addition, when appropriate, the interventions were appraised as part of combination regimens.

Population

The population is children and adolescents aged ≤ 18 years undergoing kidney transplantation. The kidney donor may be living related, living unrelated or deceased. Patients receiving multiorgan transplants and those who have received transplants and immunosuppression previously were excluded.

Outcomes

The outcome measures to be considered are:

- patient survival
- graft survival
- graft function
- time to and incidence of AR
- severity of AR
- growth
- adverse effects (AE) of treatment
- HRQoL.

Screening

All records were dual screened. First, titles and abstracts returned by the search strategy were screened for inclusion. The screening was distributed across a team of five researchers (TJ-H, LC, MHa, MB and HC). Update searches were screened by two reviewers (MHa and JV-C) and disagreements were resolved by discussion, with involvement of a third reviewer (TJ-H or MHa) if necessary. Full texts of identified studies were obtained and screened in the same way. Studies reported only as abstracts were included provided sufficient methodological details were reported to allow critical appraisal of study quality. In addition, studies included in the review conducted by Yao *et al.*[2] were screened for inclusion.

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

Data extraction

Information from new studies (not included in TA99) was extracted and tabulated; information included details of the study design and methodology, baseline characteristics of participants and results including HRQoL and any AEs if reported (see *Appendix 1*). All included studies (including those in TA99) were quality appraised.

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

Critical appraisal strategy

Randomised control trials

Four reviewers (LC, MHa, HC and TJ-H) independently assessed the quality of all studies included in the clinical effectiveness review. The internal and external validity of RCTs was assessed according to criteria based on Centre for Reviews and Dissemination (CRD) guidance[69] (*Table 8*).

Non-randomised control trials

There is no agreed recommended appraisal tool for the assessment of non-randomised studies.[70] The CRD handbook suggests considering the study design, risk of bias, other issues related to study quality, choice of outcome measure, statistical issues, quality of reporting, quality of the intervention and generalisability.[69] Therefore, the internal and external validity of non-RCTs was assessed according to criteria based on CRD guidance[69] (*Table 9*).

Methods of data synthesis

Data were tabulated and discussed in a narrative review. The subgroups defined in *Chapter 2*, *Populations including subgroups*, were considered in the analyses.

TABLE 8 Critical appraisal checklist for randomised control studies

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

ITT, intention to treat.
Note
Criteria were based on CRD guidance.[69]

TABLE 9 Critical appraisal checklist for non-randomised control studies

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

Note
Criteria were based on CRD guidance.[69]

Meta-analyses

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

A random-effects model was assumed for all meta-analyses. For binary data, an odds ratio (OR) was used as a measure of treatment effect and the DerSimonian–Laird method was used for pooling.[71] For continuous data (e.g. graft function), mean differences were calculated if the outcome was measured on the same scale in all trials. If applicable, publication bias was assessed using funnel plots, the Harbord test was used for binary outcomes [OR, log-standard error (SE)] and the Egger test for continuous data. All analyses were performed in Stata 13 (StataCorp LP, College Station, TX, USA).

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

Results of the systematic review

Quantity and quality of research available

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

Randomised control trials

Our searches returned 5079 unique titles and abstracts, with 784 papers retrieved for detailed consideration. To ensure the inclusion of trials with mixed child/adolescent and adult populations that reported separate results for children and adolescents, the searches and title and abstract screening were not limited to children and adolescents. Update searches conducted on 7 January 2015 returned 416 unique titles and abstracts. Forty papers were retrieved for detailed consideration.

Of the 824 full-text papers retrieved, 793 were excluded (a list of these records with reasons for their exclusion can be found in *Appendix 2*, *Table 135*). Although RCTs in mixed populations were identified, none included subgroup analysis by age – providing separate results for children/adolescents and adults – and were therefore excluded from the review (a list of these records can be found in *Appendix 2*, *Table 136*). Three RCTs (published in one abstract[72] and seven papers[73–79]) met the inclusion criteria.

Only one abstract[72] was included in the review. This abstract included new data related to Offner *et al.*[73] and sufficient methodological information to inform the quality appraisal. In addition, there were 23 articles that were systematic reviews and all eligible systematic reviews were tabulated (see *Appendix 3*, *Table 137*).

The process is illustrated in detail in *Figure 8*.

In summary, three RCTs (published in seven papers[73–79] and one abstract[72]) were found eligible and are included in this review (*Table 10*).

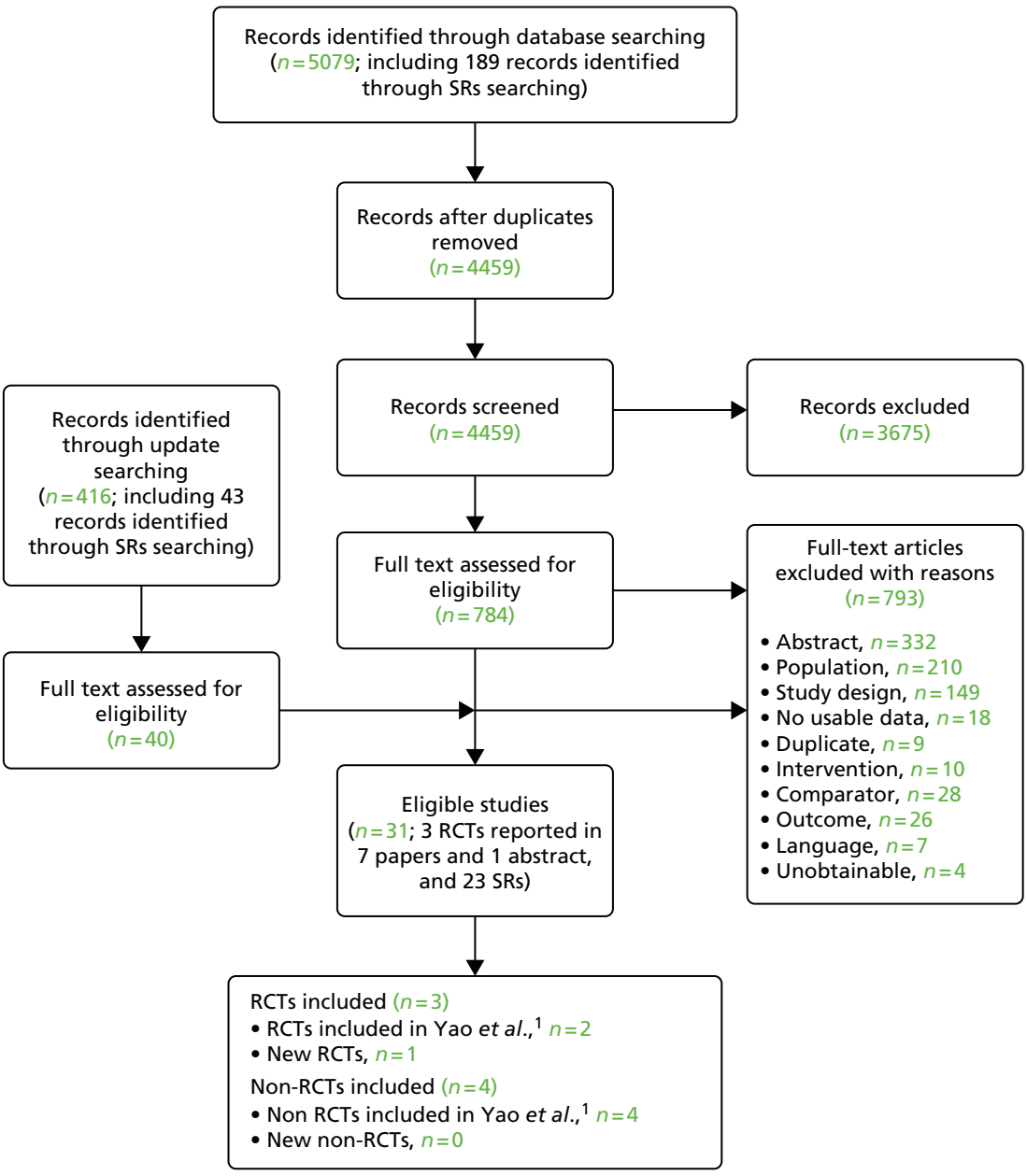

FIGURE 8 Clinical effectiveness review: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. SR, systematic review.

TABLE 10 Summary table of included randomised controlled studies

Study	*n*[a]	Agent (*n*)	Control (*n*)	Outcomes	Multiple publications
Induction therapy					
Offner *et al.*[73]	192	BAS + CSA + MMF + CCS (100)	PBO + CSA + MMF + CCS (92)	Mortality, graft loss, graft function, BPAR, AE	Höcker *et al.*,[74] Jungraithmayr *et al.*[72]
Grenda *et al.*[75]	192	BAS + TAC + AZA + CCS (99)	NI + TAC + AZA + CCS (93)	Mortality, graft loss, graft function, BPAR, AE	Webb *et al.*[76]
Maintenance therapy					
Trompeter *et al.*[77]	196	TAC + AZA + CCS (103)	CSA + AZA + CCS (93)	Mortality, graft loss, graft function, BPAR, AE	Filler *et al.*,[78] Filler *et al.*[79]

BPAR, biopsy-proven acute rejection; NI; no induction.
a Intention-to-treat population.

Non-randomised trials

The systematic reviews were used to identify non-RCTs. We screened the titles and abstracts of 226 unique references identified by the PenTAG systematic review searches (including 43 records from update searches) and retrieved 38 papers for detailed consideration. All eligible systematic reviews were tabulated (see *Appendix 3*, *Table 137*).

In total, four non-RCTs met the inclusion criteria and were considered eligible for inclusion (*Table 11*). All of these were included in the previous HTA by Yao *et al.*[2] so no new non-RCTs were identified. However, in 2007 one of the four non-RCT studies[83] published 5-year follow-up data[85] that were not included in the previous HTA.

TABLE 11 Summary table of included non-randomised studies

Study	*n*[a]	Treatment	Outcomes	Multiple publications
Induction and maintenance therapy				
Garcia *et al*[80]	24	BAS + TAC + AZA + CCS vs. BAS + CSA + MMF + CCS	Mortality, graft loss, graft function, BPAR, AE	N/A
Maintenance therapy				
Antoniadis *et al.*[81]	14	CSA + MMF + CCS vs. CSA + AZA + CCS[b]	Graft function, BPAR, AE	N/A
[c]Benfield *et al.*[82]	67	(OKT3 or CSA) + MMF + CCS vs. (OKT3 or CSA) + AZA + CCS	Mortality, graft loss, graft function, BPAR	N/A
Staskewitz *et al.*[83]	139[d]	CSA + MMF + CCS[e] vs. CSA + AZA + CCS	Mortality, graft loss, graft function, BPAR, AE	Jungraithmayr *et al.*,[84] Jungraithmayr *et al.*[85]

BPAR, biopsy-proven acute rejection; N/A, not applicable; OKT3, a murine monoclonal antibody muromonab-CD3.
a Intention-to-treat population.
b Methylprednisolone induction in all participants.
c This was a randomised trial of OKT3 vs. CSA at the time of transplantation. First 31 participants were given AZA and subsequent 36 participants were given MMF. In addition, participants were randomly assigned to receive two different CSA preparations: (Sandimmun®, Novartis) and (Neoral®, Novartis). Only a subgroup of participants was considered in this review.
d Staskiewitz *et al.*[83] reported results for 65 MMF and 54 AZA participants; however, the following two publications (Jungraithmayr *et al.*[84] and Jungraithmayr *et al.*[85]) report on 85 MMF and 54 AZA participants.
e Participants received prednisone/methylprednisolone induction in this arm, no induction reported for the historical control arm (CSA + AZA + CCS).

Ongoing studies

Eleven ongoing trials were considered relevant to this review and were investigated further. An overview of the 11 trials with reasons for inclusion/exclusion in PenTAG review is provided in *Appendix 4*, *Table 138*. Only one of these ongoing trials was identified as potentially eligible for inclusion. The methods and design of this trial (A2314) were reported as conference abstracts.[86–89] This international trial investigates the efficacy, tolerability and safety of early introduction of EVL, reduced CNIs and early steroid elimination compared with standard CNI, MMF and steroid regimen in paediatric renal transplant recipients and is sponsored by Novartis. The estimated date of completion is December 2016, so it was not included in this review. The search of ongoing studies in trial registries did not identify any additional RCTs for inclusion in the PenTAG systematic review.

The previous assessment report

The assessment report published as Yao *et al.*[2] informed the current NICE guidance TA99.[1] The aim of the previous HTA was to establish the clinical effectiveness (harms and benefits) and cost-effectiveness of four of the newer immunosuppressive drugs for renal transplantation, namely BAS, DAC, TAC and mycophenolate (mofetil and sodium), and of SRL in children and adolescents.

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

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

The current PenTAG systematic review aims to establish the clinical effectiveness and cost-effectiveness of immunosuppressive regimens including BAS and r-ATG as an induction therapy in renal transplantation in children and adolescents, and of immunosuppressive regimens including TAC-IR, TAC-PR, MMF, MPS, BEL, SRL, and EVL as a maintenance therapy in renal transplantation in children and adolescents (including review of TA99).

The current PenTAG review included:

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

In addition, the PenTAG review compares results in children and adolescents with those from the parallel HTA 09/46/01 appraisal 'Immunosuppressive therapy for kidney transplantation in adults'.[68]

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

Randomised control trials

Children and adolescents

The previous TA99[1] included three paediatric RCTs: the unpublished Wyeth 0468E1–217-US study (Wyeth submission 2005), Trompeter *et al.*,[77] and an abstract by Grenda *et al.*[90] (*Table 12*). The Wyeth submission 2005 compared an addition of SRL to a CNI maintenance therapy [(CSA or TAC) + CCS], with a triple maintenance therapy [(CSA or TAC) + (MMF or AZA) + CCS] in children and adolescents (≤ 20 years of age) who experienced one or more episodes of AR or chronic rejection after kidney transplantation.[2] Because of the trial design (treatment combinations were allowed) and population characteristics (age and time from transplantation) this study is not eligible to be included in the current review. The other two paediatric RCTs included in Yao *et al.*[2] are included in the PenTAG review.[77,90] Additional publications of Grenda *et al.*[90] were identified in our searches (the previous HTA included only 6-month follow-up data; see *Table 12*). We identified one new RCT[73] that was not included in Yao *et al.*[2]

Non-randomised studies

An overview of the nine non-randomised studies included in Yao *et al.*[2] with reasons for inclusion/exclusion in the current review is provided in *Table 13*. Five studies were excluded from the PenTAG review (see *Table 13*):

- Duzova *et al.*[91] (compared BAS with no induction) administered triple therapy of (CSA or TAC) + (AZA or MMF) + CCS; however, a breakdown of the numbers (and results) in each combination was not reported and the mean recipient age was 14.9 ± 3.6 years (range 7–21 years).
- Pape *et al.*[92] recruited a child with a combined kidney–liver transplantation.
- Swiatecka-Urban *et al.*[93] included children, adolescents and adults (inclusion criteria aged < 21 years).
- Neu *et al.*[94] included children, adolescents and adults (inclusion criteria aged > 2 years and < 21 years) and the use of induction therapy varied in the study.
- Steffen *et al.*[95] was published as an abstract only and did not include enough information to allow critical appraisal.

In summary, four non-randomised studies were included in the PenTAG review and all were also included in the previous HTA review by Yao *et al.*[2] No new non-randomised studies were identified in PenTAG systematic review searches.

TABLE 12 Previous HTA review included children and adolescents RCTs

Number	Study	Multiple publications	Treatments	Published	Included in PenTAG (reason)
1	Grenda *et al.*[90]	Fijusawa/Astellas 2005	BAS vs. PBO	Abstract only; full trial provided in Fujusawa/Astellas' submission	Yes, trial was published as Grenda *et al.*[75] and Webb *et al.*[76]
2	Trompeter *et al.*[77]	Filler *et al.*[78,79]	TAC vs. CSA	Yes	Yes
3	Wyeth submission 2005	0468E1–217-US, NCT00005113 (study was terminated)	Addition of SRL	No; full trial provided in Fujusawa/Astellas' submission	No (population, design)

TABLE 13 Previous HTA review included children and adolescents non-randomised studies

Number	ID	*n*[a]	Treatments	Included in PenTAG (reason)
Induction therapy				
1	Duzova *et al.*[91]	43	BAS + (CSA or TAC) + (AZA or MMF) + CCS vs. (CSA or TAC) + (AZA or MMF) + CCS	No (design and population)
2	Pape *et al.*[92]	77	BAS + CSA + CCS vs. CSA + CS	No (population)[b]
3	Swiatecka-Urban *et al.*[93]	32	BAS + TAC + CCS vs. TAC + CCS[c]	No (population)
Maintenance therapy				
4	Garcia *et al.*[80]	24	BAS + TAC + AZA + CCS vs. BAS + CSA + MMF + CCS	Yes
5	Neu *et al.*[94]	986	TAC + MMF + CCS vs. CSA + MMF + CS	No (population)
6	Antoniadis *et al.*[81]	14	CSA + MMF + CCS vs. CSA + AZA + CCS[d]	Yes
7	Steffen *et al.*[95]	NR		No (abstract)
8	Staskewitz *et al.*[83] (Jungraithmayr *et al.*[84])	120	CSA + MMF + CCS[e] vs. CSA + AZA + CCS	Yes
9	[f]Benfield *et al.*[82]	678	(OKT3 or CSA) + MMF + CCS vs. (OKT3 or CSA) + AZA + CCS	Yes

ID, identification; NR, not reported; OKT3, a murine monoclonal antibody muromonab-CD3.
a An intention-to-treat population.
b One child had a combined kidney–liver transplantation.
c A single AZA dose perioperatively in seven out of eight participants in the non-BAS group.
d Methylprednisolone induction in all participants.
e Participants received prednisone/methylprednisolone induction in this arm, no induction reported for the historical control arm (CSA + AZA + CCS).
f This was randomised trial of OKT3 vs. CSA at the time of transplantation. First 31 participants were given AZA and subsequent 36 participants were given MMF. In addition participants were randomly assigned to receive Sandimmun or Neoral CSA preparations.

Adults

The previous TA99 included evidence from 25 adult RCTs. In comparison, the updated HTA 09/46/01 appraisal 'Immunosuppressive therapy for kidney transplantation in adults' included 86 trials: 11 induction studies, 73 maintenance studies and two studies of both induction and maintenance treatment. An overview of the 25 adult RCTs included in Yao *et al.*[2] with reasons for inclusion/exclusion in the parallel HTA review[68] is provided in *Appendix 5* (see *Table 139*).

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

Quality of included studies

We appraised both newly identified trials and those included in the previous HTA review.[2] The reasons for reappraising trials were first to ensure consistency with appraisal of the new study and, second, because we have access to new information from papers published after the inclusion date for the previous review. Only primary research studies were appraised (i.e. not systematic reviews). If a trial was reported in multiple publications, only one quality assessment of the trial was conducted (all publications for that trial were assessed together).

Randomised controlled trials

In total, three RCTs were assessed: two induction studies and one maintenance study.[73,75,77]

Overall assessment

For all three RCTs, fewer than half of the items constituting the quality appraisal assessment were rated as being of 'adequate' quality (*Table 14*). All of these trials either did not report, or lacked clarity on, at least 5 out of the 10 quality appraisal items. It is possible that items that were not clearly reported in the papers were in fact adequately conducted in the trials. Nevertheless, all three RCTs were rated as 'inadequate' for at least one item of the quality appraisal assessment.

Treatment allocation

Random allocation: the method of random allocation, including the method of sequence generation, was clearly stated and adequate in only one trial[73] and unclear in the other two trials.[75,77]

Concealment of allocation: the method of concealment of allocation was clearly reported in only one trial[77] and unclear in the other two trials.[73,75]

Similarity of groups

Baseline characteristics: all three RCTs stated that baseline characteristics were similar between treatments arms on a range of prognostic factors (see *Table 16* for a summary of baseline characteristics). However, one trial appeared to have a higher percentage of males in the PBO arm than the BAS arm (67.4% vs. 56%, respectively).[73]

Implementation of masking

Treatment allocation masked from providers: the method was clearly stated and adequate in only one trial.[73] In the other two trials,[75,77] care providers were not blinded to treatment allocation.

Treatment allocation masked from outcome assessors: none of the three trials clearly reported whether or not treatment allocation was masked from outcome assessors.[73,75,77]

Treatment allocation masked from participants: the method was clearly stated and adequate in only one trial.[73] In the other two trials, participants were not blinded to treatment allocation.

Completeness of trials

In all three studies,[73,75,77] it was not clear whether or not all reported outcomes were the same as those in the trial protocol and the reporting of loss to follow-up, withdrawals and dropouts was also not clearly reported.

Intention-to-treat (ITT) analysis: none of the trials was rated as adequate. One induction trial investigating the effectiveness of BAS excluded eight participants who received a 'commercially available formulation of the drug instead of the blinded study drug Simulect' and was, therefore, rated as 'inadequate' for this item of the quality appraisal assessment.[73] Similarly, one study excluded participants who did not receive study medication and excluded an additional four participants because of reporting issues and so was also rated as 'inadequate' for this item.[77] The remaining study[75] did not clearly report the initial number of participants who were randomised, so it was unclear whether or not all randomised and transplanted participants were included in the analyses.

Applicability of trials to the NHS

Applicability to the current NHS in England: all three studies were considered to be applicable to the NHS because no specific limitations with regards applicability were found in the study.[73,75,77] All three trials were conducted in Europe, patient and donor characteristics were largely representative of the NHS in England and doses of the drug under investigation were similar to current recommended doses, although Trompeter *et al.*[77] administered 10 mg of BAS for participants who were < 40 kg, and 20 mg for participants who were ≥ 40 kg, whereas the recommended cut-off for increasing the dose from 10 mg to 20 mg is currently 35 kg.

TABLE 14 Quality assessment: RCT

Study	Was the assignment to the treatment groups really random?	Was the treatment allocation concealed?	Were the groups similar at baseline in terms of prognostic factors?	Were the care providers blinded to the treatment allocation?	Were the outcome assessors blinded to the treatment allocation?	Were the participants blinded to the treatment allocation?	Were all a priori outcomes reported?	Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?	Did the analyses include an ITT analysis?	Are there any specific limitations that might limit the applicability of this study's findings to the current NHS in England?
Offner *et al.*[73]	Adequate	Unclear	Adequate	Adequate	Unclear	Adequate	Unclear	Unclear	Inadequate	Adequate
Grenda *et al.*[75]	Unclear	Unclear	Adequate	Inadequate	NR	Inadequate	Unclear	Unclear	Unclear	Adequate
Trompeter *et al.*[77]	Unclear	Adequate	Partial[a]	Inadequate	NR	Inadequate	Unclear	Unclear	Inadequate	Adequate

NR, not reported; ITT, intention to treat.
a The reported percentages of males in the BAS arm compared with the PBO arm was 56.0% and 67.4%, respectively.

Non-randomised trials

In total, four non-randomised studies were assessed.[80–83]

Overall assessment

For all four non-randomised studies, fewer than half of the items constituting the quality appraisal assessment were adequately addressed (*Table 15*). However, for all studies, at least 5 out of the 10 quality appraisal items were either not applicable (owing to study design), not reported, or not clearly reported. It is possible that items that were not clearly reported in the papers were in fact adequately conducted in the studies.

Treatment allocation

Allocation to groups: three of the non-randomised studies adequately described what the treatment and control groups were and the general basis for allocating participants to a particular treatment.[80,82,83] In two studies,[82,83] allocation to groups was dictated by changes to the treatment protocol in the study centres (i.e. they were historically controlled studies). One study compared two retrospective cohorts (for which treatment allocation was unrelated to the study design).[80] Despite being a prospective non-randomised, controlled trial, the remaining study did not report the basis for allocation to treatment groups.[81]

Avoidance of selection bias: none of the four studies provided evidence that selection bias (to the study overall and to treatment groups) was minimised within the context of the study design. All four studies were rated as 'unclear' with regards minimisation of selection bias. Two studies did not confirm whether or not all eligible participants were recruited for either group.[82,83] The other two studies did state that all transplanted children and adolescents were included in the study but did not clearly describe how participants were allocated to treatment groups, so the extent of possible selection bias to groups is not clear.[80,81]

Similarity of groups

Baseline characteristics: three out of the four studies did not clearly report whether or not treatment groups were similar at baseline on a range of prognostic factors and they omitted descriptive statistical information (see *Table 17* for a summary of baseline characteristics).[80–82] In two studies,[80,83] the age of participants statistically significantly differed between treatment groups. In addition, although the groups were reported not to be significantly different for gender, the percentages of males appeared to be different (6/12, 50% and 8/12, 66.7%, respectively) in one small study.[83]

Implementation of masking

None of the four non-randomised studies reported whether or not treatment allocation was masked from treatment providers, outcome assessors or participants. However, for three of the studies this was not applicable, because blinding could not be reasonably expected given the study design.[80,82,83] The remaining study was a prospective non-RCT, therefore, masking of care providers, outcome assessors (by using independent assessors) and participants could be done but was not reported.[81]

Length of follow-up

Three of the non-randomised studies had an adequate length of follow-up, with all participants followed for at least 6 months.[81–83] The remaining study was rated as 'partial' because not all participants were followed for at least 6 months but DGF was included as an outcome (this outcome would usually be assessed within the first month of transplantation).[80]

Completeness of trials

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

TABLE 15 Quality assessment: non-randomised studies

Study	Design	Was the allocation to group(s) reported?	Is the allocation to groups or to the study a source of selection bias?	Were the groups similar at baseline in terms of prognostic factors?	Were the care providers blinded to the treatment allocation?	Were the outcome assessors blinded to the treatment allocation?	Were the participants blinded to the treatment allocation?	Was follow-up long enough for outcomes to occur?	Were complete data reported, e.g. was attrition and exclusion (including reasons) reported for all outcomes?	Were statistical analyses adjusted to account for any between-group differences?	Was the group(s) representative of NHS renal transplant patients?
Antoniadis *et al.*[81]	Non-RCT	NR	Unclear	Unclear	NR	NR	NR	Adequate	Adequate	NR	Inadequate
Benfield *et al.*[82]	Historically controlled study[a]	Adequate	Unclear	Unclear	N/A	N/A	N/A	Adequate	Adequate	Inadequate	Unclear
Garcia *et al.*[80]	Retrospective cohort study	Adequate	Unclear	Inadequate[b]	N/A	N/A	N/A	Partial	Adequate	NR	Unclear
Staskewitz *et al.*[83]	Historically controlled study	Adequate	Unclear	Partial[c]	N/A	N/A	N/A	Adequate	Adequate	Inadequate	Inadequate

N/A; not applicable; NR, not reported; OKT3, a murine monoclonal antibody muromonab-CD3; SD, standard deviation.

a This was randomised trial of OKT3 vs. CSA at the time of transplantation. The first 31 participants were given AZA and the subsequent 36 participants were given MMF. In addition, participants were randomly assigned to receive Sandimmun or Neoral CSA preparations. Therefore, we consider there to be two additional studies embedded within the original RCT, one of which is applicable to this review.

b The reported age at transplantation in the TAC + AZA group and the CSA + MMF group was 11.3 ± 9.3 years and 9.0 ± 6 years, respectively ($p = 0.01$) and the reported percentages of males in the TAC + AZA group and the CSA + MMF group was 50% and 66.7%, respectively (groups did not differ significantly in terms of gender).

c The reported mean age at transplantation in the MMF group and the AZA group was 11.5 years (SD 3.6 years) and 9.9 years (SD 4.7 years), respectively ($p < 0.05$).

Adjustment for bias in non-randomised studies

This item of the quality appraisal assessment was applicable to all four studies. However, two of the studies did not perform any adjustment for bias in their analyses.[82,83] For the other two studies, analyses were not fully reported, so this could not be assessed.[80,81]

Applicability of trials to the current NHS in England

None of the non-randomised studies was considered to be clearly applicable to the NHS in England. Two studies were rated as inadequate because the study population was not representative of the current NHS in England. In one of these studies, all kidneys were from living related donors[81] and in the other, > 90% of kidneys were from cadaveric donors.[83] The other two studies were both rated as unclear because the populations were not recruited from the European Union, but it was not clear to what extent the population characteristics could generalise to the NHS in England.[80,82]

Baseline characteristics

Randomised controlled studies

Baseline characteristics of the three included RCTs[73,75,77] are summarised in *Table 16*. All three studies were conducted over multicentres in Europe. Only Offner *et al.*[73] reported the countries involved (Germany, France and Switzerland).[73] Mean age across the studies' arms ranged from 10.1 years to 11.5 years. The proportion of adolescents (with 12 or 13 years old being the cut-off point for adolescence in the three studies; see *Table 16* for details) is 36.6% to 54.4% across the study arms. Boys represented 56.0–67.4% of participants. Two studies had a high proportion of white participants (87–95%),[73,77] with one trial not reporting ethnicity.[75] The proportion of living donors across the study arms ranges from 15.5% to 35.8%. The proportion of first transplants is high, ranging from 85% to 96% across the arms. Finally, HLA antigen mismatch ranges from 2.3 to 2.7 across the three trials. A close antigen match is no longer considered critical owing to the more effective immunosuppressive therapy, but a better HLA match may lead to longer graft survival.

Non-randomised studies

Similarly, baseline characteristics of the four included non-randomised studies [Antoniadis *et al.*[81] (non-RCT), Benfield *et al.*[82] (historically controlled study), Garcia *et al.*[80] (retrospective cohort study) and Staskewitz *et al.* 2001[83] (historically controlled study)] are summarised in *Table 17*.[80–83] The Antoniadis *et al.*[81] study was conducted in one Greek centre, the Benfield *et al.*[82] study was conducted in two centres in the USA and the Staskewitz *et al.*[83] study was conducted in 12 German centres. Garcia *et al.*[80] did not report where or within how many centres their study was performed, but the authors are all based in Brazil and, therefore, it is likely that this study was completed in Brazil. Not surprisingly, the baseline characteristics of the non-RCTs vary not only across the studies, but also within the studies. Mean age across the study arms ranges from 9.0 years to 11.5 years; however, none of the non-RCTs reports the proportion of adolescents included. Boys represented 50.0–66.7% of participants. Two studies had a high proportion of white participants (75–100%),[80,83] one study reported that between 19% and 25% of participants were black (dependent on treatment group),[82] while one study did not report ethnicity.[81] Most studies included a high proportion of living donors (75 –100%). However, one study reported only 6% living donors in one treatment group and 9% in the other treatment group.[83] This was the only study reporting mean HLA mismatches (2.69–2.89).[83]

TABLE 16 Baseline characteristics: RCTs

Study	Induction	Maintenance	*n*[a]	Mean age, years (SD)	Adolescents *n/N*, %	First transplant *n/N*, %	Male *n/N*, %	Donor type *n/N*, %		Ethnic group[b] *n/N*, %	Mean HLA mismatches Mean (SD)
								Living	Deceased		
Offner *et al.*[73]	BAS	CSA + MMF + CCS	100	10.7 (4.6)	43/100, 43[c]	96/100, 96	56/100, 56.0	30/100, 30	70/100, 70	95/100 white, 95 5/100 other, 5	2.6 (1.2)
	PBO		92	10.8 (4.9)	43/92, 46.7[c]	88/92, 96	62/92, 67.4	32/92, 34.8	60/92, 65.2	84/92, white 91.3 8/92, other 8.7	2.2 (1.0)
Grenda *et al.*[75]	BAS	TAC + AZA + CCS	99	11.5 (4.1)	53/99 53.5[d]	95/99, 96	62/99, 62.6	20/99 20.2	79/99 79.8	NR	2.5 (NR)
	NI		93	11.3 (4.0)	51/93 54.4[d]	87/93, 93.5	57/93, 61.3	16/93 17.2	77/93 82.8	NR	2.3 (NR)
Trompeter *et al.*[77]	Methylprednisolone	TAC + AZA + CCS	103	10.5 (4.6)	41/103 39.8[e]	94/103, 91	64/103, 62.1	16/103, 15.5	87/103, 84.5	90/103, white 87.4 1/103, black 1 1/103, oriental 1 11/103, other 10.7	2.5 (NR)
		CSA + AZA + CCS	93	10.1 (4.5)	34/93, 36.6[e]	79/93, 85	56/93, 60.2	15/93, 16.1	78/93, 83.1	82/92, white 88.2 0/92, black 0 3/92, oriental 3.2 8/92, other 8.6	2.7 (NR)

N/A, not applicable, NI; no induction; NR, not reported; SD, standard deviation.
a ITT population.
b Ethnic group descriptions are reported as coded in the individual papers.
c Adolescents defined as > 12 years and < 19 years.
d Adolescents defined as 12–18 years.
e Adolescents defined as 13–18 years.

TABLE 17 Baseline characteristics: non-randomised studies

Study	Induction	Maintenance therapy	*N*[a]	Mean age, years (SD)	Adolescents *n/N*, %	First transplant *n/N*, %	Male *n/N*, %	Donor type *n/N*, %		Ethnic group *n/N*, %	Mean HLA mismatches (SD)
								Living	Deceased		
Antoniadis *et al.*[81]	Methylprednisolone	CSA + MMF + CCS	7	10 (4–12)[b]	NR	NR	NR	7/7, 100	N/A	NR	NR
		CSA + AZA + CCS	7		NR	NR	NR	7/7, 100	N/A	NR	NR
[c]Benfield *et al.*[82]	OKT3	CSA + MMF + CCS	17	10.7 (5.3)	NR	NR	20/36, 55	25/36, 69	11/36, 31	9/36, 25 black	NR
	CSA	CSA + MMF + CCS	19		NR	NR					NR
	OKT3	CSA + AZA + CCS	17	9.4 (5.1)	NR	NR	19/31, 61	24/31, 77	12/31, 39	6/31, 19 black	NR
	CSA	CSA + AZA + CCS	14		NR	NR					NR
Garcia *et al.*[80]	BAS	TAC + AZA + CCS	12	11.3 (9.3)	NR	NR	6/12, 50%	8/12, 66.7	4/12, 33.3	11/12, 91.7	NR
		CSA + MMF + CCS	12	9.0 (6)	NR	NR	8/12, 66.7	7/12, 58.3	5/12, 41.7	9/12, 75	NR
Staskewitz *et al.*[83]	Prednisone/ methylprednisolone	CSA + MMF + CCS	85[d]	11.5 (3.6)	NR	61/65, 94	42/65, 65	4/65, 6	61/65, 94	65/65, 100 Caucasian	2.69 (0.87)
	NR	CSA + AZA + CCS	54	9.9 (4.7)	NR	53/54, 98	32/54, 59	5/54, 9	49/54, 91	54/54, 100 Caucasian	2.89 (0.96)

DCD, donation after cardiac death; N/A, not applicable; NR, not reported; OKT3, a murine monoclonal antibody muromonab-CD3; SD, standard deviation.

a ITT population.

b Only median and (range) reported.

c This was randomised trial of OKT3 vs. CSA at the time of transplantation. First 31 participants were given AZA and subsequent 36 participants were given MMF. In addition, participants were randomly assigned to receive Sandimmun or Neoral CSA preparations. Only arms with CSA induction were considered in the analyses. Numbers of participants in the OKT3 group were reported from text (17 and 19); however, numbers reported in a table differed (16 and 20; numbers from text were reported because they were relevant to outcomes reported in this section).

d Staskiewitz *et al.*[83] reported results for 65 MMF and 54 AZA participants and the following two publications (Jungraithmayr *et al.*[84] and Jungraithmayr *et al.*[85]) report on 85 MMF and 54 AZA participants.

Results of the included studies

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

A summary comparing our results with those of the adult kidney transplant population (using evidence from parallel HTA appraisal 'Immunosuppressive therapy for kidney transplantation in adults'[68]) is made at the end of this section. Briefly, 11 induction trials, 73 maintenance trials and two trials of both induction and maintenance were included in the parallel HTA.

Induction therapy

Two RCTs of induction therapy[73,75] (reported in four publications[73–76] and one abstract[72]) in children and adolescents were identified in the review; the population characteristics are summarised in *Table 16*. Offner *et al.*[73] compared BAS induction therapy with PBO: BAS + CSA + MMF + CCS versus PBO + CSA + MMF + CCS. Grenda *et al.*[75] compared BAS induction therapy with no induction: BAS + TAC + AZA + CCS versus TAC + AZA + CCS. No RCTs were identified that evaluated r-ATG in children and adolescents.

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

Mortality

Both RCTs[73,75] provided data on mortality for BAS versus no induction or PBO (*Table 18*). Grenda *et al.*[75] reported the longest follow-up data at 2 years post transplant. No evidence of a statistically significant difference in overall survival between BAS and comparator arms was reported at any time point.

Summary

In summary, there was no evidence that BAS improved survival when compared with PBO or no induction. This is similar to the conclusions of the previous HTA.[2]

Graft loss

Both RCTs[73,75] provided data on graft loss for BAS versus no induction or PBO (*Table 19*). Grenda *et al.*[75] reported the longest follow-up data of 2 years. No evidence of a significant difference between the BAS and control arms was reported for any data point.

The pooled results at 6-month follow-up did not find any significant difference between BAS and control arms for graft loss [OR = 93 favours BAS; 95% confidence interval (CI) 0.29 to 2.97, $I^2 = 0\%$, $\tau^2 = 0$; *Figure 9*].

Summary

In summary, there was no evidence that BAS lowered graft loss when compared with PBO or no induction. This is similar to the conclusions of the previous HTA.[2]

TABLE 18 Mortality: RCTs

Study	Treatment	3 months		6 months		1 year		2 years	
		n events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)
[a]Offner *et al.*[73]	BAS + CSA + MMF + CCS	1/100, 1	2.79 (0.11 to 69.31)	2/100, 2	4.69 (0.22; 99.10)	3/100, 3	6.64 (0.34 to 130.33)	NR	N/A
	PBO + CSA + MMF + CCS	0/92, 0		0/92, 0		0/92, 0		NR	
Grenda *et al.*[75]	BAS + TAC + AZA + CCS	NR	N/A	0/99, 0	N/A	NR	N/A	0/99, 0	0.33 (0.01 to 8.20)
	NI + TAC + AZA + CCS	NR		0/93, 0		NR		1/93, 1	

CI, confidence interval; N/A, not applicable; NI; no induction; NR, not reported;
a Two additional deaths in BAS arm: one at day 21 (this participant was excluded from ITT as death occurred before transplantation) and one at day 397 (not included as 2 years data were not reported). All ORs were calculated by PenTAG. OR < 1 favours BAS.

TABLE 19 Graft loss: RCTs

Study	Treatment	6 months		1 year		2 years	
		n events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)
Offner *et al.*[73]	BAS + CSA + MMF + CCS	1/100, 1	0.92 (0.06 to 14.92)	1/100, 1	0.92 (0.06 to 14.92)	NR	N/A
	PBO + CSA + MMF + CCS	1/92, 1		1/92, 1		NR	
Grenda *et al.*[75]	BAS + TAC + AZA + CCS	5/99, 5	0.94 (0.26 to 3.34)	NR	N/A	5/99, 5	0.50 (0.16 to 1.54)
	NI + TAC + AZA + CCS	5/93, 5		NR		9/93, 10	

CI, confidence interval; N/A, not applicable; NI; no induction; NR, not reported.
All ORs were calculated by PenTAG. OR < 1 favours BAS.

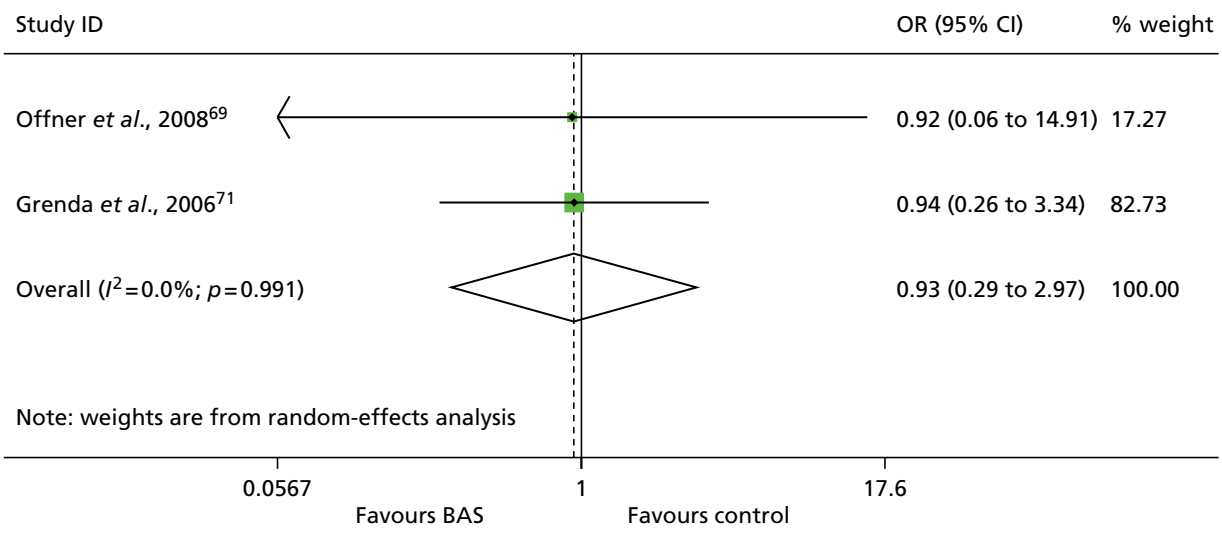

FIGURE 9 Graft loss: randomised control trials. Control, no induction/PBO control arms. $\tau^2 = 0$. Studies included were Offner *et al.*[73] and Grenda *et al.*[75]

Graft function

Both RCTs[73,75] reported graft function estimated using the Schwartz equation (ml/minute/1.73 m^2; *Table 20*). There were no statistically significant differences between BAS and control arms at any data point (between 6 months and 2 years). Both RCTs reported 6-month and 2-year follow-ups, no standard deviation (SD) was reported at 2 years by Offner *et al.*[73] and no SD was reported at 6 months or 2 years by Grenda *et al.*[75]

To allow for combining the results at 6-month and 2-year follow-ups, a SD of 26 ml/minute/1.73 m^2 was used ('average' SD calculated from SD available at 6-month and 2-year follow-ups; *Figure 10*). The pooled results do not suggest any difference for eGFR between BAS and control arms: weighted mean difference (WMD) = –4.20 (favours controls; 95% CI –9.60 to 1.20, $I^2 = 0\%$) at 6 months and WMD = –1.38 (favours controls; 95% CI –7.20 to 4.44, $I^2 = 0\%$) at 2 years. Grenda *et al.*[75] also reported incidences of DGF (defined as requiring dialysis for more than 1 day during the first study week). The rate of DGF was not statistically significantly different between the two arms: 11 out of 99 participants (11%) and 5 out of 93 participants (5%) in BAS and no induction arms, respectively (*p*-value was not reported).[75]

TABLE 20 Graft function (eGFR): RCTs

		6 months		1 year		2 years	
Study	Treatment	Mean (SD)	*t*-test (*p*-value)	Mean (SD)	*t*-test (*p*-value)	Mean (SD)	*t*-test (*p*-value)
[a]Offner *et al.*[73]	BAS + CSA + MMF + CCS	80 (27)	–1.73 (0.08)	79 (23)	–0.88 (0.38)	80 (NR)	–0.92 (0.36)
	PBO + CSA + MMF + CCS	87 (29)		82 (24)		84 (NR)	
[b]Grenda *et al.*[75]	BAS + TAC + AZA + CCS	77.6 (NR)	–0.48 (0.63)	NR	N/A	66.7 (NR)	0.22 (0.82)
	NI + TAC + AZA + CCS	79.4 (NR)		NR		65.8 (NR)	

N/A, not applicable; NI; no induction; NR, not reported; SD, standard deviation.
a The number of participants evaluated at 2-year follow-up was 79 in BAS arm and 65 in PBO arm.
b The number of participants evaluated at 2-year follow-up was 84 in BAS arm and 80 in NI arm. *t*-tests were calculated by PenTAG, for data points with no SD reported a SD of 26 was used. Graft function was estimated using the Schwartz equation (ml/minute/1.73 m^2).

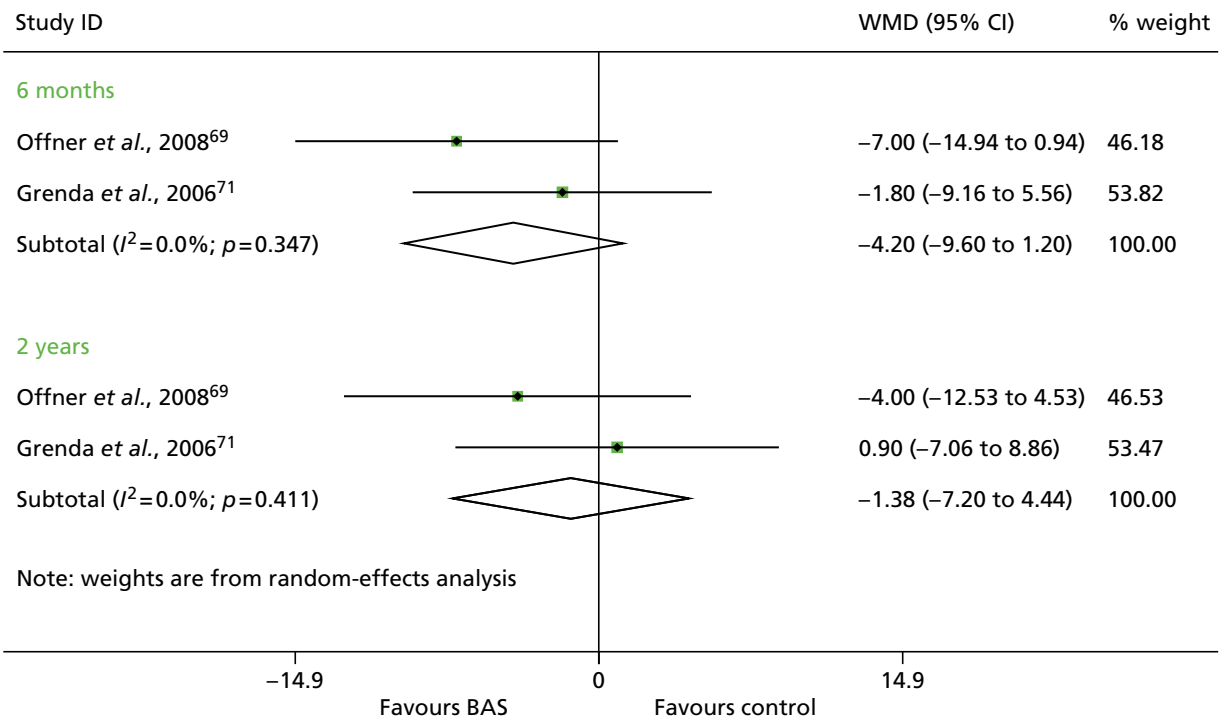

FIGURE 10 Graft function (eGFR): randomised control trials. Control, no induction/PBO control arms. For data points with no SD reported, a SD of 26 was used. Graft function was estimated using the Schwartz equation (ml/minute/1.73 m^2). Studies included were Offner *et al.*[73] and Grenda *et al.*[75]

Summary

In summary, there was no evidence that BAS lowered graft function when compared with PBO or no induction. The child/adolescent RCT evidence identified in the previous HTA review[2] concluded that BAS did not increase serum creatinine levels at 1-year follow-up when compared with no induction.

Acute rejection

Both RCTs[73,75] provided data on biopsy-proven acute rejection (BPAR) for BAS versus no induction or PBO (*Table 21*). Grenda *et al.*[75] reported the longest follow-up data of 2 years. No evidence of a statistically significant difference between the BAS and the comparators arms was reported for any data point. The pooled results at 6 months did not find any difference between BAS and control arms for BPAR: OR = 0.71 (favours BAS; 95% CI 0.40 to 1.27, $I^2 = 15.7\%$, $\tau^2 = 0.03$; *Figure 11*).

In addition, Grenda *et al.*[75] also reported BPAR separately for younger and older age groups (< 12 years and ≥ 12 years, respectively). The incidence of BPAR was lower in the patients < 12 years in the no induction arm (4/42, 10%) than the same age group with BAS (6/46, 13%), although this difference was not statistically significant (Wilcoxon–Gehan test, *p*-value was not reported). Conversely, incidences of BPAR were higher for the patients ≥ 12 years with no induction (15/51, 29%) than the same age group with BAS (13/53, 25%); however, again, this difference was not statistically significant (Wilcoxon–Gehan test, *p*-value was not reported).

Finally, the data from Offner *et al.*[75] of 79 BAS and 65 PBO on study participants (reported in an abstract by Jungraithmayr *et al.*[72]) found a cumulative AR rate of 33% versus 35% in the BAS and PBO arms, respectively, at 2 years and a cumulative AR rate of 41% versus 45% in the BAS and PBO arms, respectively, at 5 years. Results were not statistically significant at either data point.[72]

TABLE 21 Biopsy-proven acute rejection: RCTs

		3 months		6 months		1 year		2 years	
Study ID	Treatment	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)
Offner *et al.*[73]	BAS + CSA + MMF + CCS	6/100, 6	0.39 (0.14 to 1.07)	11/100, 11	0.51 (0.23 to 1.14)	13/100, 13	0.51 (0.24; 1.08)	NR	N/A
	PBO + CSA + MMF + CCS	13/92, 14		18/92, 20		21/92, 23		NR	
Grenda *et al.*[75]	BAS + TAC + AZA + CCS	NR	N/A	19/99, 19	0.93 (0.46 to 1.87)	NR	N/A	23/99, 23	0.74 (0.39 to 1.40)
	NI + TAC + AZA + CCS	NR		19/93, 20		NR		27/93, 29	

N/A, not applicable; NI, no induction; NR, not reported.

Note

All ORs were calculated by PenTAG. OR < 1 favours BAS.

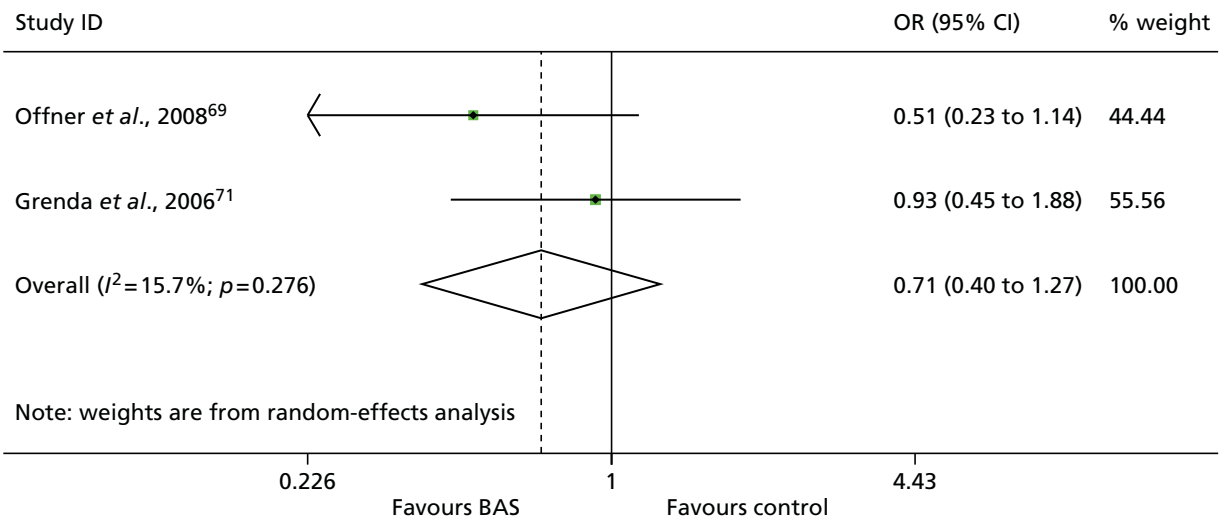

FIGURE 11 Biopsy-proven acute rejection: RCTs. Control, no induction/PBO control arms. $\tau^2 = 0.03$. Studies included were Offner *et al.*[73] and Grenda *et al.*[75]

Time to BPAR (*Table 22*) was only reported by Grenda *et al.*[75] The median time to BPAR appears to be similar between the two arms (*p*-values were not reported in the study).[75] Time to first BPAR episode or treatment failure within the first 6 months post transplant was the primary efficacy end point in Offner *et al.*[73] The proportion of children and adolescents (Kaplan–Meier estimates) achieving this efficacy point was 16.7% in the BAS arm and 21.7% in the PBO arm. The difference was not statistically significant; HR of 0.72 (favours BAS; 95% CI 0.42 to 1.26).[73]

Severity of BPAR was reported by Offner *et al.*[73] and Grenda *et al.*[75] (*Table 23*). All BPAR episodes in BAS treated patients were mild (grade IA or IB), whereas 8 out of 18 episodes in the PBO group were moderate (grade IIA) in Offner *et al.*[73] Similarly, there seemed to be more moderate BPAR episodes (Banff 2) in the no induction group than the BAS group in Grenda *et al.*[75] However, Offner *et al.*[73] also performed biopsies in children who had not recently experienced clinical signs of rejection or undergone biopsy (at 6 months, $n = 64$ and $n = 60$ in BAS and PBO groups, respectively) to identify subclinical rejections. The rate ($p = 0.055$) and severity (*p*-value not reported) of subclinical rejections was higher in the BAS group (25.0%) than in the PBO group (11.7%).[73]

Summary

In summary, there was no evidence that BAS reduced incidences of, severity and time to BPAR when compared with PBO or no induction. This is similar to the conclusions of the previous HTA; no significant differences in BPAR for BAS versus no therapy in children were found.[2]

TABLE 22 Time to BPAR: RCTs

Study	Treatment	Time to AR median (range), days
Grenda *et al.*[75]	BAS + TAC + AZA + CCS	41 (2–176)
	NI + TAC + AZA + CCS	43 (1–150)

NI, no induction.

TABLE 23 Severity of AR: RCTs

	BAS + CSA + MMF + CCS *n* events/ *N* participants (%)				PBO/NI + CSA + MMF + CCS *n* events/ *N* participants (%)				
Study	BPAR	Banff 1	Banff 2	Banff 3	BPAR	Banff 1	Banff 2	Banff 3	*p*-value
Grenda *et al.*[75]	19/99 (19.2)	15/99 (15)	3/99 (3)	1/99 (1)	19/93 (20.4)	11/93 (12)	7/93 (8)	1/93 (1)	NR
[a]Offner *et al.*[73]	11/100 (11)	Grade IA: 8/100 (8)	Grade IIA: 0/100 (0)	0/100 (0)	18/92 (19.6)	Grade IA: 9/92 (10)	Grade IIA: 8/92 (9)	0/92 (0)	0.308[b]
		Grade IB: 3/100 (3)	Grade IIB: 0/100 (0)			Grade IB: 1/92 (1)	Grade IIB: 0/92 (0)		

NI, no induction.
a One patient in the PBO group experienced two episodes of BPAR.
b Wilcoxon signed-rank test.[73,96]

Adverse events

Two RCTs[73,75] provided data on AEs for BAS versus no induction or PBO. Offner *et al.*[73] reported AEs that occurred in at least 10% of the safety population. Grenda *et al.*[75] reported AEs that occurred in at least 10% in either treatment arm. The AEs reported in these trials are summarised in *Table 24*.

In one trial,[73] more infections were found with BAS than with PBO (OR = 2.23; favours PBO; 95% CI 1.03 to 4.68).[73] In Grenda *et al.*[75] toxic nephropathy was higher in the BAS arm than in the no induction arm (14.1% vs. 4.3%, respectively; $p = 0.03$). Similarly, abdominal pain was higher in the BAS arm than no induction (11.1% vs. 2.2%, respectively; $p = 0.02$).[75]

Grenda *et al.*[75] also reported changes in glucose metabolism disorders. None of the children and adolescents had a glucose metabolism disorder {described as glucose tolerance decreased, hyperglycaemia or diabetes mellitus using the modified coding symbols for a thesaurus of adverse reaction terms [The Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary]} at baseline. However, during the study, 13 patients (13.1%) in the BAS arm and 10 patients (10.8%) in the no induction arm developed a glucose metabolism disorder within the first 6 months. One new case of impaired glucose metabolism was noted at 1 year; this new case resolved at 2 years.

Summary

In summary, more infections were found with BAS than with PBO (OR = 2.23, favours PBO; 95% CI 1.03 to 4.68).[73] In addition, Grenda *et al.*[75] found that toxic nephropathy and abdominal pain were higher in the BAS arm than in the no induction arm ($p = 0.03$ and $p = 0.02$, respectively). The previous HTA reported post-transplant diabetes mellitus in only one study[90] and the rest of the data were confidential and were, therefore, omitted from the report.

Maintenance therapy

One RCT[77] and four non-RCTs[80–83] of maintenance therapy in children and adolescents were included in the review. RCT evidence evaluating TAC and non-RCT evidence on the use of TAC and MMF was identified.

The population characteristics from the one RCT of maintenance treatment identified in the review are summarised in *Table 16*. Trompeter *et al.*[77] compared the use of TAC + AZA + CCS with CSA + AZA + CCS.[77] No RCTs evaluated TAC-PR, MMF, MPS, EVL, SRL and BEL in children and adolescents.

TABLE 24 Adverse events, induction regimens: RCTs

AE	Follow-up	[a]Offner *et al.*[73] BAS *n* events/ *N* participants, %	[a]Offner *et al.*[73] PBO *n* events/ *N* participants, %	[a]Offner *et al.*[73] OR (95% CI)	[b]Grenda *et al.*[75] BAS *n* events/ *N* participants, %	[b]Grenda *et al.*[75] NI *n* events/ *N* participants, %	[b]Grenda *et al.*[75] OR (95% CI)
Any infections	1 year	104/109, 95	84/93, 90	2.23 (1.03 to 4.68)	NR	NR	N/A
	1–2 years	13/79, 16	12/65, 12	0.87 (0.37 to 2.06)	NR	NR	N/A
Serious infections	1 year	58/109, 53	45/93, 48	1.21 (0.72 to 2.05)	NR	NR	N/A
	2 years	NR	NR	N/A	NR	NR	N/A
UTI	6 months	NR	NR	N/A	19/99, 19	26/93, 28	0.61 (0.31 to 1.20)
	1 year	38/109, 29	21/93, 23	1.84 (0.99 to 3.40)	NR	NR	N/A
Bacterial infections	6 months	NR	NR	N/A	32/99, 32	30/93, 32	1.00 (0.55 to 1.81)
	2 years	NR	NR	N/A	47/99, 45	45/93, 48	0.96 (0.56 to 1.65)
Viral infections	6 months	NR	NR	N/A	15/99, 15	15/93, 16	0.93 (0.43 to 2.02)
	2 years	NR	NR	N/A	26/99, 26	24/93, 26	1.02 (0.54 to 1.93)
CMV infections	6 months	NR	NR	N/A	7/99, 7	2/93, 2	3.46 (0.70 to 17.11)
	1 year	14/109, 13	8/93, 9	1.57 (0.63 to 3.92)	NR	NR	N/A
EBV infections	1 year	10/109, 9	11/93, 12	0.75 (0.30 to 1.86)	NR	NR	N/A
Solid tumour	6 months	NR	NR	N/A	0/99, 0	0/93, 0	N/A
	1 year	1/109, 1	0/93, 0	2.58 (0.10 to 64.19)	NR	NR	N/A
PTLD	6 months	NR	NR	N/A	0/99, 0	2/93, 2	0.18 (0.01 to 3.88)
	1 year	2/109, 2	5/93, 5	0.33 (0.06 to 1.74)	NR	NR	N/A
	2 years	NR	NR	N/A	1/99, 1	2/93, 2	0.46 (0.04 to 5.21)
Hypertension	6 months	NR	NR	N/A	34/99, 34	36/93, 39	0.83 (0.47 to 1.47)
Any AE	6 months	NR	NR	N/A	91/99, 92	84/93, 90	1.22 (0.58 to 2.57)
	1 year	108/109, 99	92/93, 99	1.17 (0.16, 8.59)	NR	NR	N/A

CMV, cytomegalovirus; EBV, Epstein–Barr virus; N/A, not applicable; NI, no induction; NR, not reported; PTLD, post-transplant lymphoproliferative disease; UTI, urinary tract infection.
a AE reported if incidence was ≥ 10% in safety population.
b AE reported if incidence was ≥ 10% in either treatment arm; 2-year follow-up data reported in Webb *et al.*[76] All ORs were calculated by PenTAG.

The population characteristics from the four non-RCTs of maintenance treatment identified in the review[80–83] are summarised in *Table 17*. Garcia *et al.*[80] compared the use of BAS + TAC + AZA + CC with BAS + CSA + MMF + CCS in a retrospective cohort study. Antoniadis *et al.*[81] compared the use of CSA + MMF + CCS with CSA + AZA + CCS in a non-RCT. Benfield *et al.*[82] reported retrospective analyses of a randomised, multicentre trial of OKT3 (a murine monoclonal antibody muromonab-CD3) versus CSA induction therapy with two types of maintenance therapies, but only the comparison of CSA + MMF + CCS with CSA + AZA + CCS was included in this review. Finally, Staskewitz *et al.*[83] compared the use of CSA + MMF + CCS with CSA + AZA + CCS in a historically controlled study. No non-randomised evidence was identified regarding the use of TAC-PR, MPS, EVL, SRL and BEL in the child/adolescent population.

Mortality

Randomised controlled trials

Trompeter *et al.*[77] compared the use of TAC + AZA + CCS with CSA + AZA + CCS. The trial reported similar survival rates in both arms, which were not significantly different at 6 months, 1 year, 2 years or 4 years (*Table 25*).

Non-randomised controlled trials

Three non-RCTs[80,81,83] provided data on mortality (*Table 26*) and two trials compared MMF with AZA.[81,83] The remaining study[80] compared TAC + AZA with CSA + MMF. Staskewitz *et al.*[83] reported long-term follow-up of up to 5 years, but no further deaths were recorded in either arm. No statistically significant difference in child/adolescent survival between MMF and AZA and between TAC + AZA and CSA + MMF was reported.

Summary

In summary, no difference in survival was found between TAC and CSA from the child/adolescent RCT. In addition, no difference was found between TAC and CSA, and between MMF and AZA, in the child/adolescent non-RCT evidence. This is similar to the conclusions of the previous HTA.[2]

TABLE 25 Mortality: RCTs

	Trompeter *et al.*[77]		
Follow-up	TAC + AZA + CCS *n* events/ *N* participants, %	CSA + AZA + CCS *n* events/ *N* participants, %	OR (95% CI)
6 months	3/103, 3	3/93, 3	0.90 (0.18 to 4.58)
1 year	3/103, 3	3/93, 3	0.90 (0.18 to 4.58)
2 years	3/103, 3	4/93, 4	0.67 (0.15 to 3.07)
4 years	5/103, 5	4/93, 4	1.14 (0.30 to 4.36)

NR, not reported.
Note
All ORs were calculated by PenTAG.

TABLE 26 Mortality: non-randomised studies

Study	Treatment	3 months		6 months		1 year	
		n events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)
Garcia *et al.*[80]	BAS + TAC + AZA + CCS	0/12, 0	N/A	NR	N/A	NR	N/A
	BAS + CSA + MMF + CCS	0/12, 0		NR		NR	
Antoniadis *et al.*[81]	CSA + MMF + CCS	NR	N/A	NR	N/A	0/7, 0	N/A
	CSA + AZA + CCS	NR		NR		0/7, 0	
[a]Staskewitz *et al.*[83]	CSA + MMF + CCS	NR	N/A	0/86, 0	0.20 (0.008 to 5.14)	0/86, 0	0.08 (0.004 to 1.67)
	CSA + AZA + CCS	NR		1/54, 2		3/54, 6	

N/A, not applicable; NR, not reported.
a No further deaths were recorded in either arm at a 5-year follow-up.
Note
All ORs were calculated by PenTAG.

Graft loss

Randomised controlled trials

Trompeter *et al.*[77] compared the use of TAC + AZA + CCS with CSA + AZA + CCS. Graft loss appeared to be higher in the CSA arm than in the TAC arm, especially at the longer follow-up (2–4 years), but the difference was not statistically significant (*Table 27*).

Non-randomised controlled trials

Three non-RCTs[80,81,83] provided data on graft loss (*Table 28*). Two trials compared MMF with AZA.[81,83] The remaining study[80] compared TAC + AZA with CSA + MMF. Staskewitz *et al.*[83] found better graft survival in MMF than with AZA in up to a 5-year follow-up,[83] while Antoniadis *et al.*[81] did not find a statistically significant difference in graft loss between MMF and AZA. No statistically significant difference in graft loss between TAC + AZA and CSA + MMF regimens was reported.[80]

Summary

In summary, no statistically significant difference was found between TAC and CSA for graft loss. However, the RCT child/adolescent evidence identified in the previous HTA review[2] concluded that TAC lowered graft loss at 2- (10/103 vs. 19/93; $p = 0.03$) and 4-year follow-ups (11/103 vs. 20/93; $p = 0.03$). This discrepancy in result is because we have excluded graft loss due to death from our analyses. This was, first, to avoid double counting with another key outcome (mortality) and, second, because death-censored graft survival is a well-established clinical outcome to which death with functioning graft (DWFG) is intrinsically related, just as mortality is to overall survival. It should be noted that after the removal of graft loss due to death from the analyses, the evidence from Trompeter *et al.*[77] suggested borderline statistically non-significantly lower graft loss in TAC than CSA (OR = 0.41, 95% CI 0.16 to 1.00, and OR = 0.43, 95% CI 0.18 to 1.01 at 2- and 4-year follow-ups, respectively). In addition, the current review and the previous HTA[2] found better graft survival in MMF than in AZA (up to 5-year follow-up) in one non-RCT.[83]

TABLE 27 Graft loss: RCTs

	Trompeter *et al.*[77]		
Follow-up	TAC + AZA + CCS *n* events/ *N* participants, %	CSA + AZA + CCS *n* events/ *N* participants, %	OR (95% CI)
6 months	6/103, 6	13/93, 14	0.38 (0.14 to 1.05)
1 year	8/103, 8	15/93, 16	0.44 (0.18 to 1.09)
2 years	8/103, 8	16/93, 17	0.41 (0.16 to 1.00)
4 years	9/103, 9	17/93, 18	0.43 (0.18 to 1.01)

Note
All ORs were calculated by PenTAG.

TABLE 28 Graft loss: non-randomised studies

		3 months		1 year		2 years		3 years		4 years		5 years	
Study	Treatment	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)	*n* events/ *N* participants, %	OR (95% CI)
Garcia *et al.*[80]	BAS + TAC + AZA + CCS	0/12, 0	0.30 (0.01 to 8.30)	NR	N/A	NR	N/A	NR	N/A	NR	N/A	NR	N/A
	BAS + CSA + MMF + CCS	1/12, 8		NR		NR		NR		NR		NR	
Antoniadis *et al.*[81]	CSA + MMF + CCS	NR	N/A	0/7, 0	N/A	NR	N/A	NR	N/A	NR	N/A	NR	N/A
	CSA + AZA + CCS	NR		0/7, 0		NR		NR		NR		NR	
Staskewitz *et al.*[83]	CSA + MMF + CCS	NR	N/A	2/86, 2	0.14 (0.03 to 0.68)	4/86, 5	0.24 (0.07 to 0.84)	4/86, 5	0.15 (0.05 to 0.51)	7/86, 8	0.25 (0.09 to 0.69)	8/86, 9	0.24 (0.09 to 0.63)
	CSA + AZA + CCS	NR		8/54, 15		9/54, 17		13/54, 24		14/54, 26		16/54, 30	

N/A, not applicable; NR, not reported.

Note

All ORs were calculated by PenTAG.

Graft function

Randomised controlled trials

Trompeter *et al.*[77] compared the use of TAC + AZA + CCS with CSA + AZA + CCS and reported graft function estimated using the Schwartz equation (ml/minute/1.73 m^2). Significantly higher graft function in the TAC arm than in the AZA arm was reported (*Table 29*). No data on DGF were reported.[77]

Non-randomised controlled trials

Only one non-RCT provided data on graft function. Garcia *et al.*[80] compared TAC + AZA with CSA + MMF and reported graft function at a 3-month follow-up (*Table 30*). There were no significant differences between the arms for graft function [eGFR, creatinine clearance (ml/minute)]. Garcia *et al.*[80] also reported incidences of DGF. The same rate of DGF was reported in the two arms [1/12 (8%) and 1/12 (8%), respectively].[80]

Summary

In summary, lower graft function was associated with TAC compared with CSA in the child/adolescent RCT. This is similar to the conclusions of the previous HTA.[2] In addition, no difference in graft function between TAC + AZA and CSA + MMF regimens was reported in the one non-RCT.[80] However, the previous HTA included a non-RCT by Neu *et al.*[94] which found significantly better graft function at 1- and 2-year follow-ups ($p < 0.01$).

TABLE 29 Graft function (eGFR): RCTs

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

a N values reported in Trompeter *et al.*[77] and Filler *et al.*[79] differed; values from Filler *et al.*[79] were used. *t*-tests were calculated by PenTAG.
Evidence suggesting a statistically significant difference between treatments is highlighted in bold.
Graft function estimated using the Schwartz equation (ml/minute/1.73 m^2).

TABLE 30 Graft function (eGFR): non-randomised studies

		3 months	
Study ID	Treatment	Mean (SD)	*t*-test (*p*-value)
Garcia *et al.* 2002[80]	BAS + TAC + AZA + CCS	71 (23)	–1.28 (0.21)
	BAS + CSA + MMF + CCS	82 (19)	

Note
t-tests were calculated by PenTAG; graft function was estimated by measuring creatinine clearance (ml/minute).

Acute rejection

Randomised controlled trials

Trompeter *et al.*[77] compared the use of TAC + AZA + CCS with CSA + AZA + CCS, reporting statistically significantly higher BPAR at a 6-month follow-up, and AR (which was not biopsy proven) at 6-month and 1-year follow-ups in the CSA arm compared with the TAC arm (*Table 31*). In addition, 2- and 4-year follow-up data are available for Trompeter *et al.*[77] in Filler *et al.*[79] However, these analyses do not take into account those who were lost to follow-up and those who died. In the second year of the trial, 7 out of 77 patients in the TAC group and 9 out of 71 patients in the CSA group experienced AR ($p = 0.6041$, Fisher's exact test).[79] In the third year, 2 out of 70 patients in the TAC group and 6 out of 57 patients in the CSA group experienced AR ($p = 0.1454$, Fisher's exact test).[79] Finally, in the fourth year, 2 out of 57 patients in the TAC group and 6 out of 42 patients in the CSA group experienced AR ($p = 0.1359$, Fisher's exact test).[79] Rejection episodes frequently occurred in the same patients that experienced AR previously. Although overall treatment group differences were maintained after the first year, the annual differences in AR were not statistically significant for years 2, 3 and 4.[79] Time to, and severity of, AR were not reported in Trompeter *et al.*[77]

Non-randomised controlled trials

Four non-RCTs[80–83] provided data on BPAR (*Table 32*)[80–83] and three studies compared MMF with AZA.[81–83] The remaining study[80] compared TAC + AZA with CSA + MMF. No statistically significant difference in BPAR was found between the MMF arm and AZA arms, and between TAC + AZA and CSA + MMF.

The pooled results at a 6-month follow-up suggested borderline statistically non-significantly lower BPAR in MMF compared with AZA (OR = 0.48, 95% CI 0.23 to 1.02, $I^2 = 0\%$, $\tau^2 = 0$; *Figure 12*).

In addition, Garcia *et al.*[80] reported the severity of AR (*Table 33*); one Banff 3 episode was reported in TAC + AZA and two Banff 1 episodes were reported in CSA + MMF. No study reported time to BPAR.

TABLE 31 Acute rejection: RCTs

			6 months		1 year[a]	
Study ID	Acute rejection	Treatment	*n* events/*N* participants, %	OR (95% CI)	*n* events/*N* participants, %	OR (95% CI)
Trompeter *et al.* 2002[77]	BPAR[b]	TAC + AZA + CCS	17/94, 18	**0.29 (0.15 to 0.57)**	NR	N/A
		CSA + AZA + CCS	37/86, 43		NR	
	AR	TAC + AZA + CCS	38/103, 37	**0.40 (0.23 to 0.71)**	42/103, 41	**0.43 (0.25 to 0.76)**
		CSA + AZA + CCS	55/93, 59		57/93, 62.3	

N/A, not applicable; NR, not reported.
a 1-year follow-up reported in Trompeter *et al.*[77] Between months 6 and 12, four TAC patients and two CSA patients experienced a first AR.
b 94 TAC and 86 CSA participants had renal biopsies; 13 out of 18 centres reported biopsy findings. In addition, biopsies were not mandatory in case of clinically suspected AR.
All ORs were calculated by PenTAG.
Evidence suggesting a statistically significant difference between treatments is highlighted in bold.

TABLE 32 Biopsy-proven acute rejection: non-randomised studies

Study	Treatment	3 months		6 months	
		n events/*N* participants, %	OR (95% CI)	*n* events/*N* participants, %	OR (95% CI)
Garcia *et al.* 2002[80]	BAS + TAC + AZA + CCS	1/12, 8	0.45 (0.04 to 5.78)	NR	N/A
	BAS + CSA + MMF + CCS	2/12, 17		NR	
Antoniadis *et al.* 1998[81]	CSA + MMF + CCS	NR	N/A	0/7, 0	0.08 (0.003 to 1.94)
	CSA + AZA + CCS	NR		3/7, 43	
Staskewitz *et al.* 2001[83]	CSA + MMF + CCS	NR	N/A	10/65, 15	0.52 (0.21 to 1.29)
	CSA + AZA + CCS	NR		14/54, 26	
Benfield *et al.* 1999[82]	CSA + MMF + CCS	NR	N/A	4/17, 24[a]	0.56 (0.13 to 2.47)
	CSA + AZA + CCS	NR		6/17, 35	

N/A, not applicable; NR, not reported.
a Reported in text as 4 out of 17, 23%.
All ORs were calculated by PenTAG.

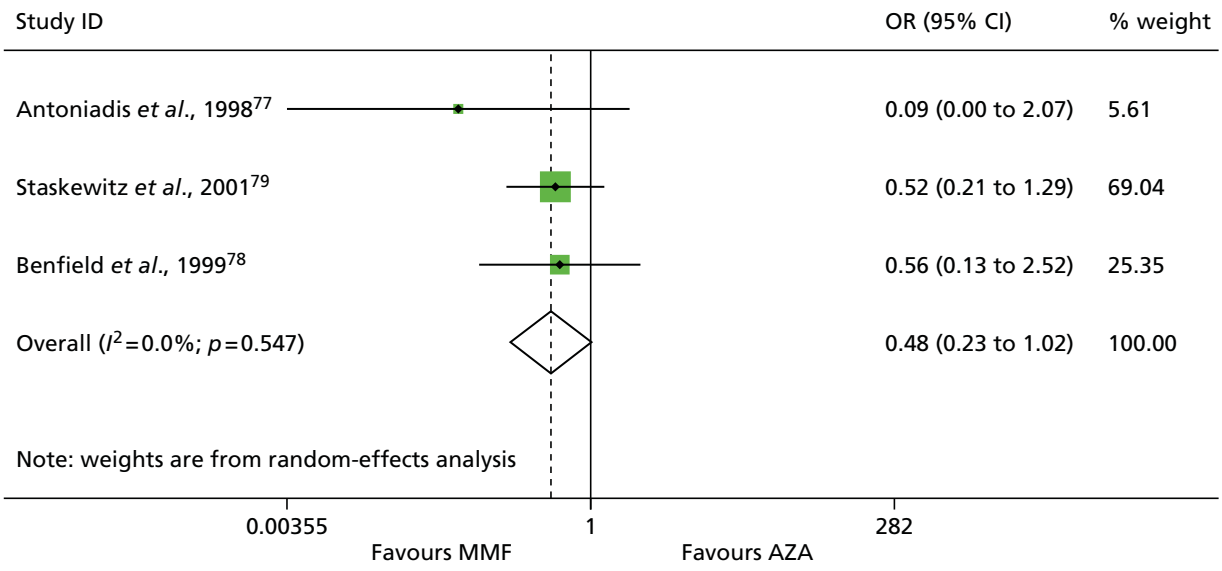

FIGURE 12 Biopsy-proven acute rejection: non-randomised studies. $\tau^2 = 0$. Studies included were Antoniadis *et al.*,[81] Staskewitz *et al.*[83] and Benfield *et al.*[82]

TABLE 33 Severity of AR: non-randomised studies

Study	Treatment	3 month *n* events/*N* participants, %		
		Banff 1	Banff 2	Banff 3
Garcia *et al.* 2002[80]	BAS + TAC + AZA + CCS	0/12, 0	0/12, 0	1/12, 8
	BAS + CSA + MMF + CCS	2/12, 17	0/12, 0	0/12, 0

Note
No Banff 2 AR was reported, assumed 0 and 0 events of Banff 2 in each arm.

Summary

In summary, higher rates of BPAR were found in CSA than TAC in the one included child/adolescent RCT with 6-month data.[77] The RCT child/adolescent evidence identified in the previous HTA review[2] also concluded more BPAR in the CSA arm than the TAC.[77] However, the limited longer follow-up data from this study did not find statistically significant differences in AR between TAC and CSA at 2- and 4-year follow-ups.[79] In addition, no statistically significant difference in BPAR was found between the MMF arm and AZA arms, and between TAC + AZA and CSA + MMF arms in the non-randomised evidence. The pooled non-RCT child/adolescent evidence identified in the previous HTA review suggested less BPAR with MMF compared with AZA [relative risk (RR) = 0.39 favours MMF; 95% CI 0.19 to 0.79]. Similarly, our analyses suggested borderline statistically non-significantly lower BPAR in MMF than AZA at 6-month follow-up (OR = 0.48, 95% CI 0.23; 1.02, $I^2 = 0\%$, $\tau^2 = 0$).

Adverse events

Randomised controlled trials

One child/adolescent RCT[77] provided data on AE for maintenance treatments. This study compared the use of TAC + AZA + CCS with CSA + AZA + CCS and reported no statistically significant differences between TAC and CSA for a range of AEs (*Table 34*). In addition, the incidence of new-onset diabetes mellitus after transplantation (NODAT) (defined as insulin use for > 30 consecutive days in previously non-diabetic patients) was not significantly different between TAC and CSA; NODAT was reported for 3 out of 100 children and adolescents (3.0%) in the TAC group and 2 out of 93 children and adolescents (2.2%) in the CSA group.[77] The proportion of children and adolescents withdrawing owing to AEs was 10% (10/103) in TAC and 15% (14/93) in CSA arms (OR = 0.61; favours TAC; 95% CI 0.25 to 1.44). Finally, Trompeter *et al.*[77] reported that a deficiency of magnesium in the blood and diarrhoea were more common with TAC than with CSA [34.0% compared with 12.9% ($p = 0.001$) and 13.6% compared with 3.2% ($p = 0.011$), respectively], while excessive hair growth, flu syndrome and swollen gums were less common with TAC than with CSA [0.0% compared with 7.5% ($p = 0.005$), 0.0% compared with 5.4% ($p = 0.023$) and 0.0% compared with 5.4% ($p = 0.023$), respectively].[77]

TABLE 34 Adverse events, maintenance studies: RCTs

	AE *n* events/*N* participants, %		
	[a]Trompeter *et al.*[77]		
Adverse events	TAC + AZA + CCS	CSA + AZA + CCS	OR (95% CI)
Any infections	71/103, 69	60/93, 65	0.88 (0.45 to 1.67)
UTI	30/103, 30	31/93, 33	0.82 (0.45 to 1.49)
Bacterial infections	43/103, 42	38/93, 41	1.04 (0.60 to 1.80)
Viral infections	23/103, 22	23/93, 25	0.88 (0.45 to 1.69)
PTLD	1/103, 1	2/93, 2	0.45 (0.04 to 5.01)
Solid tumour	1/103, 1	0/93, 0	2.73 (0.11 to 67.99)
Hypertension	71/103, 69	57/93, 61	1.40 (0.83 to 2.36)
Any AE	98/103, 95	93/93, 100	0.10 (0.01 to 1.57)

PTLD, post-transplant lymphoproliferative disease; UTI, urinary tract infection.
Note
a All ORs were calculated by PenTAG.

Non-randomised controlled trials

Three non-RCTs provided data on AEs (*Table 35*)[80,81,83] and two trials compared MMF with AZA.[81,83] The remaining study[80] compared TAC + AZA with CSA + MMF.[80] Staskewitz *et al.*[83] reported AEs only for the MMF group and not for the historic control AZA group. No statistically significant between-group differences in AEs were found (see *Table 35*) in the non-RCTs that did compare treatment groups.

In addition, Staskewitz *et al.*[83] reported AEs up to 5 years of follow-up for the MMF group (see *Appendix 5*, *Table 140*).[84,85]

TABLE 35 Adverse events, maintenance studies: non-randomised studies

Adverse events	Follow-up	AE *n* events/*N* participants, %						
		Garcia *et al.*[80]			Antoniadis *et al.*[81]			Staskewitz *et al.*[83]
		TAC + AZA	CSA + MMF	OR (95% CI)	MMF	AZA	OR (95% CI)	MMF
UTI	3 months	NR	NR	N/A	NR	NR	N/A	13/65, 20
	6 months	NR	NR	N/A	2/7, 28	5/7, 71	0.16 (0.02 to 1.55)	14/65, 22
CMV infections	3 months	4/12, 33.3	0/12, 0	13.80 (0.67 to 286.1)	NR	NR	N/A	9/65, 14
	6 months	NR	NR	N/A	3/7, 43	5/7, 71	0.30 (0.04 to 2.51)	10/65, 15
Respiratory infections	3 months	NR	NR	N/A	NR	NR	N/A	15/65, 23
	6 months	NR	NR	N/A	1/7, 14	3/7, 42	0.22 (0.02 to 2.92)	20/65, 31
Herpes simplex	3 months	NR	NR	N/A	NR	NR	N/A	6/65, 9
	6 months	NR	NR	N/A	2/7, 28	1/7, 14	2.40 (0.17 to 33.52)	8/65, 12
Oral thrush	3 months	NR	NR	N/A	NR	NR	N/A	2/65, 3
	6 months	NR	NR	N/A	1/7, 14	1/7, 14	N/A	2/65, 3
Diarrhoea	3 months	NR	NR	N/A	NR	NR	N/A	11/65, 17
	6 months	NR	NR	N/A	1/7, 14	0/7, 0	3.55 (0.12 to 103.51)	13/65, 20
Abdominal pain	3 months	NR	NR	N/A	NR	NR	N/A	14/65, 22
	6 months	NR	NR	N/A	NR	NR	N/A	16/65, 25
NODAT	3 months	1/12, 8.3	0/12, 0	3.29 (0.12 to 89.20)	NR	NR	N/A	NR

CMV, cytomegalovirus; N/A, not applicable; NR, not reported; UTI, urinary tract infection.

Notes

Staskewitz *et al.*[83] did not report any AE for the historic control AZA group; only AE for MMF group were reported.

All ORs were calculated by PenTAG.

Summary

The RCT results suggested no statistically significant differences between TAC and CSA for a range of AEs [any infections, urinary tract infections (UTIs), bacterial infections, viral infections, post-transplant lymphoproliferative disease (PTLD), solid tumour, hypertension, any AE and NODAT].[77] This is similar to the conclusions of the previous HTA.[2] In addition, no statistically significant differences between MMF and AZA for UTI, cytomegalovirus (CMV) infections, respiratory infections, herpes simplex, oral thrush and diarrhoea were identified in the non-randomised evidence.[81] Similarly, no statistically significant differences between TAC + AZA and CSA + MMF in CMV infections and NODAT were identified in the non-randomised evidence.[80] In contrast, the previous HTA found significantly more CMV infection in TAC + AZA than CSA + MMF (4/12 vs. 0/12, respectively; $p = 0.04$) in the same non-RCT.[80] This discrepancy in results is due to different statistical analyses used as the current review calculated OR (OR = 13.80, favours CSA + MMF; 95% CI 0.67 to 286.10). This inconsistency highlights the small size of this study[80] ($n = 24$) and the uncertainties of its results.

Comparing children and adolescents, and adult evidence

The results from the current review are contrasted with those from the parallel HTA appraisal 'Immunosuppressive therapy for kidney transplantation in adults'.[68]

Induction therapy

The current review identified two RCTs[73,75] evaluating BAS induction therapy in children and adolescents. Offner *et al.*[73] compared BAS induction therapy with PBO and Grenda *et al.*[75] compared BAS induction therapy with no induction.

Mortality

Adult randomised controlled trial evidence

In the adult evidence identified by the parallel HTA, three RCTs comparing BAS and no induction reported mortality[97–99] and four studies compared BAS with PBO.[100–103] Six studies reported results at 1-year follow-up.[98–103] The pooled results at 1 year with four studies[98,100–102] suggest no difference between BAS and PBO or no induction: OR = 0.95 (favours BAS; 95% CI 0.49 to 1.87, $I^2 = 0.7\%$, $\tau^2 = 0.004$);[98,100–102] two studies reported zero events in both arms.[99,103]

Summary

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

Graft loss

Adult randomised controlled trial evidence

In the adult evidence identified by the parallel HTA, three studies comparing BAS and no induction reported graft loss[97–99] and four studies compared BAS with PBO.[100–103] Six studies reported results at 1-year follow-up.[98–103] The pooled results at 1 year with five studies[98,100–103] suggest no difference between BAS and PBO or no induction: OR = 0.82 (favours BAS; 95% CI 0.56 to 1.21, $I^2 = 0.0\%$, $\tau^2 = 0.0$);[98,100–103] one study reported zero events in both arms.[99]

Summary

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

Graft function

Adult randomised controlled trial evidence

In the adult evidence identified by the parallel HTA, graft function was reported by four studies at 1 year comparing BAS with PBO.[99–102] The pooled analysis for graft function implied no beneficial effect of BAS compared with controls: WMD = 1.93 (favours BAS; 95% CI –0.97 to 4.83, $I^2 = 23.9\%$).[99–102] One study comparing BAS and no induction reported data on graft function from 1 year to 10 years.[99] It was summarised that up to 7 years, graft function appeared to be slightly better for participants who received BAS; however, the effect reduced over time and the reverse was true at 10 years. Furthermore, the difference across all time points was not statistically significant.[99]

Summary

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

Acute rejection

Adult randomised controlled trial evidence

In the adult evidence identified by the parallel HTA, three studies comparing BAS and no induction[97–99] and four studies comparing BAS with PBO reported AR.[100–103] The pooled results at 1 year with five studies[98,100–103] suggest less BPAR in BAS than PBO or no induction (OR = 0.53; favours BAS; 95% CI 0.40 to 0.70, $I^2 = 0.0\%$, $\tau^2 = 0.0$). Furthermore, Sheashaa *et al.*[99] reported BPAR at 10 years, at which time BAS continues to show a beneficial effect compared with no induction (OR = 0.41, 95% CI 0.18 to 0.96).

In addition, six studies reported severity of BPAR.[97,99–103] The results do not suggest that BAS is associated with more severe BPAR than no induction or PBO (*Table 36*).

TABLE 36 Adult RCT evidence: severity of AR BAS versus PBO/no induction

Study	Time point (years)	BAS					PBO/no induction				
		n	BPAR	Banff 1	Banff 2	Banff 3	*n*	BPAR	Banff 1	Banff 2	Banff 3
Albano *et al.* 2013[97]	0.5	283	36	16	18	2	302	31	13	15	3
[a]Lawen *et al.* 2003[103]	0.5	59	9	5	1	2	64	17	4	11	1
Nashan *et al.* 1997[101]	0.5	190	51	20	26	5	186	73	31	31	11
Ponticelli *et al.* 2001[102]	0.5	168	31	15	12	4	172	49	16	25	8
Kahan *et al.* 1999[100]	1	173	61	26	31	4	173	85	38	37	10
[b]Sheashaa *et al.* 2003[99]	1	50	29	27	2		50	45	35	10	
[b]Sheashaa *et al.* 2003[99]	5	50	27	24	3		50	36	25	11	
[b]Sheashaa *et al.* 2003[99]	7	50	41	3	2		50	55	44	11	
[b]Sheashaa *et al.* 2003[99]	10	50	41	3	2		50	55	44	11	

a In addition to reported Banff 1–3, there was one BPAR of unknown classification in both study arms.
b Numbers of BPAR episodes were reported and Banff 2 and 3 were reported together, while episodes recorded as Banff 1 also included borderline BPAR.

Summary

In summary, the adult evidence suggested less BPAR in BAS than PBO or no induction, but no difference in severity of BPAR was found. Similarly, there was no evidence that BAS reduced incidences of, severity and time to BPAR when compared with PBO or no induction in the child/adolescent RCTs.[73,75]

Adverse events

Adult randomised controlled trial evidence

Five adult RCTs comparing BAS with PBO or no induction identified by the parallel HTA reported AEs at 1-year follow-up.[98,100,101,103,104] No significant differences in NODAT, PTLD, malignancy, infections and CMV infections were found between BAS and PBO or no induction arms (*Table 37*).

Summary

In summary, the adult RCT evidence identified in the parallel HTA did not find any significant differences in NODAT, PTLD, malignancy, infections and CMV infections between BAS and PBO or no induction conditions. However, the child/adolescent RCTs found more infections with BAS than with PBO in one study (OR = 2.23, favours PBO; 95% CI 1.03 to 4.68).[73]

Maintenance therapy

The current review identified one RCT[77] and four non-RCTs[80–83] evaluating maintenance therapy in children and adolescents. Trompeter *et al.*[77] compared the use of TAC and CSA. Garcia *et al.*[80] compared the use of TAC+AZA and CSA+MMF. Antoniadis *et al.*,[81] Benfield *et al.*[82] and Staskewitz *et al.* 2001[83] compared the use of MMF and AZA.

TABLE 37 Adults induction therapy RCTs: pooled results at 1-year follow-up

AE	Studies	OR	95% CI	I^2	t^2
NODAT[a]	Kyllönen *et al.* 2007[98]	3.79	0.43 to 33.64	N/A	N/A
Malignancy[b]	Kahan *et al.* 1999[100]	0.62	0.22 to 1.76	0%	0
	Kyllönen *et al.* 2007[98]				
	Nashan *et al.* 1997[101]				
PTLD[b]	Nashan *et al.* 1997[101]	0.98	0.06 to 15.77	N/A	N/A
Infections[a]	Kahan *et al.* 1999[100]	0.98	0.80 to 1.20	0%	0
	Nashan *et al.* 1997[101]				
	Lawen *et al.* 2003[103]				
CMV[a]	Kahan *et al.* 1999[100]	0.8	0.56 to 1.13	0%	0
	Kyllönen *et al.* 2007[98]				
	Nashan *et al.* 1997[101]				
	Lawen *et al.* 2003[103]				

N/A, not applicable.
a Bingyi *et al.*[104] reported zero events in each arm.
b Bingyi *et al.*[104] and Lawen *et al.*[103] reported zero events in each arm.

Mortality

Parallel Health Technology Assessment adult randomised controlled trial evidence

Ten adult RCTs comparing TAC + AZA with CSA + AZA identified by the parallel HTA reported mortality.[105–114] The pooled results at 1 year with eight studies[106–111,113,114] found no statistically significant difference between TAC and CSA (OR = 1.51; favours CSA; 95% CI 0.75 to 3.06, $I^2 = 14.8\%$). One study[107] reported mortality up to 5 years, but the results are consistent with earlier time points and indicated no statistically significant difference between arms (OR 1.20; favours CSA; 95% CI 0.69 to 2.07).[107]

Seven adult RCTs comparing MMF + CSA and AZA + CSA identified by the parallel HTA reported mortality.[114–120] The pooled results at 1 year with five studies[114,116–119] suggest no significant difference between MMF and AZA (OR = 1.19; favours AZA; 95% CI 0.47 to 3.02, $I^2 = 0\%$, $\tau^2 = 0$). In addition, two studies reported mortality at a 3-year follow-up, suggesting no difference between MMF and AZA (OR = 0.56 favours MMF; 95% CI 0.23 to 1.23, $I^2 = 0\%$, $\tau^2 = 0$).[115,118] The study reported by Tuncer *et al.*[118] provided data at 5 years, which also indicated no preference for either MMF or AZA (OR 0.73, 95% CI 0.15 to 3.50).

Summary

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

Graft loss

Parallel Health Technology Assessment adult randomised controlled trial evidence

Eleven adult RCTs comparing TAC + AZA with CSA + AZA identified by the parallel HTA reported graft loss.[105–114,121] The pooled results at 1 year with eight studies[107–111,113,114,121] found no significant difference between TAC and CSA (OR = 0.83; favours TAC; 95% CI 0.54 to 1.27, $I^2 = 12.3\%$; in addition, one study reported zero events in both arms[108]). As with mortality, the results for graft loss suggest no statistically significant difference between TAC and CSA. This lack of preference for either treatment remained at 2- (OR 0.71, 95% CI 0.40 to 1.25)[107,121], 4- (OR 0.96, 95% CI 0.62 to 1.48)[107] and 5-year follow-ups (OR 0.92, 95% CI 0.61 to 1.40).[107] However, the pooling of two trials at 6 months gives an OR of 0.45 with 95% CI 0.24 to 0.84, which is statistically significant in favour of TAC.[110,112]

Five adult RCTs comparing MMF + CSA with AZA + CSA identified by the parallel HTA reported graft loss.[114–117,120] The pooled results at 1 year with four studies[114–117] suggest no significant difference between MMF and AZA (OR = 0.76; favours MMF; 95% CI 0.38 to 1.50, $I^2 = 32.3\%$, $\tau^2 = 0.120$).

Summary

In summary, 1-year follow-up data found no statistically significant difference in graft loss between TAC and CSA and between MMF and AZA in the adult evidence. Similarly, no statistically significant difference was found between TAC and CSA for graft loss in the child/adolescent RCT evidence. However, it should be noted that the evidence from Trompeter *et al.*[77] suggested borderline statistically non-significantly lower in graft loss with TAC compared with CSA (OR = 0.41, 95% CI 0.16 to 1.00, and OR = 0.43, 95% CI 0.18 to 1.01 at 2- and 4-year follow-ups, respectively). In addition, the current review found better graft survival in MMF than in AZA in a 5-year follow-up from one child/adolescent non-RCT.[83]

Graft function

Parallel Health Technology Assessment adult randomised controlled trial evidence

Four adult RCTs comparing TAC with CSA identified by the parallel HTA reported graft function.[105,110,122,123] No meta-analysis was conducted because the results were presented in a number of ways and were not appropriate for pooling. One study[110] suggested lower graft function for TAC, as opposed to CSA at 1- and 2-year follow-ups, but not at a 3-year follow-up. Another study[122] did not find statistically significant difference between TAC and CSA at 1-year follow-up. Conflicting results were reported by all four trials across all time points (1 month to 3 years).

Summary

In summary, conflicting adult evidence was reported in the parallel HTA across all time points (1 month to 3 years) and it is not clear if there is any difference between TAC and CSA with regard to graft function. In contrast, better graft function was associated with TAC compared with CSA in the one child/adolescent RCT.[77] In addition, no difference in graft function between TAC + AZA and CSA + MMF regimens was reported in the one non-RCT.[80]

Acute rejection

Parallel Health Technology Assessment adult randomised controlled trial evidence

TAC versus CSA Nine adult RCTs comparing TAC with CSA identified by the parallel HTA reported AR at 1 year.[107–111,113,114,121,124] The pooled results at 1 year with all nine studies found significantly higher BPAR in the CSA arm than the TAC arm (OR = 0.50; favours TAC; 95% CI 0.39 to 0.64, $I^2 = 8.1\%$).[107–111,113,114,121,124] In addition, Mayer *et al.*[107] reported BPAR at 4 years, for which the beneficial effect of TAC appeared to be maintained (OR 0.38 favours TAC, 95% CI 0.25 to 0.57).

Time to first BPAR was reported by two studies[109,121] which suggested that BPAR may occur quicker for participants receiving TAC (35 days, SD 13) than CSA (59 days, SD 38); however, no statistical tests were reported.[121] Campos *et al.*[109] reported that the mean time to BPAR was comparable between the TAC and CSA groups (14.5 days, SD 47.3, and 12.0 days, SD 21.0, respectively).

Severity of BPAR was reported by four studies (*Table 38*).[110,112,113,121] At 6 months, Charpentier *et al.*[112] report the proportion of people with BPAR classified as Banff 3 as 10.7% for TAC and 15.4% for CSA and by 2 years Margreiter *et al.*[110] report 6.4% and 16.8% of people with BPAR experiencing Banff 3, for TAC and CSA, respectively.

TABLE 38 Adult RCT evidence: severity of AR TAC + AZA versus CSA + AZA

Study	Time point (years)	TAC + AZA					CSA + AZA				
		n	BPAR	Banff 1	Banff 2	Banff 3	*n*	BPAR	Banff 1	Banff 2	Banff 3
Margreiter *et al.* 2002 [110]	0.5	286	56	21	31	4	271	101	34	49	18
Charpentier *et al.* 2003[112]	0.5	186	28	18	7	3	184	39	14	19	6
Baboolal *et al.* 2002[121]	1	27	5	3	2	0	24	8	5	3	0
Hardinger *et al.* 2005[113]	1	134	6	3	3	0	66	4	1	3	0
[a]Margreiter *et al.* 2002[110]	1	286	60	23	33	4	271	111	39	54	18
[a]Margreiter *et al.* 2002[110]	2	286	62	23	35	4	271	113	40	54	19

a Recorded Banff 1 BPAR include two and one borderline BPAR in TAC + AZA and CSA + AZA groups, respectively.

MMF versus AZA Six adult RCTs comparing MMF and AZA identified by the parallel HTA reported BPAR.[114–117,119,120] The pooled results from three studies[115,119,120] at 6-month follow-up suggested less BPAR in the MMF than the AZA arm (OR = 0.50; favours MMF; 95% CI 0.35 to 0.72, $I^2 = 35.1\%$, $\tau^2 = 0.036$), while pooled results of four RCTs[114–117] at 1-year follow-up suggested no statistically significant between-group differences for BPAR (OR = 0.67; 95% CI 0.37 to 1.22, $I^2 = 58.3\%$, $\tau^2 = 0.198$).

In addition, three RCTs identified by the parallel HTA reported severity of BPAR (*Table 39*).[115,117,120] Overall, at 0.5 years, the more severe classification of Banff 3 appears to be more likely in the AZA arm for people with BPAR (CSA 9.1%, AZA 15.9% for Sollinger *et al.*[120] and CSA 5.9%, AZA 11.9% for the Tricontinental Group 1996[115]).

Insufficient data were provided for time to BPAR to allow pooled analysis as only Merville *et al.*[117] reported time to BPAR as 48.5 days for MMF and 43.7 days for AZA.

Summary

In summary, pooled results of nine adult RCTs identified by the parallel HTA at 1-year follow-up suggested less BPAR with TAC compared with CSA. Similarly, higher rates of BPAR were found in CSA compared with TAC in the one included child/adolescent RCT at a 6-month follow-up.[77] No statistically significant differences were found between TAC and CSA in the adult RCT evidence with regard to time to BPAR, and severity of BPAR. No child/adolescent evidence on severity and time to BPAR was identified.

In addition, pooled results of three adult RCTs identified by the parallel HTA at 6-months follow-up suggested less BPAR with MMF than AZA (OR = 0.50; favours MMF; 95% CI 0.35 to 0.72, $I^2 = 35.1\%$); however, the pooled results of four adult RCTs at 1-year follow-up suggested no statistical significance between-group differences (OR = 0.67; 95% CI 0.37 to 1.22, $I^2 = 58.3\%$). Similarly in the child/adolescent non-randomised evidence, no statistically significant differences in BPAR were found between the MMF and AZA arms, and between TAC + AZA and CSA + MMF.

Adverse events

Parallel Health Technology Assessment adult randomised controlled trial evidence

Ten adult RCTs comparing TAC with CSA identified by the parallel HTA reported AEs at 1-year follow-up,[106–109,113,114,121,125–127] six studies compared TAC + AZA + CCS with CSA + AZA + CCS regimens,[106–109,113,121] two studies compared TAC + MMF + CCS with CSA + MMF + CCS regimens,[114,125] one study compared TAC + SRL + CCS with CSA + SRL + CCS regimens,[126] and one study (Symphony study comparing four regimens[127]) compared low TAC + MMF + CCS with low CSA + MMF + CCS regimens.[127] No difference in PTLD, malignancy, infections and CMV infection was found between TAC and CSA regimens at 1-year follow-up. The meta-analysis (including eight studies[106–109,113,125–127]) suggested more cases of NODAT in TAC regimens compared with CSA (OR = 2.22; favours CSA; 95% CI 1.42 to 3.46, $I^2 = 0\%$). All meta-analyses are summarised in *Table 40*.

TABLE 39 Adult RCT evidence: severity of AR MMF + CSA versus AZA + CSA

Study	Time point (years)	MMF + CSA					AZA + CSA				
		n	BPAR	Banff 1	Banff 2	Banff 3	*n*	BPAR	Banff 1	Banff 2	Banff 3
Sollinger *et al.* 1995[120]	0.5	167	33	18	12	3	166	63	29	24	10
Tricontinental study 1996[115]	0.5	173	34	16	16	2	166	59	26	26	7
[a]Merville *et al.* 2004[117]	1	37	5	4	1	0	34	7	2	3	2

a Incidences of BPAR were reported.

TABLE 40 Adults maintenance therapy RCTs: pooled results at 1-year follow-up

AE	Study	OR	95% CI	I^2	t^2
NODAT	Laskow *et al.* 1996[106]	2.22	1.42 to 3.46	0%	0
	Mayer *et al.* 1997[107]				
	Jarzembowski *et al.* 2005[108]				
	Campos *et al.* 2002[109]				
	Hardinger *et al.* 2005[113]				
	Yang *et al.* 1999 [125]				
	Symphony[127]				
	Chen *et al.* 2008[126]				
Malignancy	Mayer *et al.* 1997[107]	1.36	0.54 to 3.39	0%	0.57
	Hardinger *et al.* 2005[113]				
	Yang *et al.* 1999[125]				
	Symphony[127]				
Infections	Mayer *et al.* 1997[107]	1.12	0.84 to 1.49	0%	0.46
	Chen *et al.* 2008[126]				
	Yang *et al.* 1999[125]				
	Symphony[127]				
CMV	Baboolal *et al.* 2002[121]	0.8	0.59 to 1.09	0%	0.6
	Mayer *et al.* 1997[107]				
	Jarzembowski *et al.* 2005[108]				
	Weimer *et al.* 2006[114]				
	Symphony[127]				
	Yang *et al.* 1999[125]				
	Hardinger *et al.* 2005[113]				

N/A, not applicable.

Three adult RCTs that compared MMF with AZA reported AEs; one study compared MMF + CSA + CCS with AZA + CSA + CCS regimens,[117] and two three-arm studies compared MMF + CSA + CCS with AZA + CSA + CCS regimens.[114,116] No difference in infections and CMV infection were found between MMF and AZA regimens at 1-year follow-up. However, only two studies[114,117] reported CMV infection and only one study reported infections.[116]

Summary

The result suggested no difference between TAC and CSA for mortality, graft loss and AEs, although more BPAR and AR, and worse graft function was reported in CSA compared with TAC.[77] The child/adolescent RCT found no statistically significant differences between TAC and CSA for a range of AEs including NODAT (e.g. any infections, UTIs, bacterial infections, viral infections, PTLD and solid tumour).

Summary

Three RCTs are included in the clinical effectiveness systematic review presented in this report: one new RCT[73] and two RCTs from the previous assessment.[75,77]

Four non-RCTs are included in our review. All of these were also included in the previous assessment by Yao *et al.*[2] No new non-randomised studies were identified in our searches.

Induction therapy

Two RCTs of induction therapy (reported in four publications and one abstract) evaluating BAS in children and adolescents were identified in the review.[73,75] No RCTs were identified that evaluated r-ATG in children and adolescents.

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

We found no significant difference in survival, graft loss, graft function, incidences of BPAR, severity of BPAR and time to BPAR between BAS and PBO/no induction.[73,75]

Comparison with the previous Health Technology Assessment and the parallel Health Technology Assessment in adults

The results of the current review are similar to the previous HTA.[2]

In addition, the child RCT evidence is similar to the conclusions of the parallel HTA in adults. However, the adult evidence found less BPAR in BAS than PBO or no induction (OR = 0.53; favours BAS; 95% CI 0.40 to 0.70, $I^2 = 0.0\%$, $\tau^2 = 0.0$; pooled results at 1-year follow-up with five studies).

The comparison of the child/adolescent RCT evidence with the previous HTA and the parallel HTA in adults is summarised in *Table 41*.

Maintenance therapy

Randomised controlled trial evidence

One RCT of maintenance therapy (reported in three publications) evaluating TAC (compared with CSA) in children and adolescents was identified.[77] No RCTs were identified that evaluated TAC-PR, MMF, MPA, SRL, EVL or BEL in children and adolescents.

From the RCTs, we found no significant difference in survival or graft loss between TAC and CSA.[77] However, a significantly higher graft function (mean eGFR of 71.5 ml/minute/1.73 m^2, SD 22.9 ml/minute/1.73 m^2, in TAC vs. mean eGFR of 53.0 ml/minute/1.73 m^2, SD 21.6 ml/minute/1.73 m^2, in CSA; *t*-test = 4.03; $p < 0.01$ at 4-year follow-up), and less BPAR (OR = 0.29, favours TAC, 95% CI 0.15 to 0.57 at 6-month follow-up) was found in TAC compared with CSA.[77]

Comparison with the previous Health Technology Assessment and the parallel Health Technology Assessment in adults

The results of the current review for survival, graft function and BPAR are similar to the previous HTA.[2] However, the RCT child and adolescent evidence identified in the previous HTA review[2] concluded that TAC lowered graft loss at 2- and 4-year follow-ups. The difference in these results is because we excluded graft loss due to death from all analyses. This was, first, to avoid double counting with another key outcome (mortality) and, second, because death-censored graft survival is a well-established clinical outcome, to which DWFG is intrinsically related. After the removal of graft loss due to death from the analyses, the evidence from Trompeter *et al.*[77] suggested a borderline (statistically non-significant) lower graft loss with TAC than CSA (OR = 0.41, 95% CI 0.16 to 1.00, and OR = 0.43, 95% CI 0.18 to 1.01 at 2- and 4-year follow-ups, respectively). In addition, while there were statistically significant treatment group differences in BPAR and AR at 6 months, the annual differences in AR were not statistically significant for years 2, 3 and 4.[77,79]

TABLE 41 Summary of RCT evidence comparing BAS with PBO and no induction

		PenTAG RCTs BAS vs. control	Yao *et al.*[2] RCTs BAS vs. control	Parallel HTA adult RCTs BAS vs. control (meta-analysis at 1-year follow-up)
Outcome	Follow-up	OR (95% CI)	RR (95% CI)	OR (95% CI)
Mortality	3 months	2.79 (0.11 to 69.31)[73]		
	6 months	4.69 (0.22 to 99.10)[73]	No deaths in either arm[75]	
		No deaths in either arm[75]		
	1 year	6.64 (0.34 to 130.33)[73]		0.95 (0.49 to 1.87); $I^2 = 0.7\%$[98,100–102]
				No deaths in either arm[99,103]
	2 years	0.33 (0.01 to 8.20)[75]		
Graft Loss	6 months	0.93 (0.29 to 2.97); $I^2 = 0\%$[73,75]	0.93 (95% CI 0.28 to 3.12)[75]	
	1 year	0.92 (0.06 to 14.92)[73]		0.82 (0.56 to 1.21); $I^2 = 0\%$[98,100–103]
				No deaths in either arm[99]
	2 years	0.50 (0.16 to 1.54)[75]		
BPAR	3 months	0.39 (0.14 to 1.07)[73]		
	6 months	0.71 (0.40 to 1.27); $I^2 = 15.7\%$[73,75]	0.93 (95% CI 0.53 to 1.65)[75]	
	1 year	0.51 (0.24 to 1.08)[73]		0.53 **(0.40 to 0.70)**; $I^2 = 0\%$[98,100–103]
	2 years	0.74 (0.39 to 1.40)[75]		
eGFR	6 months	WMD[a] –4.20 (–9.60 to 1.20); $I^2 = 0\%$[73,75]	WMD[b] 4.5 (95% CI –6.26 to 5.26)[75]	
	1 year	Mean (SD)[a]: 79(23) vs. 82 (24); $p = 0.38$[d,73]		WMD[c] 1.93 (–0.97 to 4.83); $I^2 = 23.9\%$[99–102]
	2 years	WMD[a] –1.38 (–7.20 to 4.44); $I^2 = 0\%$[73,75]		

a eGFR estimated using Schwartz equation (ml/minute/1.73 m^2).
b Serum creatinine (mmol/l).
c Various equations (ml/minute).
d Result of *t*-test comparing means and SDs.

Notes
The previous HTA by Yao *et al.*[2] had only 6 months follow-up data for Grenda *et al.*[75] (as included in Fujusawa/Astellas' submission and an abstract by Grenda *et al.*[90]).
Evidence suggesting a statistically significant difference between treatments highlighted in bold. OR > 1 favours BAS; RR > 1 favours BAS; WMD > 0 favours BAS.

In addition, the child RCT evidence is similar to the conclusions of the parallel HTA in adults. The pooled result of nine studies at 1-year follow-up found less BPAR in TAC than CSA (OR = 0.50, favours TAC; 95% CI 0.39 to 0.64, $I^2 = 8.1\%$). The comparison of the child/adolescent RCT evidence with the previous HTA and the parallel HTA in adults is summarised in *Table 42*.

Non-randomised controlled trial evidence

Three non-RCTs evaluating MMF (compared with AZA) in children and adolescents were identified.[81–83] One non-RCT compared TAC + AZA with CSA + MMF.[80] No non-RCTs were identified that evaluated TAC-PR, MPA, SRL, EVL or BEL in children and adolescents.

TABLE 42 Summary of RCT evidence comparing TAC with CSA

		PenTAG RCTs TAC vs. CSA	Yao *et al.*[2] RCTs TAC vs. CSA	Parallel HTA adult RCTs TAC vs. CSA (meta-analysis at 1 year follow-up)
Outcome	**Follow-up**	**OR (95% CI)**	**RR (95% CI)**	**OR (95% CI)**
Mortality	6 months	0.9 (0.18 to 4.58)[77]	0.9 (0.21 to 3.84)[77]	
	1 year	0.9 (0.18 to 4.58)[77]	*n/N*: 3/103 vs. 3/93 ($p = 0.90$)[77]	1.51 (0.75 to 3.06); $I^2 = 14.8\%$[106–111,113,114]
	2 years	0.67 (0.15 to 3.07)[77]	*n/N*: 3/103 vs. 4/93 (NS)[77]	
	4 years	1.14 (0.30 to 4.36)[77]	*n/N*: 5/103 vs. 4/93 ($p = 0.90$)	
Graft loss[a]	6 months	0.38 (0.14 to 1.05)[77]	0.48 (0.22 to 1.08)[77]	
	1 year	0.44 (0.18 to 1.09)[77]	*n/N*: 10/103 vs. 17/93 ($p = 0.082$)[77]	10.83 (0.542 to 1.27); $I^2 = 12.3\%$[106,107,109–111,113,114,121]
	2 years	0.41 (0.16 to 1.00)[77]	*n/N*: 10/103 vs. 19/93 **($p = 0.03$)**[77]	
	4 years	0.43 (0.18 to 1.01)[77]	*n/N*: 11/103 vs. 20/93 **($p = 0.03$)**[77]	
BPAR	6 months	0.29 **(0.15 to 0.57)**[77]	0.42 **(0.26 to 0.69)**[77]	
	1 year			0.50 **(0.39 to 0.64)**; $I^2 = 8.1\%$[107–111,113,114,121,124]
eGFR[b]	6 months	Mean (SD):[c] 65.6 (19.9) vs. 61.2(15.8); [d]$p = 0.11$[77]	Mean (SD):[c] 90.91 (34.2) vs. 86.09 (26.8)[77]; [d]**$p = 0.09$**[77]	No meta-analysis was performed; conflicting results were reported by all four trials across all time points (1 month to 3 years)[99–102]
	1 year	Mean (SD):[c] 64.9 (20.7) vs. 57.8 (21.9); [d]**$p = 0.04$**[77]	Mean (SD):[c] 62.5 vs. 56.4; [d]**$p < 0.01$**[77]	
	2 years	Mean (SD):[c] 64.9 (19.8) vs. 51.7 (20.3); [d]**$p < 0.01$**[77]	Mean (SD):[c] 64.9 vs. 51.7; [d]**$p < 0.01$**[77]	
	3 years	Mean (SD):[c] 66.7 (26.4) vs. 53.0 (23.3); [d]**$p < 0.01$**[77]		
	4 years	Mean (SD):[c] 71.5 (22.9) vs. 53.0 (21.6); [d]**$p < 0.01$**[77]	Mean (SD):[c] 71.5 vs. 53.0; [d]**$p < 0.01$**[77]	

NS, not significant.

a The discrepancy in graft loss result between PenTAG and the previous HTA is because we have excluded graft loss owing to death from our analyses. This was, first, to avoid double counting with another key outcome (mortality) and, second, because death-censored graft survival is a well-established clinical outcome, to which DWFG is intrinsically related just as mortality is to overall survival. It should be noted that after the removal of graft loss owing to death from the analyses the child/adolescent RCT evidence suggested borderline statistically non-significantly lower graft loss in TAC compared with CSA.

b eGFR values reported in Trompeter *et al.*[77] and the 4-year follow-up paper by Filler *et al.*[79] differ, we used data reported in Filler *et al.*[79]

c eGFR estimated using Schwartz equation (ml/minute/1.73 m^2).

d Result of *t*-test comparing means and SDs.

Note

Evidence suggesting a statistically significant difference between treatments highlighted in bold. OR > 1 favours TAC; RR > 1 favours TAC; WMD > 0 favours TAC.

Tacrolimus versus ciclosporin

We found no statistically significant difference in survival between MMF and AZA in the non-RCTs.[81,83] Similarly, no statistically significant difference in BPAR between MMF and AZA in the non-RCTs was identified.[81–83] A significantly lower graft loss was found in MMF compared with AZA at 1- to 5- year follow-ups in one of the two non-RCTs[83] (OR = 0.24 at 5-year follow-up; favours MMF; 95% CI 0.09 to 0.63). However, this was not confirmed by the other non-RCT at 1-year follow-up.[81] Graft function (eGFR) was not measured in the three included non-RCTs comparing MMF and AZA.[81–83]

In addition, conflicting evidence was found in the parallel HTA in adults. No difference in graft loss was found between MMF and AZA in the adult evidence; OR = 0.76 (favours MMF; 95% CI 0.38 to 1.50, $I^2 = 32.3\%$, $\tau^2 = 0.120$; pooled results of four studies a 1-year follow-up).[114–117,120] The pooled results of three adult RCTs at 6-month follow-up suggested less BPAR with MMF than AZA (OR = 0.50; favours MMF; 95% CI 0.35 to 0.72, $I^2 = 35.1\%$);[115,119,120] however, the pooled results of four adult RCTs at 1-year follow-up suggested no statistically significant between-group differences (OR = 0.67; 95% CI 0.37 to 1.22, $I^2 = 58.3\%$).[114,116–119] Finally no significant difference in survival between MMF and AZA was found in the adult evidence (OR = 1.19; favours AZA; 95% CI 0.47 to 3.02, $I^2 = 0\%$, $\tau^2 = 0$; pooled results of five studies at 1-year follow-up).[114,116–119]

Tacrolimus ± azathioprine versus ciclosporin ± mycophenolate mofetil

We found no statistically significant difference in survival, graft loss, BPAR, graft function and DGF between TAC + AZA and CSA + MMF in the non-RCT.[80]

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

Adverse events

Induction

More infections were found in children treated with BAS than in those treated with PBO (OR = 2.23, favours PBO; 95% CI 1.03 to 4.68).[73] In addition, Grenda *et al.*[75] found that toxic nephropathy and abdominal pain was higher in the BAS arm than no induction ($p = 0.03$ and $p = 0.02$, respectively).[75] The previous HTA reported only post-transplant diabetes mellitus[90] and the rest of the data were confidential and were omitted from the report.[2]

In addition, the child RCT evidence is largely similar to the conclusions of the parallel HTA in adults. The adult 1-year follow-up RCT evidence identified in the parallel HTA did not find any significant differences in NODAT, PTLD, malignancy, infections and CMV infections between BAS and PBO or no induction.[98,100,101,103,104]

Maintenance therapy

There were no statistically significant differences between TAC and CSA for a range of AEs (any infections, UTIs, bacterial infections, viral infections, PTLD, solid tumour, hypertension, any AEs and NODAT).[77] This is similar to the conclusions of the previous HTA.[2] However, Trompeter *et al.*[77] also reported that a deficiency of magnesium in the blood and diarrhoea were more common with TAC than with CSA, while excessive hair growth, flu syndrome and swollen gums were less common with TAC than with CSA.[77] In addition, there were no statistically significant differences between MMF and AZA for UTI, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhoea identified in the non-randomised evidence.[81] Similarly, no statistically significant differences between TAC + AZA and CSA + MMF in CMV infections and NODAT were identified in the non-randomised evidence.[80]

However, the parallel HTA in adults found more cases of NODAT in TAC than CSA (OR = 2.22; favours CSA; 95% CI 1.42 to 3.46, $I^2 = 0\%$; pooled results of eight studies at 1-year follow-up).[106–109,113,125–127] In addition, no difference in CMV infections[114,117] and infection[116] were found between MMF and AZA regimens in the adult evidence at 1-year follow-up.

Companies' reviews of clinical effectiveness

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

Astellas submitted a systematic review summarising evidence on the clinical effectiveness and safety of TAC-IR therapy compared with current alternative treatments [TAC-PR (Advagraf), CSA, SRL, BEL, and EVL] as primary immunosuppressive therapies in patients undergoing renal transplantation. The submission did not address the study question in full.

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

Only one child/adolescent RCT[77] and two child/adolescent non-RCTs[80,94] were included in the company submission. In addition, adult RCT evidence was summarised; an overview of adult RCTs included in Astellas' submission with reasons for inclusion/exclusion in the PenTAG parallel review is provided in *Appendix 6*, *Table 141*.

Tacrolimus versus ciclosporin

Trompeter *et al.*[77] is the only child/adolescent RCT comparing TAC with CSA that is included both in the Astellas submission and in the PenTAG review. Astellas reported a significantly higher graft function, BPAR and better graft survival in TAC than AZA.[77] However, we have excluded graft loss due to death from our analyses. This was, first, to avoid double counting with another key outcome (mortality) and, second, because death-censored graft survival is a well-established clinical outcome to which DWFG is intrinsically related, just as mortality is to overall survival. After the removal of graft loss due to death from the analyses, the evidence from Trompeter *et al.*[77] suggested borderline statistically non-significantly lower graft loss in TAC than in CSA (OR = 0.41, 95% CI 0.16 to 1.00, and OR = 0.43, 95% CI 0.18 to 1.01, at 2- and 4-year follow-ups, respectively).

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

Tacrolimus versus sirolimus

No child/adolescent evidence comparing TAC and SRL was identified. Astellas' clinical effectiveness results from adult RCTs suggest better graft survival and less AR with TAC compared with SRL, but they included a trial comparing TAC and no induction-based regimen with SRL + r-ATG induction regimen.[128] The parallel PenTAG review found fewer incidences of BPAR for TAC compared with SRL. In addition, Astellas pooled results from studies comparing SRL with MMF in TAC-based regimens and significantly more drug discontinuations were found in the SRL + TAC regimen than in the MMF + TAC regimen.

Immediate-release tacrolimus versus prolonged-release tacrolimus

No child/adolescent evidence comparing immediate-release TAC and prolonged-release TAC formulations was identified. Astellas' clinical effectiveness results from adult RCTs suggest no difference between TAC and TAC-PR. The results do not conflict with conclusions in the parallel HTA review.[68]

Tacrolimus versus belatacept

No child/adolescent evidence comparing TAC and BEL was identified. In addition, no adult RCTs comparing TAC and BEL were identified. Astellas performed an indirect treatment comparison to compare Advagraf with Prograf, with more intensive and less intensive BEL regimens. Evidence of less AR with Prograf compared with both BEL regimens was presented. In addition, better graft survival was found with Prograf compared with the more intensive BEL regimen, and better survival was found with Prograf compared with the less intensive BEL regimen. Finally, evidence of less AR with Advagraf compared with the less intensive BEL regimen was presented. However, it was not clear what TAC evidence was included and the results presented seem to be conflicted. The parallel HTA network meta-analyses results suggested that BEL + MMF may be more effective at reducing the odds of mortality than TAC + MMF and SRL + MMF. In addition, a study directly comparing BEL and TAC regimens was identified in the parallel HTA.[129]

Tacrolimus versus everolimus

No child/adolescent evidence comparing TAC and EVL was identified. In addition, no adult RCTs comparing TAC and EVL were identified. Astellas performed an indirect treatment comparison to compare TAC with EVL. It is not clear what TAC evidence was included and why the results were not reported separately for TAC and TAC-PR (as they were presented in the TAC vs. BEL comparison). No statistically significant differences between TAC and EVL were identified in the submission. The parallel HTA network meta-analyses results did not find any difference between TAC and EVL regimens for clinical effectiveness outcomes.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

The purpose of this section of the report is to review existing evidence on the cost-effectiveness of immunosuppressive regimens [BAS and r-ATG as induction therapies, and TAC-IR, TAC-PR, MMF, MPS, SRL, EVL and BEL as maintenance therapies (including a review of TA99)] in renal transplantation in children and adolescents.

Methods

Searches

Bibliographic literature searching was conducted on 8 April 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 15 January 2015. The search was not limited by language and it was not limited to human-only studies.

The following databases were searched: MEDLINE and MEDLINE In-Process (via Ovid), EMBASE (via Ovid), NHS EED (via Wiley Online Library), Web of Science (ISI – including conference proceedings), Health Economic Evaluations Database (HEED) (via Wiley) and EconLit (via EBSCO*host*). The search strategies are recorded in *Appendix 1*.

Screening

Inclusion and exclusion criteria were the same as for the clinical effectiveness systematic review (see *Chapter 3, Inclusion and exclusion criteria*), 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 that report only average cost-effectiveness ratios were included only 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 the UK, the USA, Canada, Australia and western Europe were included as these settings may include data generalisable to the UK.

All records were dual screened. 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.

Quality assessment

Studies meeting the criteria for inclusion were assessed by one reviewer (RMM) using the checklist developed by Evers *et al.*[130] When studies were based on decision models they were also quality assessed using the checklist developed by Philips *et al.*[131,132]

Synthesis

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

Results

Identified studies

The electronic database search for cost-effectiveness evidence, including update searches conducted on 18 November 2014, identified 2090 records. After deduplication 1378 records remained, all of which were screened by title and abstract. Of these, 86 full texts were assessed for eligibility. Thirty-eight full texts were deemed to meet the eligibility criteria for the review. The process is illustrated in detail in *Figure 13*.

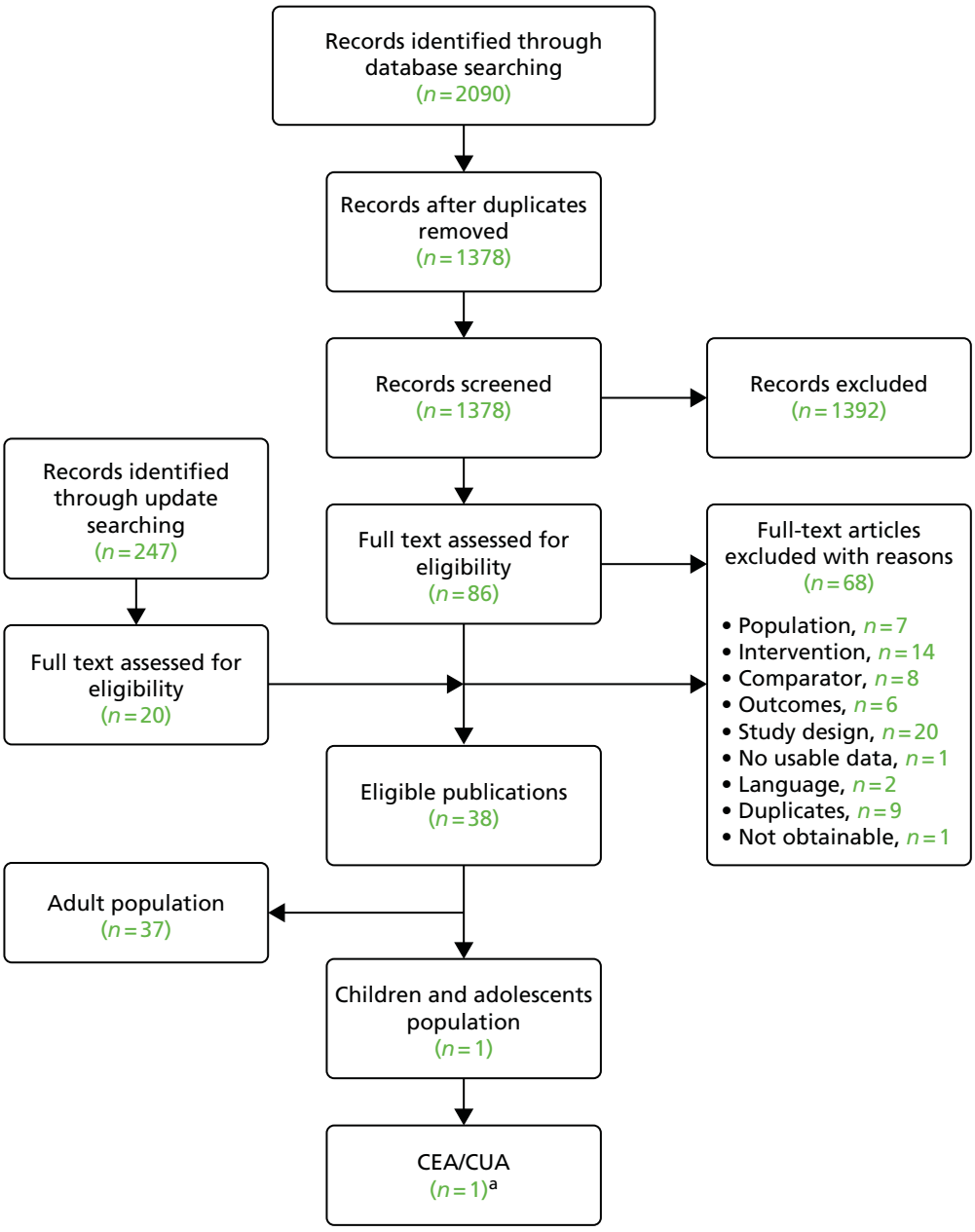

FIGURE 13 Cost-effectiveness review: PRISMA flow diagram. CEA, cost-effectiveness analyses; CUA, cost–utility analyses. a, The previous HTA review by Yao *et al.*;[2] includes child, adolescent and adult evidence.

Only one study[2] was identified that met the inclusion criteria. This was the HTA report of the previous NICE appraisal on the topic in children or adolescent patients. The rest of the subsection is devoted to reviewing this study.

Yao *et al.*[2] reports the methods and results of economic analyses submitted to the previous NICE appraisal on the topic by three sponsoring companies. All of these analyses used an equation estimated from regression analysis (meta-model) of child/adolescent simulation outcomes of immunosuppressive regimens derived from a model originally developed by one company (Novartis) for informing its submission to the corresponding NICE review on adult patients. The adult metamodel was developed by the Technology Assessment Group at Birmingham and the individual companies adapted it to children and adolescents. After critically appraising the evidence submitted by the companies, the group at Birmingham then produced its own analysis by adapting the metamodel to children and adolescents.

Briefly, the Birmingham model was a Markov model spanning a 10-year horizon after the initial transplant. It consisted of three states: functioning graft, graft failed (dialysis) and death. In common with models in this clinical area, surrogate outcomes were used to extrapolate beyond the end of follow-up in the RCT evaluating the relative effects of immunosuppressive regimens in terms of BPAR. The model used a HR of 1.41 for graft failure up to 7 years post transplant for children and adolescents ($\leq$ 18 years) treated for an AR before discharge versus those not treated. The Birmingham group then used this surrogate relationship to translate 12-month differences in BPAR rates between immunosuppressive regimens from RCT studies in children and adolescents for therapies other than MMF and DAC, for which adult RCT data were used, into 10-year graft survival differences. The study also adjusted the resource use and costs for age–weight immunosuppressive doses in children and adolescents.

Table 43 presents the characteristics of the analysis by Yao *et al.*[2] Results were presented for two pairwise comparisons of induction regimens and two pairwise comparisons of initial and maintenance immunosuppressive regimens. In the comparisons of induction therapy regimens, BAS was found to result in lower total costs and higher quality-adjusted life-years (QALYs) than no induction in patients managed with either TAC or CSA in a CNI-containing triple immunosuppressive therapy including AZA and steroids. In terms of the initial and maintenance immunosuppressive regimens, TAC was found to have an incremental cost per QALY gained of £145,540 relative to CSA, while the corresponding figure for MMF relative to AZA was £194,559 when these therapies were combined with CSA and steroids. It is worth noting that the latter comparison was based on efficacy data from studies on MMF use in adults. *Table 44* summarises the base-case results. However, altering the hazard (risk) ratio of graft loss with AR from 1.41 (which was based on a single observational study in children and adolescents) to a HR of 1.96 (derived from a pooled analysis of adult observational studies) and arbitrarily increasing the cost of dialysis from the base-case value of £21,000 (which was estimated from data on adults) to £50,000, as a way of accounting for the higher staff-to-patient ratios in children and adolescents, resulted in a cost per QALY gained of £34,000.[2]

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

TABLE 43 Characteristics of analysis by Yao *et al.*[2]

Author and country	Regimens	Population	Study type	Perspective	Outcomes considered	Horizon	Model based?	Sponsor
Yao *et al.*,[2] UK	Induction: BAS + CSA + AZA + CCS vs. CSA + AZA + CCS BAS + TAC + AZA + CCS vs. TAC + AZA + CCS Initial and maintenance: TAC + AZA + CCS vs. CSA + AZA + CCS CSA + MMF + CCS vs. CSA + AZA + CCS	Children and adolescents with renal transplant	Cost–utility analysis	NHS and PSS	QALYs	10 years	Yes	Adapted model by independent Technology Assessment Group from model originally developed by Novartis for adult patients

PSS, Personal Social Services.

TABLE 44 Base-case results of analyses presented by Yao *et al.*[2]

Regimens compared	BTAS vs. TAS	BCAS vs. CAS	TAS vs. CAS	CMS vs. CAS
Initial age range	3–13 years			
Time horizon	10 years			
Discounted incremental QALYs	0.038	0.074	0.090	0.049
Discounted incremental costs (£)	–451	–1103	13,716	9543
ICER, incremental cost per QALY gained	Dominant	Dominant	145,540	194,559
Notes	Costs discounted at 6%; QALYs discounted at 1.5%, costs are in 2005 prices			Cost discounted at 6%, QALYS 1.5%. Efficacy data were based on meta-analysis that included studies of MMF in adults

ICER, incremental cost-effectiveness ratio.

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

As for the methodology behind this evidence, the assessment was based on a meta-analysis of the evidence on AR rates, although for MMF this included studies in adult patients. The study did not account for costs and HRQoL effects of changes in graft function and omitted the effect of differences between regimens in terms of the graft function on longer-term prognosis. Recent evidence from studies in adults suggest that quality of life[133] and costs[60] do vary significantly with renal function and this casts some doubt on the conclusion by the Birmingham group that small QALY differences are generally found between regimens. It is also questionable whether or not the surrogate relationship between AR and graft survival was validly implemented, because the estimated HR used to predict graft survival was estimated from AR rates occurring before discharge post transplantation, while the efficacy data used to model treatment differences were based on 12-month outcomes post transplantation. In addition, lack of data prevented the analysis from accounting for side effect differences between regimens, to which results were found to be sensitive. The quality assessment of these analyses are summarised in *Table 45*.

Critical appraisal of company submissions

Astellas' submission

The submission compared

- twice-daily TAC-IR (Prograf) with
- once-daily TAC-PR,

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

- twice-daily TAC-IR (Prograf) with
- Modigraf (TAC granules for oral solution – for 3 years, then switch to Prograf)
- TAC specials (oral suspensions)
- EVL

TABLE 45 Quality assessment Evers checklist[2,130]

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

Y, Yes; N, No; ?, unclear.

- BEL
- SRL with low-dose CSA (CNI minimisation)
- SRL with MMF (CNI avoidance).

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

Astellas' analysis found that Prograf was cost-effective compared with all comparators, except SRL (avoidance), which the company argues is not a treatment option that is routinely considered of use for children and adolescents in general. Further, Advagraf was considered cost-effective relative to Prograf and recommended by the company to be adopted as the new standard of care. Owing to limited information on children and adolescents, the model was populated with information from adult KTRs from a meta-analysis and network meta-analysis of evidence on short-term outcomes from comparative clinical studies in adults.

The submission pointed to evidence on the relationship between adherence, acute and long-term graft rejection, and graft failure. In particular, it is stated that adherence to immunosuppressant regimens positively affects graft survival by preventing the development of de novo donor specific antibodies, which have been associated with a reduction in 10-year graft survival.[134] This is the stated justification for translating the observed improvement in adherence with once-daily TAC relative to twice-daily TAC[135] into graft and patient survival benefits in the Astellas model.[135] In addition, the company claims that once-daily TAC-PR has a better pharmacokinetic profile than twice-daily TAC (lower intra-patient variability,[136] which results in a lower risk of long-term graft failure[137]). The company also cites analyses from the Collaborative Transplant Study for Europe (2011–13 data) presented at the 2014 World Transplant Congress, which shows that Advagraf-treated patients had higher patient and graft survival rates than Prograf-treated patients over the 12 months following renal transplantation. However, this observation was not robust to the adjustment for multiple confounders (HR 0.76; $p = 0.14$, 95% CI was not stated).

The submission also cites the results of a meta-analysis pointing to increased risk of NODAT with TAC (RR at 12 months 1.72, 95% CI 1.17 to 2.52; RR at 36 months 2.71, 95% CI 1.61 to 4.57) relative to CSA and acknowledges the evidence on the association between NODAT and reduced graft survival (RR 1.63, 95% CI 1.46 to 1.84).[138] The company argues that these estimates may have been the result of patients treated with high doses of TAC relative to current practice. To support this claim, the submission cites the results of a Phase III study comparing Advagraf with Prograf,[139] which used lower doses of TAC and found lower incidence rates of NODAT than those in the studies included in the meta-analysis report.[139] However, it is noted that the Krämer *et al.*[139] evidence is not relevant to the meta-analysis finding of a higher RR of NODAT with TAC than CSA.

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 Library, MEDLINE and other sources not specified) it identified and included 12 studies in its review (although the Astellas submission states that 11 studies were included). No details were provided about the inclusion criteria for the review of economic studies but all of the reviewed studies were conducted in adults.

One of the included studies compared TAC-IR with TAC-PR (US study[140]); four studies compared TAC with CSA (two in continental Europe,[141,142] one in the UK[143] and the remaining study was from the USA and measured only costs of medication[113]); seven studied SRL in CNI avoidance or minimisation strategies versus TAC (one from the USA,[144] another from the UK,[145] two more from Germany[146,147] and three studies from Colombia, Mexico and Poland[148–150]).

The submission briefly described the main results of these studies without critically assessing their validity and applicability to a UK setting, although it mentions the limited transferability of results from non-UK studies (10 out of the 12). It concludes that the evidence supports the view that TAC is cost-effective when compared with CSA, but that it is ambiguous in relation to the comparison against SRL in a CNI avoidance or minimisation strategy. The submission also includes a section where three published models are described.[144,148,149] No assessment of their strengths and weakness was presented. These models are all of adult patient populations and are therefore not included in the review of cost-effectiveness studies of this monograph.[144,148,149]

Economic evaluation by the company

The cost-effectiveness analysis submitted by Astellas is an adaptation of a published Markov model-based assessment of the cost-effectiveness of TAC, in either its extended release formulation, Advagraf, or the current standard therapy of immediate-release (Prograf[151]) in adult KTRs. The model describes the annual transitions between four health states starting from kidney-only transplantation: functioning graft without history of AR, functioning graft having experienced AR, graft failure (dialysis) and death (*Table 46*). Owing to the lack of child/adolescent data, the Astellas submission is based on a review of short-term safety and efficacy outcomes of immunosuppression in adults, reported by RCTs published study until June 2014. These were then extrapolated using registry data on child/adolescent graft and patient survival. The base-case analyses submitted by the company discount costs and QALY outcomes at an annual rate of 3.5%.

Efficacy data

The model accounts for differences in outcomes between regimens that originate in their differing impact on BPAR at 12 months post transplant. These differences in BPAR between the regimens evaluated were estimated from RCTS of adult KTRs (*Table 47*). The model was based on the assumption that the effects of treatment on this surrogate outcome lasted for only the first year post transplantation. In fact, the model allowed BPAR to occur only in the first 12 months post transplantation. This assumption was combined with (1) the estimated RR of graft failure for a functioning graft with previous BPAR versus no previous BPAR and (2) the 1-year post-transplant BPAR frequency, both from estimates reported by Opelz *et al.*,[153] to derive the graft survival curves for grafts without prior AR and grafts with history of AR from the child 5-year graft survival profile in UK registry data (including graft survival rates for years 3 and 4 derived by linear interpolation[32]). The model extrapolation was complemented by using exponential survival curves to extend graft survival from 5 years up to 16 years post transplantation.

With regard to patient survival, the model used the 1-, 2- and 5-year post-transplantation survival rates in children and adolescents from the NHS Blood and Transplant (NHSBT) Report 2013–2014[32] as the estimated survival rates with a functioning graft. To populate survival probabilities in the state of graft failure, the model used annual survival rates of adult patients on dialysis followed for 10 years from the UK Renal Registry.[154] The patient survival rates were extrapolated until 18 years of age (i.e. 10 years post transplant in the base case) by linear extrapolation of the available data, projecting survival rates from the last observed rate. There is no mention in the submission about adjusting survival for increases in background mortality as the cohort in the model ages. For patients in the state of graft failure, which was assumed to be associated with the use of dialysis, the probability of receiving a retransplant was populated with data from adults treated at a centre in Cardiff, Wales.[155]

In addition to the difference in efficacy, measured in terms of AR rates (see *Table 47*), the model allowed for differences in effectiveness between the TAC arms through the differences in adherence associated with the once daily, prolonged-release formulations of the drug (Advagraf) versus the twice-daily immediate-release formulations of the drug (Prograf). The model employed comparative estimates on adherence with Advagraf versus Prograf of 88.2% versus 78.8% from a published randomised study[135] and combined them with an estimated RR of graft failure in non-adherent versus adherent patients of 3.47 derived from a meta-analysis[15] to obtain a RR 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.[15,135]

TABLE 46 Characteristics of the Astellas model

Population	Comparators (initial and maintenance therapy)	Horizon	Model structure	Surrogates to model long term	Health states/events modelled	Risk factors	AEs	Model drivers (sensitivity analysis)	Comments
Age 8 years (minimum 2 years); 26.0 kg (female); 25.6 kg (male) starting weight); England and Wales	• TAC-IR (Prograf) • TAC-PR (Advagraf) • Modigraf • TAC specials • BEL • EVL [CNI minimisation (60% CSA reduction)] • SRL [CNI minimisation (80% CSA reduction) and CNI avoidance] • All maintenance regimens are given with BAS induction and AZA + CCSs	10 years (maximum 16 years; i.e. for starting age 2 years: analysis ended at age 18 years in all cases)	Markov model of annual cycles with tunnel states extrapolation of 1 year trial outcomes	AR	Functioning graft – no previous BPAR Functioning graft – previous BPAR Failed graft (dialysis) Functioning regraft – no previous BPAR Functioning regraft –previous BPAR Death	BPAR	Malignancies CMV infections NODAT Wound-healing disorders Anaemia HMGCoA Hypertension	Improved adherence with PR medication TAC-IR vs. SRL: Graft survival (scenario with graft survival in Symphony trial [CNI minimisation] with DAC induction)	Assumes that BPAR only occur in the first 12 months. Graft and patient survival were estimated from UK 5-year survival statistics in children and adolescents with renal transplant (UK NHSBT Report 2012–13) extrapolated to 10 years post-transplant by exponential and linear function of time, respectively. Survival in dialysis was estimated from 10-year UK survival statistics in adults, extrapolated by exponential function. Utility values of AEs not accounted for. Model has flaws of implementation, especially in relation to retransplants

HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A.

TABLE 47 Acute graft rejection rates used in the Astellas model

Product	Rate, %	Comment
Prograf (base comparator)	12.6	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139]
Modigraf/TAC specials	12.6	Assumed the same as Prograf owing to lack of data
Advagraf	14.6	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139] and meta-analysis
BEL	30.7	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139] and meta-analysis
EVL (CNI minimisation)	18.0	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139] and meta-analysis
SRL (CNI minimisation)	16.5	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139] and meta-analysis
SRL (CNI avoidance)	28.7	Silva *et al.*,[152] Albano *et al.*,[97] Krämer *et al.*[139] and meta-analysis

Adverse events

The model allows for seven types of AE following transplantation: malignancy, diabetes mellitus, anaemia, CMV infection, hypertension, wound-healing disorders and the need for 3-hydroxy-3-methylglutaryl-coenzyme A. These events were assigned costs (except for the last type of event which had zero cost and, thus, was effectively omitted from the analysis) but no disutility. The AE incidence rates used in the model, reproduced in *Table 48*, 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 AEs were derived from a systematic review and meta-analysis published in 2006,[156] the values adopted by the published economic model for adults in Germany by Jurgensen *et al.*[146] and trial outcomes from the BENEFIT and BENEFIT-EXT trials.[157,158]

The rates of AEs were assumed to be the same with Advagraf and Prograf and for the two SRL regimens (CNI avoidance and CNI minimisation). According to the incidence rates figures in this model, TAC has the lowest annual incidence of malignancy (except for SRL from the third post-transplantation year onwards), CMV, anaemia (except for BEL which had the same annual incidence rates as those of TAC), dyslipidaemia and hypertension, but was associated with an excess incidence of NODAT over the other options.

Utilities

Health-related quality of life and QALY outcomes were calculated from time spent in the graft functioning state and the graft failure state, which involved dialysis. Based on published European Quality of Life-5 Dimensions (EQ-5D) estimates,[159] the functioning state was associated with a utility value of 0.71, regardless of any prior experience of AR, and the graft failure state was associated with a utility of 0.459, which was equal to the weighted average of the utility of haemodialysis (0.44), experienced by 82% of dialysis patients, and peritoneal dialysis (0.53), received by the rest.[159]

Retransplantation

The model allows for the occurrence and effects of retransplantation, using the time to retransplantation data reported by McEwan *et al.*[145,155] for adult patients. However, the states following the first retransplantation (i.e. functioning graft with prior AR on the current retransplant, functioning graft without prior AR on the current retransplant – regardless of AR of any previous transplant and graft failure) face the same transition probabilities, utility values and costs as the corresponding states before retransplantation. This is likely biasing the analysis in favour of treatments with higher rejection rates in the model (as higher AR rates 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 TAC over the comparators.

TABLE 48 Adverse events used in the Astellas model (%)

Product	AE	Year 1	Year 2	Year 3 and later
Advagraf/Prograf/Modigraf/TAC specials	Malignancies	0.00	0.00	0.43
	CMV infections	3.62	3.62	0.04
	NODAT	6.07	6.07	6.27
	Wound-healing disorders	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
EVL	Malignancies	2.43	2.43	0.64
	CMV infections	3.19	3.19	0.04
	NODAT	5.58	5.58	5.77
	Wound-healing disorders	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
SRL (CNI minimisation and avoidance regimens)	Malignancies	0.20	0.20	0.05
	CMV infections	2.11	2.11	0.03
	NODAT	5.88	5.88	6.07
	Wound-healing disorders	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
BEL	Malignancies	2.32	2.32	0.61
	CMV infections	7.65	7.65	0.09
	NODAT	4.00	4.00	4.19
	Wound-healing disorders	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

HMGCoA, 3-hydroxy-3-methylglutaryl-coenzyme A.
Source: Webster *et al.*,[156] Jürgensen *et al.*,[146] Vincenti *et al.*[157] and Durrbach *et al.*[158]

Resource utilisation and unit costs

The amount of drug use for TAC was age dependent and imputed according to weight by age distributions in observational data by associating body surface area with mean weight by age statistics from UK growth charts.[160,161] Dosages per kg of body weight for all medications were based on adult dosages as detailed in the *British National Formulary* (BNF)[162] and the corresponding Summary Product Characteristics, with the exception of MMF, which was based on body surface area parameters, and EVL, which was based on data from a study in children and adolescents.[163]

The model used BNF prices for both interventions and comparators. The cost per mg of Advagraf used was 23% lower than that of Prograf, based on the BNF list prices and information on the market share of pack sizes for Prograf. [The authors present sensitivity analyses of discounts on TAC list prices limited to the first (commercial-in-confidence information has been removed) days post transplantation.] Prices for other immunosuppressant regimens were based on BNF *prices. Table 49* reproduces table 38 in the submission, which details the prices used by the Astellas model. The submission says that TAC prices were not available in the electronic market information tool (eMIT), apparently to justify its deviation from the NICE methods guide (section 5.5.2)[165] which specifies that, if available, reduced prices should be used in the reference case, that is, eMIT prices reflecting the prices paid by NHS trusts. The submission does not give any further reason for their using list prices for TAC and all the other drug regimens.

TABLE 49 Unit costs of immunosuppressive therapies in the Astellas model (£)

Variable	Value	Comment
Cost per mg: Simulect®	£42.12	Injection, powder for reconstitution, BAS, net price 10-mg vial = £758.69, 20-mg vial = £842.38 (both with water for injections). For i.v. infusion
Cost per mg: Prograf®	£1.62	Concentrate for i.v. infusion, 5 mg/ml of TAC, net price 1-ml ampoule = £58.45. Capsules, TAC (as monohydrate) 500 µg (yellow), net price 50-capsule pack = £61.88; 1 mg (white), 50-capsule pack = £80.28, 100-capsule pack = £160.54; 5 mg (greyish-red), 50-capsule pack = £296.58 and using market distribution of pack sizes
Cost per mg: Advagraf®	£1.24	Capsules, m/r, TAC (as monohydrate) 500 µg (yellow/orange), net price 50-capsule pack = £35.79; 1 mg (white/orange), 50-capsule pack = £71.59, 100-capsule pack = £143.17; 3 mg (orange), 50-capsule pack = £214.76; 5 mg (red/orange), 50-capsule pack = £266.92
Cost per mg: BEL	£1.42	i.v. infusion, powder for reconstitution, BEL, net price 250-mg vial = £354.52
Cost per mg: EVL	£5.87	No UK price available price at the time of this submission. Estimated price of EVL based on the price of Afinitor® (EVL) white-yellow, EVL, 5 mg, net price 30-tablet pack = £2250.00; 10 mg, 30-tablet pack = £2970.00 and assuming use of cheapest in terms of cost per mg
Cost per mg: Modigraf	£7.22	Granules, TAC (as monohydrate), 200 µg, net price 50-sachet pack = £71.30; 1 mg, 50-sachet pack = £356.65
Cost per mg: specials	£3.83	TAC 2.5 mg/5 ml oral suspension, 100 ml = £232.44; TAC 5 mg/5 ml oral suspension, 100 ml = £301.96[164]
Cost per mg: SRL (Rapamune®)	£3.45	Tablets, coated, SRL 500 µg (tan), net price 30-tablet pack = £69.00; 1 mg (white), 30-tablet pack = £86.49; 2 mg (yellow), 30-tablet pack = £172.98
Cost per mg: BEL (Nulojix®)	£1.42	i.v. infusion, powder for reconstitution, BEL, net price 250-mg vial = £354.52
Cost per mg: Neoral	£0.03	Capsules, 10 mg of CSA (yellow/white), net price 60-capsule pack = £19.40; 25 mg (blue/grey), 30-capsule pack = £19.52; 50 mg (yellow/white), 30-capsule pack = £38.23; 100 mg (blue/grey), 30-capsule pack = £72.57
Cost per mg: CellCept	£0.003	Capsules, blue/brown, MMF 250 mg, net price 100-capsule pack = £82.26
Cost per mg: Thymoglobuline®	£6.35	i.v. infusion, powder for reconstitution, r-ATG, net price 25-mg vial = £158.77

Reproduced from Astellas' submission to NICE, Patel S, Astellas Pharma Ltd, 2014, unpublished data.
Note
Prices of pharmaceutical products from BNF.[162]

Treatment of AR was assigned costs of i.v. steroids and, for the 20% of steroid-resistant BPAR cases, a regimen of r-ATG and the cost of an inpatient hospital stay for acute kidney injury without complications (£1737 overall mean cost). This assumed zero medical management costs for the 80% of patients with steroid-sensitive AR, which ignores any follow-up costs to monitor treatment efficacy. The cost per year of dialysis was £31,806 and the cost of retransplant was £26,639. Although the latter was based on UK *NHS Reference Costs 2013 to 2014*,[58] the former was based on a microcosting study in seven hospital units in the UK.[166] The study measured the average costs of dialysis per year for a 'typical patient', who is likely to be an adult. These costs were measured from the service provider's perspective and included direct costs and the costs of transport and medication usage. They excluded the costs of access surgery and managing dialysis complications. In addition, capital costs of the hospital building were not included. The costs of AEs adopted are presented in *Table 50*, which reproduces table 35 in the Astellas submission to NICE. The major elements of costs are summarised in *Table 51*.

Results

The base-case results presented by Astellas are displayed in *Table 52*. The expected discounted (at 3.5%) QALYs (censored after 10 years) were 5.569 for TAC-IR (Prograf), 5.565 for SRL CNI minimisation, 5.564 for EVL, 5.553 for SRL CNI avoidance, and 5.551 for BEL, in a cohort of patients of mean age 8 years. For TAC once-daily prolonged-release formulation (Advagraf), discounted QALYs were 5.569. The Modigraf and TAC specials regimens were assumed to result in the same health outcomes as Prograf.

In the base-case results, results comparing TAC immediate-release (Prograf) with non-TAC immunosuppressive regimens, Prograf produced more QALYs than any of the comparators and lower costs than BEL and EVL, SRL avoidance, Modigraf and TAC specials whereas it had higher cost than the SRL minimisation regimen. The ICER against SRL CNI minimisation strategy was in excess of £1M. In the comparison of TAC regimens, Advagraf dominated Prograf, given its lower costs and higher QALYs (both discounted and undiscounted).

TABLE 50 Costs of AEs used in the Astellas model (per year)

Variable	Value	Comment
Malignancies	£1388 to £4452 depending on body surface area (m^2)	PTLD/skin/non-Hodgkin's lymphoma. Mabthera concentrate for i.v. infusion, 10 mg/ml of rituximab, net price 10-ml vial = £174.63, 50-ml vial = £873.15. No costs included of other treatment modalities
CMV infections	£221 to £1151 depending on weight (kg)	i.v. ganciclovir 14–21 days then maintenance for 8 weeks. Cymevene® i.v. infusion, powder for reconstitution, ganciclovir (as sodium salt). Net price 500-mg vial = £29.77
NODAT	£17.38	Tablets, coated, metformin hydrochloride 500 mg, net price 28-tablet pack = 87p, 84-tablet pack = £1.00; 850 mg, 56-tablet pack = £1.36
Wound-healing disorders	£0.00	–
Anaemia	£16.88/kg	Binocrit® injection maintenance dose 17–33 units/kg three 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-tablet pack = £18.03; 20 mg (tan), 28-tablet pack = £29.69; 40 mg (red), 28-tablet pack = £29.69; 80 mg (red), 28-tablet pack = £29.69
Hypertension	£15.51	Capsules, Ramipril 1.25 mg, net price 28-capsule pack = 99p; 2.5 mg, 28-capsule pack = £1.05; 5 mg, 28-capsule pack = £1.12; 10 mg, 28-capsule pack = £1.19

Reproduced from Astellas' submission to NICE, Patel S, Astellas Pharma Ltd, 2014, unpublished data.
Source: BNF 2014.[162]

TABLE 51 Major cost elements in the Astellas model (£)

Cost elements	Astellas[a]
TAC-IR therapy (per year)	1559 (first year)
	1366 (second year+)[b]
TAC-PR therapy (per year)	1322 (first year)
	1112 (second year+)
Modigraf	13,654 (first year)
	13,580 (second year+)
TAC administration	0
MMF therapy (per year)	1326[c]
CSA therapy	N/A[d]
EVL (per year)	5086
EVL administration	0
SRL (per year)	2536 (first year)
	2522 (second year+)
SRL administration	0
BEL (per year)	4018 (first year)
	2374 (second year+)
BEL administration	0
CCSs	176 (first year)
	139 (second year+)
AR (event)	889[e]
Dialysis (per year)	31,806[f]
Retransplantation	26,639[g]
Retransplantation: organ procurement	0

a Adopted a 11–12 kg weight and body-surface area for representative patient in the model. The cost of BAS induction (20 mg within 2 hours before transplantation and at 4 days post transplant; BNF 2014 prices[162] £1685) was included in all arms.
b Prograf.
c Based on 600 mg/m^2 twice daily, valued at £82.26 price for 500 mg, 50-capsule pack from BNF 2014.[162]
d Astellas does not evaluate CSA with MMF in their submission. The model only includes CSA as part of the SRL (minimisation) comparator regimen.
e Based on BNF prices.[162]
f From Baboolal *et al.*[166] and included direct costs and the costs of transport and medication usage. They excluded the costs of access surgery and managing dialysis complications. In addition, capital costs of the hospital building were not included.
g *NHS Reference Costs – Renal Transplant and Dialysis*.[167]

TABLE 52 Results of model-based analyses submitted by Astellas

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

The results were found to be sensitive to the starting age (base case started at 8 years, while sensitivity analyses started at 2, 10 and 13 years) and the discount rate, AEs and half-cycle corrections. The results against SRL were found to change significantly when graft survival parameters in the model were populated with data from the Symphony study[127] instead of the NHSBT Service data[32] used in the base-case analyses: low dose TAC was found to dominate SRL as CNI avoidance regimen when both were given with DAC induction, 2 g of MMF and steroids. In discussing these findings, the authors note that the Symphony study[127] has reported outcomes up to 3 years and is the largest prospective study in the de novo kidney transplantation to date, which showed TAC to result in lower AR, better renal function and graft survival outcomes at 1 year than the SRL regimen.

On the basis of these results, the company submission concludes that TAC is cost-effective and that Advagraf should become the standard of care as it produces lower costs and better health outcomes than Prograf. The latter statement is further supported, the submission claims, by the expected benefits (not accounted for in the Astellas model) arising from the improved pharmacokinetic profile of Advagraf relative to Prograf. Despite the apparent cost-effectiveness of its CNI minimisation mode, the submission states that the results of the Symphony trial have discouraged the general use of SRL and that BEL's high cost and high AR rate may do likewise, citing a report by the All Wales Medicines Strategy Group[168] as supportive evidence for this assertion.

Critical appraisal

The analysis presented by Astellas (*Table 53* shows the quality checklist) covers a number of appropriate comparators, including new regimens BEL and regimens with modes of action different from that of CNIs (i.e. EVL and SRL), as well alternative TAC formulations that are believed by the company to be used in routine practice (i.e. Modigraf and specials). However, it omits one relevant comparator: CSA. There is no justification in the submission as to why this drug regimen was not considered. This suggests that the results presented may be misleading owing to the exclusion of a relevant comparator. In addition, all of the regimens analysed by Astellas were evaluated in combination with MMF. This seems to contradict the assertion in the company's submission that 'Most children in the UK receive triple immunosuppression therapy with a CNI (CSA or TAC), a DNA proliferation inhibitor (usually azathioprine), and a CCS following kidney transplantation' (Astellas' submission, page 1). Astellas also reported the results of sensitivity

TABLE 53 Quality assessment Evers checklist;[130] Astellas' submission

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

analyses that varied the mean starting age of patients in the cohort modelled, but as the analysis was censored/stopped at age 18 years, it is difficult to assign any meaningful interpretation to their findings that the results were sensitive to such variation.

There are two logical concerns with the Astellas model-based analysis. First, by accounting for the advantages in adherence of Advagraf in its comparison with Prograf, it makes the comparison of outcomes of Advagraf with those of other immunosuppressive regimens in the model invalid, as 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 AR.[169] Thus, regardless of the validity of the comparative analysis of Advagraf and Prograf, indirect comparisons of model results between advagraf and SRL, and EVL and BEL are invalid. Second, although the model was adjusted to include the effect of adherence on graft survival in the Advagraf versus Prograf comparison, the patient survival curves (for the functioning and failed graft states) were left unchanged, thus the same set of patient survival curves was applied to all immunosuppressive options analysed. This implies the empirically questionable assumption that improvements in graft survival, such as those obtained with Advagraf relative to Prograf (and indeed relative to all other model arms), do not translate in direct patient survival benefits. This inconsistent logic in turn leads to underestimating the benefits of Advagraf and overestimating its costs.

Inspection of the Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) model spreadsheets revealed that the TAC drug regimen options (Advagraf and Prograf) and EVL were the only treatment arms populated by actual data on immunosuppressive drug use from the RCT sample that served as the source for the respective efficacy data; drug consumption values for BEL and SRL regimens were based on treatment guidelines (BNF or SPC). Adult dosages (per kg body weight) of these treatments were used to estimate costs in the model. The only therapies for which child-specific doses were used in calculating resource utilisation in the analysis were MMF and EVL. There are important distinctions with adults that are likely to cast doubt on these drug dosage values. In particular, as acknowledged by the authors in relation to TAC pharmacokinetic studies, children and adolescents appear to eliminate the drug more rapidly than older adults. Further, in relation to steroids, there are concerns about the effects of the medication on growth, which are likely to lead to its more limited use in children and adolescents than in adults.

There is inadequate use of the registry data used to extrapolate short-term efficacy outcomes from RCT in the model. The model used the data from the NHSBT report 2013–14[32] on patient survival rates for kidney-only transplant recipients in the UK (table 28, p. 35, Astellas' submission) to populate the patient survival parameters of patients with a functioning graft, ignoring the fact that such data on survival rates were likely to include deaths from both patients with a functioning and a failed graft. Instead, the probability of death in the graft functioning state should have been calculated as the remainder of the annual probability of death from the NHSBT patient survival data minus the product of probability of mortality in the graft failure state and the proportion of patients with a failed graft. In other words, the Astellas model is likely to overestimate mortality in the functioning graft states, which, in turn, underestimates the benefits of gains in efficacy (i.e. reductions in AR in the model) that any regimen may have over another, for example TAC over the comparators. Thus, the results reported by Astellas in the submission may be treated as conservative estimates of the costs and benefits of its TAC regimes. In relation to the evidence presented in support of Advagraf, its quality is limited by the omission of CSA as a comparator therapy and the fact that the Advagraf versus Prograf comparison is based on what is, in effect, a different model of the outcomes of renal transplantation from that used to compare Prograf with all the other regimens. In fact, the model used for comparing Advagraf with Prograf contradicts the fundamental premise of the model used to compare Prograf with all regimens other than Advagraf: that AR captures all important drivers of clinically meaningful outcomes.

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

In addition, Astellas chose to use values of time to retransplantation for patients on dialysis that were obtained from adult studies, whose mean wait for a retransplant was 3 years.[155] This was in contradiction with the company's submission, which stated that 'Children tend to be prioritised in deceased donor organ allocation systems: the median wait for a kidney in the UK during 2003–2006 for patients aged < 18 years was 277 days'.[170]

There is also an anomaly with regards to the timing of transplantation. Markov models typically imply that transitions occur at the end of the period represented by each cycle. In the present case, the cycle length was 1 year and the authors of the Astellas model correctly decided on using half-cycle corrections to reduce the inaccuracy in expected costs and QALY calculations arising from more frequent average state transitions. However, the model assumed that a proportion of patients undergo retransplantation in the very first cycle and that these made a transition from the failed graft state to a functioning graft post retransplantation state as if the retransplant had occurred at the start of the period so that they spent the whole cycle length (6 months, owing to the half-cycle correction) with a functioning graft after retransplantation in the first cycle. However, this is incorrect as in a cohort of de novo kidney transplant patients, the discrete Markov process transition from a functioning first graft to a functioning retransplant

requires two sequential intervening events to occur (i.e. graft failure and retransplantation) and a minimum of two cycles, one for each event.

In terms of the values used to populate the model, the costs of dialysis – one of the most influential parameters in the analysis – was derived from a microcosting study of the treatment pathway of a typical (i.e. adult) patient at six hospital units. This study[166] sought to inform the introduction of Payment by Results in the NHS.[171] It did not include the costs of access surgery, managing dialysis complications and capital building costs. Reference costs for dialysis are now available that may reflect more representative data.[58] On this basis of this feature and the observation that children and adolescents tend to require higher staff-to-patient ratios than adults,[2] it is expected that the costs of dialysis have been underestimated by the Astellas analysis.

The analysis does not account for discounts in price paid by hospitals for TAC-IR (Prograf), MMF, steroids and CSA (in the SRL CNI minimisation regimen), which were found to be one-third, one-tenth, one-tenth and a half of the list prices, respectively (see *Tables 49* and *97*). The implications of these differences are further explored in the next section (see *Chapter 5*).

Chapter 5 Independent economic assessment

Introduction

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

What is the cost-effectiveness of immunosuppressive regimens in renal transplantation in children and adolescents, of BAS and r-ATG as an induction therapy and TAC-IR, TAC-PR, MMF, MPS, SRL, EVL and BEL as a maintenance therapy?

We are aware of only one published economic evaluation that partially addresses the study question, which is the economic evaluation conducted to support current NICE guidance TA99, published by Yao *et al.*[2] This evaluation did not include the interventions rabbit antihuman thymocyte, EVL or BEL. Astellas submitted an economic evaluation which also does not address the study question in full.

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

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

Methods

Summary of changes from Peninsula Technology Assessment Group model for adults

This economic assessment was conducted using an economic model originally developed by PenTAG to evaluate the cost-effectiveness of immunosuppressive agents in adult KTRs. A summary of changes is provided here as a reference for readers familiar with the original model for adult KTRs (*Table 54*).

Modelling approach

Target population and subgroups

The target population was children and adolescents undergoing kidney-only transplantation (i.e. people receiving multiorgan transplants are not included). The upper age limit for the population 'children and adolescents' is not always clear as young people aged 16–18 years may receive their treatment in child/adolescent or adult centres.[172] Although some data sets include only young people aged < 16 years, the population for the economic assessment is children and adolescents aged < 18 years. The vast majority of transplant kidneys for this population come from DBD and living related donors (UK Transplant Registry standard data set, see *Appendix 10* for further details) (Cathy Hopkinson, NHSBT, 15 October 2014, personal communication).

TABLE 54 Summary of changes from PenTAG model for adults

Type of change	Description	Detailed description and justification in *Chapter 5*
Structural	Addition of two new arms: BAS + TAC + AZA and r-ATG + TAC + AZA	*Interventions and comparators*
	Change of assumed baseline regimen from BAS + TAC + MMF to BAS + TAC + AZA	*Model structure*
	Removal of DCD and living unrelated donors for first graft	*Graft survival, Baseline*
	Addition of extra retransplantation	*Markov model*
	Inclusion of six new arms (three pairs), based on child/adolescent RCTs identified in *Chapter 3* (summarised in *Table 10*)	*Decision tree*
	Inclusion of body weight and surface area as age-dependent variables affecting doses	*Target population and subgroups*
Natural history parameters	Baseline graft survival re-estimated for those under 18 years and according to age group (< 6 years, 6–12 years, > 12 years)	*Graft survival, Baseline*
	Increased rate of retransplantation while < 18 years	*Interventions and comparators*
	Surrogate relationship between eGFR and graft survival re-estimated from a child/adolescent study	*Graft survival, Graft function at 12 months*
	Baseline eGFR at 12 months re-estimated from a child/adolescent study	*Graft survival, Graft function at 12 months*
	Probability of pre-emptive retransplantation at loss of first graft set to 20%	*Graft survival, Use of graft survival in the model*
	Re-estimated baseline risks of AR, cytomegalovirus infection and NODAT	*Adverse events*
	Re-estimated risk profiles for cytomegalovirus and Epstein–Barr virus	*Tables 91* and *93*
	Mortality rate while receiving dialysis estimated for those < 18 years	*Overall survival, Mortality after graft loss*
Cost parameters (resource use)	Dosages for TAC-IR, CSA, MMF, AZA and prednisolone updated with estimates from child/adolescent studies	*Resource use, Maintenance therapy*
	Cytomegalovirus prophylaxis resource use updated	*Resource use, Infection prophylaxis*
	Post-transplant monitoring resource use updated	*Resource use, Monitoring*
	Mix of haemodialysis and peritoneal dialysis estimated for those < 18 years	*Resource use, Dialysis*
Cost parameters (unit costs)	Cost of temporary access for haemodialysis estimated for those < 19 years[a]	*Unit cost, Dialysis*
	Ongoing costs of haemodialysis and peritoneal dialysis updated for those < 19 years	*Unit cost, Dialysis*
	Cost of 10 mg of BAS dose added for KTRs who weigh < 35 kg	*Unit cost, Induction*
	Costs estimated for differing severity of AR (spontaneously resolving, steroid sensitive and steroid resistant)	*Unit costs, Acute rejection*
	Cost of PTLD estimated	*Unit costs, Post-transplant lymphoproliferative disease*
	Costs of hypertension and hypomagnesaemia estimated	*Unit costs, Hypomagnesaemia* and *Hypertension*
	Costs of explant surgery estimated for those < 19 years	*Unit costs, Explant surgery*
	Costs of pre-transplant workup and transplantation estimated for those < 19 years	*Unit costs, Subsequent transplant*

a Costs are estimated for those < 19 years rather than those < 18 years as this is how *NHS Reference Costs 2013 to 2014*[58] are reported.

The UK Transplant Registry standard data set contains data on all solid organ transplants in the UK between 1995 and 2012. It allows linkage of multiple transplants for a single recipient and includes graft and patient survival (measured in days). A total of 34,803 records refer to kidney-only transplants, of which 29,759 recorded both graft and patient survival, 4937 recorded graft survival only (although it may be inferred that the patient survived at least as long as the graft), 24 recorded patient survival only, and 83 recorded neither graft nor patient survival.

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

To explore the impact of age at time of transplantation on cost-effectiveness, subgroups were identified by age (*Table 55*). In addition to this, the average cost-effectiveness of interventions was calculated by determining weighted average total discounted costs and QALYs for each year of age. It was assumed that the same number of transplants would be conducted in 16- and 17-year-olds as for 15-year-olds in order to estimate the cost-effectiveness for those under 18 years. No other subgroups were analysed as there was no evidence from child/adolescent RCTs identified in the systematic review of clinical effectiveness to support economic evaluation of these subgroups.

The weight and body surface area of child/adolescent KTRs are important for dosing and are highly dependent on age. It was assumed that the weight of child/adolescent KTRs would follow the median weight of UK children and adolescents[160,161] (*Figure 14*). In scenario analyses it was assumed instead that the weight of child/adolescent KTRs would follow the ninth centile weight of UK children and adolescents to reflect the possibility that child/adolescent KTRs may have had their growth impaired by renal failure.

TABLE 55 Age distribution of child/adolescent KTRs in the UK

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

Source: UK Renal Registry. The data reported here have been supplied by the UK Renal Registry of the Renal Association (Anna Casula, UK Renal Registry, personal communication, 26 February 2015). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

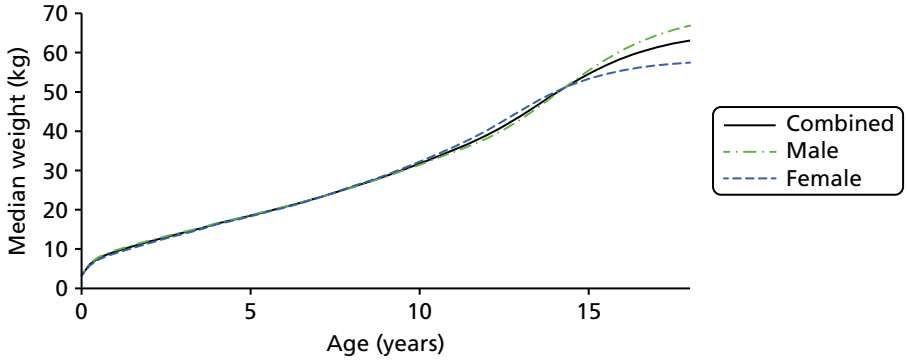

FIGURE 14 Median weight of UK children and adolescents according to age.

Body surface area was then calculated from weight based on the table for body surface area estimation in the BNF for Children,[173,174] as shown in *Table 56*.

Setting and location

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

Study perspective

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

TABLE 56 Estimated body surface area for given weight

Weight (kg)	BSA (m^2)
1.0	0.10
1.5	0.13
2.0	0.16
2.5	0.19
3.0	0.21
3.5	0.24
4.0	0.26
4.5	0.28
5.0	0.30
5.5	0.32
6.0	0.34
6.5	0.36
7.0	0.38
7.5	0.40
8.0	0.42
8.5	0.44
9.0	0.46
9.5	0.47

TABLE 56 Estimated body surface area for given weight (*continued*)

Weight (kg)	BSA (m^2)
10.0	0.49
11.0	0.53
12.0	0.56
13.0	0.59
14.0	0.62
15.0	0.65
16.0	0.68
17.0	0.71
18.0	0.74
19.0	0.77
20.0	0.79
21.0	0.82
22.0	0.85
23.0	0.87
24.0	0.90
25.0	0.92
26.0	0.95
27.0	0.97
28.0–29.0	1.00
30.0–34.0	1.10
35.0–38.0	1.20
39.0–43.0	1.30
44.0–48.0	1.40
49.0–53.0	1.50
54.0–58.0	1.60
59.0–64.0	1.70
65.0–69.0	1.80
70.0–75.0	1.90
76.0–81.0	2.00
82.0–87.0	2.10
88.0–90.0	2.20

BSA, body surface area.
Source: BNF for Children.[173]
Adapted by permission from Macmillan Publishers Ltd on behalf of Cancer Research UK: *Journal of Cancer*, Sharkey I, Boddy AV, Wallace H, Mycroft J, Hollis R, Picton S. Body surface area estimation in children using weight alone: application in paediatric oncology. *British Journal of Cancer* 2001;**85**(1):23,[174] copyright 2001.

Interventions and comparators

As the immunosuppressive agents are used in combination and in sequence, we used treatment regimens as interventions and comparators rather than individual agents, although the cost-effectiveness of an individual agent versus another individual agent can then be evaluated by considering the cost-effectiveness of regimens which are identical but for the use of the intervention agent or the comparator.

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

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

Table 57 presents the regimens considered in this analysis as well as an indication of whether or not the Assessment Group believes the regimen to be a licensed combination for children and adolescents (however, no warranty or representation is given as to the correctness of the information presented in this regard, which reflects the Assessment Group's understanding of the marketing authorisation as stated in the summaries of product characteristics; this understanding has not been confirmed by a clinician or pharmacist and, therefore, its accuracy cannot be guaranteed, particularly as regards drug combinations).

TABLE 57 Immunosuppressive regimens included in independent economic assessment

Identifier	Induction therapy	Maintenance therapy[a]	Licensed
CSA + MMF	None	CSA and MMF	Y
TAC + MMF	None	TAC-IR and MMF	U
CSA + AZA	None	CSA and AZA	Y
TAC + AZA	None	TAC-IR and AZA	Y
CSA + EVL	None	CSA and EVL	N
TAC + SRL	None	TAC-IR and SRL	N
TAC-PR + MMF	None	TAC-PR and MMF	N
BAS + CSA + MMF	BAS	CSA and MMF	Y
BAS + TAC + MMF	BAS	TAC-IR and MMF	U
BAS + CSA + AZA	BAS	CSA and AZA	Y
BAS + TAC + AZA	BAS	TAC-IR and AZA	U
BAS + SRL + MMF	BAS	SRL and MMF	U
BAS + BEL + MMF	BAS	BEL and MMF	N
BAS + CSA + MPS	BAS	CSA and MPS	N
r-ATG + CSA + MMF	R-ATG	CSA and MMF	Y
r-ATG + TAC + MMF	R-ATG	TAC-IR and MMF	U
r-ATG + CSA + AZA	R-ATG	CSA and AZA	Y
r-ATG + TAC + AZA	R-ATG	TAC-IR and AZA	Y

N, no; Y, yes; U, uncertain.
a All maintenance regimens also included CCSs.

In its submission, Astellas also included the following regimens, which we have not modelled:

- SRL and CSA (with BAS induction) – note that we have modelled SRL and TAC without BAS induction (although the SPC for SRL specifies it is to be used in combination with CSA, we found significantly more RCT evidence in the adult population for which it was used in combination with TAC)
- EVL and CSA (with BAS induction) – note that we have modelled this without BAS induction because there were slightly more patients in adult RCTs receiving this regimen without induction
- TAC-IR ('specials' for first 3 years followed by Prograf for remaining life of graft) and MMF (with BAS induction)
- TAC-IR (Modigraf for first 3 years followed by Prograf for remaining life of graft) and MMF (with BAS induction).

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

Time horizon

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

Discount rate

In line with the NICE reference case, the discount rate for costs and health effects was 3.5% per annum.[165]

Choice of health outcomes

The primary health outcome of the independent economic assessment was QALYs for each comparator regimen, in line with the NICE reference case.[165]

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 AR
- likelihood of developing NODAT
- likelihood of receiving a second, third or fourth transplant.

Model structure

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

The first type of analysis was based on actual RCT evidence in the child/adolescent kidney transplant population meeting the inclusion criteria for our systematic review of clinical effectiveness evidence (see *Chapter 3, Inclusion and exclusion criteria*). For each RCT, a decision tree was used to model the expected costs incurred and QALYs accrued for the duration of the trial (see *Decision tree*), followed by extrapolation using the Markov model (see *Markov model*), as shown in *Figure 15*. These analyses allow for an estimation of the cost-effectiveness of the interventions BAS and TAC-IR while relying on as little evidence from the adult population as possible, but do not allow for estimation of the cost-effectiveness of other interventions.

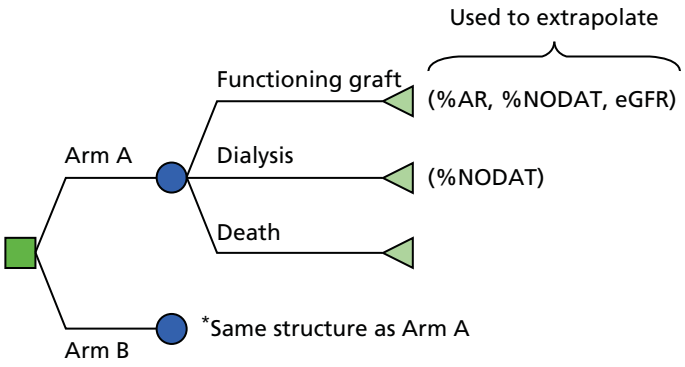

FIGURE 15 Simplified diagram of decision tree used for economic analyses based on child/adolescent RCTs.

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

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

All analyses were constructed in Microsoft Excel 2010.

Decision tree

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

- costs (discounted and undiscounted) of immunosuppression, AR and AEs during the trial duration
- life-years up to the trial duration with functioning graft and with dialysis
- QALYs (discounted and undiscounted) during the trial duration
- for extrapolation using the Markov model
    - proportion of KTRs alive with functioning graft at the end of the trial duration
    - proportion of KTRs who are dialysis-dependent at the end of the trial duration
    - probability of AR within 12 months
    - probability of NODAT within 12 months
    - graft function (mean eGFR) at 12 months.

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

For simplicity, it was assumed that no KTRs losing their graft would be retransplanted within the trial duration. For Offner *et al.*,[73] with follow-up of only 1 year, this is likely to be a very reasonable assumption. For Grenda *et al.*[75] and Trompeter *et al.*,[77] with follow-up of 2 and 5 years, respectively, this may result in a bias against the arm with greater graft loss.

Methods for estimating costs

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

Immunosuppression resource use was frequently reported as dose per kg body weight or per m^2 body surface area, so these were estimated and were modelled to increase over the course of the trial duration in line with child/adolescent growth curves. If baseline body weight was not reported, it was estimated based on age at baseline.

Methods for estimating life-years

For each RCT, we estimated the numbers and times of KTRs losing their grafts (any cause, including DWFG) and the numbers and times of KTRs dying. It was then assumed that all KTRs not losing their graft or dying were censored at the end of the trial duration. Restricted mean survival was calculated (restricted to the trial duration) as shown in *Table 58*. The estimated life-years with functioning graft was then the restricted mean graft survival (not censored for DWFG). Restricted mean patient survival minus restricted mean graft survival gave the estimated life-years on dialysis.

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

$$\begin{aligned} T_{diff} &= T_{max} - T \\ \mathrm{E}[T_{diff}] &= T_{max} - \mathrm{E}[T] \\ \mathrm{SE}[T_{diff}] &= \mathrm{SE}[T] \\ T_{diff} &\sim \Gamma(\alpha, \beta) \\ \alpha &= (\mathrm{E}[T_{diff}]/\mathrm{SE}[T_{diff}])^2 \\ \beta &= (\mathrm{SE}[T_{diff}])^2/\mathrm{E}[T_{diff}]. \end{aligned} \quad (1)$$

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

TABLE 58 Restricted mean overall and graft survival in child/adolescent RCTs (years)

Trial	Trompeter *et al.*[77]		Grenda *et al.*[75]		Offner *et al.*[73]	
Arm	TAC + AZA	CSA + AZA	TAC + AZA	BAS + TAC + AZA	BAS + CSA + MMF	CSA + MMF
Overall survival						
T_{max}	4		2		1	
E[*T*]	3.921	3.852	1.996	2.000	0.984	1.000
SE[*T*]	0.0383	0.0733	0.0018		0.0057	
Graft survival						
T_{max}	4		2		1	
E[*T*]	3.769	3.609	1.840	1.884	0.975	0.994
SE[*T*]	0.0748	0.1030	0.0550	0.0503	0.0123	0.0055

E, expected value; *T*, time; T_{max}, time at follow-up duration.

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

Outcomes for extrapolation

Overall survival (Kaplan–Meier) as reported by the RCTs was used to estimate the proportion of children and adolescents dead at the end of the trial duration, that is, at the start of extrapolation using the Markov model (*Table 59*). Kaplan–Meier graft survival (this time censored for DWFG) was used to estimate the proportion of those alive who would still have a functioning graft (see *Table 59*).

Markov model

A Markov model structure was used with three main states: *functioning graft, graft loss* and *death*.

The KTRs start in the *functioning graft* unless they suffer PNF, in which case they start in the *graft loss* state. Transitions can occur from *functioning graft* to *graft loss*, reflecting disease progression; transitions are not permitted in the opposite direction except through retransplantation. Up to three retransplantations are possible and, therefore, there are four substates for *functioning graft* and *graft loss* reflecting the graft number (1–4). As with the initial graft, it is possible that PNF will occur and, therefore, transitions can occur directly to *graft loss* following second, third or fourth graft. Pre-emptive retransplantation can occur from the original *functioning graft* state, but not from *functioning graft* states 2–4. Death can occur from any state but the rate of mortality is greater in the *graft loss* state (see *Overall survival*, *Mortality after graft loss*) 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), as this was judged the most likely regimen for kidney transplantation in adults (and most retransplantations are expected to occur after KTRs reach adulthood).

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

In addition to these health states, for each regimen the incidence of AR, CMV infection, dyslipidaemia and NODAT was estimated.

TABLE 59 Outcomes from decision trees for extrapolation with Markov models

Trial	Trompeter *et al.*[77]		Grenda *et al.*[75]		Offner *et al.*[73]	
Arm	**TAC + AZA**	**CSA + AZA**	**TAC + AZA**	**BAS + TAC + AZA**	**BAS + CSA + MMF**	**CSA + MMF**
Kaplan–Meier overall survival	0.94	0.92	0.989	1.000	0.972	1.000
Kaplan–Meier graft survival (censored for DWFG)	0.954	0.792	0.896	0.949	0.981	0.989
AR within 12 months[a]	0.43	0.62	0.26	0.24	0.13	0.23
NODAT within 12 months	0.019	0.011	0.011	0.040	0.0	0.0
eGFR at 12 months (ml/minute/1.73 m^2)	64.9	57.8	74.9	74.0	79	82

Note

a The proportions with AR in Trompeter *et al.*[77] and Grenda *et al.*[75] are estimated Kaplan–Meier method (i.e. cumulative incidence) while proportions in Offner *et al.*[72] are estimated as simple proportions.

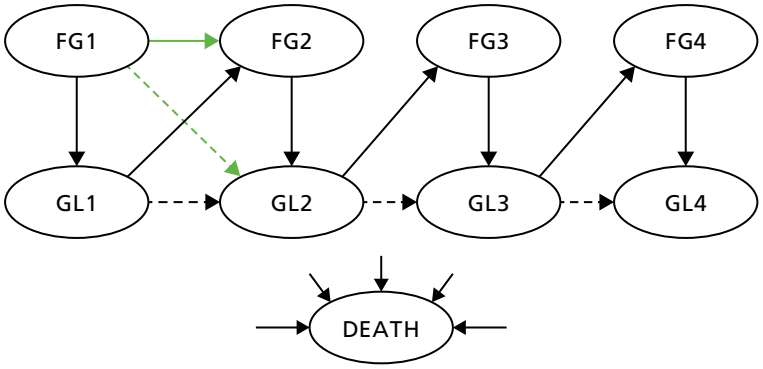

FIGURE 16 Markov model diagram. Note that green arrows indicate pre-emptive retransplantation while dashed arrows signify PNF of a subsequent retransplantation. FR, *functioning graft*; GL, *graft loss*.

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

$$p_i = (r_i/R) \times (1-e^{-R\Delta t}), \quad (2)$$

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).

Table 60 gives a summary of how the transition rates were dependent on factors such as age, AR and NODAT. BAS + TAC + AZA was assumed to be the baseline regimen for the initial graft, for the following reasons:

- Only two of the four regimens in current use in the NHS (TAC + AZA and BAS + TAC + AZA) are consistent with current NICE guidance TA99.[1]
- Although the most common regimen in use is TAC + AZA, this is also expected to result in worse outcomes than BAS + TAC + AZA, TAC + MMF and BAS + TAC + MMF (except death within 12 months, for which it is expected to be superior to TAC + MMF, and eGFR at 12 months, for which it is expected to be superior to TAC + MMF and BAS + TAC + MMF) according to network meta-analyses of adult RCT evidence, and so TAC + AZA may not be as close to average UK outcomes as BAS + TAC + AZA.

Factors included in the model

Overall survival

Overall survival was not explicitly included as an input to the model and, therefore, emerges from the two modelled rates of mortality (see *Overall survival*, *Death with functioning graft* and *Mortality after graft loss*).

The exception to this is that the rate of DWFG in the first year was adjusted using an individual HR for each regimen to achieve the desired OR of patient mortality as derived from the mixed-treatment comparison (MTC) and head-to-head comparisons.

Although 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 rerun Solver every time relevant parameters were changed) and would greatly slow down PSAs.

TABLE 60 Summary of determining factors for transition rates within the Markov model

Transition	Corresponding clinical outcome	Dependent on
Functioning graft to *graft loss* (first graft)	Disease progression (graft loss/survival)	First year
		Time since transplantation
		Regimen-specific OR 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)	DWFG	First year
		Time since transplantation
		Regimen-specific HR based on OR of patient death within 12 months
		Subsequent years
		Time since transplantation
		Age
		NODAT
Functioning graft to *death* (subsequent graft)	DWFG	Age
		NODAT
Graft loss to subsequent *functioning graft*	Retransplantation	Age
Graft loss to *death*	Mortality while receiving dialysis	Age

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

For each OR of graft loss, linear regression of ln(odds of patient mortality) versus ln(HR of DWFG) was performed and the values of the linear regression coefficients were found to be linearly dependent on the OR of graft loss (*Figure 18*).

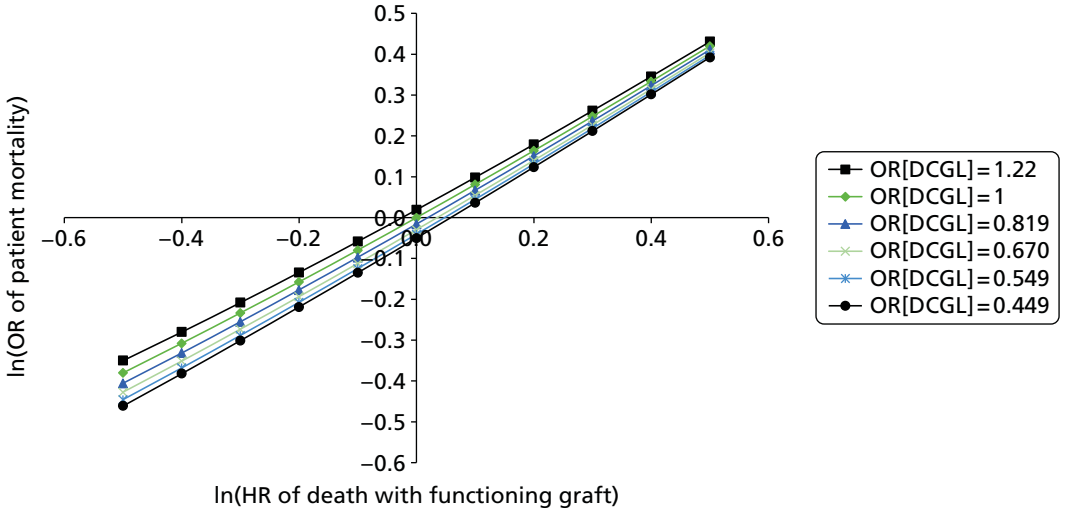

FIGURE 17 Odds ratio of patient mortality is dependent on HR of DWFG and OR of DCGL. DCGL, death-censored graft loss.

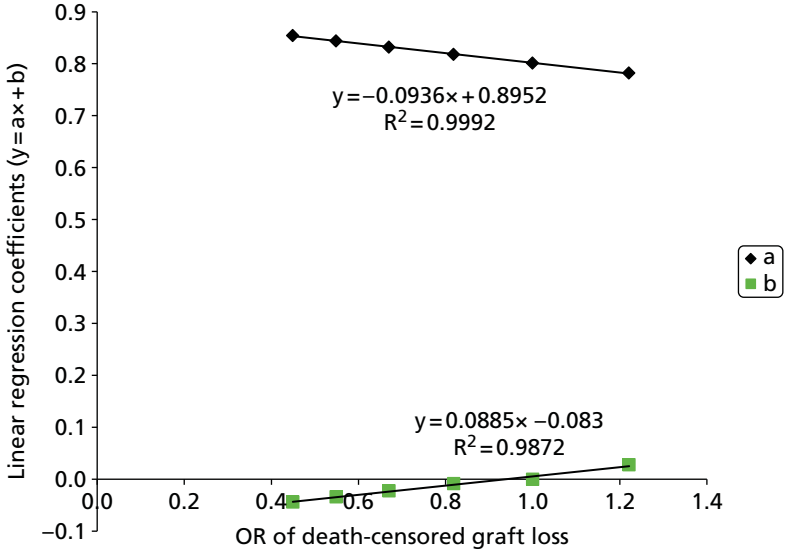

FIGURE 18 Linear regression coefficients for ln(OR of patient death) versus ln(HR of DWFG) plotted versus OR of graft loss.

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

$$\begin{aligned} a_i &= 0.8952 - 0.0936 \times OR_{DCGL,i} \\ b_i &= 0.0885 \times OR_{DCGL,i} - 0.083 \\ HR_{DWFG,i} &= \exp\left\{ \frac{\ln(OR_{PD,i}) - b_i}{a_i} \right\}. \end{aligned} \quad (3)$$

As can be seen in *Table 61*, the regression formulae perform well in most instances.

TABLE 61 Comparison of HRs for DWFG from regression and calculated using Solver

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

Death with functioning graft

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

More KTRs die from infection and malignancy than dialysis recipients and the risk of both is increased by greater immunosuppression.[175] CVD 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 that are adjusted for when comparing survival across different centres.[96]

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).[176] The use of steroids is also linked to increased risk of death from CVD and infection.[177]

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 1 year post transplantation.[177]

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 data set for each donor type (DBD, DCD, living related, living unrelated) after adjusting for transplant period (adjusted to 2007–12) and age group (adjusted to 31–50 years). The Kaplan–Meier survival function was directly used for the first 19 years, followed by an extrapolation based on the estimated rate of DWFG from 9–19 years. The baseline survivor function is shown in *Figure 19*.

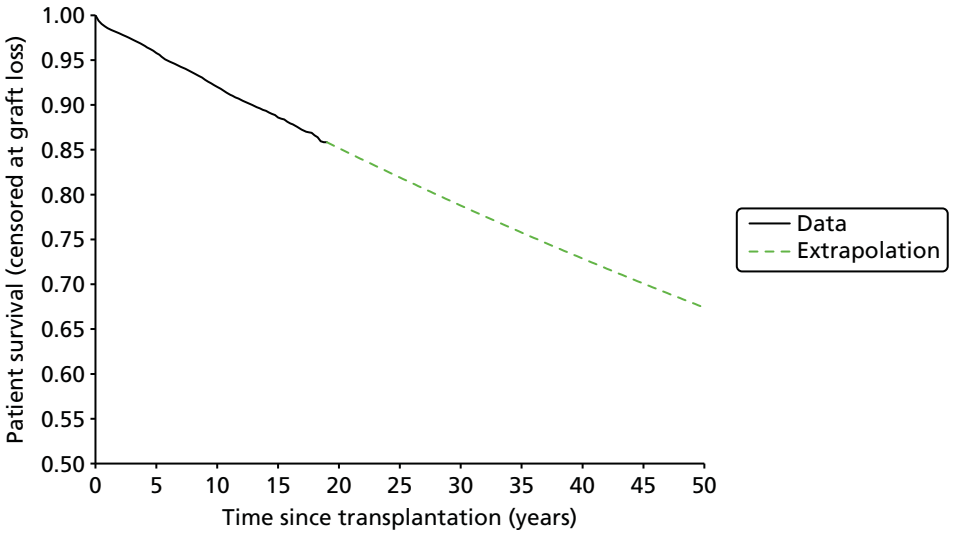

FIGURE 19 Baseline survivor function for DWFG.

The rate of DWFG was then adjusted by sex, donor type and age based on a Cox proportional-hazards analysis of the UK Transplant Registry data set (*Table 62* and see *Appendix 10*). For the first 12 months an individual HR was applied for each regimen to achieve a target OR of patient mortality (see *Overall survival*) and thereafter a HR for NODAT was applied according to Cole *et al.*[178]

TABLE 62 Hazard ratios applied to rate of DWFG

Covariate	HR
NODAT	1.41
Sex: female	0.865
Donor type	
DBD	1
DCD	1.083
Living related	0.551
Living unrelated	0.703
Age (years)	
< 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 retransplantation, KTRs will be placed on dialysis. Some KTRs will be waitlisted for retransplantation while others will be judged not fit for retransplantation owing 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.[154]

It was assumed that mortality rates following graft loss would be the same as mortality rates for dialysis recipients and dependent on age group (*Table 63*). It is notable that the rate of mortality for children and adolescents on dialysis is higher than the rates for KTRs aged 18–49 years.

For the PSA, the SE of mortality rate in each group was estimated by dividing the square root of the number of observed deaths by the estimated exposure.

Graft survival

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

Use of graft survival in the model

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

TABLE 63 Mortality rate for dialysis recipients

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

Note
Calculated from results in table 8.18 of Pruthi *et al.*[154]

The transitions for the first graft are calculated by first estimating a graft survival curve (censored for DWFG) 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:

$$r_{GL}(t_i) = [\ln(S(t_i)) - \ln(S(t_{i+1}))]/\Delta t, \quad (4)$$

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

The details for how the survival curves are estimated were given earlier (see *Overall survival*), but briefly:

- Graft survival censored for DWFG is estimated by adjusting baseline graft survival from the UK Transplant Registry standard data set in the first year according to the OR of graft loss within 12 months and thereafter according to a surrogate relationship based on AR within 12 months, NODAT within 12 months and eGFR at 12 months.
- Death with functioning graft is estimated by adjusting baseline patient survival estimated from the UK Transplant Registry standard data set in the first year according to the OR of patient death within 12 months and thereafter according to a surrogate relationship based on NODAT within 12 months.

To account for the possibility of pre-emptive retransplantation, the rate of *graft loss* is partitioned between transitions from first *functioning graft* to *graft loss* following first graft; first *functioning graft* to second *functioning graft* (successful pre-emptive retransplantation); and first *functioning graft* to *graft loss* following second graft (unsuccessful pre-emptive retransplantation). It was assumed that 20% would receive pre-emptive retransplantation,[179] of which 1.6% would result in PNF (based on the UK Transplant Registry standard data set, see *Appendix 10*).

Estimation of graft survival

It has been established in adults that AR, NODAT and graft function measured at 12 months are predictive of graft survival.[178,180–184]

For children and adolescents we identified far fewer studies estimating the relationship between the potentially predictive attributes identified for adults (AR, NODAT and graft function at 12 months) and graft survival.

Muscheites *et al.*[185] considered a number of potentially predictive factors for death-censored graft loss in 104 children and adolescents receiving kidney transplants in one out of four German centres: recipient age (< 6 years, 6–12 years, > 12 years); recipient gender; donor type; number of HLA mismatches; number of rejection episodes; underlying renal disease; transplant period (1989–95, 1996–2000); change in GFR (between 30 days and 12 months; between 6 and 12 months); and GFR at 30 days, 6 months and 12 months. KTRs with graft survival of < 1 year were excluded and the mean follow-up was 8.3 years. They found that in univariate Cox analyses only the absolute GFR values at 30 days, 6 months and 12 months were predictive of graft survival with a significance level of 0.05. Furthermore, when considering a multivariate Cox analysis only GFR at 12 months was predictive of long-term graft survival. This study concludes that AR is not predictive (in univariate or multivariate analyses, significance level 0.05), but does not report any central estimates for the HR due to AR. It is possible that the study was insufficiently powered to estimate the effect of AR on graft survival with precision and it is also possible that excluding patients with graft survival < 1 year would also limit the predictive power of AR. The study also does not include NODAT as a covariate.

Tejani and Sullivan[186] considered the relationship between AR and 'chronic rejection graft loss' (which accounted for 30.8% of failed grafts). Although they found that AR is a significant predictor of chronic rejection graft loss, they do not report the relationship between AR and graft loss overall.

It was decided that the relationship between eGFR and graft survival would be estimated based on the results of Muscheites *et al.*[185] as these appear to be in the relevant population and estimated using appropriate statistical methodology. It was decided that for AR and NODAT, the same relationship as used for the adult population would be used, as this is consistent with TA99[1] (where the Committee in their consideration of the evidence accepted an AR surrogate relationship based on adult evidence).

It could be argued that as no statistically significant evidence for a relationship between AR and graft survival was found by Muscheites *et al.*,[185] that no such relationship should be included in the model, but it was felt that if two regimens were predicted to result in the same eGFR but one regimen was predicted to reduce the rate of AR, that this should be reflected in the predicted graft survival. In addition, as Muscheites *et al.*[185] did not report the central estimate for the HR according to AR, it is possible that the central estimate may not be too different from the HR for adults.

It may also be noted that the HR of graft loss (for KTRs experiencing BPAR in the first 12 months versus KTRs not experiencing BPAR) assumed in this model (1.60 on the basis of adult evidence) is less than the HR assumed to inform TA85 and TA99 (1.96), although it is greater than a HR proposed by the Assessment Group for TA99 and rejected by the NICE Appraisal Committee at that time (a value of 1.41).

Throughout this section it should be noted that graft survival (and the underlying event, graft failure) does not include DWFG, that is, 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 data set using the Kaplan–Meier method, restricting to the first graft for each recipient and adjusting to the year 2012 (using Cox proportional hazards on transplant year). Graft survival was estimated separately for DBD and living related donors (DCD and living unrelated donors are very rare in child/adolescent transplantation). KTRs with graft failure on the day of transplant were assumed to have PNF and were excluded. Any KTRs dying with a functioning graft were censored at the time of death. *Figure 20* gives the baseline graft survival.

Baseline graft survival was extrapolated by fitting a Weibull curve to conditional survival from 1 year for first graft (i.e. fitted to KTRs whose first grafts survived at least 1 year), with proportional hazards covariates for donor type and transplant year. The fit of this Weibull curve was verified with a graphical test of the Cox–Snell residuals (*Figure 21*), which demonstrated that the fit was good as there was little deviation from the diagonal except for long follow-up (when censoring tends to cause such deviations).

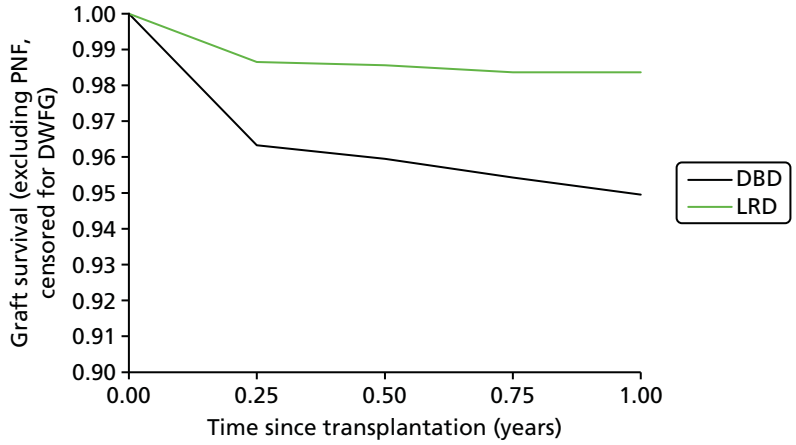

FIGURE 20 Graft survival in first year according to donor type. LRD, living related donors.

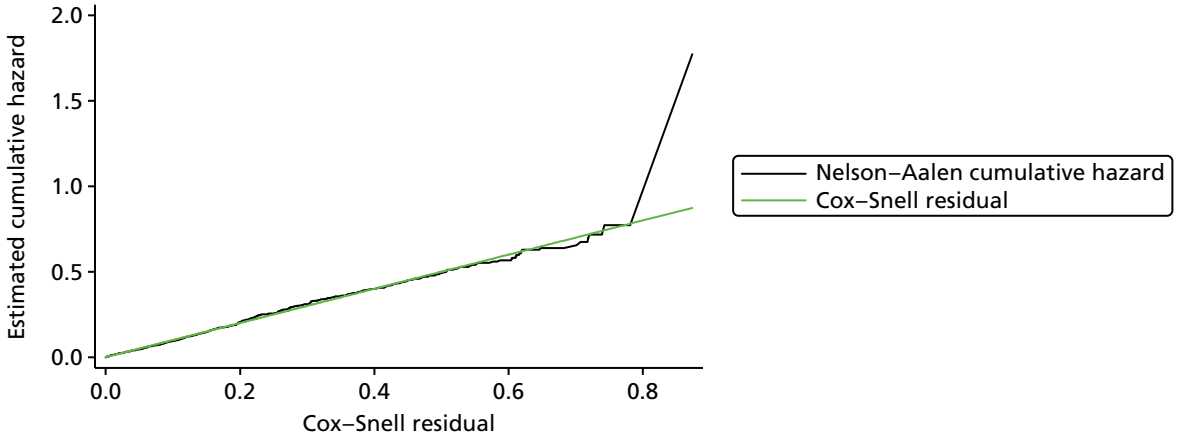

FIGURE 21 Graphical verification of the fit to graft survival.

Other parametric survival distributions were not explored owing to the adequacy of the Weibull fit and for consistency with the parallel HTA (in which a Weibull curve was further indicated owing to the need to apply HRs derived from a separate Weibull fit reported by Levy *et al.*[182]).

The baseline model for conditional graft survival from 1 year is then:

$$S(t) = \exp\{-\lambda t^{\gamma}\}, \quad (5)$$

where t is time after 1 year, λ is the rate parameter and γ is the shape parameter (with a value of 1.103, implying increasing hazard rate with time).

A different rate parameter is obtained for different covariate values (proportional hazards model), the baseline rate parameter was obtained by assuming the following covariate values: donor type = [(DBD, 0.638), (living related, 0.362)]; transplant year = 2012. These led to a baseline rate parameter value of 0.02187.

The resulting baseline graft survival in the PenTAG model is shown in *Figure 22*.

Results presented by Hudson and Collett[187] at the British Transplantation Society Congress (February 2014) suggest that for deceased donors the median graft survival (death censored) for DBD grafts is 21–22 years (and higher for grafts from living donors), while estimated 30-year graft survival is 36% for DBD grafts (and expected to be higher for living donor grafts). These results serve as external validation of the extrapolation in the PenTAG model.

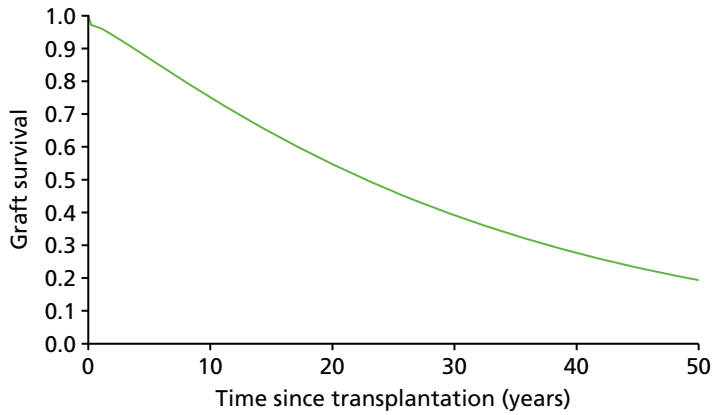

FIGURE 22 Baseline graft survival in the PenTAG model.

Adjustments during the first year Graft survival for the first year was adjusted using the proportional odds method such that for each regimen the ORs of graft loss (excluding death and PNF) throughout the first year matched the ORs of graft loss as detailed in *Based on adult randomised controlled trial evidence*.

Adjustments after the first year Graft survival for the first graft after the first year was modelled using the surrogate end points renal function at 12 months, AR within 12 months and NODAT within 12 months.

The surrogate relationship was implemented using proportional hazards and summarised in *Table 64* and expanded in sections below. The rate parameters for all regimens (after adjusting according to the surrogate relationship) are given in *Table 65*. The resulting graft survival (excluding DWFG) at 1, 3, 5 and 10 years for each regimen is given in *Table 66*.

TABLE 64 Surrogate relationship HRs for graft survival

Relationship	HR	Source
AR within 12 months	1.60	Cole *et al.*[178]
Renal function (eGFR ml/minute/1.73m^2) at 12 months	1 for eGFR > 80	Muscheites *et al.*[185]
	1.59 for 45 < eGFR ≤ 80	
	55.9 for eGFR ≤ 45	
NODAT within 12 months	1.12	Cole *et al.*[178]

TABLE 65 Rate parameters for graft survival after 1 year

Regimen	Rate parameter (λ)
CSA + MMF	0.0391
TAC + MMF	0.0300
CSA + AZA	0.0461
TAC + AZA	0.0269
CSA + EVL	0.0331
TAC + SRL	0.0424
TAC-PR + MMF	0.0303
BAS + CSA + MMF	0.0323
BAS + TAC + MMF	0.0247
BAS + CSA + AZA	0.0375
BAS + TAC + AZA	0.0219
BAS + SRL + MMF	0.0286
BAS + BEL + MMF	0.0210
BAS + CSA + MPS	0.0272
r-ATG + CSA + MMF	0.0346
r-ATG + TAC + MMF	0.0267
r-ATG + CSA + AZA	0.0397
r-ATG + TAC + AZA	0.0236

TABLE 66 The 1-, 3-, 5- and 10-year graft survival for each regimen

	Graft survival (excluding DWFG and PNF) (%)			
Regimen	1 year	3 years	5 years	10 years
CSA + MMF	97.01	89.19	80.97	62.34
TAC + MMF	97.24	91.16	84.65	69.27
CSA + AZA	96.02	86.97	77.62	57.06
TAC + AZA	95.47	90.10	84.30	70.42
CSA + EVL	97.51	90.81	83.69	67.09
TAC + SRL	95.37	87.06	78.40	59.06
TAC-PR + MMF	96.70	90.60	84.07	68.66
BAS + CSA + MMF	97.47	90.94	83.98	67.69
BAS + TAC + MMF	97.66	92.61	87.14	73.88
BAS + CSA + AZA	96.63	89.15	81.27	63.27
BAS + TAC + AZA	96.16	91.74	86.92	75.11
BAS + SRL + MMF	96.52	90.76	84.56	69.84
BAS + BEL + MMF	97.91	93.59	88.87	77.26
BAS + CSA + MPS	97.81	92.25	86.26	71.92
r-ATG + CSA + MMF	97.67	90.66	83.23	66.04
r-ATG + TAC + MMF	97.85	92.39	86.49	72.36
r-ATG + CSA + AZA	96.88	88.96	80.66	61.88
r-ATG + TAC + AZA	96.45	91.69	86.51	73.91

Graft function at 12 months The average graft function (eGFR) at 12 months for each regimen was estimated by estimating the baseline average eGFR at 12 months. We were unable to find these figures in the UK Renal Registry annual reports; the best available estimate is 82 ml/minute/1.73 m^2 (SD 27 ml/minute/1.73 m^2) from a German multicentre observational study.[185] This study, by Muscheites *et al.*,[185] also informs the surrogate relationship between graft function at 12 months and graft survival. Dividing eGFR into three categories (< 45 ml/minute/1.73 m^2, 45–80 ml/minute/1.73 m^2 and > 80 ml/minute/1.73 m^2) the authors found that compared with KTRs in the highest eGFR category at 12 months, those in the lowest had significantly worse graft survival (HR 55.9, 95% CI 5.29 to 591), and those in the middle category had worse graft survival, but this was not shown to be statistically significant (HR 1.59, 95% CI 0.52 to 4.87).

The regimen-specific proportion of KTRs in each eGFR category at 12 months was estimated by first calculating the expected mean eGFR for the regimen by adding the regimen-specific mean eGFR difference (see *Based on adult randomised controlled trial evidence*) to the baseline mean eGFR, then assuming a normal distribution with a SD of 27 ml/minute/1.73 m^2.

Acute rejection within 12 months Acute rejection rates within 12 months were estimated using effectiveness estimates as described in *Based on adult randomised controlled trial evidence* and a baseline AR rate for BAS + TAC + AZA.

The baseline AR rate for BAS + TAC + AZA was estimated as 19 out of 99 = 19.2% from Grenda *et al.*[75]

The effect of AR on graft survival after the first year was estimated using the HR of 1.60 from Cole *et al.*[178] A regimen-specific raw HR was then calculated according to the weighted average of the HRs for AR (1.60) and no rejection (1.00) with the weights equal to the AR rate for each regimen. These were then normalised to give HRs versus the baseline (BAS + TAC + AZA), as shown in *Table 67*.

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 mellitus*.

The effect of NODAT on graft survival after the first year was estimated using the HR of 1.12 from Cole *et al.*[178] (based on the adult population) and incorporated using the same methodology as for graft function and AR. *Table 68* demonstrates that the impact of NODAT on graft survival is fairly small, which is to be expected given the conclusions of Cole *et al.*[178] that NODAT primarily increases the rate of DWFG, which is not considered here.

Adverse events

Synthesis of AE data is rarely conducted across studies owing to typically low incidence (resulting in low statistical power to detect differences) and heterogeneity of reporting. The challenge of synthesising such data is impossible in the case of child/adolescent kidney transplantation owing to the paucity of RCT evidence. Even so, for this model and in the model for the adult population it was judged important to consider the possible impact of different regimens on AE rates because the profile of AEs is considered highly clinically relevant.

TABLE 67 Acute rejection rates and HR for graft survival due to AR for each regimen

Regimen	AR rate	Raw HR	HR vs. baseline
CSA + MMF	27.83%	1.167	1.046
TAC + MMF	24.57%	1.147	1.029
CSA + AZA	44.98%	1.270	1.139
TAC + AZA	32.09%	1.193	1.069
CSA + EVL	27.19%	1.163	1.043
TAC + SRL	23.89%	1.143	1.025
TAC-PR + MMF	24.11%	1.145	1.026
BAS + CSA + MMF	16.24%	1.097	0.984
BAS + TAC + MMF	14.07%	1.084	0.972
BAS + CSA + AZA	29.13%	1.175	1.053
BAS + TAC + AZA (baseline)	19.19%	1.115	1.000
BAS + SRL + MMF	15.22%	1.091	0.979
BAS + BEL + MMF	24.88%	1.149	1.031
BAS + CSA + MPS	22.37%	1.134	1.017
r-ATG + CSA + MMF	11.98%	1.072	0.961
r-ATG + TAC + MMF	10.31%	1.062	0.952
r-ATG + CSA + AZA	22.40%	1.134	1.017
r-ATG + TAC + AZA	14.30%	1.086	0.974

TABLE 68 Incidence of NODAT and effect on graft survival for each regimen

Regimen	Incidence of NODAT	Raw HR	HR vs. baseline
CSA + MMF	1.83%	1.002	0.997
TAC + MMF	4.04%	1.005	1.000
CSA + AZA	1.83%	1.002	0.997
TAC + AZA	4.04%	1.005	1.000
CSA + EVL	1.74%	1.002	0.997
TAC + SRL	6.33%	1.008	1.003
TAC-PR + MMF	4.75%	1.006	1.001
BAS + CSA + MMF	1.83%	1.002	0.997
BAS + TAC + MMF	4.04%	1.005	1.000
BAS + CSA + AZA	1.83%	1.002	0.997
BAS + TAC + AZA (baseline)	4.04%	1.005	1.000
BAS + SRL + MMF	3.22%	1.004	0.999
BAS + BEL + MMF	0.79%	1.001	0.996
BAS + CSA + MPS	1.71%	1.002	0.997
r-ATG + CSA + MMF	1.83%	1.002	0.997
r-ATG + TAC + MMF	4.04%	1.005	1.000
r-ATG + CSA + AZA	1.83%	1.002	0.997
r-ATG + TAC + AZA	4.04%	1.005	1.000

Owing to the lack of RCT evidence in children and adolescents, it was decided that in the analysis for which effectiveness estimates are drawn from adult RCT evidence, the impact of regimens on AEs should also be drawn from those adult RCTs. However, in the analyses based on child/adolescent RCTs, estimates of incidence were taken from those child/adolescent RCTs when possible, even when this meant a different set of AEs was included.

In this section and subsections we describe how the incidences of NODAT, CMV infection, dyslipidaemia and anaemia are estimated in the analysis based on adult RCT evidence.

Cytomegalovirus infection is assumed to be a one-off event occurring in the first year, whereas NODAT, dyslipidaemia and anaemia are chronic conditions modelled for the full time horizon while patients are alive. All AEs incur costs while NODAT additionally results in a utility decrement (see *Disutility due to diabetes mellitus*).

Diabetes mellitus

The incidence of diabetes mellitus 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.[188] Kidney transplantation appears to result in a significant increase in the incidence of diabetes mellitus in the first year post transplant (and especially in the first 6 months), after which incidence falls to similar levels to those seen in people on dialysis (see figure 2 of Woodward *et al.*[188]). TAC has been repeatedly associated with the development of NODAT[5,178] and the same incidence pattern is observed of significantly elevated incidence in the first year post transplant.[188]

Pre-existing diabetes mellitus in the cohort was not modelled, only NODAT within 12 months. Based on a visual inspection of figure 1 of Woodward *et al.*,[188] it was assumed that 75% of NODAT in the first year would occur within the first 6 months. Incidence of NODAT after the first year was not modelled, as the results of Woodward *et al.*[188] suggest that after the first year the incidence of diabetes mellitus returns to pre-transplantation levels.

As in the model for adult KTRs, we assume that after the first year there is no change in the prevalence of NODAT in the population.

Baseline 12-month incidence of NODAT for BAS + TAC + AZA was estimated to be 4.0% from Grenda *et al.*[75]

In the model for adult KTRs it was assumed that the effect of changing regimen from baseline (BAS + TAC + AZA) could be estimated by multiplying the effects of changing the agents TAC and AZA. In fact, no RCTs were identified comparing MMF and AZA which reported NODAT and, therefore, it was assumed that AZA and MMF would lead to the same incidence of NODAT.

Tables 69 and *70* list the studies (RCTs from the systematic review of clinical effectiveness in adults) informing the impact of replacing TAC-IR and MMF, respectively, on 12-month NODAT incidence. The corresponding network diagrams are given in *Figures 23* and *24*.

Mixed-treatment comparisons were conducted for both and in both cases a fixed-effects model was considered to be more appropriate owing to a lower deviance information criterion (DIC) (58.28 vs. 60.39 and 25.52 vs. 27.04). The results of the MTCs are presented in *Tables 71* and *72*.

The mean log-ORs were combined from the MTCs to estimate an overall OR for each regimen, as shown in *Table 73*, 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 74*.

TABLE 69 Studies included to estimate the impact on NODAT incidence of replacing MMF

Study	Compares	NODAT in 12 months
Ciancio *et al.* 2008[189]	MMF vs. MPS	7/61 vs. 6/55
[a]Ferguson *et al.* 2011[129]	MMF vs. SRL	0/33 vs. 2/26
Takahashi *et al.* 2013[190]	MMF vs. EVL	3/61 vs. 7/61
Tedesco Silva *et al.* 2010[191]	MMF vs. EVL	19/273 vs. 14/274
Anil Kumar *et al.* 2005[192]	MMF vs. SRL	2/75 vs. 2/75
Gonwa *et al.* 2003[193]	MMF vs. SRL	9/176 vs. 10/185
Sampaio *et al.* 2008[194]	MMF vs. SRL	6/50 vs. 12/50

a TAC + MMF arm excluded.

TABLE 70 Studies included to estimate the impact on NODAT incidence of replacing TAC-IR

Study	Compares	NODAT in 12 months
Laskow *et al.* 1996[106]	TAC vs. CSA	12/67 vs. 1/20
Mayer *et al.* 1997[107]	TAC vs. CSA	17/303 vs. 3/145
Campos and Abbud Filho 2002[109]	TAC vs. CSA	10/85 vs. 3/81
Hardinger *et al.* 2005[113]	TAC vs. CSA	5/134 vs. 1/66
Raofi *et al.* 1999[195]	TAC vs. CSA	3/14 vs. 4/21
Yang *et al.* 1999[125]	TAC vs. CSA	1/24 vs. 1/21
Krämer *et al.* 2010[139]	TAC vs. TAC PR	20/336 vs. 22/331
Tsuchiya *et al.* 2013[196]	TAC vs. TAC PR	0/52 vs. 1/50
[a]Vincenti *et al.* 2005[197]	CSA vs. BEL	6/73 vs. 1/71
[a]BENEFIT[198]	CSA vs. BEL	16/221 vs. 7/226
[a]BENEFIT-EXT[199]	CSA vs. BEL	11/184 vs. 7/175
[b]Ferguson *et al.* 2011[129]	TAC vs. BEL	1/30 vs. 0/33
Lebranchu *et al.* 2009[200]	CSA vs. SRL	2/97 vs. 3/96
Buchler *et al.* 2007[201]	CSA vs. SRL	3/74 vs. 9/71
Kreis *et al.* 2000[202]	CSA vs. SRL	1/38 vs. 1/40
Guba *et al.* 2010[203]	CSA vs. SRL	4/71 vs. 5/69
Martinez-Mier *et al.* 2006[204]	CSA vs. SRL	1/21 vs. 1/20
Schaefer *et al.* 2006[205]	TAC vs. SRL	5/39 vs. 6/41
Groth *et al.* 1999[206]	CSA vs. SRL	1/42 vs. 1/41
Chen *et al.* 2008[126]	TAC vs. CSA	1/21 vs. 1/20
Symphony[127]	TAC vs. CSA vs. SRL	34/403 vs. 17/408 vs. 25/380

a Less intensive BEL arm only (more intensive BEL arm excluded).
b BEL + SRL arm excluded.

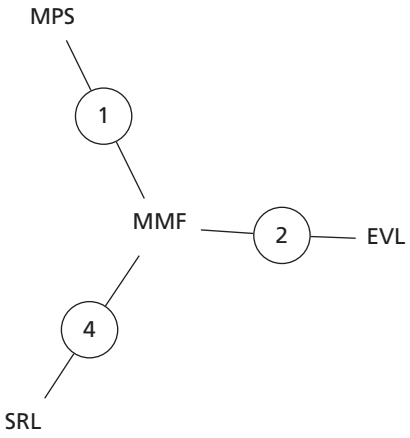

FIGURE 23 Network diagram for network meta-analysis estimating the impact on NODAT incidence of replacing MMF.

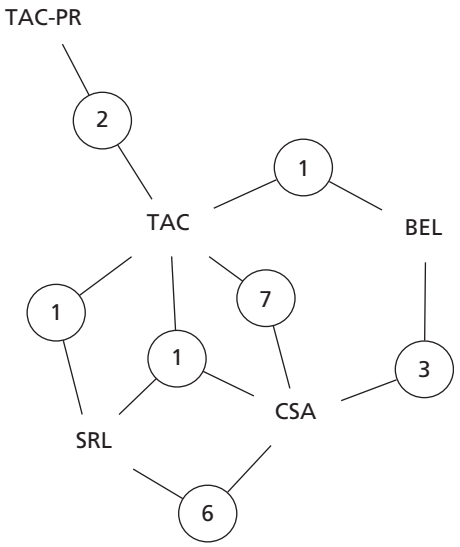

FIGURE 24 Network diagram for network meta-analysis estimating the impact on NODAT incidence of replacing TAC-IR.

TABLE 71 Mixed-treatment comparison estimates of impact on NODAT incidence of replacing TAC-IR [WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK); fixed-effects model]

	OR vs. baseline (natural logarithmic scale)					OR vs. baseline (linear scale)		
Agent	Mean	SD	Median	95% CrI		Median	95% CrI	
TAC	(Baseline)							
TAC-PR	0.1694	0.3199	0.1687	–0.4546	0.8003	1.184	0.635	2.226
CSA	–0.8162	0.2086	–0.8136	–1.231	–0.4129	0.443	0.292	0.662
BEL	–1.671	0.381	–1.665	–2.431	–0.9394	0.189	0.088	0.391
SRL	–0.2345	0.2239	–0.2339	–0.6734	0.2016	0.791	0.510	1.223

CrI, credible interval.

TABLE 72 Mixed-treatment comparison estimates of impact on NODAT incidence of replacing MMF (WinBUGS; fixed-effects model)

	OR vs. baseline (natural logarithmic scale)					OR vs. baseline (linear scale)		
Agent	Mean	SD	Median	95% CrI		Median	95% CrI	
MMF	(Baseline)							
MPS	–0.07041	0.6122	–0.0656	–1.291	1.126	0.937	0.275	3.083
SRL	0.4739	0.3318	0.4719	–0.1688	1.131	1.603	0.845	3.099
EVL	–0.05221	0.3194	–0.05309	–0.6831	0.5742	0.948	0.505	1.776

CrI, credible interval.

TABLE 73 Calculations for the OR of NODAT in 12 months

Regimen	Replace TAC	OR	Replace MMF	OR	Overall OR
CSA + MMF	CSA	0.442	–	1.000	0.442
TAC + MMF	–	1.000	–	1.000	1.000
CSA + AZA	CSA	0.442	AZA	1.000 (assumed)	0.442
TAC + AZA	–	1.000	AZA	1.000 (assumed)	1.000
CSA + EVL	CSA	0.442	EVL	0.949	0.420
TAC + SRL	–	1.000	SRL	1.606	1.606
TAC-PR + MMF	TAC-PR	1.185	–	1.000	1.185
BAS + CSA + MMF	CSA	0.442	–	1.000	0.442
BAS + TAC + MMF	–	1.000	–	1.000	1.000
BAS + CSA + AZA	CSA	0.442	AZA	1.000 (assumed)	0.442
BAS + TAC + AZA	–	1.000	AZA	1.000 (assumed)	1.000
BAS + SRL + MMF	SRL	0.791	–	1.000	0.791
BAS + BEL + MMF	BEL	0.188	–	1.000	0.188
BAS + CSA + MPS	CSA	0.442	MPS	0.932	0.412
r-ATG + CSA + MMF	CSA	0.442	–	1.000	0.442
r-ATG + TAC + MMF	–	1.000	–	1.000	1.000
r-ATG + CSA + AZA	CSA	0.442	AZA	1.000 (assumed)	0.442
r-ATG + TAC + AZA	–	1.000	AZA	1.000 (assumed)	1.000

TABLE 74 Estimated 12-month incidence of NODAT for each regimen

Regimen	NODAT incidence (%)
CSA + MMF	1.83
TAC + MMF	4.04
CSA + AZA	1.83
TAC + AZA	4.04
CSA + EVL	1.74
TAC + SRL	6.33
TAC-PR + MMF	4.75
BAS + CSA + MMF	1.83
BAS + TAC + MMF	4.04
BAS + CSA + AZA	1.83
BAS + TAC + AZA	4.04
BAS + SRL + MMF	3.22
BAS + BEL + MMF	0.79
BAS + CSA + MPS	1.71
r-ATG + CSA + MMF	1.83
r-ATG + TAC + MMF	4.04
r-ATG + CSA + AZA	1.83
r-ATG + TAC + AZA	4.04

Cytomegalovirus infection

Cytomegalovirus infection was judged on the basis of examining the incidence of CMV infection in RCTs included in the systematic review in the adult population and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster *et al.*[156,207] that CMV infection could be affected by the use of mammalian/mechanistic target of rapamycin inhibitor (mTOR-I) (SRL and EVL) and that the impact could vary depending on whether replacing a CNI or antimetabolite in the 'standard triple-therapy'.

Table 75 lists the studies (RCTs from the systematic review of clinical effectiveness) that could inform the estimate of the impact on CMV infection incidence of using mTOR-I. The corresponding network diagram for these studies is given in *Figure 25*.

Fixed-effects and random-effects MTCs were conducted and the random-effects model was judged to be superior on the basis of DIC (54.02 vs. 59.54 for fixed-effects model). The results of the random-effects MTC are shown in *Table 76*.

TABLE 75 Studies included to estimate the impact on CMV infection incidence of using mTOR-I (SRL and EVL)

Study	Compares	CMV infection within 12 months
Vitko *et al.* 2004[208]	No mTOR-I vs. mTOR-I replacing antimetabolite	38/196 vs. 10/194
Takahashi *et al.* 2013[190]	No mTOR-I vs. mTOR-I replacing antimetabolite	21/61 vs. 3/61
Tedesco Silva *et al.* 2010[191]	No mTOR-I vs. mTOR-I replacing antimetabolite	16/273 vs. 2/274
Chadban *et al.* 2013[209]	No mTOR-I vs. mTOR-I replacing antimetabolite	2/47 vs. 4/30
Sampaio *et al.* 2008[194]	No mTOR-I vs. mTOR-I replacing antimetabolite	6/50 vs. 6/50
Mjörnstedt *et al.* 2012[210]	No mTOR-I vs. mTOR-I replacing CNI	13/100 vs. 9/102
Flechner *et al.* 2002[211]	No mTOR-I vs. mTOR-I replacing CNI	2/30 vs. 3/31
Lebranchu *et al.* 2009[200]	No mTOR-I vs. mTOR-I replacing CNI	6/97 vs. 4/96
Büchler *et al.* 2007[201]	No mTOR-I vs. mTOR-I replacing CNI	17/74 vs. 4/71
Kreis *et al.* 2000[202]	No mTOR-I vs. mTOR-I replacing CNI	8/38 vs. 2/40
Guba *et al.* 2010[203]	No mTOR-I vs. mTOR-I replacing CNI	20/71 vs. 5/69
Martinez-Mier *et al.* 2006[204]	No mTOR-I vs. mTOR-I replacing CNI	0/21 vs. 1/20
Symphony[127]	No mTOR-I vs. No mTOR-I vs. mTOR-I replacing CNI	39/403 vs. 45/408 vs. 23/380

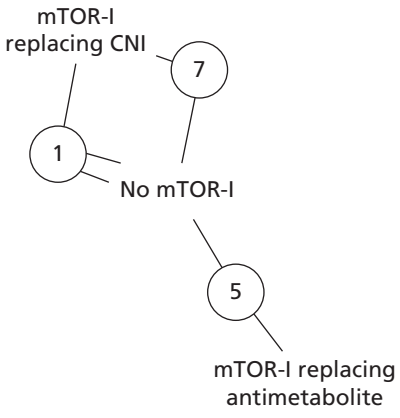

FIGURE 25 Network diagram for network meta-analysis estimating the impact on CMV incidence of mTOR-I use.

TABLE 76 Mixed-treatment comparison estimates of impact on CMV infection incidence of using mTOR-I (WinBUGS; random-effects model)

	OR vs. baseline (natural logarithmic scale)					OR vs. baseline (linear scale)		
mTOR-I use	Mean	SD	Median	95% CrI		Median	95% CrI	
No mTOR-I	(Baseline)							
mTOR-I replacing CNI	–0.7981	0.3889	–0.806	–1.558	0.01047	0.447	0.211	1.011
mTOR-I replacing antimetabolite	–1.153	0.4916	–1.175	–2.091	–0.1184	0.309	0.124	0.888
σ (random effects parameter)	0.7915	0.4085	0.7538	0.08925	1.705			

CrI, credible interval.

The baseline incidence of CMV infection was estimated from Jongsma *et al.*[212] who found that 25.8% of transplantations in 159 Dutch children and adolescents were followed by CMV infection within 1 year. The typical regimens were CSA + MMF and BAS + CSA + MMF.

Combining the baseline incidence with the treatment effects results in the incidence rates for each regimen as shown in *Table 77*.

Dyslipidaemia

Dyslipidaemia was judged on the basis of examining the incidence of CMV infection in RCTs in the adult population and on the basis of the Cochrane systematic reviews of maintenance immunosuppression by Webster *et al.*[156,207] 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 CNI or with an antimetabolite. Therefore, to increase statistical power the effect of mTOR-I use on dyslipidaemia incidence was estimated as the OR of dyslipidaemia incidence for mTOR-I use versus no mTOR-I use.

Table 78 details the adult population RCTs that compared regimens with and without mTOR-I and that reported dyslipidaemia. The direction of effect is consistent across the studies and the corresponding network diagram of these studies is given in *Figure 26*. Fixed- and random-effects meta-analyses were conducted and it was judged on the basis of DIC (28.267 vs. 29.897) that a fixed-effects analysis was appropriate. The results of the fixed-effects meta-analysis are shown in *Table 79*.

The baseline incidence of dyslipidaemia (without mTOR-I use) was estimated by Bonthuis *et al.*[213] based on European registry data for child/adolescent RRT recipients. The incidence of dyslipidaemia was 55.5% (313/564) for transplant recipients, versus 85.1% and 76.1% for haemodialysis and peritoneal dialysis recipients, respectively. This study also highlighted that SRL was associated with significantly increased lipid levels versus TAC and CSA. The incidence of dyslipidaemia with mTOR-I use was therefore estimated as 68.5%.

TABLE 77 CMV infection incidence rates used in the model

Regimen	CMV incidence within 12 months (%)
CSA + EVL	9.88
TAC + SRL	9.88
BAS + SRL + MMF	13.53
No mTOR-I	25.79

TABLE 78 Studies used to estimate the impact on dyslipidaemia of mTOR-I use

Study	Compares	Dyslipidaemia within 12 months
Vitko *et al.* 2004[208]	No mTOR-I vs. mTOR-I use	24/196 vs. 51/194
Takahashi *et al.* 2013[190]	No mTOR-I vs. mTOR-I use	19/61 vs. 28/61
Tedesco Silva *et al.* 2010[191]	No mTOR-I vs. mTOR-I use	43/273 vs. 57/274
Sampaio *et al.* 2008[194]	No mTOR-I vs. mTOR-I use	8/50 vs. 11/50
Mjörnstedt *et al.* 2012[210]	No mTOR-I vs. mTOR-I use	9/100 vs. 13/102
Flechner *et al.* 2002[211]	No mTOR-I vs. mTOR-I use	16/30 vs. 20/31
Lebranchu *et al.* 2009[200]	No mTOR-I vs. mTOR-I use	4/97 vs. 8/96
Büchler *et al.* 2007[201]	No mTOR-I vs. mTOR-I use	38/74 vs. 50/71
Guba *et al.* 2010[203]	No mTOR-I vs. mTOR-I use	5/71 vs. 14/69
Symphony[127]	No mTOR-I vs. mTOR-I use	91/811 vs. 60/380

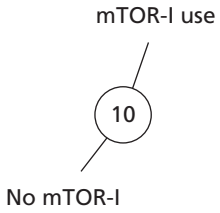

FIGURE 26 Network diagram for network meta-analysis estimating the impact on dyslipidaemia incidence of mTOR-I use.

TABLE 79 Fixed-effects meta-analysis of the impact on dyslipidaemia incidence of mTOR-I use

	OR vs. baseline (natural logarithmic scale)					OR vs. baseline (linear scale)		
mTOR-I use	Mean	SD	Median	95% CrI		Median	95% CrI	
No mTOR-I	(Baseline)							
mTOR-I use	0.5566	0.1005	0.5555	0.3604	0.7533	1.743	1.434	2.124

CrI, credible interval.

Anaemia

Anaemia is an AE that affects KTRs and people on dialysis. As 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 (ESAs) was estimated as 5.2%, based on a study by Vanrenterghem *et al.*[214] This prevalence was assumed to be the same regardless of time since transplantation, age, or other factors.

Retransplantation

In the parallel HTA to evaluate the cost-effectiveness of immunosuppressive agents for adult KTRs,[68] the rate of retransplantation was estimated for those under 65 years as 0.1037 from the UK Transplant Registry standard data set. To estimate the rate of retransplantation specifically for children and adolescents (who generally receive priority in DBD allocation) this rate was multiplied by 3.422 for those under 18 years, to reflect that median waiting time for adults is 3.422 times greater than median waiting time for children and adolescents (1160 days vs. 339 days).

Pre-emptive retransplantations were also included, as described in *Use of graft survival in the model*.

Subsequent grafts

Owing to limitations of Markov modelling imposed by the memoryless assumption, there is reduced flexibility in the modelling of costs and outcomes for subsequent grafts. It was 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;[215,216] the UK Renal Registry data set does not include BAS 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 r-ATG if received as induction for first graft or for treatment of steroid-resistant AR, thus it was judged to be less likely to be used as induction than BAS.

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 80* summarises the parameters affecting subsequent grafts.

Effectiveness estimates

The key effectiveness parameters driving cost-effectiveness in the model are:

- graft loss within 12 months
- patient death within 12 months
- AR within 12 months
- graft function at 12 months
- NODAT at 12 months
- CMV infection within 12 months
- dyslipidaemia at 12 months.

TABLE 80 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 UK Transplant Registry standard data set (see *Appendix 10*) (first graft and PNF excluded)
Resource use		
TAC 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, TAC TDM, blood test, renal profile, liver function tests)	Once monthly	Assumption

TDM, therapeutic drug monitoring.

As explained in *Model structure*, it was not possible to estimate these for all interventions based on RCT evidence in the child/adolescent kidney transplant population. Therefore, it was decided that separate analyses would be conducted based on adult RCT evidence (allowing comparison of all interventions) and on child/adolescent RCT evidence (only allowing a very limited number of comparisons).

The analyses based on child/adolescent RCT evidence differ somewhat from the analyses based on adult RCT evidence as they utilise a decision tree to estimate costs and QALYs in the trial duration followed by extrapolation with the Markov model. As such, graft loss and patient death are estimated at the study end and additionally the restricted mean survival of the patient and the graft are estimated (restricted to the trial duration), as described in *Decision tree*.

Based on adult randomised controlled trial evidence

Graft loss, patient death, AR and graft function were primarily estimated from network meta-analyses of adult RCT evidence for induction and maintenance regimens, assuming independence of treatment effects (i.e. that the clinical 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 81*.

Head-to-head comparisons for TAC-PR versus TAC-IR and for MPS versus MMF were additionally used to identify any differences in effectiveness between these agents. In the network meta-analysis, MMF and MPS 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 clinical effectiveness. The effectiveness of MMF was assumed to be that of mycophenolate in the network meta-analysis and the

TABLE 81 Summary of mean treatment effects from network meta-analyses of adult RCT evidence

Arm	Mortality within 12 months[a] (lower is better)	Graft loss within 12 months[a] (lower is better)	eGFR at 12 months[b] (higher is better)	BPAR within 12 months[b] (lower is better)
Induction (vs. no induction)				
BAS	–0.1168	–0.1712	+2.615	–0.6878
R-ATG	–0.4605	–0.2534	+0.7524	–1.041
Maintenance (vs. 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

a Presented as log-ORs.
b Presented as mean difference.
Note
The comparators here are the comparators in the network meta-analysis rather than the baseline used in the model.

effectiveness of MPS was estimated by combining the network meta-analysis and head-to-head effectiveness estimates (y_{MPA} and $y_{MPS-MMF}$, respectively) as follows (on the appropriate scale, i.e. log-odds for dichotomous outcomes, linear scale for eGFR):

$$y_{MMF} = y_{MPA} \quad (6)$$

$$y_{MPS} = y_{MPA} + \Delta y_{MPS-MMF}. \quad (7)$$

The effectiveness of TAC-PR was similarly estimated:

$$y_{TAC-PR} = y_{TAC} + \Delta y_{TAC-PR-TAC}. \quad (8)$$

The effectiveness estimates were combined with the following estimated baseline values (for BAS + TAC + AZA): mortality within 12 months (odds) = 0.0052 (based on the model with baseline graft loss and DWFG rates); graft loss within 12 months (odds) = 0.0400 (based on UK Transplant Registry standard data set); eGFR at 12 months (ml/minute/1.73 m^2) = 82 (based on Muscheites *et al.*[185]); AR within 12 months (odds) = 0.2375 (based on Grenda *et al.*[75]). The resulting absolute effectiveness estimates are given in *Table 82*.

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 (see sections *Diabetes mellitus*, *Cytomegalovirus infection* and *Dyslipidaemia* in *Adverse events*).

TABLE 82 Summary of absolute effectiveness estimates for each regimen based on adult RCT evidence

Regimen	Mortality within 12 months (odds)	Graft loss within 12 months (odds)	Mean eGFR (ml/minute/1.73 m^2)	BPAR within 12 months (odds)
CSA + MMF	0.0039	0.0245	71.7	0.386
TAC + MMF	0.0063	0.0225	76.6	0.326
CSA + AZA	0.0041	0.0329	70.1	0.818
TAC + AZA	0.0058	0.0376	79.4	0.472
CSA + EVL	0.0058	0.0203	74.9	0.373
TAC + SRL	0.0057	0.0384	69.7	0.314
TAC-PR + MMF	0.0082	0.0270	76.4	0.318
BAS + CSA + MMF	0.0035	0.0206	74.3	0.194
BAS + TAC + MMF	0.0056	0.0190	79.2	0.164
BAS + CSA + AZA	0.0037	0.0277	72.7	0.411
BAS + TAC + AZA	0.0052	0.0317	82.0	0.238
BAS + SRL + MMF	0.0064	0.0286	76.5	0.180
BAS + BEL + MMF	0.0020	0.0170	83.2	0.331
BAS + CSA + MPS	0.0024	0.0178	78.2	0.288
r-ATG + CSA + MMF	0.0026	0.0190	72.4	0.136
r-ATG + TAC + MMF	0.0040	0.0175	77.4	0.115
r-ATG + CSA + AZA	0.0028	0.0256	70.8	0.289
r-ATG + TAC + AZA	0.0037	0.0292	80.1	0.167

Health measurement and valuation

The EQ-5D (3-level version) is the preferred instrument to measure HRQoL in the NICE reference case,[165] but it is designed for use in adults. An adapted version of EQ-5D, the European Quality of Life-5 Dimensions Youth version (EQ-5D-Y), has been developed for children and adolescents (aged 8–17 years), but there is currently no method to value states measured in EQ-5D-Y (except naively applying the EQ-5D value set which is cautioned against).[217] Furthermore, we attempted to systematically identify any HRQoL studies in the child/adolescent kidney transplant population and did not find any.

In the absence of any studies measuring HRQoL in the child/adolescent population, it was assumed that the formula estimating the utility of general population health, the utility decrements for the different methods of RRT and the utility decrement for diabetes mellitus would be the same as for the adult population, as follows.

Utility was estimated for KTRs by first estimating age-dependent baseline utility for the general population, then applying a utility decrement according to whether KTRs were in the *functioning graft* or *graft loss* state. In addition, the proportion of the population with NODAT was estimated and a utility decrement was applied to both *functioning graft* and *graft loss* states to reflect the decreased HRQoL for KTRs with NODAT.

In the PSA utility decrements were drawn from gamma distributions to ensure that they did not result in increased utility.

With the exception of the source for baseline utility (see *Utility of general population*), 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 HRQoL, with population search terms for renal transplant, dialysis and ESRD. No study design filter was used.

The search yielded 1311 titles and abstracts, which were screened by an experienced HTA researcher (RA). Only 99 were studies that 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.

Utility of general population

Baseline utility was modelled using the following equation:

$$Utility = 0.967981 - 0.001807 \times age - 0.000010 \times age^2 + 0.023289 \times male, \quad (9)$$

where *male* is equal to 1 for men and 0 for women. This equation was derived from the Health Survey for England (2012)[218] using the well-established methodology of Ara and Brazier.[219] The data set includes 16- and 17-year-olds but does not appear to include utility estimates for younger individuals (all of whom had utility recorded as exactly 1) and, therefore, this is an extrapolation.

Utility with dialysis

A systematic review and meta-analysis by Liem *et al.*[220] reported pooled estimates of utility for various health states of people undergoing RRT. It reported random-effects meta-analyses of six studies[159,221–224] which had produced EQ-5D index scores (either explicitly based on the UK utility tariff or assumed to be so by the authors) for haemodialysis (range 0.44–0.62) and of four studies[159,221,223,224] for peritoneal dialysis (range 0.53–0.65). The estimates used in our model are shown in *Table 83*.

TABLE 83 The EQ-5D index utility weights for dialysis[220]

Type of dialysis	Pooled mean (95% CI)	Number of studies	Number of people
Haemodialysis	0.56 (0.49 to 0.62)	6	1315
Peritoneal dialysis	0.58 (0.50 to 0.67)	4	192

These estimates were then converted into utility decrements from baseline age-related general health (assuming age 60.4 years and 58% male for haemodialysis, and age 57.9 and 55% male for peritoneal dialysis) in order that the utility of those on dialysis would always be lower than in people in the general population of the same age and sex.

The estimated utility decrements were [mean (SE)]: haemodialysis [0.277 (0.034)] and peritoneal dialysis [0.264 (0.044)].

Utility with functioning graft

The same systematic review and meta-analysis by Liem *et al.*[220] reported pooled estimates of utility for people living with a functioning renal graft. It reported a random-effects meta-analysis of five studies[159,223,225–227] that had produced EQ-5D index scores (either explicitly based on the UK utility tariff or assumed to be so by the authors) for people living with a functioning renal graft (range of means, some medians, 95% CI 0.71 to 0.86; *Table 84*).

It was assumed that the HRQoL for KTRs would not exceed that of members of the general population (aged 51.4 years and 60% male), so this absolute estimate was converted into a utility decrement from baseline of 0.053 (SE 0.049).

Disutility due to diabetes mellitus

Our literature search for utilities revealed one study looking specifically at disutility of NODAT in renal transplantation patients.[228] This is a recent study in the adult RRT population and reports EQ-5D utility data, with an estimated disutility of 0.06 associated with NODAT. This figure does not adjust for people with CVD complications and, therefore, is appropriate to how we model NODAT. We note that the study was conducted in only one hospital in USA and the valuation set for the utility values is US based[229] so the outcomes may not be generalisable to the UK population. It has been demonstrated by Johnson *et al.*[230] 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. 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 mellitus compared with general population using Health Survey for England data.[218] This would be a broader population of comparison and is unlikely to reflect the true utility impact of diabetes mellitus on someone who has received a kidney transplant.

In their submission to the parallel technology appraisal to evaluate the cost-effectiveness of immunosuppressive agents for adult KTRs,[68] Bristol-Myers Squibb incorporated disutility of 0.041 for NODAT citing Currie *et al.*[231] as its source, which is a study looking at costs. We believe Bristol-Myers Squibb intended to cite the other Currie *et al.* paper from 2005,[232] but it is still not clear how it calculated this value. In its model, the deterministic value for disutility of NODAT appears to be 0.06, which corresponds with our chosen value.

TABLE 84 The EQ-5D index utility weights for functioning graft[220]

Health state	Pooled mean (95% CI)	Number of studies	Number of people
Functioning graft	0.81 (0.72 to 0.90)	5	673

Astellas (in its submission to this technology appraisal) reports the findings of Wyld *et al.*[233] which does report utilities, deriving a disutility of 0.10 between no diabetes mellitus and diabetes mellitus groups of people with CKD. However, this is not restricted to the renal transplant population and it is not clear which utility elicitation method is used.

Estimating resources and costs

Costs are incurred in the model either in the form of events (e.g. induction therapy, AR, 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
- AR (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.

Currency, price date and conversion

Costs are all in 2014/15 pounds sterling. Costs in earlier financial years are inflated based on the Hospital and Community Health Services pay and prices index (*Table 85*).[234]

No costs were included in different currencies so conversion was not necessary.

TABLE 85 HCHS pay and prices index

Year	HCHS pay and prices index	Inflation factor
2008/9	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 3 years)	1.000

HCHS, Hospital and Community Health Services.

Resource use

Induction therapy

Basiliximab can be administered by i.v. infusion or i.v. injection but it was assumed that it would be administered by i.v. infusion in accordance with Brennan *et al.*[235] As i.v. infusion is a more costly method of administration than i.v. injection, this may overestimate the costs of BAS administration.

Rabbit anti-human thymocyte immunoglobulin is administered only by i.v. infusion and it was assumed it would be administered as in Brennan *et al.*,[235] which was conducted in adults. We found no RCT evidence in children or adolescents for r-ATG to inform dosages. We assumed no wastage of r-ATG, which may result in the costs being underestimated.

The dosage for BAS is 10 mg if the recipient's weight is < 35 kg and 20 mg if the recipient's weight is ≥ 35 kg.[63] This cut-off was used by Offner *et al.*,[73] while a higher cut-off of 40 kg was used by Grenda *et al.*[75] *Table 86* describes resource use for induction therapy.

In the base case, recipients are aged 10 years with expected body weight 32 kg and, therefore, they receive 10 mg doses rather than 20 mg doses.

TABLE 86 Resource use for induction therapy

Parameter	Value	Source
BAS induction		
BAS 10 mg doses	1.964	Brennan *et al.*[235]
BAS 20 mg doses	0	(Weight < 35 kg)
Administration (i.v. infusion)	1.964	Brennan *et al.*[235]
R-ATG induction		
R-ATG mg/kg	6.5	Brennan *et al.*[235]
Administration (i.v. infusion)	4.525	Assumption based on Brennan *et al.*[235]

Number of doses	People
1	2
2	6
3	10
4	24
5	97
6	1
7	1

Actual breakdown not reported but given that 87.9% were initiated before reperfusion, 68.8% received the intended five doses, one patient received six doses, also one patient received six doses. At least four doses were received by 87.2% of people

Maintenance therapy

Dosages for those under 18 years were estimated from child/adolescent RCTs when possible. When this was not possible, dosing guidelines for adults were followed when they were already weight based. When they were not weight based, it was assumed that the dose for children and adolescents would be lower and would be proportional to their weight or body surface area. *Table 87* describes resource use for maintenance therapy.

Tacrolimus, SRL, EVL and CSA are titrated to achieve target whole blood trough concentrations, as numerous factors can affect their absorption and removal from the bloodstream and therapeutic windows can be narrow.

TABLE 87 Resource use for maintenance therapy

Parameter	Value	Source
TAC-IR		
With AZA	Those < 18 years	Trompeter *et al.*[77]
	Time / **Dosage (mg/m²/day)** 0–6 months / 7.57 6–12 months / 5.61 Thereafter / 4.89	
	Those > 18 years	Margreiter[110]
	Time / **Dosage (mg/kg/day)** 12–36 months / 0.09 Thereafter / 0.08	
With MMF	Those < 13 years: 0.18 mg/kg/day Those 13–17 years: 0.13 mg/kg/day Those > 18 years: 0.08 mg/kg/day	Grenda *et al.*[24] (assumed no higher than AZA)
With SRL	**Time** / **Dosage (mg/kg/day)** 0–1 month / 0.175 1–3 months / 0.110 3–6 months / 0.104 6–12 months / 0.080 12+ months / 0.070	Starting dose from Gonwa *et al.*[193] (0–1 month); assumed no higher than with MMF (1–6 months); Gonwa *et al.*,[193] Anil Kumar *et al.*[236] (6+ months)
TAC-PR		
With MMF	As for TAC-IR plus 0.015 mg/kg/day for 12 months	Wlodarczyk *et al.*,[237] Krämer *et al.*,[139] Tsuchiya *et al.*[196] and Oh *et al.*[238]

TABLE 87 Resource use for maintenance therapy (*continued*)

Parameter	Value	Source
CSA		
With AZA	< 18 years	Trompeter *et al.*[77]
	Time / **Dosage (mg/m²/day)** 0–6 months / 251 6–12 months / 192 Thereafter / 180	
	> 18 years	Margreiter[110]
	Time / **Dosage (mg/kg/day)** 12–36 months / 2.93 Thereafter / 2.84	
With MMF or MPS	< 18 years (with induction)	Offner *et al.*[73]
	Time / **Dosage (mg/kg/day)** 0–3 months / 7.80 3–6 months / 7.15 6–12 months / 6.65 Thereafter / 6.20	
	< 18 years (no induction)	
	Time / **Dosage (mg/kg/day)** 0–3 months / 7.67 3–6 months / 6.85 6–12 months / 6.20 Thereafter / 5.90	
	> 18 years: 2.82 mg/kg/day	Rowshani *et al.*[239]
With EVL	**Time** / **Dosage (mg/kg/day)** 0–12 months / 3.9 12+ months / 2.1	Vitko *et al.*[208]
AZA		
With TAC	< 18 years: 1.80 mg/kg/day	Trompeter *et al.*[77]
	> 18 years: 1.20 mg/kg/day	Laskow *et al.*[106]
With CSA	< 18 years: 1.80 mg/kg/day	(Assumed equal to TAC)
	> 18 years: 1.22 mg/kg/day	Vacher-Coponat *et al.*[240]

continued

TABLE 87 Resource use for maintenance therapy (*continued*)

Parameter	Value	Source
MMF		
With TAC	< 13 years: 0.54 g/m²/day	Grenda *et al.*[24]
	13–17 years: 0.60 g/m²/day	
	> 18 years: 1.47 g/day	Ekberg *et al.*[127]
With CSA	< 18 years (with induction)	Offner *et al.*[73]

Time	Dosage (g/m²/day)
0–3 months	1.06
3–6 months	1.01
6–12 months	0.95
Thereafter	0.93

< 18 years (no induction)

Time	Dosage (g/m²/day)
0–3 months	1.04
3–6 months	0.93
6–12 months	0.83
Thereafter	0.82

	> 18 years: 1.67 g/day	Ekberg *et al.*[127]
With SRL		Ekberg *et al.*[127] (assuming adult body surface area 1.73 m²)

Time	Dosage (g/m²/day)
0–3 months	1.16
3–12 months	1.00
Thereafter	0.85

With BEL	1.16 g/m²/day	Vincenti *et al.*[198] (assuming adult body surface area 1.73 m²)

TABLE 87 Resource use for maintenance therapy (*continued*)

Parameter	Value		Source
MPS			
With CSA	**Time**	**Dosage (mg/kg/day)**	Mjörnstedt *et al.*[210] (assuming adult body weight 63 kg)
	0–3 months	22.8	
	3–9 months	19.2	
	9+ months	17.5	
SRL			
With TAC	**Time**	**Dosage (mg/kg/day)**	Anil Kumar *et al.*[236] (assuming adult body weight 63 kg)
	0–12 months	0.059	
	12–60 months	0.044	
	Thereafter	0.029	
With MMF	**Time**	**Dosage (mg/kg/day)**	Lebranchu *et al.*[200] (assuming adult body weight 63 kg)
	0–3 months	0.082	
	3–6 months	0.071	
	6–9 months	0.055	
	9–12 months	0.051	
	12–48 months	0.046	
	48+ months	0.041	
EVL			
With CSA	**Time**	**Dosage (mg/kg/day)**	Tedesco Silva *et al.*[191] and Lorber *et al.*[241] (assuming adult body weight 63 kg)
	0–3 months	0.047	
	3–6 months	0.044	
	6–9 months	0.040	
	9–12 months	0.041	
	12–24 months	0.041	
	24+ months	0.032	

continued

TABLE 87 Resource use for maintenance therapy (*continued*)

Parameter	Value	Source
BEL		
Drug acquisition	(Round up to nearest 250 mg)	Dosing schedule: 10 mg/kg on days 1 and 5, weeks 2, 4, 8 and 12, then 5 mg/kg every 4 weeks thereafter
	Doses per quarter year: Time / 10 mg/kg / 5 mg/kg 0–3 months: 5 / 0 3–6 months: 1 / 2 Thereafter: 0 / 3.26	
Drug administration (i.v. infusion)	Time / Infusions per quarter 0–3 months: 5 3–6 months: 3 Thereafter: 3.26	
Prednisolone		
With CSA	< 18 years	Trompeter *et al.*[77]
	Time / Dosage (mg/kg/day) 0–6 months: 2.4 Thereafter: 0.3	
Without CSA	< 18 years	
	Time / Dosage (mg/kg/day) 0–6 months: 2.1 Thereafter: 0.3	
All maintenance regimens	> 18 years: 16.3 mg/day	Ekberg *et al.*[127]

Belatacept is administered intravenously according to a prescribed schedule. It was assumed that the 'less intensive' regimen from the BENEFIT[198] (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial) and BENEFIT-EXT[199] (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-Extended criteria donors) studies would be used. We were advised that vial sharing would most likely not be feasible and, therefore, we assumed full wastage of excess BEL.

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 88*). The haemodialysis mix was reflected in incident and prevalent people on dialysis, but conversion costs (between dialysis modes) were not included.

TABLE 88 Proportion of dialysis patients receiving haemodialysis by age group

Age group (years)	Proportion receiving haemodialysis (%)
0–1	45.5
2–3	46.4
4–7	55.6
8–11	64.5
12–15	70.5
16–17	62.5
18–24	79.1
25–34	80.4
35–44	84.5
45–54	84.3
55–64	85.2
65–74	85.8
75–84	89.0
85+	91.5

Source: Reproduced with permission from UK Renal Registry 16th Annual Report (figure 2.7)[242] and UK Renal Registry 17th Annual Report (table 4.4).[4] The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.

Acute rejection

The number of KTRs suffering at least one AR episode was derived as detailed in *Acute rejection within 12 months* and *Based on adult randomised controlled trial evidence*.

To account for the fact that some KTRs may experience more than one AR episode, a study[112] was identified that gave both the number of people experiencing at least one AR episode and the total number of episodes. From this, it was estimated that there would be 1.19 ARs expected per person suffering at least one AR event.

Grenda *et al.*[75] and Trompeter *et al.*[77] report ARs in the first 6 months according to their response to treatments as either 'spontaneously resolving' (i.e. not requiring changes to treatment), 'steroid sensitive' (i.e. resolving after a short course of high-dose CCSs) or 'steroid resistant' (i.e. not resolving after a short course of high-dose CCSs). ARs between 6 and 24 months were not reported by those categories, so it was assumed that 80% were steroid sensitive and 20% steroid resistant. *Table 89* gives the numbers of ARs in the RCTs in children and adolescents.

Infection prophylaxis

Cytomegalovirus prophylaxis was included for KTRs at high risk of CMV infection (D+/R–; i.e. donor is seropositive, recipient is seronegative) following the Birmingham Children's Hospital Renal Unit protocol (Fiona Gamston, Birmingham Children's Hospital, 15 July 2014, personal communication). It was assumed that all high-risk patients would receive valganciclovir (Valcyte®, Roche Products Ltd) at a once-daily dose calculated using the formula:

$$\text{Dose (mg)} = 7 \times \text{body surface area} \times \text{eGFR}. \quad (10)$$

Doses are rounded to 450 mg or 900 mg (whichever is nearest). For example, a KTR with body surface area of 1.2 m^2 and eGFR 40 ml/minute/1.73 m^2 would have a target dose of 336 mg, rounded up to 450 mg.

TABLE 89 Acute rejection and response to treatment in child/adolescent RCTs

Trial	Trompeter *et al.*[77]		Grenda *et al.*[75]		Offner *et al.*[73]	
Arm	TAC + AZA ($n = 103$)	CSA + AZA ($n = 93$)	TAC + AZA ($n = 93$)	BAS + TAC + AZA ($n = 99$)	BAS + CSA + MMF ($n = 100$)	CSA + MMF ($n = 92$)
0–6 months					11	19
Spontaneously resolving	2	0	2	1		
Steroid sensitive	45	65	14	15		
Steroid resistant	8	26	3	3		
6–12 months	4	2	8	4	2	3
12–24 months	7	9				
24–36 months	2	6				
36–48 months	2	6				

According to the Birmingham protocol, prophylaxis is for 3 months, followed by a month at half dose if quantitative polymerase chain reaction (PCR) at 3 months is negative, followed by discontinuation if quantitative PCR at 4 months is negative. Relevant data on the proportions having negative PCR at 3 or 4 months were not available and were therefore estimated.

Humar *et al.*[243] report a comparison of 100-day and 200-day CMV prophylaxis in adults (aged ≥ 16 years). Figure 3 of Humar *et al.*[243] suggests that, at 90 days, approximately 10% of patients have developed CMV viraemia and in the month after discontinuation (100-day arm), approximately 14% of patients developed CMV viraemia. It was therefore assumed that 10% would receive 3 months' prophylaxis plus 2 months' pre-emptive treatment (at the same dose), 76% of patients would receive 4 months' planned prophylaxis while the remaining 14% would receive 4 months' planned prophylaxis plus 2 months' pre-emptive treatment at the full target dose (*Table 90*).

Half dosage was implemented assuming that alternate day dosing was acceptable, meaning the effective target daily dose was rounded to 225 mg, 450 mg or 900 mg (whichever is nearest).

Cytomegalovirus prophylaxis was not included for intermediate- or low-risk KTRs (*Table 91*), except in the case of intermediate-risk KTRs receiving r-ATG, who were assumed to receive 3 months' CMV prophylaxis (based on the Royal and Exeter protocol for adults[244]).

Pneumocystis jirovecii pneumonia (PJP) and UTI prophylaxis was assumed to be 480 mg of co-trimoxazole (Septrin®, Aspen Pharma Trading Ltd) daily for 3 months.

TABLE 90 Modelled CMV prophylaxis for high-risk KTRs

Proportion of CMV high-risk patients (%)	Time at full dose	Time at half dose
10	5 months	None
76	3 months	1 month
14	5 months	1 month

TABLE 91 CMV risk for children and adolescents receiving kidney transplantation[212]

CMV risk category	Proportion of child/adolescent KTRs
High risk (D+/R–)	54/209 = 25.8%
Intermediate risk (D±/R+)	84/209 = 40.2%
Low risk (D–/R–)	71/209 = 34.0%

D–/R–, donor is seronegative, recipient is seronegative; D+/R–, donor is seropositive, recipient is seronegative; D±/R+, donor is seropositive/seronegative, recipient is seropositive.

Monitoring

The 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 (TAC, CSA, SRL and EVL)
- viral quantitative PCR [CMV, BK virus (BKV), Epstein–Barr virus (EBV)].

In addition, KTRs attend regular outpatient clinics. KTRs with degraded or deteriorating graft function receive more intensive monitoring to maximise graft survival.

It was assumed that children and adolescents would attend clinics and receive monitoring according to the Birmingham protocol (Fiona Gamston, Birmingham Children's Hospital, 15 July 2014, personal communication), and this was assumed to taper after a number of years to quarterly visits (*Table 92*).

Kidney transplant recipients at high risk of CMV infection (D+/R–; i.e. donor is seropositive, recipient is seronegative) were assumed to receive monthly CMV quantitative PCR for 4 months and CMV serology at 3 months, following the Birmingham protocol (Fiona Gamston, Birmingham Children's Hospital, 15 July 2014, personal communication).

TABLE 92 Frequency of attendances at clinic and monitoring

Time	Visits per month
Month 1	12
Month 2	8
Month 3	4
Months 4–6	2
Months 7–12	1
Year 2	1 (assumed)
Year 3	2/3 (assumed)
Thereafter	1/3 (assumed)

According to the Birmingham protocol, all CMV seronegative patients (high risk and low risk) should receive annual CMV serology until they are seropositive. It was assumed that, on average, this would require two annual tests for high-risk patients (50.9% of high-risk adult patients in Humar *et al.*[243] were PCR positive at 12 months) and five annual tests for low-risk patients.

It was also assumed that intermediate-risk patients would receive weekly CMV quantitative PCR for 3 months [based on the Bristol Royal Hospital for Children and the Royal Devon and Exeter protocols[244] (Jan Dudley, Bristol Royal Hospital for Children, 25 June 2014, personal communication)] unless they received induction with r-ATG, in which case they would receive CMV prophylaxis for 3 months.

The BKV quantitative PCR was assumed to be conducted for all children and adolescents at 3, 6 and 12 months (based on the Royal Devon and Exeter protocol[244]).

The EBV quantitative PCR was assumed to be conducted for children and adolescents at high risk of EBV infection (*Table 93*) monthly for months 1–6, then at 9 months and 12 months (based on the Royal Devon and Exeter protocol[244]).

Explant surgery

Not all grafts are explanted on failure, with the likelihood of nephrectomy decreasing with time since transplantation. NHSBT provided data on the probability of nephrectomy as a function of time since transplantation for the PenTAG assessment report for NICE guidance TA165,[18] which we have reproduced in *Table 94* 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 on failure by applying the proportions of grafts explanted for the first graft to the exponential graft survival curve for subsequent grafts.

TABLE 93 The EBV risk for children and adolescents receiving kidney transplantation[245]

EBV risk category	Proportion of child/adolescent KTRs
High risk (D+/R–)	28/82 = 34.1%
Intermediate risk (D±/R+)	48/82 = 58.5%
Low risk (D–/R–)	6/82 = 7.3%

D–/R–, donor is seronegative, recipient is seronegative; D+/R–, donor is seropositive, recipient is seronegative; D±/R+, donor is seropositive/seronegative, recipient is seropositive.

TABLE 94 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 NHSBT. Statistics prepared by NHSBT for TA165 (table 33, p.53).[18] Contains information licensed under the Non-Commercial Government Licence v1.0.

Subsequent retransplantation

Based on the *NHS Reference Costs 2013 to 2014*,[58] 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 mellitus medication

It was assumed that KTRs with NODAT would receive three 500-mg metformin tablets daily. Although this may not be a sophisticated or accurate estimate of the cost of diabetes mellitus medication, it is considered that the costs of complications incurred in and out of hospital will significantly exceed the cost of diabetes mellitus 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.*[246]

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.*[246]

It was assumed that 10% of people would receive simvastatin as there have been safety warnings with respect to CSA. A dosage of 10 mg per day was assumed, again as this is the starting dose in Riella *et al.*[246]

Medical management for dyslipidaemia was assumed to be one dietetics outpatient attendance per year and one GP appointment per year.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease was not included in the analyses based on adult effectiveness estimates, but was reported as an outcome in all three paediatric RCTs (*Table 95*).

Hypomagnesaemia

Trompeter *et al.*[77] reported hypomagnesaemia as an AE occurring significantly more frequently in the TAC arm than in the CSA arm. Hypomagnesaemia requiring medication occurred within 6 months in 42 out of 103 TAC patients and in 21 out of 93 CSA patients.

Hypomagnesaemia was assumed to last from incidence for the trial duration (4 years).

TABLE 95 Post-transplant lymphoproliferative disease in RCTs in children and adolescents

Trial	Trompeter *et al.*[77]		Grenda *et al.*[75]		Offner *et al.*[73]	
Arm	TAC + AZA (*n* = 103)	CSA + AZA (*n* = 93)	TAC + AZA (*n* = 93)	BAS + TAC + AZA (*n* = 99)	BAS + CSA + MMF (*n* = 100)	CSA + MMF (*n* = 92)
PTLD	3	3	2	1	3[a]	5[a]
Time to event (years)	Mean 0.41	Mean 1.09	0–0.5	0.5–1	0–1	0–1

a PTLD/malignancy.

Hypertension

Hypertension was the most frequent AE reported by Trompeter *et al.*,[77] with 91 out of 103 TAC patients and 81 out of 93 CSA patients requiring antihypertensive medication within 6 months.

Hypertension was assumed to last from incidence for the trial duration (4 years).

Anaemia

According to Vanrenterghem *et al.*,[214] 207 out of 3969 (5.2%) adult KTRs required ESA treatment for anaemia, with a mean weekly dose of 5832 IU. Therefore, it was assumed that child and adolescent KTRs would, on average, receive 3967 IU of ESA per quarter-year cycle while they were not dependent on dialysis.

The *NHS Reference Costs 2013 to 2014*[58] indicates that the costs of ESA treatment for anaemia (and of drug treatments for bone mineral disorders) should be included in Healthcare Resource Group (HRG) costs. Therefore, it was assumed that additional ESA therapy would not be included for people in the *graft loss* state.

Unit costs

The following sources were used to identify unit costs for drug acquisition:

- Commercial Medicines Unit eMIT[62]
- *BNF* Volume 68 (January 2015 online update)[63]
- *BNF* for Children Volume 68 (January 2015 online update).[173]

The eMIT national database was the preferred source as it represents the average cost actually paid by NHS hospitals, including any negotiated discounts.

For procedures, the *NHS Reference Costs 2013 to 2014*[58] (inflated to 2014/15 prices) were the preferred source of unit costs. When 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 96*.

Maintenance immunosuppression

Although historically the prescribing of maintenance immunosuppression has, in some cases, been transferred to primary care physicians through shared care arrangements and dispensing in the community, at present paediatric KTRs are not being transferred out of hospital care and hospital prescribing and KTRs previously transferred out are being repatriated (Fiona Gamston, Birmingham Children's Hospital, 10 March 2015, personal communication). A similar process is under way for adult KTRs. As a result, in this analysis it is assumed that hospital prescribing and dispensing is appropriate and, therefore, eMIT costs are preferred when available.

TABLE 96 Drug acquisition costs for induction therapy

Agent	Pack details	Units	Unit cost	Source
BAS	Single 10-mg vial = £758.69	10-mg doses	£758.69	BNF 68[63]
BAS	Single 20-mg vial = £842.38	20-mg doses	£842.38	BNF 68[63]
R-ATG	Single 25-mg vial = £158.77	mg	£6.35	BNF 68[63]

For TAC-PR, there is a significant difference in unit price between 5-mg capsules (£1.07 per mg) and smaller 1-mg and 3-mg capsules (£1.43 per mg). In the absence of data on relative quantities purchased, it was assumed that virtually all KTRs receiving TAC-PR 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. Drug acquisition costs for maintenance therapy are given in *Table 97*.

Dialysis

Costs of haemodialysis and peritoneal dialysis are broken down in NHS Reference Costs by mode (haemodialysis, peritoneal dialysis), age (≥ 19 years, ≤ 18 years), 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 Healthcare Resource Group version 4 (HRG4) codes (and corresponding currencies in the NHS Reference Costs) for dialysis in total (including four for acute kidney injury).

The costs of haemodialysis and peritoneal dialysis were estimating by dividing the HRG4s currencies by mode and age, making assumptions about the number of currency units per week and then calculating a weighted average cost based on activity.

Haemodialysis was assumed to be performed three times weekly unless at home, in which case it was assumed to be performed 3.23 times per week on average (based on inspection of reported average number of sessions per week after removing clearly erroneous outliers). Peritoneal dialysis is explicitly costed per day according to the Reference Costs Guidance[247] 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 costs correspond to £6093 and £6000 per quarter-year cycle, in 2014/15 prices, for haemodialysis and peritoneal dialysis, respectively.

It was estimated for children and adolescents (in 2013/14 prices) that haemodialysis would cost £1529.53 per week and peritoneal dialysis £793.09 per week. These costs correspond to £20,278 and £10,515 per quarter-year cycle, in 2014/15 prices, for haemodialysis and peritoneal dialysis, respectively.

Dialysis access surgery Dialysis access costs were estimated per procedure from *NHS Reference Costs 2013 to 2014* and inflated to 2014/15 prices (*Table 98*).

Acute rejection

The only estimates of the cost of treating AR in children and adolescents are:

- Yao *et al.*:[2] £4644 (price year not stated), which appears to be based on an amalgamation of the company submitted costs for TA85 (i.e. for the adult population).
- Astellas (estimate for TA99):[2] 'around £1000' (price year not reported).
- Astellas (estimate for current appraisal): £889 [£38.40 for steroid-sensitive AR (80% of cases), £4292 for steroid-resistant AR (20% of cases)] (presumed 2012/13 prices).

TABLE 97 Drug acquisition costs for maintenance therapy

Agent	Pack details	Units	Unit cost	Source
TAC-IR	50 × 1 mg = £28.81	mg	£0.5201 (based on eMIT market share)	CMU eMIT[62]
	100 × 1 mg = £55.05			
	50 × 0.5 mg = £24.90			
	50 × 5 mg = £88.57			
TAC-PR	50 × 0.5 mg = £35.79	mg	£1.0677 (based on 50 × 5-mg pack)	BNF 68[63]
	50 × 1 mg = £71.59			
	100 × 1 mg = £143.17			
	50 × 3 mg = £214.76			
	50 × 5 mg = £266.92			
CSA	30 × 100 mg = £46.15	mg	£0.0165 (based on eMIT market share)	CMU eMIT[62]
	60 × 10 mg = £16.61			
	30 × 25 mg = £14.55			
	30 × 50 mg = £25.26			
MMF	50 × 500 mg = £9.17	g	£0.3774 (based on eMIT market share)	CMU eMIT[62]
	100 × 250 mg = £10.94			
MPS	120 × 180 mg = £96.72	mg	£0.004478 (based on 120 × 180-mg pack)	BNF 68[63]
	120 × 360 mg = £193.43			
AZA	28 × 25 mg = £1.63	mg	£0.001075 (based on eMIT market share)	CMU eMIT[62]
	100 × 25 mg = £9.43			
	56 × 50 mg = £2.53			
	100 × 50 mg = £5.03			
SRL	30 × 0.5 mg = £69.00	mg	£2.8830 (based on 30 × 2-mg pack)	BNF 68[63]
	30 × 1 mg = £86.49			
	30 × 2 mg = £172.98			
EVL	60 × 0.25 mg = £148.50	mg	£9.9000	Novartis' submission
BEL	Single 250-mg vial = £354.52	Vial	£354.52	BNF 68[63]
Prednisolone	28 × 1 mg = £0.15	mg	£0.003286 (based on eMIT market share)	CMU eMIT[62]
	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			

TABLE 98 Unit costs for dialysis access surgery in 2014/15 prices

Procedure	Unit cost (< 19 years)	Unit cost (≥ 19 years)
Temporary access for haemodialysis	£1747	£823
Long-term access for haemodialysis	£1946	£1946
Long-term access for peritoneal dialysis	£1101	£1101

It was decided that none of these estimates were appropriate because they were not recent, in the wrong patient population or omitted important cost components (such as the cost of administration and hospitalisation for steroid-sensitive AR in the more recent estimate by Astellas). In the absence of any appropriate costs for children and adolescents, it was decided that the cost estimated by Bristol–Myers Squibb in its submission to the parallel technology appraisal to update NICE guidance TA85 (kidney transplantation in adults) would be used, as it was judged the most appropriate cost for the PenTAG assessment in that technology appraisal. The cost of AR was estimated as £3217 in 2009 Great British pounds, which was inflated to £3557 in 2014/15 prices.

It is possible that the cost of treating AR could be greater in children and adolescents than in adults because often hospitalisation costs are greater in children and adolescents. On the other hand, it may be that reduced drug costs (owing to reduced dosage requirements) counter this. Furthermore, it may be that some expensive treatments are also deemed to be inappropriate for children and adolescents. Nevertheless, £3557 is deemed to be an appropriate central estimate for the cost of treating AR in children and adolescents.

By response to treatment Grenda *et al.*[75] and Trompeter *et al.*[77] report ARs in the first 6 months according to their response to treatments, as either 'spontaneously resolving' (i.e. not requiring changes to treatment), 'steroid sensitive' (i.e. resolving after a short course of high-dose CCSs), or 'steroid resistant' (i.e. not resolving after a short course of high-dose CCSs).

We assumed that the cost of spontaneously resolving AR would be £145 (the cost of a clinic visit) and that the cost of steroid-sensitive AR could be approximated by HRG4 currency LA07P (acute kidney injury without treatment complication and comorbidity score 0–3),[48] as the cost of high-dose CCSs is not significant (in 2014/15 prices, this is £1274).

We assumed that steroid-resistant AR would be treated by a course of 7 days' r-ATG infusion at 1.5 mg/kg, plus the cost of steroid-sensitive AR. The total medical management cost for steroid-resistant AR was estimated to be £3456 and the drug acquisition cost to be £44.46 per kg body weight. This may be an underestimate of the true cost of AR.

New-onset diabetes mellitus after transplantation

To our knowledge the only estimated costs for NODAT are:

- Astellas/Fujisawa, in their submission for NICE guidance TA99, proposed a one-off cost of £533 for diabetes mellitus followed by treatment switching (although notably this switching was mostly from CSA + AZA to TAC + AZA or from TAC + AZA to TAC + MMF).[2]
- Yao *et al.*[2] did not specifically cost for NODAT, but do include a one-off cost for side effects (including NODAT) of £200 followed by treatment switching.
- Astellas, in its submission for this appraisal, propose a yearly cost of £17.38 for NODAT, comprising metformin tablets only.

We considered that the costs estimated for NICE guidance TA99 are not appropriate as sources are not given and the costs are not recent. We also considered that the costs estimated by Astellas for this appraisal are not appropriate as they do not include any possible complications resulting from NODAT.

We assumed that the costs estimated for NODAT in the adult population could be a reasonable approximation to costs in children and adolescents. Although these costs would be likely to include certain costs that are unlikely to be incurred in young patients (particularly cardiovascular complications), there would also be likely to be increased costs of medical management for children and adolescents with NODAT and greater costs in the event of any complications requiring hospitalisation. The cost of diabetes mellitus in adults in the general population was estimated as £2028 per year (£1352 inpatient costs, £676 non-inpatient costs).[248] This was inflated to £2084 per year in 2014/15 prices.

Dyslipidaemia

Statin acquisition costs for the treatment of dyslipidaemia are given in *Table 99* and medical management costs are given in *Table 100*.

Infection prophylaxis

Drug acquisition costs for infection prophylaxis are given in *Table 101*. Costs for CMV prophylaxis (valganciclovir) are clearly much higher than costs for PJP and UTI prophylaxis.

TABLE 99 Medication (statin) unit costs for dyslipidaemia

Statin	Pack details	Units	Unit cost	Source
Fluvastatin	28 × 20 mg = £1.59	mg	£0.002216 (weighted by eMIT market share)	CMU eMIT[62]
	28 × 40 mg = £1.79			
Pravastatin	28 × 10 mg = £4.32	mg	£0.002561 (weighted by eMIT market share)	CMU eMIT[62]
	28 × 20 mg = £1.85			
	28 × 40 mg = £0.79			
Simvastatin	28 × 10 mg = £0.15	mg	£0.000339 (weighted by eMIT market share)	CMU eMIT[62]
	28 × 20 mg = £0.24			
	28 × 40 mg = £0.34			

TABLE 100 Medical management unit costs for dyslipidaemia

		Unit cost	
Attendance	Source	2013/14 prices	2014/15 prices
Dietetics outpatient	*NHS Reference Costs 2013 to 2014*:[58] dietetics outpatients service (service code 654)	£61.69	£62.70
General practice	PSSRU unit costs 2014:[234] GP (excluding direct care staff costs, without qualification costs, per 17.2-minute clinic)	£50.00	£50.82

TABLE 101 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[63]
Valganciclovir (Valcyte)	60 × 450 mg = £1081.46	Per 450-mg tablet	£18.02	BNF 68[63]

Cytomegalovirus infection treatment

In the parallel HTA to inform the update to NICE guidance TA85,[68] Bristol–Myers Squibb submitted a microcosting study[249] in which the cost of CMV infection was estimated to be £2271 in 2009 prices. This was inflated to £3009 in 2014/15 prices.

Astellas, in its submission for this appraisal, proposes a cost of £221–1151 depending on body weight. This cost includes drug acquisition [ganciclovir (Cymevene®, Roche Products Ltd)] but does not include any other costs, including drug administration and other medical management (e.g. hospitalisation costs).

It was decided that the costs derived from adults would be more appropriate because, if anything, the costs of treating CMV infection could be greater in children and adolescents than in adults.

Post-transplant lymphoproliferative disease

Post-transplant lymphoproliferative disease was assumed to incur £1206 in drug administration (four i.v. infusions) and £3040/m^2 body surface area in drug acquisition [four × 375 mg/m^2 rituximab (Mabthera®, Roche Products Ltd), £1.7463/mg].

Hypomagnesaemia

The cost of hypomagnesaemia requiring treatment was estimated to be £290.18 per year (one sachet of Magnaspartate daily, £0.80 per sachet).[173]

Hypertension

The annual cost of hypertension requiring medication was estimated to be £120.10 (*Table 102*), based on resource use in John and Domingo.[250]

Anaemia

Costs of 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; *Table 103*). Based on the BNF list prices epoetin alfa (Binocrit®, Sandoz) is the cheapest ESA, although it is possible that local pharmacy negotiations may result in reduced costs to the NHS in practice.

Drug administration

All maintenance agents except BEL are administered orally (unless people are unable to take medication orally) and this was assumed to not incur any cost.

Basiliximab is administered by i.v. infusion or injection and r-ATG is administered by i.v. infusion. BAS is administered on the day of transplantation and 4 days after transplantation. It is very likely that KTRs will still be inpatients for the latter administration. R-ATG is administered by i.v. infusion for 3–9 days. It is likely that KTRs will be inpatients for all of these infusions (a typical adult patient is estimated to require 10 days' inpatient stay[251] and children and adolescents are unlikely to require significantly shorter duration).

TABLE 102 Costs of hypertension

Item	Resource use	Unit cost	Item cost (per year)
Dietetics clinic	1 per year	£62.70	£62.70
Amlodipine	5 mg per day	£0.0071 per mg	£13.04
Bendroflumethiazide	1 tablet per day	£0.0344 per 2.5-mg tablet	£12.56
Captopril	25 mg per day	£0.0035 per mg	£31.81
Total			£120.10

TABLE 103 Drug acquisition costs for anaemia

Agent	Pack details	Units	Unit cost	Source
Epoetin alfa (Binocrit)	1000 IU = £4.33	Per 1000 IU	£4.33 (based on 1000-IU prefilled syringe)	BNF 68[63]
	2000 IU = £8.65			
	3000 IU = £12.98			
	4000 IU = £17.31			
	5000 IU = £21.64			
	6000 IU = £25.96			
	8000 IU = £40.73			
	10,000 IU = £43.27			

Belatacept is administered by i.v. 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 i.v. 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 i.v. administration of BAS, r-ATG and BEL 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 104*). 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.

Monitoring

The unit cost of viral quantitative PCR was assumed to be the same for CMV, EBV and BKV. The most appropriate recent cost estimate that could be found was from University College London Hospitals provider-to-provider service 2013/14 tariff.[252] This is a recent cost from an NHS provider. The tariffs are likely to be slightly higher than the costs of in-house laboratory tests but this was assumed to be a small effect and it was also considered that some centres might not have in-house quantitative PCR facilities. The tariff for CMV quantitative PCR was £46 in 2013/14 prices and this was inflated to £46.75 in 2014/15 prices for use in the model. The cost of CMV serology was estimated from the same source which, when inflated to 2014/15 prices, is £18.29.

The unit costs of therapeutic drug monitoring were estimated from the Department of Biochemistry and Immunology, University Hospital of Wales, therapeutic drug monitoring test repertoire. CSA, TAC and SRL 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 SRL.

TABLE 104 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	85,206	£185.95
		Follow-up	652,678	£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	109,174	£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

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,[251] as shown in *Table 105*.

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,[253] by mapping from NHS Classification of Interventions and Procedures (OPCS-4) code M026 (excision of rejected transplanted kidney) to groups LB61, LB62 and LB63.

The average cost (weighted by activity) for adults (from HRGs LB61 and LB62) was £4886 in 2013/14 prices (£4966 in 2014/15 prices). The average cost (weighted by activity) for children and adolescents (from HRG LB63) was £4751 in 2013/14 prices (£4829 in 2014/15 prices).

Subsequent transplant

Living donor costs fall under three HRG4 currencies:

1. LA10Z: live donor kidney screening
2. LA11Z: kidney pre-transplantation workup of live donor
3. 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 £8770.60 per live kidney donation in 2013/14 prices (*Table 106*).

TABLE 105 Unit costs for other monitoring tests

Test	Unit cost (2008/9 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

TABLE 106 Reference costs informing the unit cost of live kidney donation

HRG4 currency	Frequency	Unit cost	Total cost
LA10Z: live kidney donor screening	801	£659.61	£528,351
LA11Z: kidney pre-transplantation workup of live donor	1524	£477.95	£728,398
LB46Z: live donation of kidney	805	£7209.43	£5803,587
Total cost			£7060,337
(Per live donation of kidney)			£8770.60

Deceased donor costs comprise the cost of retrieval, which may be divided into staffing, consumables and transport. NHSBT performed a service evaluation of the National Organ Retrieval Service and reported various costs.[254] Staffing costs were reported separately for abdominal retrieval teams and these were used to estimate the staffing cost of retrieval at £6093.49 in 2012/13 prices (*Table 107*). The average cost of consumables per retrieval was reported as £1770.30, although it should be noted that this also included cardiothoracic retrievals. 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 £2005.12 per retrieval. The total cost of retrieval was therefore estimated to be £9869 in 2012/13 prices, which was inflated to £10,142 in 2014/15 prices for the model. The average cost of retransplantation was estimated as £20,576 (*Table 108*) and *Table 109* gives a summary of all costs relating to subsequent retransplantation.

Summary of model parameters

See *Appendix 7* for base-case values and PSA distributions for the parameters in the model.

Model verification

The decision model was tested by an independent academic decision modeller (AS). Extreme value testing and other black box testing techniques were applied to ensure the model performed as expected.[185]

TABLE 107 Abdominal retrieval team staffing costs

Abdominal retrieval team	Number of retrievals	Average staffing cost per retrieval
University Hospitals Birmingham NHS Foundation Trust	215	£4440.56
Cambridge University Hospitals NHS Foundation Trust	245	£4082.34
University Hospital of Wales	72	£5979.36
King's College Hospital NHS Foundation Trust	246	£2865.03
Leeds Teaching Hospitals NHS Trust/Central Manchester and Manchester Children's Foundation Hospitals NHS Trust	251	£8645.29
Newcastle upon Tyne NHS Foundation Trust	179	£5158.09
Oxford Radcliffe Hospitals NHS Trust	126	£6912.76
Royal Free Hampstead NHS Trust	122	£10,800.90
Royal Infirmary of Edinburgh (SORT)	117	£10,366.39
Average		£6093.49

SORT, Scottish Organ Retrieval Team.

TABLE 108 Unit costs for subsequent transplants

Procedure	HRG4 currency	Unit cost	
		2013/14 prices	2014/15 prices
Recipient workup	LA12 A: Kidney Pre-Transplantation Workup of Recipient, 19 years and over	Adults: £835.06	Adults: £848.72
	LA12B: Kidney Pre-Transplantation Workup of Recipient, 18 years and under	Children and adolescents: £496.61	Children and adolescents: £504.73
Living donor costs	See *Table 106*	£8,770.60	£8,914.05
Deceased donor costs	See *Unit costs, Subsequent transplant*	£9,868.92	£10,142.05
Transplant surgery	See *Table 108*	Adults: £15,772.38	Adults: £16,030.35
		Children and adolescents: £20,576.15	Children and adolescents: £20,912.68

TABLE 109 Reference costs informing the unit cost of transplant surgery

HRG4 currency	Activity	Unit cost	Total cost
LA01A: kidney transplant, 19 years and over, from cadaver non-heart-beating donor	553	£13,603.01	£7,522,463
LA02A: kidney transplant, 19 years and over, from cadaver heart-beating donor	991	£15,520.53	£15,380,850
LA03A: kidney transplant, 19 years and over, from live donor	826	£17,526.91	£14,477,231
Average (adults)		£15,772.38	
LA01B: kidney transplant, 18 years and under, from cadaver non-heart-beating donor	11	£27,496.72	£302,464
LA02B: kidney transplant, 18 years and under, from cadaver heart-beating donor	47	£18,502.00	£869,594
LA03B: kidney transplant, 18 years and under, from live donor	55	£20,964.49	£1,153,047
Average (children and adolescents)		£20,576.15	

Results

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

- total costs
- incremental costs versus previous regimen
- total QALYs
- incremental QALYs versus previous regimen
- ICER (vs. 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 is 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

Based on child/adolescent randomised controlled trials

Trompeter *et al.*[77]

In the deterministic analysis based on Trompeter *et al.*[77] we found that TAC-IR dominated CSA whether restricting attention to the reported duration of the trial (4 years) or additionally extrapolating to a maximum time horizon of 50 years using the Markov decision model (*Table 110*).

During the trial period, costs were predicted to be lower in the TAC arm owing to significant savings in dialysis costs (£5897 savings) as well as in the costs of immunosuppression and AR (£638 and £1508 savings, respectively), offset in part by increased costs of AEs (£225 greater). *Table 111* gives further details.

Costs were also predicted to be lower in the TAC arm during the extrapolation period, mainly owing to savings in dialysis (*Table 112*).

Discounted QALYs were predicted to be greater in the TAC arm in both the trial duration and extrapolation periods, due, in part, to extended life expectancy (3.92 and 39.51 years with 4- and 50-year time horizons, respectively, vs. 3.85 and 38.68 years for CSA). Increased graft survival also contributed to QALY gains for TAC versus CSA.

TABLE 110 Cost-effectiveness results based on Trompeter *et al.*[77] (deterministic analysis)

Regimen	TAC + AZA	CSA + AZA
Trial duration (4 years)		
Discounted costs	£17,731	£25,550
Discounted QALYs	3.3290	3.2530
ICER (cost/QALY)	Dominant	–
INHB at £20,000/QALY	0.4669	–
INHB at £30,000/QALY	0.3366	–
Extrapolation (46 years)		
Discounted costs	£159,214	£195,939
Discounted QALYs	13.3895	12.9169
Combined (50 years)		
Discounted costs	£176,946	£221,489
Discounted QALYs	16.7185	16.1698
ICER (cost/QALY)	Dominant	–
INHB at £20,000/QALY	2.7758	–
INHB at £30,000/QALY	2.0334	–

INHB, Incremental Net Health Benefit.

TABLE 111 Predicted costs during trial duration of Trompeter *et al.*[77] (deterministic analysis)

Regimen	TAC + AZA	CSA + AZA
Undiscounted costs		
Immunosuppression	£5965	£6652
AR	£1232	£2756
AEs	£1158	£921
Dialysis	£10,710	£17,167
Total	£19,065	£27,496
Discounted costs		
Immunosuppression	£5650	£6288
AR	£1219	£2728
AEs	£1082	£857

TABLE 112 Extrapolated discounted costs following Trompeter *et al.*[77] (deterministic analysis)

Regimen	TAC + AZA	CSA + AZA
Maintenance immunosuppression (initial graft)	£8277	£5914
Monitoring (initial graft)	£5145	£3096
Dialysis	£105,979	£136,719
Retransplantation	£14,703	£18,717
Maintenance immunosuppression (subsequent grafts)	£8684	£11,220
Monitoring (subsequent grafts)	£13,122	£16,973
Other costs	£3304	£3299
Total	£159,214	£195,939

Probabilistic analysis

When the average costs and QALYs from the probabilistic analysis are considered, as in the deterministic analysis TAC-IR is dominant over CSA (*Table 113*). Costs are predicted to be lower with TAC-IR, particularly those of dialysis, and QALYs are predicted to be greater.

As shown in the scatter cloud (*Figure 27*), the vast majority of probabilistic simulations predict that TAC-IR is cost saving when compared with CSA, and a significant number also predict that TAC-IR results in greater QALYs. TAC-IR is predicted to be cost-effective at £20,000 per QALY in 100.0% of simulations and at £30,000 per QALY in 100.0% of simulations (*Figure 28*).

Scenario analyses

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

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

TABLE 113 Cost-effectiveness results based on Trompeter *et al.*[77] (probabilistic analysis)

Regimen	TAC + AZA	CSA + AZA
Trial duration (4 years)		
Discounted costs	£17,979	£25,749
Discounted QALYs	3.3267	3.2512
ICER (cost/QALY)	Dominant	–
INHB at £20,000/QALY	0.4640	–
INHB at £30,000/QALY	0.3345	–
Extrapolation (46 years)		
Discounted costs	£156,878	£192,962
Discounted QALYs	13.3755	12.8957
Combined (50 years)		
Discounted costs	£174,857	£218,711
Discounted QALYs	16.7022	16.1469
ICER (cost/QALY)	Dominant	–
INHB at £20,000/QALY	2.7480	–
INHB at £30,000/QALY	2.0171	–

INHB, incremental net health benefit.

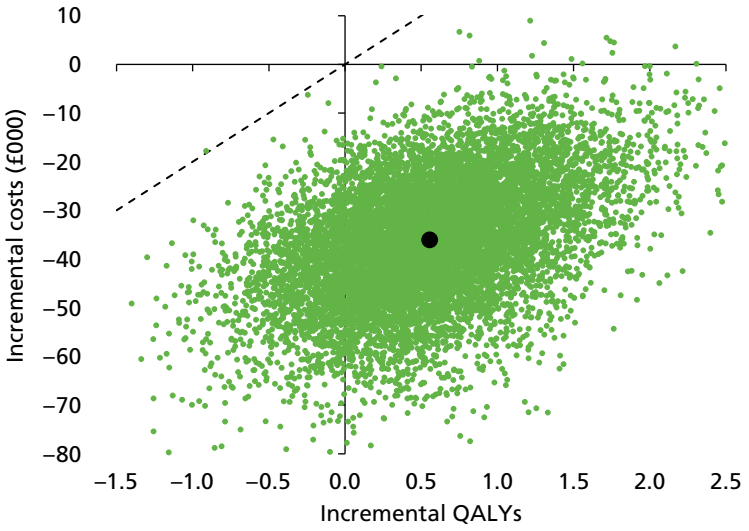

FIGURE 27 Probabilistic sensitivity analysis scatter cloud for Trompeter *et al.*[77] (TAC vs. CSA). Note: dashed line indicates £20,000 per QALY threshold; points to south-east of this line indicate that TAC is cost-effective vs. CSA at £20,000 per QALY. The black dot indicates mean incremental costs and QALYs.

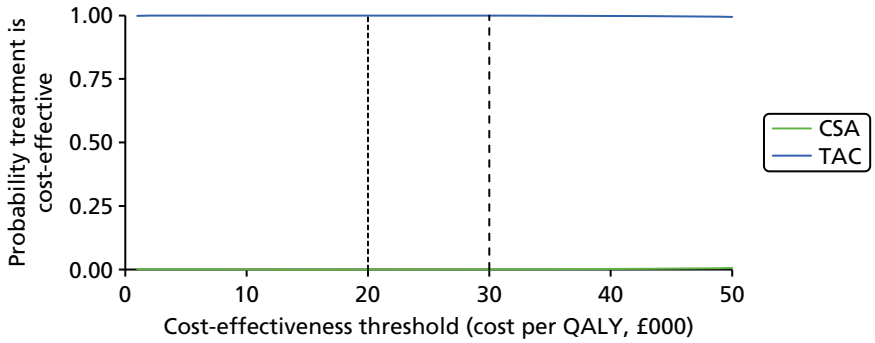

FIGURE 28 Cost-effectiveness acceptability curves for Trompeter *et al.*[77]

Surrogate relationship between AR and graft survival removed When the surrogate relationship between AR and graft survival is removed (leaving eGFR at 12 months as the dominant determinant of graft survival), TAC-IR continues to dominate CSA in the deterministic analysis.

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

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

Grenda *et al.*[75]

In the deterministic analysis based on Grenda *et al.*,[75] we found that induction with BAS was more effective and less costly than no induction, whether looking at just the trial duration (2 years) or extrapolating to a 50-year time horizon. BAS dominated no induction with a 2- or 50-year time horizon (*Table 114*).

The additional £2481 cost of induction in the BAS arm (and the £269 additional cost of AEs) in the trial duration are marginally outweighed by savings (£2776 from dialysis and £99 from AR costs), as shown in *Table 115*.

Cost savings are also realised in the extrapolation period by reducing future expenditure on dialysis and subsequent grafts, partially offset by increased cumulative immunosuppression costs for the initial graft and increased costs associated with NODAT (*Table 116*).

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

Probabilistic analysis

When the average costs and QALYs from the probabilistic analysis are considered, as in the deterministic analysis BAS is dominant over no induction (*Table 117*).

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

TABLE 114 Cost-effectiveness results based on Grenda *et al.*[75] (deterministic analysis)

Regimen	TAC + AZA	BAS + TAC + AZA
Trial duration (2 years)		
Discounted costs	£13,757	£13,631
Discounted QALYs	1.7319	1.7436
ICER (cost/QALY)	–	Dominant
INHB at £20,000/QALY	–	0.0179
INHB at £30,000/QALY	–	0.0159
Extrapolation (48 years)		
Discounted costs	£127,256	£121,684
Discounted QALYs	15.7609	15.9309
Combined (50 years)		
Discounted costs	£141,012	£135,315
Discounted QALYs	17.4928	17.6745
ICER (cost/QALY)	–	Dominant
INHB at £20,000/QALY	–	0.4665
INHB at £30,000/QALY	–	0.3716

INHB, incremental net health benefit.

TABLE 115 Predicted costs during trial duration of Grenda *et al.*[75] (deterministic analysis)

Regimen	TAC + AZA	BAS + TAC + AZA
Undiscounted costs		
Immunosuppression	£2266	£4758
AR	£531	£428
AEs	£242	£515
Dialysis	£11,264	£8361
Total	£14,304	£14,063
Discounted costs		
Immunosuppression	£2220	£4702
AR	£525	£426
AEs	£240	£508
Dialysis	£10,772	£7996
Total	£13,757	£13,631

TABLE 116 Extrapolated discounted costs following Grenda *et al.*[75] (deterministic analysis)

Regimen	TAC + AZA	BAS + TAC + AZA
Maintenance immunosuppression (initial graft)	£13,334	£14,021
Monitoring (initial graft)	£9167	£9630
Dialysis	£75,689	£69,730
Retransplantation	£10,567	£9799
Maintenance immunosuppression (subsequent grafts)	£6121	£5640
Monitoring (subsequent grafts)	£9279	£8538
NODAT	£424	£1611
Other costs	£2676	£2715
Total	£127,256	£121,684

TABLE 117 Cost-effectiveness results based on Grenda *et al.*[75] (probabilistic analysis)

Regimen	TAC + AZA	BAS + TAC + AZA
Trial duration (2 years)		
Discounted costs	£13,751	£13,636
Discounted QALYs	1.7302	1.7419
ICER (cost/QALY)	–	Dominant
INHB at £20,000/QALY	–	0.0174
INHB at £30,000/QALY	–	0.0155
Extrapolation (48 years)		
Discounted costs	£129,696	£124,073
Discounted QALYs	15.6259	15.8008
Combined (50 years)		
Discounted costs	£143,447	£137,708
Discounted QALYs	17.3562	17.5427
ICER (cost/QALY)	–	Dominant
INHB at £20,000/QALY	–	0.4734
INHB at £30,000/QALY	–	0.3778

INHB, incremental net health benefit.

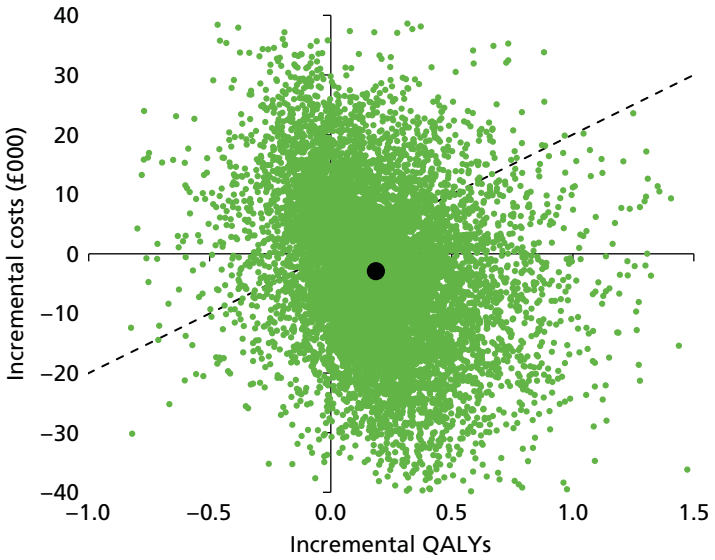

FIGURE 29 Probabilistic sensitivity analysis scatter cloud for Grenda *et al.*[75] (BAS vs. no induction). Note: dashed line indicates £20,000 per QALY threshold; points to south-east of this line indicate that BAS is cost-effective versus no induction at £20,000 per QALY. The black dot indicates mean incremental costs and QALYs.

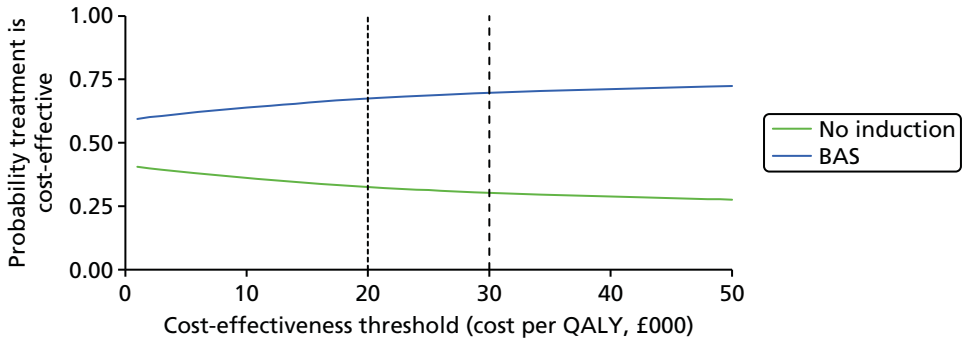

FIGURE 30 Cost-effectiveness acceptability curves for Grenda *et al.*[75]

Scenario analyses

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

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

Surrogate relationship between AR and graft survival removed Removing the surrogate relationship between AR and graft survival marginally increases graft survival in both arms, reducing costs and increasing QALYs.

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

Offner *et al.*[73]

Contrary to analyses based on Grenda *et al.*,[75] analyses based on Offner *et al.*[73] suggest that BAS is more costly and less effective than no induction, whether with a time horizon of 1 year (trial duration) or 50 years (*Table 118*).

During the trial duration BAS was predicted to result in lower AR costs (saving of £387) but also increased costs of immunosuppression, AEs and dialysis (increases of £2203, £19 and £276, respectively), as shown in *Table 119*.

When extrapolated beyond the trial duration, BAS was expected to result in greater costs of dialysis and costs associated with retransplantation (*Table 120*).

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

TABLE 118 Cost-effectiveness results based on Offner *et al.*[73] (deterministic analysis)

Regimen	BAS + CSA + MMF	CSA + MMF
Trial duration (2 years)		
Discounted costs	£5408	£3297
Discounted QALYs	0.8839	0.8992
ICER (cost/QALY)	Dominated	–
INHB at £20,000/QALY	–0.1208	–
INHB at £30,000/QALY	–0.0857	–
Extrapolation (48 years)		
Discounted costs	£129,804	£123,387
Discounted QALYs	16.9461	17.4765
Combined (50 years)		
Discounted costs	£135,212	£126,684
Discounted QALYs	17.8300	18.3757
ICER (cost/QALY)	Dominated	–
INHB at £20,000/QALY	–0.9721	–
INHB at £30,000/QALY	–0.8299	–

INHB, incremental net health benefit.

TABLE 119 Predicted costs during trial duration of Offner *et al.*[73] (deterministic analysis)

Regimen	BAS + CSA + MMF	CSA + MMF
Undiscounted costs		
Immunosuppression	£3795	£1591
AR	£462	£851
AEs	£500	£481
Dialysis	£683	£401
Total	£5441	£3323
Discounted costs		
Immunosuppression	£3778	£1575
AR	£461	£849
AEs	£500	£481
Dialysis	£669	£393
Total	£5408	£3297

TABLE 120 Extrapolated discounted costs following Offner *et al.*[73] (deterministic analysis)

Regimen	BAS + CSA + MMF	CSA + MMF
Maintenance immunosuppression (initial graft)	£15,715	£16,481
Monitoring (initial graft)	£9807	£10,606
Dialysis	£73,825	£68,017
Retransplantation	£11,706	£10,770
Maintenance immunosuppression (subsequent grafts)	£6003	£5522
Monitoring (subsequent grafts)	£9933	£9093
Other costs	£2815	£2899
Total	£129,804	£123,387

Probabilistic analysis

Results from the probabilistic analysis are consistent with the deterministic analysis; BAS is still expected to be dominated by no induction (*Table 121*).

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

Scenario analyses

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

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

TABLE 121 Cost-effectiveness results based on Offner *et al.*[73] (probabilistic analysis)

Regimen	BAS + CSA + MMF	CSA + MMF
Trial duration (2 years)		
Discounted costs	£5423	£3301
Discounted QALYs	0.8789	0.8941
ICER (cost/QALY)	Dominated	–
INHB at £20,000/QALY	–0.1212	–
INHB at £30,000/QALY	–0.0859	–
Extrapolation (48 years)		
Discounted costs	£130,442	£124,886
Discounted QALYs	16.8328	17.3400
Combined (50 years)		
Discounted costs	£135,865	£128,187
Discounted QALYs	17.7117	18.2341
ICER (cost/QALY)	Dominated	–
INHB at £20,000/QALY	–0.9062	–
INHB at £30,000/QALY	–0.7783	–

INHB, incremental net health benefit.

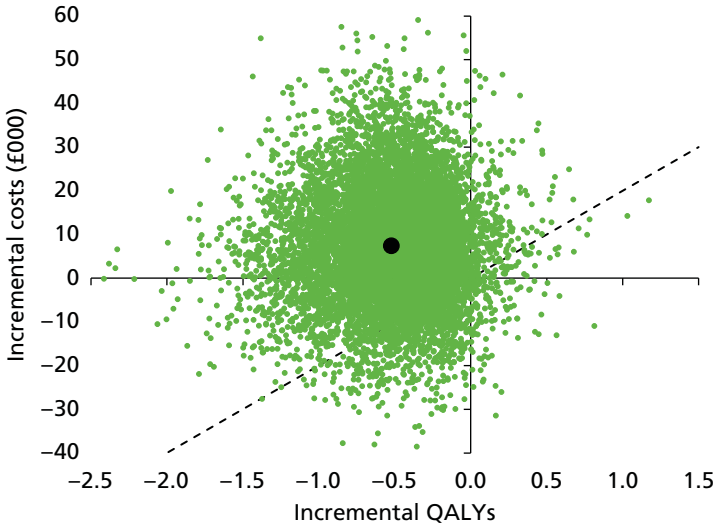

FIGURE 31 Probabilistic sensitivity analysis scatter cloud for Offner *et al.*[73] (BAS vs. no induction). Note: dashed line indicates £20,000 per QALY threshold; points to south-east of this line indicate that BAS is cost-effective versus no induction at £20,000 per QALY. The black dot indicates mean incremental costs and QALYs.

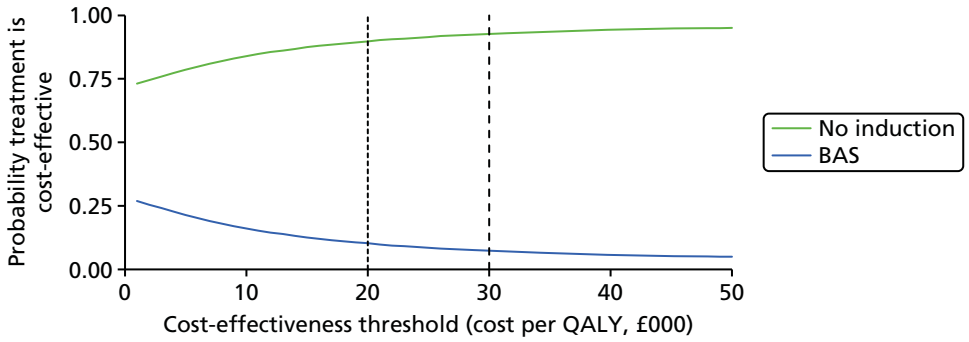

FIGURE 32 Cost-effectiveness acceptability curves for Offner *et al.*[73]

Surrogate relationship between AR and graft survival removed Removing the surrogate relationship between AR and graft survival marginally decreases graft survival in the BAS arm, increasing costs and reducing QALYs, while increasing graft survival in the no induction arm.

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

Summary of results from analyses based on child/adolescent randomised controlled trials

The analysis based on Trompeter *et al.*[77] suggested that TAC-IR would be cost-effective versus CSA at £20,000 or £30,000 per QALY as it was more effective and cost-saving both in the trial duration and when extrapolated.

The analyses based on Grenda *et al.*[75] and Offner *et al.*[73] produced contradictory results for the cost-effectiveness of BAS versus no induction. The analyses based on Grenda *et al.*[75] suggested that BAS would result in reduced costs and increased QALYs (i.e. BAS was dominant) while the analyses based on Offner *et al.*[73] suggested that BAS would result in increased costs and decreased QALYs (i.e. BAS was dominated). These results were robust to scenario analyses.

Using effectiveness estimates from adult studies

Further results for these analyses are given in *Appendix 9*.

Deterministic results

Induction agents

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

Basiliximab was found to be less costly and more effective (and, therefore, dominant) over no induction and r-ATG in all comparisons (*Table 122*). R-ATG was also found to be more costly and effective than no induction (i.e. no induction dominated r-ATG).

The differences in QALYs from r-ATG to no induction and from no induction to BAS are explained by increased life expectancy overall and by more projected time with functioning graft and less projected time dependent on dialysis (*Table 123*). Graft life expectancy for the first graft was greater for BAS than for r-ATG and no induction. The gains in graft survival for the first graft do not fully translate to gains in projected time with functioning graft or life expectancy because when a graft is lost later in life there is less time to achieve retransplantation and the mortality rate while on dialysis is greater.

TABLE 122 Summary of cost-effectiveness results for induction agents when adult RCTs are used to estimate effectiveness

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY
With CSA + AZA						***vs. BAS***	
R-ATG	£216,114	–	17.9721	–	Dominated	–1.0123	–0.7278
No induction	£210,097	–£6017	18.0031	+0.0310	Dominated	–0.6804	–0.4962
BAS	£199,042	–£11,055	18.1308	+0.1277	–	–	–
With CSA + MMF						***vs. BAS***	
R-ATG	£209,097	–	18.0702	–	Dominated	–1.0887	–0.7846
No induction	£199,910	–£9188	18.1269	+0.0567	Dominated	–0.5726	–0.4217
BAS	£190,856	–£9053	18.2468	+0.1200	–	–	–
With TAC + AZA						***vs. BAS***	
R-ATG	£183,191	–	18.2468	–	Dominated	–1.1228	–0.8082
No induction	£174,989	–£8202	18.2970	+0.0502	Dominated	–0.6625	–0.4846
BAS	£164,316	–£10,673	18.4259	+0.1288	–	–	–
With TAC + MMF						***vs. BAS***	
R-ATG	£189,637	–	18.1763	–	Dominated	–1.1560	–0.8317
No induction	£179,719	–£9918	18.2398	+0.0635	Dominated	–0.5966	–0.4377
BAS	£170,182	–£9537	18.3596	+0.1198	–	–	–

TABLE 123 Projections of expected life-years for induction agents when adult RCTs are used to estimate effectiveness

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

Finally, we compared these analyses to the analyses based on Grenda *et al.*[75] and Offner *et al.*[73] (reported in *Based on child/adolescent RCTs*). The analyses based on Grenda *et al.*[75] suggested that BAS (with TAC + AZA) was dominant compared with no induction regimen, while the analyses based on Offner *et al.*[73] suggested that BAS (with CSA + MMF) was dominated by no induction regimen. In summary, the deterministic results based on adult data were consistent with the analyses based on Grenda *et al.*[75] but not with the analyses based on Offner *et al.*[73]

Maintenance agents

Table 124 shows the summary of cost-effectiveness results for maintenance agents. It shows that TAC-IR is dominant over CSA, TAC-PR and SRL, but is less effective and less costly than BEL. Because the ICER of BEL versus TAC-IR is > £500,000 per QALY, only TAC-IR is cost-effective in these comparisons at £20,000 and £30,000 per QALY. Comparing these results to the results based on Trompeter *et al.*,[77] the regimen of TAC + AZA (vs. TAC + CSA) was dominant in both analyses (see *Tables 110* and *124*).

Table 124 also shows that when considering AZA, MMF, MPS, EVL and SRL, the results are less simple. SRL is dominated by MMF and AZA, but EVL and MPS are both the most effective and most costly treatments in their comparisons. The ICER for EVL is > £600,000 per QALY and, therefore, EVL is not predicted to be cost-effective at £20,000 or £30,000 per QALY, while the ICER for MPS is slightly > £50,000 per QALY. The cost-effectiveness of MMF appears to be dependent on the concomitant treatments: when MMF is used in combination with CSA it is dominant over AZA (and cost-effective at £20,000 and £30,000 per QALY), while when it is used in combination with TAC-IR, AZA is dominant (and MMF is therefore not cost-effective at £20,000 or £30,000 per QALY).

Table 125 gives further details in terms of projected life-years (overall and in certain health states).

TABLE 124 Summary of cost-effectiveness results for maintenance agents when adult RCTs are used to estimate effectiveness

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY
With MMF						***vs. TAC***	
CSA	£199,910	–	18.1269	–	Dominated	–1.1224	–0.7859
TAC-PR	£196,165	–£3744	18.1854	+0.0586	Dominated	–0.8767	–0.6026
TAC	£179,719	–£16,446	18.2398	+0.0544	–	–	–
With AZA						***vs. TAC***	
CSA	£210,097	–	18.0031	–	Dominated	–2.0494	–1.4642
TAC	£174,989	–£35,108	18.2970	+0.2940	–	–	–
With BAS + MMF						***vs. TAC***	
SRL	£198,631	–	18.2423	–	Dominated	–1.5397	–1.0655
CSA	£190,856	–£7,775	18.2468	+0.0045	Dominated	–1.1464	–0.8019
TAC	£170,182	–£20,674	18.3596	+0.1127	–	–	–
BEL	£293,175	+£122,993	18.5901	+0.2306	£533,449	–5.9191	–3.8692

TABLE 124 Summary of cost-effectiveness results for maintenance agents when adult RCTs are used to estimate effectiveness (*continued*)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit	
	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY
With BAS + AZA						***vs. TAC***	
CSA	£199,042	–	18.1308	–	Dominated	–2.0314	–1.4526
TAC	£164,316	–£34,726	18.4259	+0.2951	–	–	–
With r-ATG + MMF						***vs. TAC***	
CSA	£209,097	–	18.0702	–	Dominated	–1.0791	–0.7548
TAC	£189,637	–£19,460	18.1763	+0.1061	–	–	–
With r-ATG + AZA						***vs. TAC***	
CSA	£216,114	–	17.9721	–	Dominated	–1.9209	–1.3722
TAC	£183,191	–£32,923	18.2468	+0.2748	–	–	–
With CSA						***vs. MMF***	
AZA	£210,097	–	18.0031	–	Dominated	–0.6332	–0.4634
MMF	£199,910	–£10,188	18.1269	+0.1238	–	–	–
EVL	£259,327	+£59,417	18.2209	+0.0940	£632,246	–2.8769	–1.8866
With TAC						***vs. AZA***	
SRL	£222,300	–	17.9553	–	Dominated	–2.7073	–1.9187
MMF	£179,719	–£42,581	18.2398	+0.2844	Dominated	–0.2938	–0.2149
AZA	£174,989	–£4730	18.2970	+0.0572	–	–	–
With BAS + CSA						***vs. MMF***	
AZA	£199,042	–	18.1308	–	Dominated	–0.5254	–0.3889
MMF	£190,856	–£8186	18.2468	+0.1161	–	–	–
MPS	£198,303	+£7447	18.3907	+0.1438	£51,770	–0.2285	–0.1044
With BAS + TAC						***vs. AZA***	
MMF	£170,182	–	18.3596	–	Dominated	–0.3596	–0.2618
AZA	£164,316	–£5866	18.4259	+0.0663	–	–	–
With r-ATG + CSA						***vs. MMF***	
AZA	£216,114	–	17.9721	–	Dominated	–0.4490	–0.3321
MMF	£209,097	–£7017	18.0702	+0.0982	–	–	–
With r-ATG + TAC						***vs. AZA***	
MMF	£189,637	–	18.1763	–	Dominated	–0.3928	–0.2853
AZA	£183,191	–£6446	18.2468	+0.0705	–	–	–

TABLE 125 Projections of expected life-years for maintenance agents when adult RCTs are used to estimate effectiveness

Maintenance agent	Graft life expectancy (first graft; years)		Life expectancy (years)		Projected years with functioning graft		Projected years receiving dialysis	
	Total	Incremental	Total	Incremental	Total	Incremental	Total	Incremental
With MMF								
CSA	17.110	–	43.374	–	34.445	–	8.929	–
TAC-PR	20.038	+2.929	43.452	+0.077	35.370	+0.925	8.082	–0.848
TAC	20.304	+0.266	43.553	+0.102	35.502	+0.132	8.051	–0.031
With AZA								
CSA	15.098	–	43.175	–	33.784	–	9.391	–
TAC	21.263	+6.164	43.649	+0.474	35.925	+2.141	7.724	–1.667
With BAS + MMF								
SRL	20.376	–	43.534	–	35.533	–	8.001	–
CSA	19.171	–1.204	43.566	+0.032	35.159	–0.374	8.407	+0.406
TAC	22.449	+3.277	43.746	+0.180	36.286	+1.127	7.460	–0.947
BEL	24.625	+2.176	44.125	+0.379	37.236	+0.950	6.889	–0.571
With BAS + AZA								
CSA	17.229	–	43.378	–	34.490	–	8.888	–
TAC	23.597	+6.367	43.858	+0.480	36.785	+2.295	7.073	–1.815
With r-ATG + MMF								
CSA	15.983	–	43.294	–	34.059	–	9.236	–
TAC	18.881	+2.898	43.467	+0.173	34.994	+0.935	8.473	–0.763
With r-ATG + AZA								
CSA	14.421	–	43.136	–	33.557	–	9.578	–
TAC	20.068	+5.647	43.582	+0.447	35.474	+1.916	8.109	–1.470
With CSA								
AZA	15.098	–	43.175	–	33.784	–	9.391	–
MMF	17.110	+2.011	43.374	+0.200	34.445	+0.661	8.929	–0.462
EVL	19.183	+2.074	43.499	+0.124	35.118	+0.673	8.380	–0.549
With TAC								
SRL	15.862	–	43.139	–	33.979	–	9.160	–
MMF	20.304	+4.442	43.553	+0.415	35.502	+1.524	8.051	–1.109
AZA	21.263	+0.959	43.649	+0.096	35.925	+0.423	7.724	–0.327
With BAS + CSA								
AZA	17.229	–	43.378	–	34.490	–	8.888	–
MMF	19.171	+1.942	43.566	+0.188	35.159	+0.669	8.407	–0.481
MPS	21.364	+2.193	43.810	+0.244	35.983	+0.824	7.827	–0.579
With BAS + TAC								
MMF	22.449	–	43.746	–	36.286	–	7.460	–
AZA	23.597	+1.148	43.858	+0.111	36.785	+0.498	7.073	–0.387

TABLE 125 Projections of expected life-years for maintenance agents when adult RCTs are used to estimate effectiveness (*continued*)

Maintenance agent	Graft life expectancy (first graft; years)		Life expectancy (years)		Projected years with functioning graft		Projected years receiving dialysis	
	Total	Incremental	Total	Incremental	Total	Incremental	Total	Incremental
With r-ATG + CSA								
AZA	14.421	–	43.136	–	33.557	–	9.578	–
MMF	15.983	+1.562	43.294	+0.159	34.059	+0.501	9.236	–0.343
With r-ATG + TAC								
MMF	18.881	–	43.467	–	34.994	–	8.473	–
AZA	20.068	+1.187	43.582	+0.115	35.474	+0.480	8.109	–0.365

Immediate-release tacrolimus Immediate-release tacrolimus was compared with CSA (six comparisons), TAC-PR (one comparison), SRL (one comparison) and BEL (one comparison).

Immediate-release tacrolimus was found to be less costly and more effective than all comparators except BEL in all comparisons. BEL was predicted to be more costly and more effective than TAC-IR with an ICER of > £500,000 per QALY.

As demonstrated in *Table 125*, TAC-IR is predicted to result in prolonged survival of the initial graft by 3.2–6.4 years compared with CSA, as well as to prolong overall survival by 0.2–0.5 years. TAC-IR is predicted to give greater graft and overall survival than CSA, TAC-PR and SRL, but reduced graft and overall survival than BEL.

Prolonged-release tacrolimus Prolonged-release tacrolimus was compared with CSA and TAC-IR, in combination with MMF and CCSs.

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

Belatacept BEL was compared with CSA, TAC-IR and SRL, in combination with BAS induction, MMF and CCSs.

Belatacept was predicted to be more costly and more effective than all comparators. As CSA and SRL were predicted to be dominated by TAC-IR, the relevant comparator for BEL is TAC-IR. The ICER of BEL was predicted to be > £500,000 per QALY.

Mycophenolate mofetil Mycophenolate mofetil was compared with AZA (six comparisons), MPS (one comparison), SRL (one comparison) and EVL (one comparison).

When used in combination with CSA (three comparisons), MMF was predicted to be less costly and more effective than AZA. However, when used in combination with TAC-IR (three comparisons), MMF was predicted to be more costly and less effective than AZA. To summarise, MMF was dominant when used in combination with CSA but was dominated when used in combination with TAC-IR.

When compared with EVL in combination with CSA and CCSs, MMF was predicted to be less costly and less effective, with the ICER of EVL predicted to be > £600,000 per QALY.

When compared with SRL in combination with TAC and CCSs, MMF was predicted to be less costly and more effective than SRL, but was itself dominated by AZA in this comparison.

When compared with MPS in combination with BAS induction, CSA and CCSs, MMF was predicted to be less costly and less effective, with the ICER of MPS predicted to be > £50,000 per QALY.

At a cost-effectiveness threshold between £20,000 and £30,000 per QALY, MMF is predicted to be cost-effective in regimens containing CSA but not in regimens containing TAC-IR.

Mycophenolate sodium Mycophenolate sodium was compared with AZA and MMF in combination with BAS induction, CSA and CCSs. It was found to dominate AZA and was predicted to be more costly and more effective than MMF with an ICER of > £50,000 per QALY.

Sirolimus Sirolimus was compared with CSA, TAC-IR and BEL, in combination with BAS induction, MMF and CCSs, and was also compared with AZA and MMF, in combination with TAC-IR and CCSs.

When compared with CSA, TAC-IR and BEL, SRL was predicted to be dominated by CSA and TAC-IR.

When compared with AZA and MMF, SRL was predicted to be dominated by AZA and MMF.

Everolimus Everolimus was compared with AZA and MMF in combination with CSA and CCSs. EVL was predicted to be more costly and more effective than AZA and mycophenolate, with the appropriate ICER of EVL (vs. MMF) predicted to be > £600,000 per QALY.

Regimens

When all 18 regimens were simultaneously compared, all regimens were predicted to be dominated by BAS + TAC + AZA, except for BAS + BEL + MMF, which was predicted to have an ICER of > £700,000 per QALY (*Table 126*).

Summary

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

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY, TAC-IR was predicted to be cost-effective when compared with CSA, TAC-PR, SRL and BEL.

At cost-effectiveness thresholds between £20,000 and £30,000 per QALY, AZA was predicted to be cost-effective (vs. MMF and SRL) when used in combination with TAC while MMF was predicted to be cost-effective (vs. AZA, MPS and EVL) when used in combination with CSA.

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

TABLE 126 Summary cost-effectiveness results of regimens not dominated

Regimen	Discounted total costs	Discounted total QALYs	ICER (cost per QALY)	INHB at £20,000/QALY	INHB at £30,000/QALY
BAS + TAC + AZA	£164,316	18.4259	–	–	–
BAS + BEL + MMF	£293,175	18.5901	£784,515	–6.2787	–4.1310

Probabilistic results

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

Induction agents

Summary cost-effectiveness results are shown in *Table 127*. In all four comparisons BAS is expected to dominate no induction, which is in turn expected to dominate r-ATG. The same pattern was observed in deterministic analyses.

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

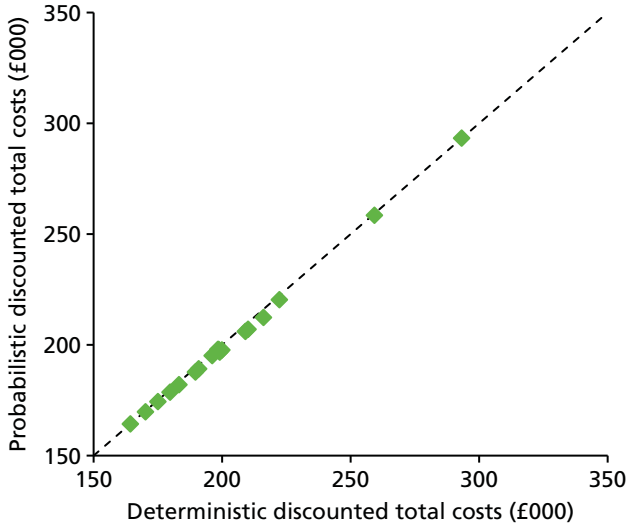

FIGURE 33 Comparison of deterministic and probabilistic total discounted costs.

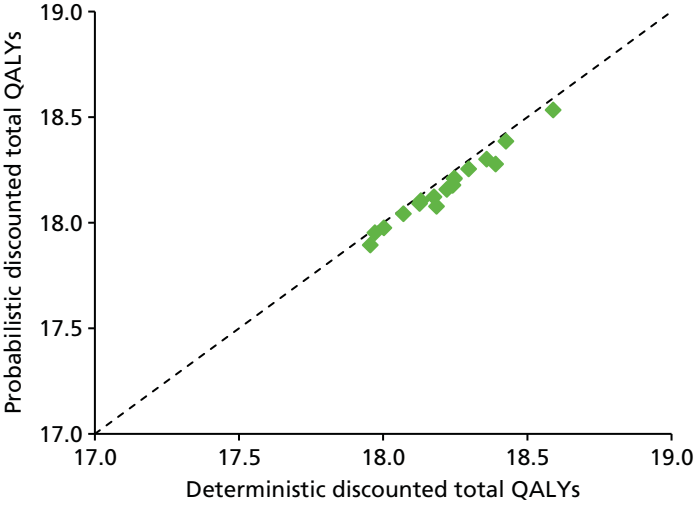

FIGURE 34 Comparison of deterministic and probabilistic total discounted QALYs.

TABLE 127 Summary cost-effectiveness results for induction agents (probabilistic analyses)

	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
Induction agent	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY	£20,000/QALY	£30,000/QALY
With CSA + AZA						***vs. BAS***			
R-ATG	£212,166	–	17.9509	–	Dominated	–0.9361	–0.6747	8.1%	8.2%
No induction	£206,855	–£5310	17.9751	+0.0242	Dominated	–0.6463	–0.4735	0.5%	0.4%
BAS	£196,484	–£10,371	18.1029	+0.1278	–	–	–	91.4%	91.4%
With CSA + MMF						***vs. BAS***			
R-ATG	£205,769	–	18.0414	–	Dominated	–1.0072	–0.7275	6.8%	7.0%
No induction	£197,421	–£8347	18.0896	+0.0482	Dominated	–0.5416	–0.4011	1.5%	1.3%
BAS	£188,991	–£8430	18.2097	+0.1201	–	–	–	91.8%	91.8%
With TAC + AZA						***vs. BAS***			
R-ATG	£181,824	–	18.2064	–	Dominated	–1.0652	–0.7696	7.4%	7.7%
No induction	£174,153	–£7671	18.2538	+0.0473	Dominated	–0.6343	–0.4666	0.7%	0.6%
BAS	£164,088	–£10,065	18.3848	+0.1311	–	–	–	91.9%	91.7%
With TAC + MMF						***vs. BAS***			
R-ATG	£187,494	–	18.1220	–	Dominated	–1.0751	–0.7760	6.7%	6.9%
No induction	£178,415	–£9079	18.1765	+0.0545	Dominated	–0.5667	–0.4188	1.4%	1.3%
BAS	£169,546	–£8870	18.2997	+0.1232	–	–	–	91.9%	91.9%

Maintenance agents

Table 128 shows the summary cost-effectiveness results for maintenance agents in the probabilistic analysis.

As in the deterministic analysis, it is predicted that TAC-IR dominates CSA (as well as TAC-PR and SRL), but is less costly and less effective than BEL (ICER £530,421 per QALY).

In addition, matching the results of the deterministic analysis it is again predicted that MMF is cost-effective when used in combination with CSA, but not when used in combination with TAC-IR.

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

Sirolimus is still not predicted to be cost-effective. As in the deterministic analyses, SRL is dominated by CSA and TAC-IR when used in combination with BAS and MMF, and is dominated by MMF and AZA when used in combination with TAC-IR.

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

Cost-effectiveness acceptability curves

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

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

Induction agents All treatment combinations with BAS induction were predicted to be cost-effective at £20,000 per QALY in at least 91.4% of the simulations and at £30,000 per QALY in at least 91.4% of simulations (*Figures 35–38*).

Maintenance agents All treatment combinations with TAC were predicted to be cost-effective at £20,000 per QALY in over 99% of the simulations and at £30,000 per QALY in over 98% of simulations (*Figures 39–44*).

Mycophenolate mofetil (in combination with CSA and no induction) was predicted to be cost-effective in 99.9% of the simulations at £20,000 and £30,000 per QALY (*Figure 45*).

Azathioprine (in combination with TAC and no induction) was predicted to be cost-effective at £20,000 per QALY in 74.1% of the simulations and at £30,000 per QALY in 74.9% of simulations (*Figure 46*).

Mycophenolate mofetil (in combination with BAS and CSA) was predicted to be cost-effective at £20,000 per QALY in 74.0% of the simulations and at £30,000 per QALY in 69.8% of simulations (*Figure 47*).

Azathioprine (in combination with BAS and TAC) was predicted to be cost-effective at £20,000 per QALY in 79.6% of the simulations and at £30,000 per QALY in 80.1% of simulations (*Figure 48*).

Azathioprine (in combination with r-ATG and CSA) was predicted to be cost-effective at £20,000 per QALY in 99.6% of the simulations and at £30,000 per QALY in 99.7% of simulations (*Figure 49*).

Azathioprine (in combination with r-ATG and TAC) was predicted to be cost-effective at £20,000 per QALY in 81.7% of the simulations and at £30,000 per QALY in 82.0% of simulations (*Figure 50*).

TABLE 128 Summary cost-effectiveness results for maintenance agents (probabilistic analyses)

	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
Maintenance agent	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY	£20,000/QALY	£30,000/QALY
With MMF						***vs. TAC***			
CSA	£197,421	–	18.0896	–	Dominated	–1.0372	–0.7204	0.5%	0.8%
TAC-PR	£194,861	–£2560	18.0765	–0.0130	Dominated	–0.9222	–0.6481	0.1%	0.3%
TAC	£178,415	–£16,446	18.1765	+0.0999	–	–	–	99.4%	98.9%
With AZA						***vs. TAC***			
CSA	£206,855	–	17.9751	–	Dominated	–1.9138	–1.3688	0.0%	0.0%
TAC	£174,153	–£32,702	18.2538	+0.2787	–	–	–	100.0%	100.0%
With BAS + MMF						***vs. TAC***			
SRL	£197,730	–	18.1774	–	Dominated	–1.5315	–1.0617	0.0%	0.0%
CSA	£188,991	–£8739	18.2097	+0.0323	Dominated	–1.0623	–0.7382	0.4%	0.6%
TAC	£169,546	–£19,445	18.2997	+0.0900	–	–	–	99.6%	99.3%
BEL	£293,117	+£123,571	18.5326	+0.2330	£530,421	–5.9456	–3.8861	0.0%	0.0%
With BAS + AZA						***vs. TAC***			
CSA	£196,484	–	18.1029	–	Dominated	–1.9018	–1.3618	0.0%	0.0%
TAC	£164,088	–£32,396	18.3848	+0.2820	–	–	–	100.0%	100.0%
With r-ATG + MMF						***vs. TAC***			
CSA	£205,769	–	18.0414	–	Dominated	–0.9943	–0.6897	0.4%	0.7%
TAC	£187,494	–£18,275	18.1220	+0.0806	–	–	–	99.6%	99.3%
With r-ATG + AZA						***vs. TAC***			
CSA	£212,166	–	17.9509	–	Dominated	–1.7727	–1.2670	0.0%	0.0%
TAC	£181,824	–£30,342	18.2064	+0.2556	–	–	–	100.0%	100.0%

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY	£20,000/QALY	£30,000/QALY
With CSA						***vs. MMF***			
AZA	£206,855	–	17.9751	–	Dominated	–0.5862	–0.4290	0.1%	0.1%
MMF	£197,421	–£9434	18.0896	+0.1145	–	–	–	99.9%	99.9%
EVL	£258,260	+£60,839	18.1562	+0.0666	£912,988	–2.9753	–1.9613	0.0%	0.0%
With TAC						***vs. AZA***			
SRL	£220,087	–	17.8930	–	Dominated	–2.6574	–1.8918	0.0%	0.0%
MMF	£178,415	–£41,672	18.1765	+0.2834	Dominated	–0.2904	–0.2194	25.9%	25.1%
AZA	£174,153	–£4262	18.2538	+0.0773	–	–	–	74.1%	74.9%
With BAS + CSA						***vs. MMF***			
AZA	£196,484	–	18.1029	–	Dominated	–0.4815	–0.3566	0.2%	0.2%
MMF	£188,991	–£7493	18.2097	+0.1068	–	–	–	74.0%	69.8%
MPS	£197,722	+£8730	18.2768	+0.0671	£130,080	–0.3694	–0.2239	25.9%	30.1%
With BAS + TAC						***vs. AZA***			
MMF	£169,546	–	18.2997	–	Dominated	–0.3581	–0.2671	20.4%	19.9%
AZA	£164,088	–£5458	18.3848	+0.0852	–	–	–	79.6%	80.1%
With r-ATG + CSA						***vs. MMF***			
AZA	£212,166	–	17.9509	–	Dominated	–0.4104	–0.3038	0.4%	0.3%
MMF	£205,769	–£6397	18.0414	+0.0905	–	–	–	99.6%	99.7%
With r-ATG + TAC						***vs. AZA***			
MMF	£187,494	–	18.1220	–	Dominated	–0.3680	–0.2735	18.3%	18.0%
AZA	£181,824	–£5670	18.2064	+0.0845	–	–	–	81.7%	82.0%

continued

TABLE 128 Summary cost-effectiveness results for maintenance agents (probabilistic analyses) (*continued*)

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	Incremental net health benefit		Probability cost-effective	
	Total	Incremental	Total	Incremental		£20,000/QALY	£30,000/QALY	£20,000/QALY	£30,000/QALY
With CSA						***vs. MMF***			
AZA	£209,016	–	17.9481	–	Dominated	–0.5872	–0.4292	0.1%	0.1%
MMF	£199,539	–£9477	18.0614	+0.1133	–	–	–	99.9%	99.9%
EVL	£259,701	+£60,162	18.1244	+0.0630	£954,838	–2.9451	–1.9424	0.0%	0.0%
With TAC						***vs. AZA***			
SRL	£221,807	–	17.8558	–	Dominated	–2.6408	–1.8824	0.0%	0.0%
MMF	£180,529	–£41,278	18.1350	+0.2792	Dominated	–0.2977	–0.2273	24.9%	23.9%
AZA	£176,305	–£4,224	18.2215	+0.0865	–	–	–	75.1%	76.2%
With BAS + CSA						***vs. MMF***			
AZA	£197,127	–	18.1019	–	Dominated	–0.4830	–0.3575	0.2%	0.2%
MMF	£189,597	–£7530	18.2083	+0.1065	–	–	–	75.0%	71.1%
MPS	£198,660	+£9063	18.2739	+0.0656	£138,196	–0.3876	–0.2365	24.8%	28.8%
With BAS + TAC						***vs. AZA***			
MMF	£170,179	–	18.2944	–	Dominated	–0.3602	–0.2696	20.0%	19.4%
AZA	£164,746	–£5433	18.3829	+0.0885	–	–	–	80.0%	80.6%
With r-ATG + CSA						***vs. MMF***			
AZA	£201,211	–	18.0837	–	Dominated	–0.4273	–0.3173	0.4%	0.3%
MMF	£194,609	–£6602	18.1809	+0.0972	–	–	–	99.6%	99.7%
With r-ATG + TAC						***vs. AZA***			
MMF	£175,703	–	18.2763	–	Dominated	–0.3816	–0.2823	17.9%	17.8%
AZA	£169,739	–£5963	18.3598	+0.0835	–	–	–	82.1%	82.2%

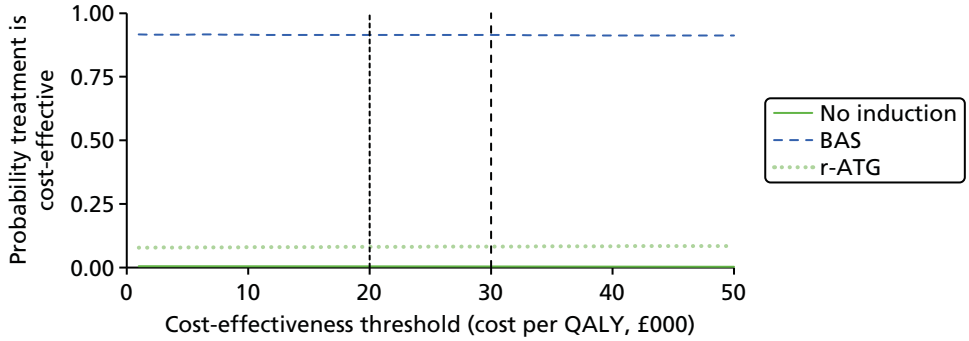

FIGURE 35 Cost-effectiveness acceptability curves for induction agents in combination with CSA and AZA.

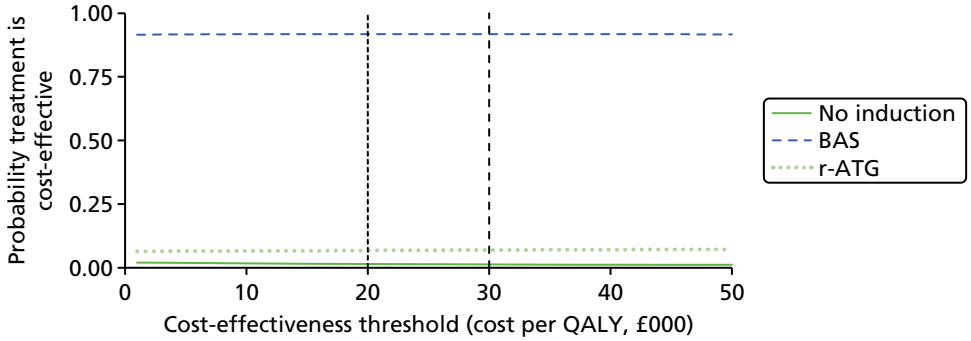

FIGURE 36 Cost-effectiveness acceptability curves for induction agents in combination with CSA and MMF.

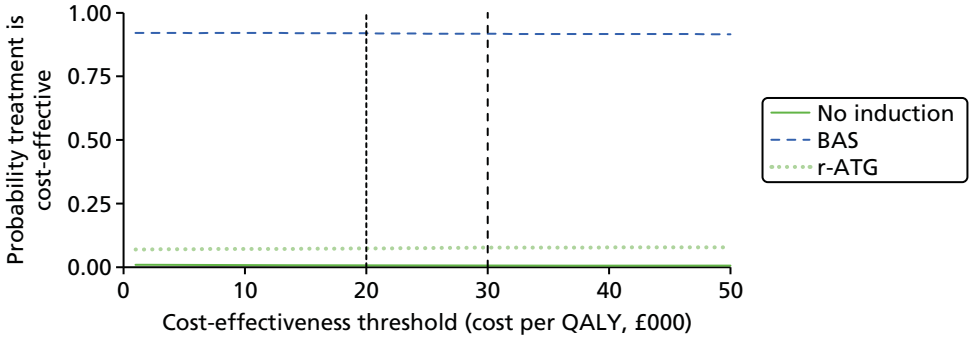

FIGURE 37 Cost-effectiveness acceptability curves for induction agents in combination with TAC-IR and AZA.

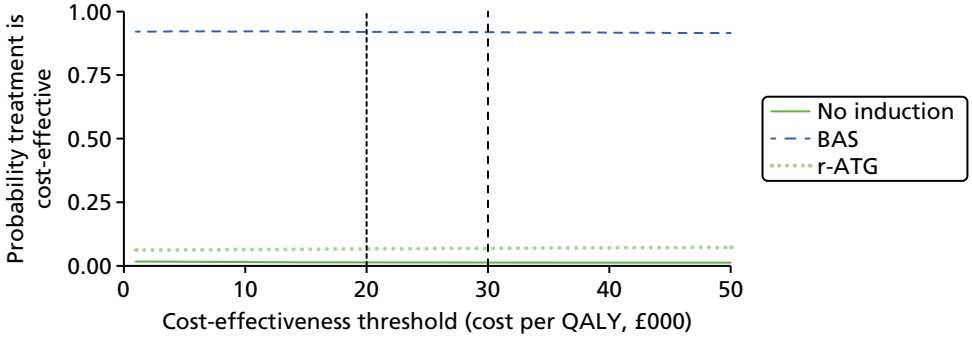

FIGURE 38 Cost-effectiveness acceptability curves for induction agents in combination with TAC-IR and MMF.

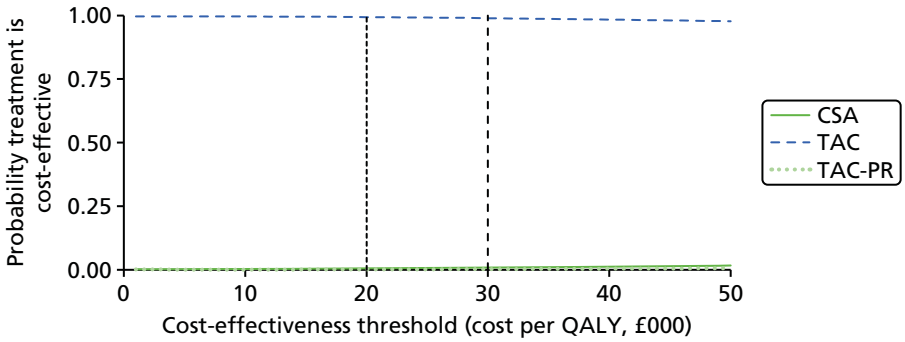

FIGURE 39 Cost-effectiveness acceptability curves for maintenance agents in combination with MMF.

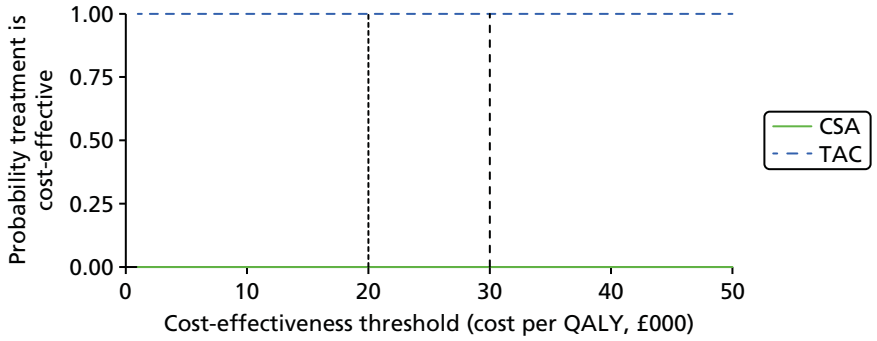

FIGURE 40 Cost-effectiveness acceptability curves for maintenance agents in combination with AZA.

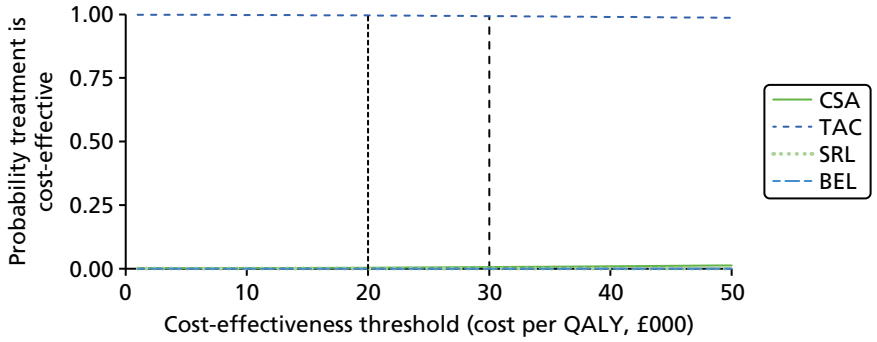

FIGURE 41 Cost-effectiveness acceptability curves for maintenance agents in combination with BAS and MMF.

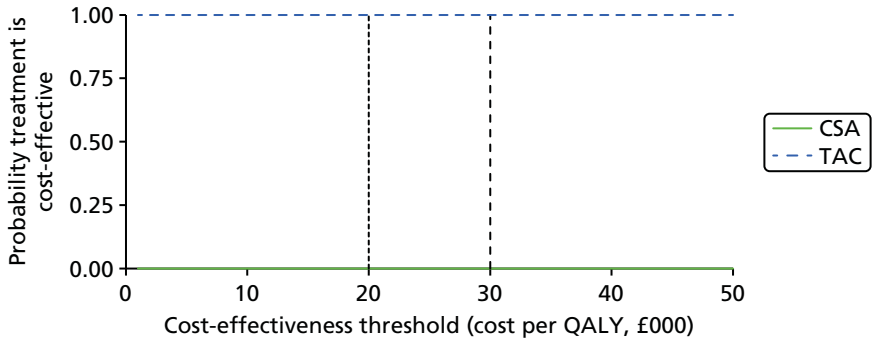

FIGURE 42 Cost-effectiveness acceptability curves for maintenance agents in combination with BAS and AZA.

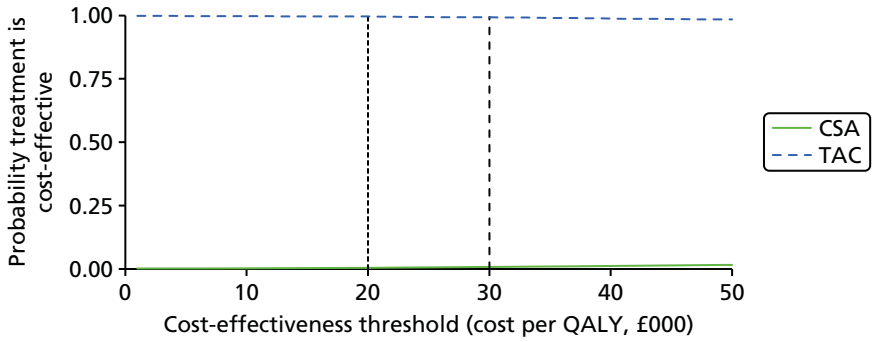

FIGURE 43 Cost-effectiveness acceptability curves for maintenance agents in combination with r-ATG and MMF.

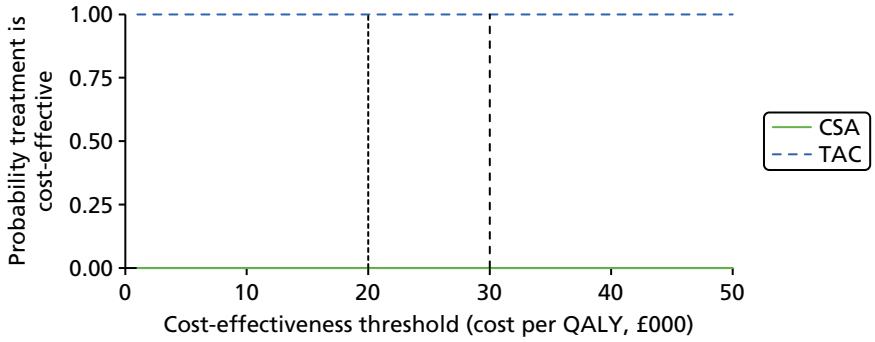

FIGURE 44 Cost-effectiveness acceptability curves for maintenance agents in combination with r-ATG and AZA.

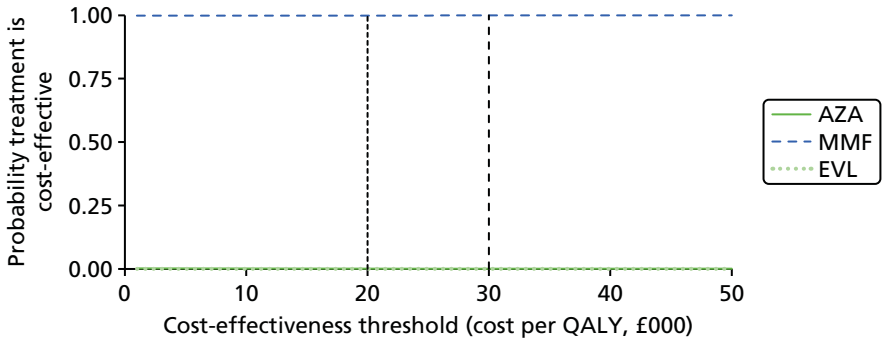

FIGURE 45 Cost-effectiveness acceptability curves for maintenance agents in combination with CSA.

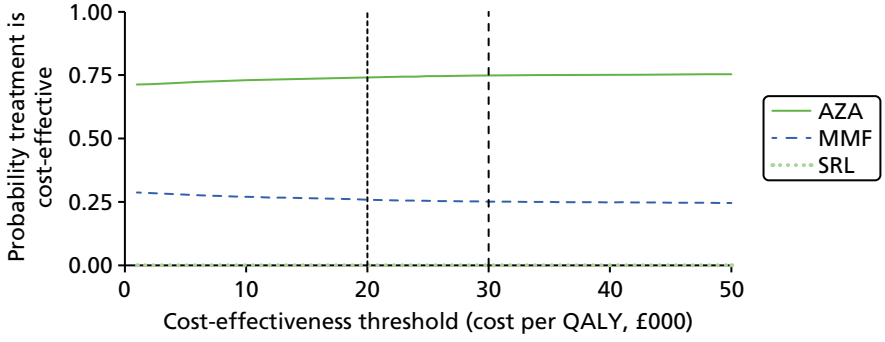

FIGURE 46 Cost-effectiveness acceptability curves for maintenance agents in combination with TAC-IR.

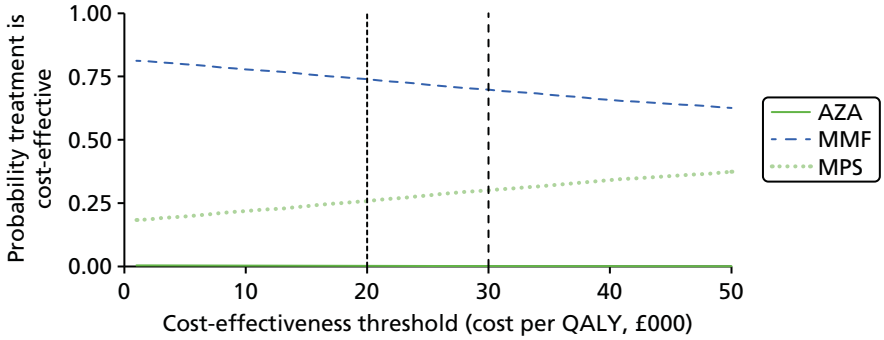

FIGURE 47 Cost-effectiveness acceptability curves for maintenance agents in combination with BAS and CSA.

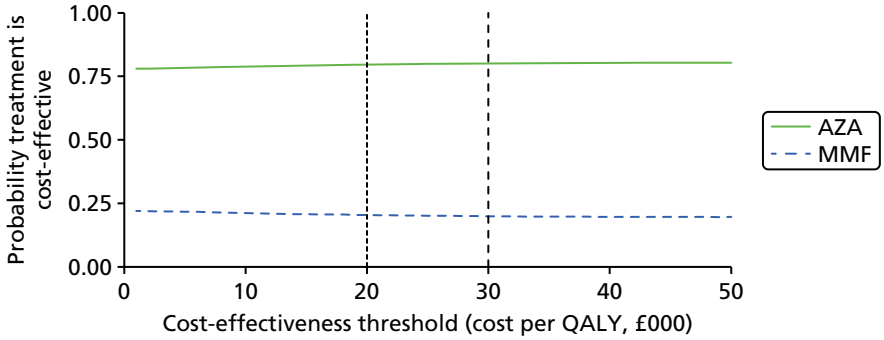

FIGURE 48 Cost-effectiveness acceptability curves for maintenance agents in combination with BAS and TAC-IR.

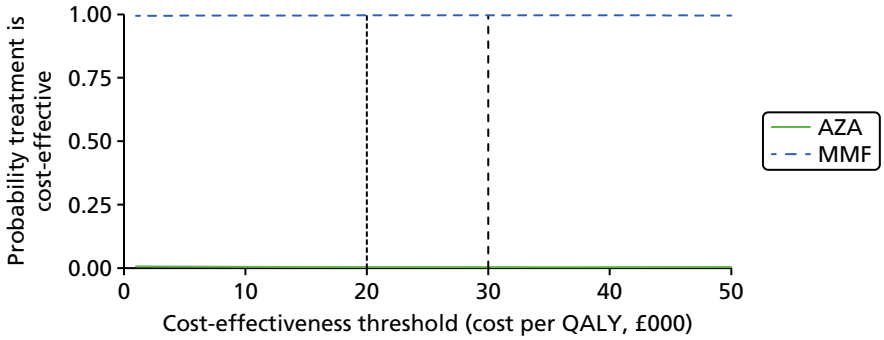

FIGURE 49 Cost-effectiveness acceptability curves for maintenance agents in combination with r-ATG and CSA.

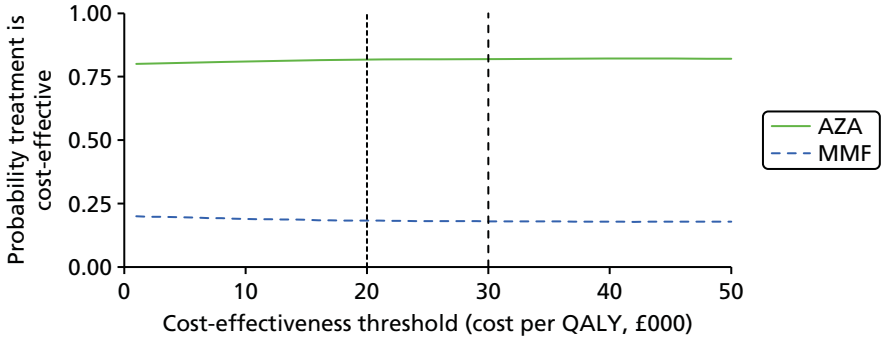

FIGURE 50 Cost-effectiveness acceptability curves for maintenance agents in combination with r-ATG and TAC-IR.

Scenario analyses

Below average weight for kidney transplant recipients

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

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

Surrogate relationship between acute rejection and graft survival removed

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

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

Subgroup analyses

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

For most regimens, discontinuities in total discounted costs were observed at age 6 years and age 13 years, which are explained by the HRs for graft survival according to age, taken from Muscheites *et al.*,[185] in which graft survival was predicted to be worse for children aged 6–12 years at the time of transplantation than for younger children or older adolescents. Reduced graft survival results in greater total costs as more recipients lose their grafts earlier and require dialysis.

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

The total discounted costs and QALYs are shown for BAS, TAC-IR and AZA in *Figure 51*. Across the age range, BAS + TAC + AZA was the most cost-effective regimen at £20,000 and £30,000 per QALY (*Figures 52* and *53*). When the weighted average total discounted costs and QALYs (weighted by number of KTRs at each age) are calculated, BAS + TAC + AZA is the cost-effective regimen at £20,000 and £30,000 per QALY (*Table 129*).

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

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

R-ATG and no induction were not predicted to be cost-effective at £20,000–30,000 per QALY compared with BAS.

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

Prolonged-release tacrolimus, SRL, BEL and CSA were not predicted to be cost-effective at £20,000–30,000 per QALY compared with TAC-IR and each other.

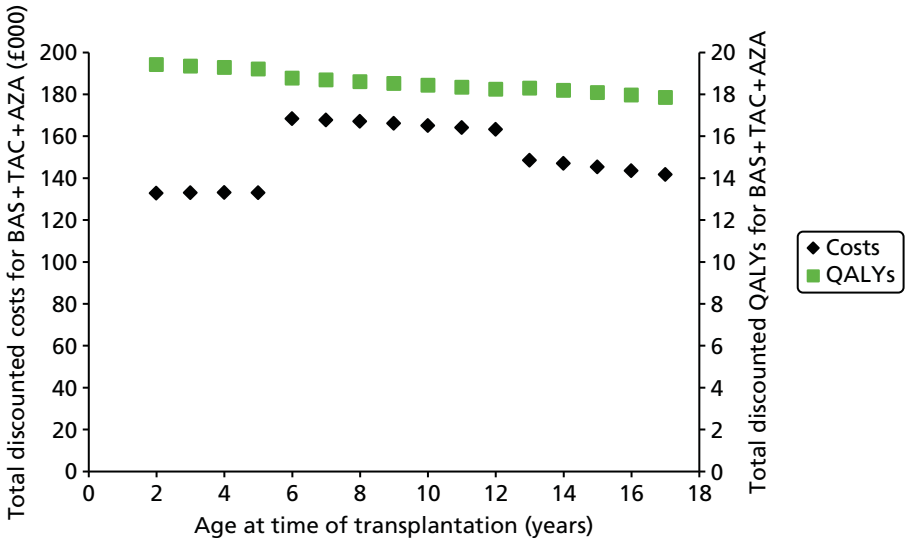

FIGURE 51 Total discounted costs and QALYs for regimen of BAS, TAC-IR and AZA as age at transplantation is varied.

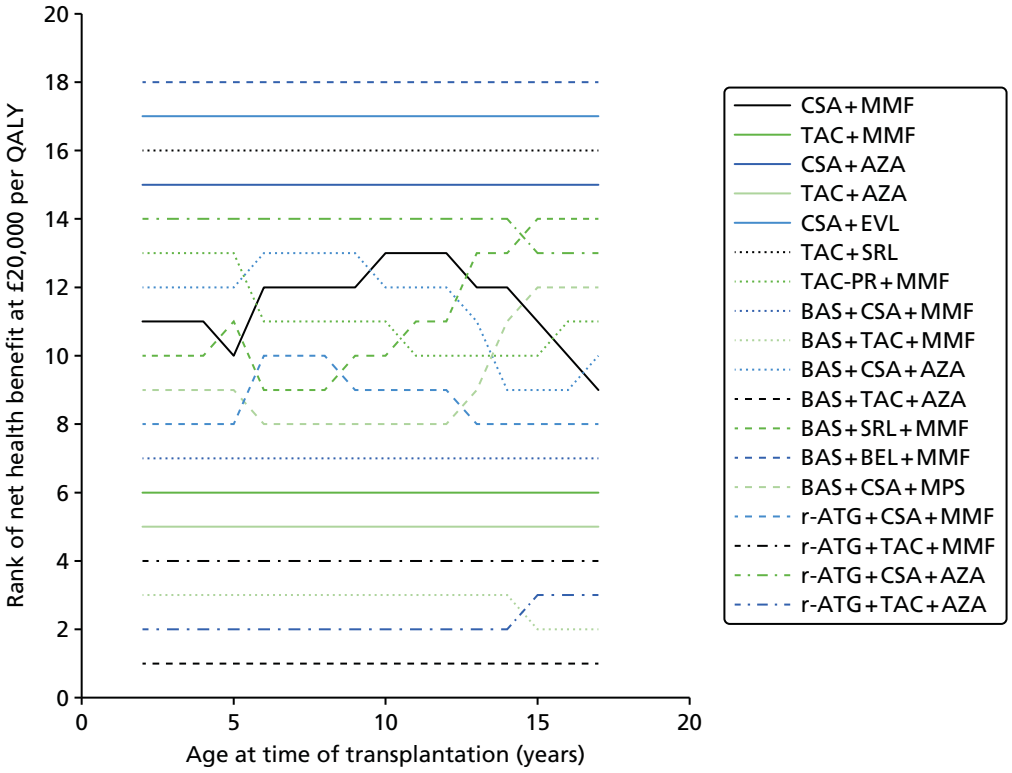

FIGURE 52 Rank of net health benefit at £20,000 per QALY for all regimens as the age at time of transplantation is varied.

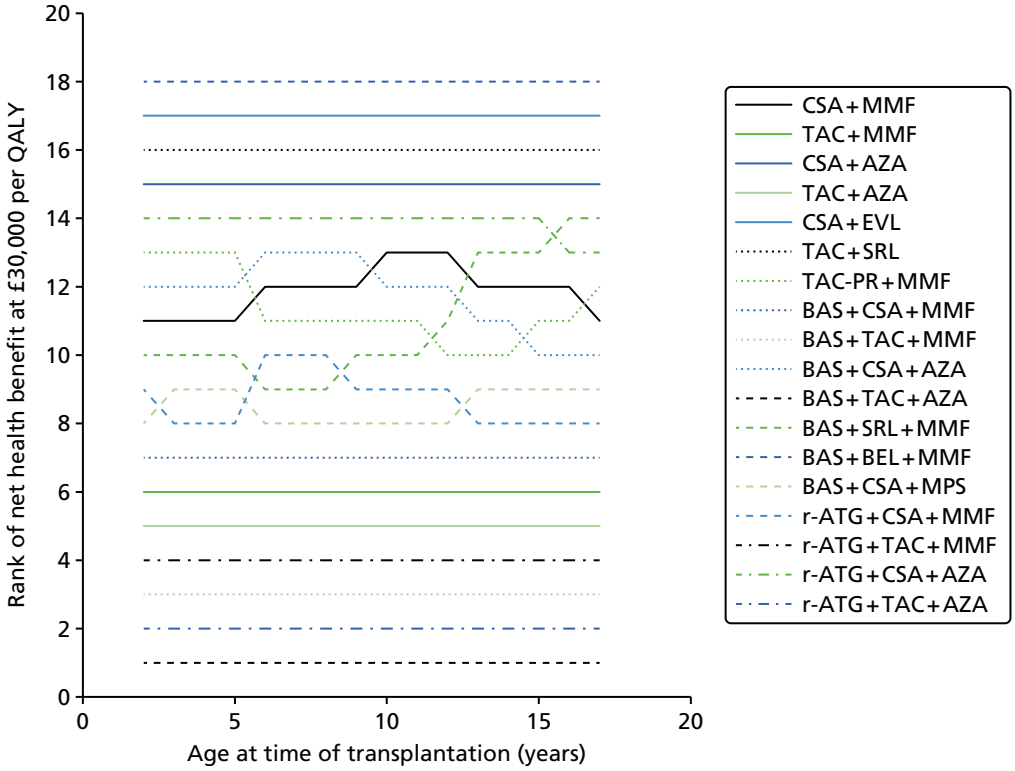

FIGURE 53 Rank of net health benefit at £30,000 per QALY for all regimens as the age at time of transplantation is varied.

TABLE 129 Net health benefit of regimens when averaged across age range

	Net health benefit	
Regimen	£20,000 per QALY	£30,000 per QALY
CSA + MMF	9.08	12.11
TAC + MMF	9.99	12.74
CSA + AZA	8.32	11.55
TAC + AZA	10.25	12.93
CSA + EVL	5.60	9.81
TAC + SRL	7.50	10.99
TAC-PR + MMF	9.10	12.13
BAS + CSA + MMF	9.59	12.49
BAS + TAC + MMF	10.65	13.23
BAS + CSA + AZA	9.08	12.11
BAS + TAC + AZA	10.95	13.45
BAS + SRL + MMF	9.02	12.10
BAS + BEL + MMF	2.33	7.76
BAS + CSA + MPS	9.23	12.29
r-ATG + CSA + MMF	9.28	12.28
r-ATG + TAC + MMF	10.34	13.02
r-ATG + CSA + AZA	8.83	11.94
r-ATG + TAC + AZA	10.69	13.27

MMF was predicted to be cost-effective at £20,000–30,000 per QALY when used in combination with CSA, but not when used in combination with TAC-IR.

Azathioprine was predicted to be cost-effective at £20,000–30,000 per QALY when used in combination with TAC-IR, but not when used in combination with CSA.

Mycophenolate sodium was not predicted to be cost-effective at £20,000–30,000 per QALY compared with MMF and AZA, but was cost-effective at £30,000 per QALY in a scenario analysis in which body weight followed the ninth centile rather than median weight for age.

Sirolimus and EVL were not predicted to be cost-effective at £20,000–30,000 per QALY compared with MMF and AZA.

Summary of results from Peninsula Technology Assessment Group economic assessment

Basiliximab was predicted to be cost-effective at £20,000–30,000 per QALY compared with no induction in one analysis based on a RCT in children and adolescents,[75] but was not predicted to be cost-effective in an analysis based on another RCT in children and adolescents.[73] BAS was predicted to be cost-effective at £20,000–30,000 per QALY compared with no induction and r-ATG in analyses based on extrapolating effectiveness estimates from the adult population.

Rabbit anti-human thymocyte immunoglobulin was not predicted to be cost-effective at £20,000–30,000 compared with BAS in analyses based on extrapolating effectiveness estimates from the adult population.

Immediate-release tacrolimus was predicted to be cost-effective at £20,000–30,000 per QALY compared with CSA in an analysis based on a RCT in children and adolescents[77] and was also predicted to be cost-effective compared with CSA, TAC-PR, SRL and BEL in analyses based on extrapolating effectiveness estimates from the adult population.

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

Prolonged-release tacrolimus, SRL, BEL, MPS and EVL were not predicted to be cost-effective at £20,000–30,000 per QALY compared with TAC-IR in analyses based on extrapolating effectiveness estimates from the adult population.

Comparison of the Peninsula Technology Assessment Group, Astellas and previous Assessment Group's model-based analyses

In this section, we compare the model-based analysis of maintenance regimens by the independent Assessment Group (PenTAG) with relevant analyses in the company submission (from Astellas) and with the previous analyses[2] which informed NICE's current guidance[1] on these technologies. *Table 130* shows which specific immunosuppression agents have been evaluated by the three models.

Table 131 summarises which combination regimens have been compared by the PenTAG and Astellas models in the child/adolescent kidney transplant populations. The Astellas submission did not provide cost-effectiveness analysis of induction therapies and only one comparison in the previous technology assessment for NICE compared induction therapies (BAS vs. no induction).

TABLE 130 Immunosuppressive agents evaluated for cost-effectiveness in PenTAG analysis, Astellas' analysis and NICE guidance TA99

Agent	TA99	PenTAG	Astellas
BAS	Y	Y	N
R-ATG	N	Y	N
(No induction)	Y	Y	N
TAC-IR	Y	Y	Y
TAC-PR	N	Y	Y
MMF	Y	Y	N
MPS	Y	Y	N
SRL	Y	Y	Y
EVL	N	Y	Y
BEL	N	Y	Y
(CSA)	Y	Y	N
(AZA)	Y	Y	N

N, no; Y, yes.
Brackets denote comparator regimens rather than interventions.

TABLE 131 Regimens compared by the PenTAG and Astellas models

PenTAG	Astellas
TAC (+ AZA) vs. CSA (+ AZA) (based on one child/adolescent RCT) In addition, based on adult RCT evidence following BAS induction: TAC (+ MMF) vs. CSA (+ MMF) vs. SRL (+ MMF) vs. BEL (+ MMF)	TAC (granules for oral solution) vs. TAC 'specials' (liquid preparations) vs. BEL vs. EVL vs. SRL + low-dose CSA (= CNI minimisation) vs. SRL + MMF (= CNI avoidance)
TAC vs. PR-TAC (based on adult RCT)	TAC vs. PR-TAC

Fully explaining the differences between the different model cost-effectiveness outputs is more challenging than usual, because

- the main assumptions in the Astellas model are different in very many respects, including:
  - 10-year time horizon versus 50 years in PenTAG analyses
  - basing effectiveness differences only on BPAR at 12 months post transplant
  - omission of CSA as a relevant comparator for maintenance therapies
  - large difference between the assumed utility of living with a functioning graft (0.71) and being on dialysis (haemodialysis 0.44, peritoneal dialysis 0.53)
  - drug unit costs were all based on *BNF* list prices in the Astellas analyses, whereas in the PenTAG analyses we used prices from the eMIT database, when possible, to reflect nationally available discounted prices (i.e. for TAC-IR, CSA, AZA, MMF, prednisolone)
  - drug consumption values for SRL regimens were based on treatment guidelines rather than trial evidence of actual dosage intensity.

- the Yao *et al.*[2] model assumptions and parameters are not fully described in any one report (and we were also unable to obtain the model files to assess it). The model used in the Yao *et al.*[2] analysis is:
  - a child-/adolescent-adapted version of an adult post-transplant immunosuppression model, which was based on:
    - a 'meta-model' developed for the previous technology assessment for NICE of immunosuppression following kidney transplantation[255] which was, in turn, based on:
      - the Novartis model submitted to the previous technology appraisal process for these drugs.

Therefore, it was not possible to know with certainty what the input parameters and other main assumptions were in the Yao *et al.*[2] model. In addition, the incremental cost-effectiveness analyses produced by the Yao *et al.*[2] model used different discount rates for costs (6% per year) and QALYs (1.5% per year), according to the NICE methods guidance at that time.[256] Like the current Astellas model, it also had a limited time horizon of 10 years. Without access to the original model, and no reporting of the model outputs for each comparator or as undiscounted costs or QALYs, it is impossible to adjust for these differences. The results, which are most different between the Yao *et al.*[2] and PenTAG modelling, are those that relied on adult RCT data – and for which the PenTAG has substantially updated the effectiveness estimates from more recent trials (*Table 132*). In contrast, the cost-effectiveness result for BAS versus no induction – which does use available child/adolescent RCT evidence in both models – arrives at the same conclusion as Yao *et al.*[2] did in 2006, that is, that BAS is both more effective and cheaper than no induction.

TABLE 132 Regimens and main results of the PenTAG and Yao *et al.* models compared

	Table 56 in Yao *et al.*[2]		PenTAG[a]	
Compared regimens	**Estimate[b]**	**ICER (£ per QALY)[b]**	**Estimate[b]**	**ICER (£ per QALY)[b]**
CAS vs. TAS (= CSA + AZA vs. TAC + AZA)				
Incremental costs (£)	13,716	145,540	–35,267	TAS dominant
Incremental QALYs	0.09		+0.2888	
CAS vs. CMS (= CSA + AZA vs. CSA + MMF)				
Incremental costs (£)	9543	194,559	–10,202	CMS dominant
Incremental QALYs	0.049		+0.1232	
CAS vs. BCAS (= CSA + AZA vs. BAS + CSA + AZA)				
Incremental costs (£)	–1103	BCAS dominant	–12,726	BCAS dominant
Incremental QALYs	0.074		+0.1522	
CAS vs. DCAS (= CSA + AZA vs. DAC + CSA + AZA)[c]				
Incremental costs (£)	–417	DCAS dominant	N/A	
Incremental QALYs	0.05		N/A	
TAS vs. BTAS (= TAC + AZA vs. BAS + TAC + AZA)				
Incremental costs (£)	–451	BTAS dominant	–12,335	BTAS dominant
Incremental QALYs	0.038		+0.1584	

B, BAS; D, DAS.
a These PenTAG analyses all based on effectiveness data from RCTs in adults.
b Note that these incremental estimated are presented as in Yao *et al.*,[2] with second regimen cost or QALY minus the first.
c DAC (D) is no longer used; the marketing authorisation has been withdrawn at the request of the manufacturer.

For reference, three larger tables in *Appendix 8* compare the main cost parameters, effectiveness parameters and main cost and effectiveness results for the three models, where they are known (see *Tables 142–144*). These show, for example, that the PenTAG model assumptions tended to include fuller costing of the administration of the maintenance therapies. In addition, although applied differently in the models, the utility difference between living with a functioning graft and living on dialysis was greater in the Astellas model (difference of between ≈0.25 and ≈0.3) than in the PenTAG and Yao *et al.*[2] models (≈0.2 difference).

Peninsula Technology Assessment Group's and Astellas' model-based analyses compared

Table 133 shows the company's and the Assessment Group's analysis of the cost-effectiveness of the two types of TAC. While the Astellas analysis estimates that TAC-PR dominates TAC-IR (estimating it to be > £5000 cheaper over 10 years and to generate 0.035 extra discounted QALYs, the PenTAG analysis produces the opposite result – based on effectiveness evidence from adult RCTs), TAC-PR is dominated by both TAC-IR and CSA. In the PenTAG analysis, TAC-PR is > £18,000 more costly than TAC-IR and generates 0.06 fewer discounted QALYs (both over a time horizon of 50 years).

This opposite result in incremental QALYs mostly arises because of the different trial data used within the two models and the fact that long-term outcomes in the Astellas model are driven entirely by rates of AR. 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.[139,196] None of the pooled ORs is statistically significant and all except the comparison for BPAR favour the TAC-IR. In contrast, the Astellas review reports using three trials;[97,139,152] including two meta-analyses of BPAR (each including two unspecified trials) which they conclude show the two types of TAC to be of 'similar efficacy and safety'. However, in their model, these data sources are then used to justify TAC-IR having a 2 percentage point higher rate of AR than TAC-PR, which then drives differences in long-term graft survival (and costs). In their modelling, they also factor in greater adherence to treatment with TAC-PR, which departs from the ITT analysis of the trials.

TABLE 133 PenTAG's and Astellas' analysis of TAC-PR compared

	Discounted costs		Discounted QALYs		
Agent	Total	Incremental	Total	Incremental	ICER
PenTAG					
CSA	£202,424	–	18.1018	–	Dominated
TAC-PR	£198,433	–£3992	18.1503	+0.0485	Dominated
TAC	£182,163	–£16,270	18.2085	+0.0581	–
Astellas					
TAC-PR	£53,395	–	5.604		–
TAC	£58,471	+£5,076	5.569	–0.035	Dominated

Table 134 shows the company's and the Assessment Group's analysis of the cost-effectiveness of TAC, BEL, SRL and CSA. In particular, it shows the impact of the very different time horizons of the two models on the accumulated costs and QALYs. The other main differences are that in the Astellas model BEL is the least effective treatment (but the most effective in the PenTAG model) and only about £20,000 more expensive than TAC (compared with £153,000 more expensive in the PenTAG model). The omission of CSA from the Astellas modelling does not invalidate comparisons between the two analyses, because in the PenTAG model the CSA regime is dominated (less effective and more costly) than TAC – and so effectively ruled out of further consideration.

Despite these substantial differences in assumptions and included comparators, in both model-based analyses TAC (immediate release) is found to be the most cost-effective regimen.

TABLE 134 PenTAG's and Astellas' analysis of TAC, BEL and SRL

	Discounted costs		Discounted QALYs		
Agent	Total	Incremental	Total	Incremental	ICER
PenTAG (all with BAS + MMF)					
SRL	£199,145	–	18.2423	–	Dominated
CSA	£191,679	–£7466	18.2468	+0.0045	Dominated
TAC	£170,915	–£20,763	18.3596	+0.0485	–
BEL	£324,708	+£153,792	18.5901	+0.0581	£667,031
Astellas					***vs. TAC***
SRL I (CNI minimisation)	£52,339	–£6132	5.565	–0.004	£1,576,937
SRL II (CNI avoidance)	£61,490	+£3019	5.553	–0.016	Dominated by TAC
TAC	£58,471	–	5.569	–	–
TAC 'specials'	£72,945	+£14,474	5.564	–0.001	Higher cost similar QALYs
BEL	£75,726	+£17,255	5.551	–0.014	Dominated by TAC

Chapter 6 Discussion

Statement of principal findings

Aim

The remit for this report was to review and update the evidence used to inform the current NICE guidance (TA99)[1] on the clinical effectiveness and cost-effectiveness of immunosuppressive therapies in renal transplantation in children and adolescents. The systematic review and economic evaluation developed to support current NICE guidance TA99 was published by Yao *et al.*[2] in 2006. We have incorporated relevant evidence presented in this previous report and report new evidence. This includes a new decision analytic model of kidney transplantation outcomes to investigate which regimen is the most cost-effective option.

In this section, we do not restate the previous evidence, but assume that the discussion is read in the context of the previous evidence summaries and the decisions which followed from them. The conclusions focus on implications of the new clinical effectiveness and cost-effectiveness evidence for service provision.

Clinical effectiveness systematic review

Three RCTs are included in the clinical effectiveness systematic review presented in this report: one new RCT[73] and two RCTs from the previous assessment.[75,77]

Four non-RCTs are included in our review.[80–83] All of these were also included in the previous assessment by Yao *et al.* 2006.[2] No new non-randomised studies were identified in our searches.

Induction therapy

Two RCTs of induction therapy (reported in four publications and one abstract) evaluating BAS in children and adolescents were identified in the review.[73,75] No RCTs were identified that evaluated r-ATG in children and adolescents.

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

We found no significant difference in survival, graft loss, graft function, incidence of BPAR or time to BPAR between BAS and PBO/no induction.[73,75]

The results of the current review are similar to those of the previous HTA.[2]

Maintenance therapy

Randomised controlled trial evidence

One RCT of maintenance therapy (reported in three publications) evaluating TAC (compared with CSA) in children and adolescents was identified.[77] No RCTs were identified that evaluated TAC-PR, MMF, MPA, SRL, EVL or BEL in children and adolescents.

From the RCT, we found no significant difference in survival or graft loss between TAC and CSA.[77] However, a significantly higher graft function [mean eGFR of 71.5 ml/minute/1.73 m^2 (SD 22.9 ml/minute/1.73 m^2) in TAC vs. mean eGFR of 53.0 ml/minute/1.73 m^2 (SD 21.6 ml/minute/1.73 m^2) in CSA; t-test = 4.03; $p < 0.01$ at 4-year follow-up), and less BPAR (OR = 0.29, favours TAC, 95% CI 0.15 to 0.57 at 6-month follow-up)] was found in TAC compared with AZA at up to 4 years' follow-up.[77]

The results of the current review for survival, graft function and BPAR are similar to those of the previous HTA.[2] However, the RCT child and adolescent evidence identified in the previous HTA review[2] concluded that TAC lowered graft loss at 2- and 4-year follow-ups. The difference in these results is because we excluded graft loss due to death from all analyses. This was, first, to avoid double counting with another key outcome (mortality) and, second, because death-censored graft survival is a well-established clinical outcome, to which DWFG is intrinsically related. After the removal of graft loss due to death from the analyses, the evidence from Trompeter *et al.*[77] suggested a borderline (statistically non-significant) lower graft loss with TAC than CSA (OR = 0.41, favours TAC; 95% CI 0.16 to 1.00; and OR = 0.43, favours TAC; 95% CI 0.18 to 1.01 at 2- and 4-year follow-ups, respectively). In addition, although there were statistically significant treatment group differences in BPAR and AR at 6 months, the annual differences in AR were not statistically significant for years 2, 3 and 4.[77,79]

Non-randomised controlled trial evidence

Three non-RCTs evaluating MMF (compared with AZA) in children and adolescents were identified.[81–83] One non-RCT compared TAC + AZA with CSA + MMF.[80] No non-RCTs were identified that evaluated TAC-PR, MPA, SRL, EVL or BEL in children and adolescents.

We found no statistically significant difference in survival between MMF and AZA in the non-RCTs.[81,83] Similarly, no statistically significant difference in BPAR between MMF and AZA in the non-RCTs was identified.[81–83] A significantly lower graft loss was found in MMF than AZA at 1- to 5-year follow-ups in one of the two non-RCTs[83] (OR = 0.24 at 5-year follow-up; favours MMF; 95% CI 0.09 to 0.63). However, this was not confirmed by the other non-RCT at 1-year follow-up.[81] In addition, we found no statistically significant difference in survival, graft loss, BPAR, graft function and DGF between TAC + AZA and CSA + MMF in the non-RCTs.[80]

Adverse events

Induction

More infections were found in children treated with BAS than in those treated with PBO (OR = 2.23, favours PBO; 95% CI 1.03 to 4.68).[73] In addition, Grenda *et al.*[75] found that toxic nephropathy and abdominal pain were higher in the BAS arm than no induction ($p = 0.03$ and $p = 0.02$, respectively).[75] The previous HTA reported only post-transplant diabetes mellitus,[90] the rest of the data they found were confidential and excluded from the report.[2]

Maintenance therapy

There were no statistically significant differences between TAC and CSA for a range of AEs (any infections, UTIs, bacterial infections, viral infections, PTLD, solid tumour, hypertension, any AE and NODAT).[77] This is similar to the conclusions of the previous HTA.[2] In addition, there were no statistically significant differences between MMF and AZA for UTI, CMV infections, respiratory infections, herpes simplex, oral thrush and diarrhoea identified in the non-randomised evidence.[81] Similarly, no statistically significant differences between TAC + AZA and CSA + MMF in CMV infections and NODAT were identified in the non-randomised evidence.[80]

Previous technology assessment

The previous assessment (TA99) in 2006[1] found scarce RCT evidence on the clinical effectiveness of immunosuppressive agents in renal transplantation in children and adolescents. Only three child and adolescent RCTs were identified,[77,90] including the Wyeth submission 2005. Child and adolescent RCT evidence was identified for TAC,[77] BAS[90] and SRL (Wyeth submission 2005). Only non-RCT evidence was identified for MMF.[81,83,95] Finally, no child and adolescent evidence was identified for MPS and DAC (since the previous assessment, the marketing authorisation of DAC has been withdrawn at the request of the manufacturer). In addition, three non-RCTs were identified for BAS,[91–93] one non-RCT for TAC,[94] and one non-RCT compared TAC + AZA with MMF + CSA.[80]

The addition of induction therapy (BAS) was not found to be beneficial. The only child and adolescent induction therapy RCT found that the addition of BAS failed to significantly improve BPAR, graft function, graft loss, mortality and AE. Similarly, a meta-analysis of adult RCTs, found no significant difference in graft loss, mortality or AE. In general, compared with a triple regimen of CSA + AZA + CCS, the newer immunosuppressive agents were found to lead to lower rates of BPAR. One included child and adolescent RCT found that TAC led to lower BPAR at 6-month follow-up (RR = 0.42, favours TAC; 95% CI 0.26 to 0.69) and higher eGFR at 1-year follow-up ($p = 0.003$; 6-month follow-up data were not statistically significantly different) than CSA. This lower rate of BPAR with TAC was also shown in the meta-analysis of six adult RCTs at 1-year follow-up (RR = 0.61, favours TAC; 95% CI 0.53 to 0.71). The total level of withdrawal in children and adolescents was reduced in those receiving TAC compared with CSA (RR = 0.61, favours TAC; 95% CI 0.39 to 0.96). Pooled results of two adult RCTs found that compared with AZA, SRL reduced BPAR (RR = 0.60, favours SRL; 95% CI 0.45 to 0.80), improved eGFR (MD = 28.7, favours SRL; 95% CI 18.8 to 38.5) and increased the level of hyperlipidaemia (RR = 1.57, favours AZA; 95% CI 1.19 to 2.07).[257,258]

In summary, important gaps in the evidence concerning the impact of the newer immunosuppressants on AEs, long-term outcomes (including graft loss and survival), growth and overall health-related quality were identified by the previous technology assessment.

Published economic evaluations

Only one previous cost-effectiveness study of immunosuppressive regimens in children and adolescents was identified.[2] It was conducted by the Technology Assessment Group at the University of Birmingham as part of the previous NICE technology appraisal process. The study evaluated the cost-effectiveness of adding BAS induction to CNI maintenance therapy with TAC or CSA combined with AZA and steroids. The study also compared CSA with TAC when given in combination with AZA and steroids, and separately, MMF compared with AZA as part of the triple therapy containing CSA and steroids.

The analysis was conducted using a Markov model of a cohort with starting age ranging between 3 years and 13 years and a 10-year horizon. The study found that BAS induction resulted in higher costs and more QALYs than the alternative of no induction in both the TAC- and CSA-containing regimens. TAC was found to have a base-case ICER (incremental cost per QALY) of £145,000 relative to CSA, while MMF had an ICER of £195,000 relative to AZA when given as part of CSA-containing triple therapy. Although some of the methodological details were not provided in the study report,[2] the sensitivity analysis showed that these results were subject to a high degree of uncertainty. In particular, when the costs of dialysis were increased to reflect high possible levels of staff requirements of dialysis treatment in children and adolescents and the estimated treatment effects on AR based on data from adults were used, the ICER for the comparison of TAC compared with CSA triple therapy reduced to £35,000. This uncertainty, and the fact that the underlying model used in this analysis accounted for BPAR only as the surrogate measure of effectiveness (ignoring the role of renal function), suggests that new evidence on the cost-effectiveness of immunosuppressive regimens in children and adolescents is warranted.

Independent economic assessment

The PenTAG economic assessment included two types of analyses.

The first type of analysis used effectiveness estimates only from RCTs in children and adolescents and, therefore, can only evaluate the cost-effectiveness of BAS (vs. no induction) and TAC-IR (vs. CSA).

The second type of analysis extrapolated effectiveness estimates from RCTs in adults and allows for the cost-effectiveness of all interventions to be evaluated. Although effectiveness estimates in these analyses were restricted to adults, a significant amount of evidence from children and adolescents was used, including baseline characteristics, costs, baseline graft and overall survival, and the relationship between graft function and graft survival. The analysis produced different results to those in the parallel HTA for adults to inform an update of NICE guidance TA85.

Neither type of analysis is presented as a preferred base case because both have their deficiencies.

Induction agents

Using effectiveness estimates from randomised controlled trials in children and adolescents

Analyses based on evidence from RCTs in children and adolescents led to contradictory conclusions regarding the cost-effectiveness of BAS versus no induction.

In the analysis based on Grenda *et al.*,[75] BAS was predicted to be more effective and less costly than no induction (in combination with TAC-IR and AZA) using either a 2-year time horizon (corresponding to the trial follow-up) or 50-year time horizon. BAS was therefore dominant over no induction using a 2- or 50-year time horizon. The probability of BAS being cost-effective at £20,000–30,000 per QALY was 67.3–69.3% (50-year time horizon).

In the analysis based on Offner *et al.*,[73] BAS was predicted to be more costly and less effective than no induction (in combination with CSA and MMF) using either a 1-year time horizon (corresponding to the trial follow-up) or 50-year time horizon. BAS was therefore dominated by no induction at either time horizon. The probability of BAS being cost-effective at £20,000–30,000 per QALY was 6.7–9.4% (50-year time horizon).

The results of both analyses were robust to scenario analyses in which the surrogate relationship between AR and graft survival was removed, and the ninth centile for body weight for age was used (instead of median weight).

No economic analyses of r-ATG could be conducted based on RCTs in children and adolescents because no such RCTs were identified.

Using effectiveness estimates from randomised controlled trials in adults

Analyses based on evidence from RCTs in the adult population suggested that BAS induction is likely to be cost-effective at £20,000–30,000 per QALY compared with no induction and r-ATG induction.

Depending on the maintenance regimen used, the probability of BAS being cost-effective at £20,000–30,000 per QALY was 67.6–72.8%, while the probability of r-ATG being cost-effective at £20,000–30,000 per QALY was 27.0–32.4%. The probability of no induction being cost-effective at £20,000–30,000 per QALY was 0.0–0.2%.

Results were robust to removal of the surrogate relationship between AR and graft survival and/or assuming ninth centile weight according to age rather than median weight.

Maintenance agents

Using effectiveness estimates from randomised controlled trials in children and adolescents

An analysis based on a RCT in children and adolescents suggested that TAC-IR is likely to be cost-effective at £20,000–30,000 per QALY. In the analysis based on Trompeter *et al.*,[77] TAC-IR in combination with AZA was predicted to be more effective and less costly than CSA, whether using a 4-year time horizon (corresponding to the trial follow-up) or a 50-year time horizon. The probability of BAS being cost-effective at £20,000–30,000 per QALY was over 99.9% (50-year time horizon).

Results were robust to removal of the surrogate relationship between AR and graft survival, and to assuming ninth centile weight according to age rather than median weight.

No economic analyses of TAC-PR, MMF, MPS, SRL, EVL or BEL could be conducted based on RCTs in children and adolescents because no such RCTs were identified.

Using effectiveness estimates from RCTs in adults

Analyses using effectiveness estimates from RCTs in adults suggested that:

- TAC-IR is likely to be cost-effective at £20,000–30,000 per QALY (99.3–100.0% of PSA simulations)
- TAC-PR is unlikely to be cost-effective at £20,000–30,000 per QALY (expected to be dominated by TAC-IR and cost-effective in only 0.2–0.3% of PSA simulations)
- MMF is likely to be cost-effective at £20,000–30,000 per QALY when used with or without induction and in combination with CSA (cost-effective in 71.1–99.9% of PSA simulations)
- MMF is unlikely to be cost-effective at £20,000–30,000 per QALY when used with or without induction and in combination with TAC-IR (expected to be dominated by AZA and cost-effective in only 17.8–24.9% of PSA simulations)
- MPS is unlikely to be cost-effective at £20,000–30,000 per QALY when used in combination with BAS induction and CSA (ICER over £50,000 per QALY and cost-effective in 24.8–28.8% of PSA simulations)
- SRL is unlikely to be cost-effective at £20,000–30,000 per QALY when used in combination with BAS induction and MMF (expected to be dominated by CSA and TAC-IR and cost-effective in only 0.1% of PSA simulations)
- SRL is unlikely to be cost-effective at £20,000–30,000 per QALY when used in combination with TAC-IR (expected to be dominated by MMF and AZA and cost-effective in 0.0% of PSA simulations)
- EVL is unlikely to be cost-effective at £20,000–30,000 per QALY when used in combination with CSA (ICER over £600,000 per QALY and cost-effective in 0.0% of PSA simulations)
- BEL is unlikely to be cost-effective at £20,000–30,000 per QALY when used in combination with BAS induction and MMF (ICER over £600,000 per QALY and cost-effective in 0.0% of PSA simulations).

If ninth centile weight according to age is assumed (instead of median weight), in the deterministic analysis MPS becomes cost-effective in the deterministic analysis at £30,000 per QALY but not at £20,000 per QALY (ICER £27,000 per QALY). However, the assumed weight–dose relationship may not be accurate (the relationship was assumed to be directly proportional, e.g. patients weighing 50% of median adult weight would require 50% of the average adult dose). In addition, this assumes that kidney transplant patients do not move from the ninth centile of weight.

Results are robust to removal of the surrogate relationship between AR and graft survival, although the deterministic ICER for MPS is lowered to £33,000 per QALY.

Company submissions

The only cost-effectiveness analysis submitted by pharmaceutical companies was that of Astellas, the sponsor of two TAC-IR formulations (Prograf and Modigraf) and TAC-PR (Advagraf). It compared TAC-IR (Prograf) with TAC oral solutions (specials), SRL with MMF (CNI avoidance regimen), SRL with CSA (CNI minimisation regimen), EVL and BEL. TAC-IR was found to have an ICER relative to SRL CNI minimisation of £1,600,000. However, the company concluded that, given the minimal use of SRL in maintenance immunosuppression for kidney transplantations in England and Wales since the publication of the Symphony study, SRL is not a relevant comparator in these countries. As TAC dominated all other regimens it was deemed to be cost-effective. In a separate analysis, TAC-IR (Prograf) was compared with TAC-PR (Advagraf) by modelling the effects of the different adherence profiles between the two regimens on BPAR and, independently, on graft survival. Advagraf was found to result in lower costs and more QALYs than Prograf and was therefore recommended as the cost-effective treatment option.

Although these analyses were set out to meet the specification of the NICE reference case, they are subject to limitations that question the validity of the results and conclusions derived from them. The most important problem is that the model uses efficacy data from RCTs conducted in adult patients. The triple regimen of CSA + MMF + CCS was an important omission from the list of comparators and for which no reason was given in the submission. The unit cost values adopted for the analysis reflect drug list prices as opposed to prices actually paid by hospitals at a discount, as evidenced from eMIT data. Moreover, the drug dosages used for regimens other than MMF and EVL in the cost analysis were derived from those

specified by national prescribing guidelines for adults (BNF). In addition, by truncating the analysis at age 18 years, the sensitivity analysis conducted by Astellas based on starting age becomes meaningless. The model ignored important recent evidence about renal graft function as an important outcome for both costs and HRQoL. Further, the Markov model structure used by Astellas was based on annual cycles and assumed that within the first year after transplantation some patients would experience graft failure and retransplantation. Although some patients may experience this in reality, the way the model implemented this effectively assumed that all such patients would experience failure and retransplantation on day 1. This suggests that the cycle length chosen by Astellas inadequately reflected the patient experience that it sought to model. These limitations cast more uncertainty on the results than seems justified by the available data and knowledge of the disease, and suggest that more evidence addressing some of those limitations would benefit NICE recommendations in this area.

Comparison of the Peninsula Technology Assessment Group, Astellas and previous assessment group's model-based analyses

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

For comparing TAC-IR with TAC-PR, the PenTAG and Astellas analyses arrive at opposite conclusions (the Astellas analysis in favour of TAC-PR). This is primarily because of reliance on BPAR at 12 months post transplant as the main surrogate outcome driving QALY differences, different unit cost sources, and using outcome data from different trials to those on which the PenTAG analysis is based. The other analysis by Astellas, comparing a larger range of maintenance therapies (but omitting CSA), showed that SRL would be the most cost-effective treatment (although its report does not highlight this) whereas the PenTAG analysis shows TAC-IR to be the most cost-effective. However, there is considerable uncertainty and the Astellas analysis is based on very small differences in estimated QALYs.

It was virtually impossible to compare our model-based analyses with those by Yao *et al.*,[2] which informed NICE's current guidance on these drugs for children and adolescents (TA99).[1] This is because the Yao *et al.*[2] model is not fully described in a single report, the model itself is not available and even the results were reported only at the level of incremental costs and QALYs (i.e. no separately reported total costs and QALYs by model comparator). Their cost-effectiveness results also reflect differential discounting of future QALYs (1.5% per year) and costs (6%), and a limited 10-year time horizon. Despite these major differences, the findings in favour of the use of BAS as an induction therapy were similar between the Yao *et al.*[2] and current PenTAG analyses. In contrast, based on more adult RCT evidence and a 50-year time horizon, the PenTAG analysis found that TAC (with AZA) was more effective and less costly than CSA, and that MMF (with CSA) was more effective and less costly than AZA.

Strengths and limitations

Systematic review of studies of clinical effectiveness

Strengths

- The systematic review is conducted by an independent research team using the latest evidence.
- The literature searches were not restricted to child/adolescent populations so as to preserve the sensitivity of the searches and enable identifying RCTs for which mixed populations may have been recruited, but outcomes were reported according to age.

Limitations

- The number of included RCTs is low; child/adolescent-specific evidence was identified only for BAS and TAC-IR. No RCT evidence from children or adolescents was identified for r-ATG, TAC-PR, MMF, MPS, SRL, EVL and BEL.
- Databases were searched to identify systematic reviews of non-RCTs; however, individual non-RCTs were not searched for directly. It is likely that some non-RCT comparative evidence was missed. In addition, results from non-randomised studies may differ from RCT evidence. It can be argued that large, prospective and comprehensive case series may achieve high external validity, but we did not search for such studies.
- There is a possibility of spuriously positive tests for statistical significance arising from conducting multiple tests; we did not formally make adjustments for multiple testing. In addition, owing to a small number of included studies, publication bias were not assessed.
- For all included studies, less than half of the items constituting the quality appraisal assessment were adequately addressed in the research articles.
- No studies reporting on quality of life, adherence and growth were identified.
- No RCTs were found to support the subgroup analyses specified in the review protocol.

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

Economic model by the Peninsula Technology Assessment Group

Strengths

- This is an analysis conducted by an independent academic group, adhering to the NICE reference case when possible.
- All interventions and relevant allowable comparators are included and evaluated for cost-effectiveness.
- The natural history of disease is based on UK data, either published by the UK Renal Registry or from new analyses of the UK Transplant Registry standard data set.
- Important differences in the costs of dialysis between those under 19 years of age and adults have been included.
- Analyses have been conducted based on all available RCTs in children and adolescents eligible for inclusion.
- Additional analyses have been conducted based on a systematic review and network meta-analysis of RCTs in the adult population to allow comparison of all interventions even when no relevant RCTs in children and adolescents were identified.
- The surrogate relationship between graft function (eGFR) at 12 months and graft survival has been estimated from a study of children and adolescents.
- Pre-emptive retransplantations are included for a minority of KTRs following failure of the initial graft (avoiding dialysis which is costly and reduces HRQoL).
- Unit costs are those relevant to the NHS (e.g. CMU eMIT costs were used when available).
- Dosages for those under 18 years of age are based, when possible, on RCTs in children and adolescents, while dosages for those over 18 years of age are estimated from RCTs in adults.
- Probabilistic sensitivity analyses are presented to reflect the possible impact of parameter uncertainty.

Limitations

- Graft function has not been modelled over time, but is only estimated at 12 months in order to estimate graft survival thereafter. Reduced graft function can have an impact on HRQoL, but this is a limited effect until graft function is significantly reduced. For most regimens this would slightly reduce total QALYs (owing to reduced utility near the end of the graft life). For non-CNI regimens, it is possible that graft function would be better sustained and these regimens would not suffer a QALY loss and would therefore become more cost-effective (but this would be unlikely to lead to them being cost-effective at £20,000–30,000 per QALY).
- The cost-effectiveness of reducing or eliminating CCSs has not been evaluated. Some regimens (particularly those with antibody induction) could make it more possible to reduce or eliminate CCSs and the side effects associated with them. Given that significant effort is already invested to minimise maintenance dosage of CCSs, and that the cost of CCSs is minimal, it may be that avoidance would have only a small impact on cost-effectiveness.
- The cost of NHS-funded transport for haemodialysis patients has not been included. Kerr *et al.*[57] estimated transport costs of £2792 per year per haemodialysis patient (almost certainly mainly estimated from adults – costs may be higher for children as they may be more likely to be reimbursed and transport for parents is also reimbursed). Including transport costs would improve cost-effectiveness for regimens with better graft survival, as this delays and reduces time on dialysis.
- Treatment discontinuation and treatment switching are not modelled except in the events of graft failure (treatment discontinuation) and retransplantation (treatment switched to BAS + TAC + MMF regardless of previous treatment). Given the uncertainty about which treatments would be switched it is difficult to predict the effect of this on cost-effectiveness.
- Independence of AR, NODAT and eGFR at 12 months was assumed when predicting graft survival. It is possible that there would be correlation between these outcomes and that the proportion of patients with particularly unfavourable outcomes at 12 months (e.g. AR, NODAT and low eGFR) is underestimated, and likewise the proportion of patients with favourable 12-month outcomes. The impact of this on cost-effectiveness is uncertain.
- The surrogate relationships from AR and NODAT to graft survival are based on the adult population. It is not possible to estimate the impact of this on cost-effectiveness.
- Continuing immunosuppression following graft loss was not modelled, although it may occur in clinical settings. This would lead to slightly increased total costs, particularly for more expensive immunosuppressive agents, and would probably improve cost-effectiveness for less expensive agents.
- A proportional hazards assumption was made for the graft survival surrogate relationship. As a Weibull model was used, this is also equivalent to an accelerated failure time assumption. Alternative assumptions could have the HR being time dependent. We have not estimated the impact of alternative assumptions for graft survival on cost-effectiveness.
- No attempt was made to explicitly model adherence to immunosuppressive agents owing to the absence of evidence on this outcome in identified RCTs; it is thought that non-adherence is a significant cause of late AR and graft loss, but any gains in clinical effectiveness owing to improved adherence attributable to any individual agent or regimen are considered speculative. If any regimen robustly demonstrated improved long-term graft survival owing to improved adherence, this would result in improved cost-effectiveness for that regimen.
- It was assumed that there would be no treatment interactions between induction and maintenance therapies affecting clinical effectiveness outcomes; however, it is known that there is a pharmacokinetic interaction between BAS and MMF that results in prolonged BAS half-life (and similar interactions may exist between other induction and maintenance therapies). It is not possible to estimate the impact of such interactions on cost-effectiveness.

- Owing to inconsistent reporting of AEs in RCTs included in our systematic review, a limited range of AEs were modelled: NODAT, CMV infection, dyslipidaemia and anaemia (of these, anaemia was assumed not to vary between regimens). Malignancy, PTLD, proteinuria, hypertension, EBV infection, BKV infection, other infections and other AEs were not modelled. In addition, induction agents were assumed not to affect the incidence of AEs. Cost-effectiveness has been overestimated for regimens with increased risk of AEs (as these generally increase costs and lower quality of life).
- No drug wastage (e.g. part used packs/vials) was assumed for any intervention except BEL; the other agent for which wastage may be likely to occur is r-ATG. The cost-effectiveness of r-ATG may have been somewhat overestimated, but given the uncertainty in dosages in children and adolescents it is unlikely to be very significant.
- The generalisability of cost-effectiveness results hinges on the generalisability of the clinical effectiveness evidence. Most of the interventions being considered (except BAS and TAC-IR) have not been evaluated in RCTs of children and adolescents, but only in adults.

Areas of uncertainty

This technology assessment was conducted by an independent academic group, builds on existing secondary research and economic evaluations and adheres to the NICE reference case when possible. However, there are some important sources of uncertainty that impact on the conclusions:

- Most of the interventions being considered (except BAS and TAC-IR) have not been evaluated in published RCTs in children and adolescents.
- Follow-up in RCTs is limited and, therefore, it has not been possible to externally validate predicted survival differences between regimens.
- Randomised controlled trials have not provided evidence to support pre-specified subgroup analyses.
- There was no evidence to support analyses of the cost-effectiveness of interventions for children and adolescents unable to swallow tablets, for whom the following may or may not be appropriate:
    - TAC-IR oral suspension (Modigraf)
    - TAC-IR liquid (from specials manufacturers)
    - CSA solution (Neoral)
    - SRL solution (Rapamune)
    - AZA oral suspension (from specials manufacturers)
    - MMF oral suspension (CellCept).
- The costs for diabetes mellitus are highly uncertain, especially as the costs relate to the general adult diabetic population.
- It is not known whether or not NHS hospitals might secure discounts from list prices when these were assumed in the model (i.e. for BAS, r-ATG, TAC-PR, MPS, SRL, EVL and BEL).
- Combinations of immunosuppressive agents other than those considered could be used in clinical practice (the PenTAG model can be extended to include additional combinations).

Chapter 7 Conclusion

Cost-effectiveness estimates for immunosuppressive agents in children and adolescents based on effectiveness estimates in children and adolescents are available only for BAS and TAC-IR. For TAC-IR, the economic analysis based on one RCT[77] suggests that TAC-IR is cost-effective (vs. CSA, in combination with AZA) at £20,000–30,000 per QALY. For BAS, the analysis based on one RCT[75] found BAS to be dominant, while the analysis based on the other RCT[73] found BAS to be dominated.

Consideration of the cost-effectiveness of immunosuppressive agents in children and adolescents by extrapolating effectiveness estimates from the adult population (when there is considerable RCT evidence) suggests that, at a cost-effectiveness threshold of £20,000–30,000 per QALY, BAS and TAC-IR are cost-effective in all considered combinations, while MMF is cost-effective only if used in combination with CSA. BAS induction, TAC-IR and AZA were predicted to be cost-effective at £20,000–30,000 per QALY when all regimens were compared.

Implications for service provision

Basiliximab is used regularly as induction therapy for child/adolescent kidney transplant patients in the NHS, but is not routinely used in all centres. BAS is recommended as an option for induction therapy by current NICE guidance (TA99).[1] Conflicting results from the new economic analyses conducted mean that it is not possible to conclude whether induction with BAS is more or less costly than no induction, but the magnitude of the cost difference is unlikely to be great because induction therapy is administered only at the time of transplantation and is not an ongoing cost.

Rabbit anti-human thymocyte immunoglobulin is not currently used routinely in the NHS and was not considered by current NICE guidance TA99.[1] Economic analyses based on extrapolation from adult effectiveness estimates suggest that induction with r-ATG is more costly than induction with BAS, but less costly than no induction.

For maintenance therapy, TAC-IR is the current standard of care in the NHS and was recommended as an option for maintenance therapy by current NICE guidance TA99.[1] If TAC-PR, SRL or BEL were to be used in place of TAC-IR this would be likely to increase costs. It is also predicted that if CSA were to be used in place of TAC-IR this would lead to increased costs.

Azathioprine and MMF are both widely and routinely used in the NHS, although current NICE guidance (TA99) recommended only MMF as an option for maintenance therapy in a restricted population.[1] Economic analyses based on extrapolation from adult effectiveness estimates suggest that MMF is likely to be more costly than AZA in combination with TAC-IR. These analyses also suggest that replacing AZA or MPS with SRL, EVL or MMF would lead to increased costs.

Belatacept, which is administered intravenously, would be expected to add an extra burden to service providers although, given the limited number of children and adolescents receiving kidney transplantation, the additional burden of drug administration may be able to be accommodated without significant changes to staffing levels.

Suggested research priorities

It is recommended that high-quality primary research into the effectiveness of immunosuppressive agents for kidney transplantation in children and adolescents is conducted. This could be experimental or observational research.

In particular, a prospective study using the UK Renal Registry data set would be beneficial. Such a study would ideally include longitudinal recording of immunosuppression (combination and doses, reflecting changes as soon as they are made), as well as recording AR episodes and regular graft function measurements. A study would also need to ensure that all covariates for effectiveness outcomes (especially potential confounders) were recorded. Such a study could also include HRQoL measurements, preferably using a generic instrument validated in the child and adolescent population such as EQ-5D-Y or Child Health Utility 9 dimensions (CHU9D), and measurements of growth.

In addition, given the perceived importance of adherence to immunosuppression, it may also be desirable to establish an objective and practical measure of adherence so that any differences in adherence between regimens can be identified, as well as any effect this has on outcomes.

Finally, although limitations of non-RCT evidence were noted above, a systematic review of non-RCTs (not limited to search for systematic reviews of non-RCTs) to map all available child and adolescents' evidence on this topic is needed.

Acknowledgements

We would like to thank Fiona Gamston, Renal Transplant Sister Birmingham Children's Hospital; Dr Paul Tappenden, Deputy Technical Director, ScHARR Technology Assessment Group; Dr Jaime Peters, Research Fellow in Health Economic Modelling, PenTAG, University of Exeter; Martin Hoyle, Associate Professor in Health Economics, PenTAG, University of Exeter; and Mr Jacob Akoh, Consultant General and Transplant Surgeon, Plymouth Hospitals NHS Trust.

We would also like to acknowledge the help of Andy Salmon, for model checking, and Sue Whiffin for her administrative support, both from the University of Exeter Medical School.

Contributions of authors

Marcela Haasova provided overall project management and led the systematic review of clinical effectiveness, including assessment of all abstracts and titles for possible inclusion and meta-analysis for clinical effectiveness outcomes. Drafted or edited all sections of the report.

Tristan Snowsill led the design, development and execution of the economic model and wrote the sections on the design and results of the economic model. Contributed to the critique of the submission from Astellas and to the writing of the general discussion and conclusions.

Tracey Jones-Hughes assessed abstracts and titles for inclusion and contributed to the writing and editing of the report.

Louise Crathorne assessed titles and abstracts for inclusion in the effectiveness and cost-effectiveness review. Contributed to writing and editing of the cost-effectiveness systematic review.

Chris Cooper led the literature searching and contributed to writing and editing the report.

Jo Varley-Campbell assessed abstracts and titles for inclusion and contributed to the writing and editing of the report.

Ruben Mujica-Mota led the systematic review of economic evaluations and provided advice on design of the model.

Helen Coelho assessed titles and abstracts for inclusion and exclusion. Contributed to writing and editing the report.

Nicola Huxley assisted with identification of model parameters and contributed to writing and editing of the report.

Jenny Lowe critiqued and wrote summaries of the literature searches for the company submissions.

Jan Dudley provided clinical input into the design of the model, and advised on clinical matters.

Stephen Marks provided clinical input into the design of the model and advised on clinical matters.

Chris Hyde extracted data for inclusion in the clinical effectiveness systematic review.

Mary Bond had oversight of project management and the clinical effectiveness systematic review and contributed to the editing of the report.

Rob Anderson contributed to the interpretation and comparison of cost-effectiveness results and the writing and editing of the report. Overall director of the project and guarantor of the report.

Data sharing statement

This is a systematic review; therefore, there are no primary data to share. Further information can be obtained from the lead author if needed.

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Appendix 1 Literature searching strategies

Clinical effectiveness searches

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: Wednesday 7 January 2015.

Hits: 95.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	81,673
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34,747
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41,731
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36,959
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46,496
6	1 or 2 or 3 or 4 or 5	115,157
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1080
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6436
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	17,526
10	Tacrolimus/	13,172
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	228
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28,566
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	22,525
14	Sirolimus/	14,642
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3203
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	75,480
17	6 and 16	9696
18	Randomized Controlled Trial.pt.	405,805
19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	863,332
20	clinical trial.pt.	503,357
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	356,127
22	18 or 19 or 20 or 21	1,343,010

#	Searches	Results
23	6 and 16 and 22	2481
24	limit 23 to yr="2014 -Current"	95

Notes: N/A.

File: N/A.

Database: EMBASE

Host: Ovid.

Data parameters: 1974 to 5 January 2015.

Date searched: Wednesday 7 January 2015.

Hits: 272.

Search strategy

#	Searches	Results
1	kidney transplantation/	97,857
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51,138
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56,254
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52,314
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66,083
6	1 or 2 or 3 or 4 or 5	154,370
7	basiliximab/	6754
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2323
9	thymocyte antibody/	20,451
10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8932
11	tacrolimus/	54,178
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.	26,496
13	belatacept/	1003
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10,124
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36,223
17	rapamycin/	36,866
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29,130
19	everolimus/	14,653
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7135
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	149,906
22	6 and 21	25,851

#	Searches	Results
23	randomized controlled trial/	358,007
24	(random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	1,039,570
25	("controlled trial$" or "clinical trial$").ti,ab,ot.	434,667
26	23 or 24 or 25	1,314,663
27	22 and 26	3526
28	limit 27 to yr="2014 -Current"	272

Notes: N/A.

File: N/A.

Database: Cochrane CENTRAL

Host: Wiley Online Library.

Data parameters: Issue 12 of 12, December 2014.

Date searched: Wednesday 7 January 2015.

Hits: 75.

#	Searches	Results
1	MeSH descriptor: [Kidney Transplantation] this term only	3313
2	(Kidney* near/3 transplant*)	5959
3	(Renal near/3 transplant*)	4492
4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5192
6	#1 or #2 or #3 or #4 or #5	9188
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")	2587
10	MeSH descriptor: [Tacrolimus] this term only	1181
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")	87
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)	3477
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989")	2199
14	MeSH descriptor: [Sirolimus] this term only	1071
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")	939
16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	7471
17	#6 and #16 Publication Year from 2014 to 2015	102

Notes: this search strategy represents the whole of The Cochrane Library but only CENTRL was downloaded in this instance (CENTRAL 75, EED 2, Groups 2, CDSR 20, DARE 3).

File: N/A.

Database: Web of Science

Host: ISI Thompson Reuters.

Data parameters: 1900–2014.

Date searched: Wednesday 7 January 2015.

Hits: 183.

#	Results	Searches
16	183	#14 AND #13
		Refined by: PUBLICATION YEARS: (2014)
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
15	2,702	#14 AND #13
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
14	1,421,223	TOPIC: ((((random* or rct* or "controlled trial*" or "clinical trial*"))))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
13	13,127	#12 AND #5
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
12	142,824	#11 OR #10 OR #9 OR #8 OR #7 OR #6
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
11	5570	TOPIC: (((Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
10	111,240	TOPIC: (((“Mycophenolic acid” or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
9	486	TOPIC: (((Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
8	23,942	TOPIC: (((Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
7	6468	TOPIC: ((((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
6	1475	TOPIC: (((Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
5	125,548	#4 OR #3 OR #2 OR #1
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
4	53,666	TOPIC: ((((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
3	50,443	TOPIC: ((((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

#	Results	Searches
2	60,478	TOPIC: (((Renal near/3 transplant*)))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
1	47,055	TOPIC: (((Kidney* near/3 transplant*)))
		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

Notes: auto suggest was turned off. No records for 2015 on date of search.

File: N/A.

Database: Health Management Information Consortium (HMIC)

Host: Ovid.

Data parameters: 1979 to November 2014.

Date searched: Wednesday 7 January 2015.

Hits: 0.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	121
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	84
3	(Renal adj3 transplant$).ti,ab,kw,ot.	81
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	152
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	28
6	1 or 2 or 3 or 4 or 5	314
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	1
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	8
10	Tacrolimus/	0
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	0
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	23
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	11
14	Sirolimus/	0
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	2
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	33
17	6 and 16	3
18	Randomized Controlled Trial.pt.	0
19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab,ot.	10,914

#	Searches	Results
20	clinical trial.pt.	0
21	("controlled trial$" or "clinical trial$").ti,ab,ot.	5640
22	18 or 19 or 20 or 21	12,174
23	6 and 16 and 22	1
24	limit 23 to yr="2014 -Current"	0

Notes: N/A.

File: N/A.

Systematic reviews search strategy: clinical effectiveness searches

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: Ovid.

Data parameters: 1946 to present.

Date searched: Thursday 8 January 2015.

Hits: 10.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	81,679
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34,743
3	(Renal adj3 transplant$).ti,ab,kw,ot.	41,731
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	36,952
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	46,489
6	1 or 2 or 3 or 4 or 5	115,148
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1080
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6435
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	17,524
10	Tacrolimus/	13,170
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	228
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	28,558
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	22,498
14	Sirolimus/	14,646
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3201

#	Searches	Results
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	75,448
17	6 and 16	9694
18	(systematic adj3 review$).ti,ab,kw,ot.	67,562
19	17 and 18	50
20	limit 19 to yr="2014 -Current"	10

Notes: N/A.

File: N/A.

Database: EMBASE

Host: Ovid.

Data parameters: 1974 to 7 January 2015.

Date searched: Thursday 8 January 2015.

Hits: 19.

Search strategy

#	Searches	Results
1	kidney transplantation/	97,867
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51,145
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56,258
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52,323
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66,091
6	1 or 2 or 3 or 4 or 5	154,387
7	basiliximab/	6757
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2323
9	thymocyte antibody/	20,454
10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8933
11	tacrolimus/	54,192
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.	26,500
13	belatacept/	1004
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10,128
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36,231
17	rapamycin/	36,874
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29,138
19	everolimus/	14,659

#	Searches	Results
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7137
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	149,945
22	6 and 21	25,858
23	(systematic adj3 review$).ti,ab,kw,ot.	79,043
24	22 and 23	127
25	limit 24 to yr="2014 -Current"	19

Notes: N/A.

File: N/A.

Database: Cochrane CDSR and Database of Abstracts of Review of Effects

Host: Wiley Online Library.

Data parameters: CDSR Issue 1 of 12, January 2015, DARE and HTA Issue 4 of 4, October 2014.

Date searched: Thursday 8 January 2015.

Hits: 23 (102 in total – CDSR 20, DARE 3, CENTRAL 75, NHS EED 2, Groups 2, HTA 0).

Search strategy

#	Searches	Results
1	MeSH descriptor: [Kidney Transplantation] this term only	3313
2	(Kidney* near/3 transplant*)	5959
3	(Renal near/3 transplant*)	4492
4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5192
6	#1 or #2 or #3 or #4 or #5	9188
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")	2587
10	MeSH descriptor: [Tacrolimus] this term only	1181
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")	87
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)	3477
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989")	2200
14	MeSH descriptor: [Sirolimus] this term only	1071
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")	940
16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	7472
17	#6 and #16 Publication Year from 2014 to 2015	102

Notes: the search strategy represents the whole of The Cochrane Library. CDSR and DARE results downloaded but not CENTRAL or NHS EEDS as hits/results would have been picked up in the effectiveness and cost-effectiveness searches.

File: N/A.

Database: Health Management Information Consortium (HMIC)

Host: Ovid.

Data parameters: 1979 to November 2014.

Date searched: Thursday 8 January 2015.

Hits: 0.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	121
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	84
3	(Renal adj3 transplant$).ti,ab,kw,ot.	81
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	152
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	28
6	1 or 2 or 3 or 4 or 5	314
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	1
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	8
10	Tacrolimus/	0
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	0
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	23
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	11
14	Sirolimus/	0
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	2
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	33
17	6 and 16	3
18	16 and 17	3
19	limit 18 to yr="2014 -Current"	0

Notes: N/A.

File: N/A.

Ongoing studies

(Basiliximab OR Basiliximabum OR Simulect OR "interleukin 2 receptor antibody") AND (kidney* OR renal)

((rabbit AND Anti-thymocyte*) OR (rabbit AND Antithymocyte*) OR (rabbit AND thymocyte*) OR (rabbit* AND polyclonal) OR (rabbit* AND ATG) OR RATG OR thymoglobulin*) AND (kidney* OR renal)

(Tacrolimus OR Fujimycin OR Prograf OR Advagraf OR Adoport OR Capexion OR Modigraf OR Perixis OR Tacni OR Vivadex OR Protopic OR Tsukubaenolide OR "FK 506" OR "FK-506" OR "FK506" OR "fr-900506") AND (kidney* OR renal)

(Belatacept OR Nulojix OR "lea29y" OR "lea 29y" OR "bms 224818") AND (kidney* OR renal)

("Mycophenolic acid" OR MPA OR Mycophenolate OR Arzip OR CellCep* OR Myfenax OR Myfortic OR Mofetil) AND (kidney* OR renal)

(Sirolimus OR Rapamune OR Rapamycin OR "ay 22-989") AND (kidney* OR renal)

(Everolimus OR Zortress OR Certican OR Afinitor OR Evertor OR "SDZ RAD") AND (kidney* OR renal)

Cost-effectiveness searches

Database: MEDLINE

Host: Ovid.

Data parameters: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present.

Date searched: Thursday 15 January 2015.

Hits: 34.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	79,778
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	34,082
3	(Renal adj3 transplant$).ti,ab,kw,ot.	40,996
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	35,985
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	45,333
6	1 or 2 or 3 or 4 or 5	112,264
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	1054
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	6278
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw,ot.	16,989
10	Tacrolimus/	12,817
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	217

#	Searches	Results
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	27,735
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	20,509
14	Sirolimus/	13,403
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	3038
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	71,697
17	6 and 16	9482
18	Economics/	26,539
19	exp Economics, Pharmaceutical/	2535
20	exp Economics, Medical/	13,480
21	exp Economics, Hospital/	19,774
22	(pharmacoeconomic* or socioeconomics or economic$).ti,ab,kw.	180,610
23	ec.fs.	339,974
24	exp "Costs and Cost Analysis"/	183,530
25	Cost of Illness/	18,219
26	(cost* or cba or cea or cua or (value adj2 money) or pric$ or fiscal or funding or financial or finance or budget$ or (expenditure$ not Energy)).ti,ab,kw.	517,055
27	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	872,822
28	17 and 27	431
29	limit 28 to yr="2014 -Current"	34

Notes: N/A.

File: N/A.

Database: EMBASE

Host: Ovid.

Data parameters: EMBASE 1974 to 14 January 2015.

Date searched: Thursday 15 January 2015.

Hits: 139.

Search strategy

#	Searches	Results
1	kidney transplantation/	97,901
2	(Kidney$ adj3 transplant$).ti,ab,kw,ot.	51,174
3	(Renal adj3 transplant$).ti,ab,kw,ot.	56,282
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw,ot.	52,361
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw,ot.	66,121

#	Searches	Results
6	1 or 2 or 3 or 4 or 5	154,466
7	basiliximab/	6765
8	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw,ot.	2325
9	thymocyte antibody/	20,465
10	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw,ot.	8936
11	tacrolimus/	54,246
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.	26,521
13	belatacept/	1006
14	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw,ot.	555
15	mycophenolic acid/	10,141
16	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw,ot.	36,267
17	rapamycin/	36,926
18	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw,ot.	29,195
19	everolimus/	14,696
20	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw,ot.	7151
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	150,139
22	6 and 21	25,879
23	exp Economics/	220,609
24	models, economic/	105,274
25	exp health economics/	636,555
26	exp "Costs and Cost Analysis"/	263,409
27	Cost of illness/	14,621
28	resource allocation/	15,767
29	pe.fs.	62,540
30	(cost$ 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.	673,305
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	1,300,678
32	22 and 31	1475
33	limit 32 to yr="2014 -Current"	139

Notes: N/A.

File: N/A.

Database: Cochrane NHS EED

Host: Wiley Online Library.

Data parameters: Issue 4 of 4, October 2014.

Date searched: Thursday 15 January 2015.

Hits: 2.

Search strategy

ID	Search	Hits
1	MeSH descriptor: [Kidney Transplantation] this term only	3313
2	(Kidney* near/3 transplant*)	5959
3	(Renal near/3 transplant*)	4493
4	((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))	3839
5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	5193
6	#1 or #2 or #3 or #4 or #5	9189
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")	522
8	((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)	364
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")	2587
10	MeSH descriptor: [Tacrolimus] this term only	1181
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818")	87
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil)	3477
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989")	2200
14	MeSH descriptor: [Sirolimus] this term only	1071
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD")	941
16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	7473
17	#6 and #16 Publication Year from 2014 to 2015	102

Notes: this search strategy represents the whole of The Cochrane Library (NHS EED 2, Groups 2, CENTRAL 75, CDSR 20, DARE 3).

File: N/A.

Database: Web of Science

Host: ISI Thompson Reuters.

Data parameters: 1900–current.

Date searched: Thursday 15 January 2015.

Hits: 55.

Search strategy

#	Results	Searches
16	55	#14 AND #13 Refined by: PUBLICATION YEARS: (2014) *Timespan=All years* *Search language=Auto*
15	697	#14 AND #13 *Timespan=All years* *Search language=Auto*
14	Approximately 3,354,783	TOPIC: (((pharmacoeconomic* or socioeconomics or economic* or pric* or cost* or cba or cea or cua or "health utilit*" or "value for money"))) *Timespan=All years* *Search language=Auto*
13	Approximately 30,726	#12 AND #5 *Timespan=All years* *Search language=Auto*
12	Approximately 261,400	#11 OR #10 OR #9 OR #8 OR #7 OR #6 *Timespan=All years* *Search language=Auto*
11	Approximately 12,458	TOPIC: (((Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD"))) *Timespan=All years* *Search language=Auto*
10	Approximately 175,118	TOPIC: (((“Mycophenolic acid” or MPA or Mycophenolate or Arzip or CellCep* or Myfenax or Myfortic or Mofetil))) *Timespan=All years* *Search language=Auto*
9	554	TOPIC: (((Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818"))) *Timespan=All years* *Search language=Auto*

#	Results	Searches
8	Approximately 65,143	TOPIC: (((Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506")))
		Timespan=All years
		Search language=Auto
7	Approximately 21,632	TOPIC: ((((rabbit* near/3 Anti-thymocyte*) or (rabbit* near/3 Antithymocyte*) or (rabbit* near/3 thymocyte*) or (rabbit* near/3 polyclonal) or (rabbit* and ATG) or RATG or thymoglobulin*)))
		Timespan=All years
		Search language=Auto
6	2,283	TOPIC: (((Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody")))
		Timespan=All years
		Search language=Auto
5	Approximately 332,469	#4 OR #3 OR #2 OR #1
		Timespan=All years
		Search language=Auto
4	Approximately 158,169	TOPIC: ((((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))))
		Timespan=All years
		Search language=Auto
3	Approximately 122,313	TOPIC: ((((kidney or renal) near/3 (recipient* or dono* or donation* or replac*))))
		Timespan=All years
		Search language=Auto
2	Approximately 145,513	TOPIC: (((Renal near/3 transplant*)))
		Timespan=All years
		Search language=Auto
1	Approximately 163,622	TOPIC: (((Kidney* near/3 transplant*)))
		Timespan=All years
		Search language=Auto

Notes: auto suggest was turned off.

File: N/A.

Database: EconLit
Host: EBSCO*host*.

Data parameters: 1886–current.

Date searched: Thursday 15 January 2015.

Hits: 0.

Search strategy
(Basiliximab or Basiliximabum or Simulect or Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or Belatacept or Nulojix or "Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep or Myfenax or Myfortic or Mofetil or Sirolimus or Rapamune or Rapamycin or Everolimus or Zortress or Certican or Afinitor or Evertor) AND (kidney or renal)

Notes: N/A.

File: N/A.

Database: Health Economic Evaluations Database (HEED)
Host: via The Cochrane Library.

Date searched: Monday 14 April 2014.

Hits: 35.

(Basiliximab or Basiliximabum or Simulect or Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or Belatacept or Nulojix or "Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep or Myfenax or Myfortic or Mofetil or Sirolimus or Rapamune or Rapamycin or Everolimus or Zortress or Certican or Afinitor or Evertor) AND (kidney or renal)

Notes: the search recorded here was our initial search. HEED had closed by the time we updated the searches, so we were unable to update our HEED searches.

File: N/A.

Searches for utility data: search strategy
The searches for utility data are recorded below. These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft or renal dialysis) AND (terms for utility questionnaires such as SF36 or CHU 9D) and were run from database inception.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
Host: Ovid.

Data parameters: 1946 to present.

Date searched: 3 September 2014.

Volume: 714.

Search strategy

#	Searches	Results
1	Kidney Transplantation/	79,870
2	(Kidney$ adj3 transplant$).ti,ab,kw.	33,553
3	(Renal adj3 transplant$).ti,ab,kw.	40,747
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	35,663
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	45,183
6	1 or 2 or 3 or 4 or 5	112,067
7	Renal Dialysis/	73,812
8	Peritoneal Dialysis/	14,950
9	((kidney or renal or peritoneal) and (dialysis or dialyses)).ti,ab,kw.	48,847
10	7 or 8 or 9	107,010
11	6 or 10	201,694
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.	17,026
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	28,980
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: 3 September 2014.

Volume: 915

Search strategy

#	Searches	Results
1	kidney transplantation/	96,703
2	(Kidney$ adj3 transplant$).ti,ab,kw.	50,181
3	(Renal adj3 transplant$).ti,ab,kw.	55,376
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	51,117
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	64,806
6	1 or 2 or 3 or 4 or 5	151,605
7	renal replacement therapy/	36,722
8	peritoneal dialysis/	23,371
9	((kidney or renal or peritoneal) and (dialysis or dialyses)).ti,ab,kw.	64,637
10	7 or 8 or 9	97,785
11	6 or 10	224,149
12	(euroqol or euro qol or eq5d or eq 5d or EQ-5D or EQ-5D-Y).ti,ab,kw.	7316
13	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,kw.	1533
14	(sf10 or sf 10 or short form 10 or shortform 10 or sf ten or sften or shortform ten or short form ten).ti, ab,kw.	109
15	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,kw.	4428
16	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	35
17	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,kw.	333
18	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	23,918
19	Short Form 36/	12,496
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	43,846
27	11 and 26	991
28	limit 27 to english language	915

Notes: N/A.

File name: EMBASE.txt.

Database: The Cochrane Library (CENTRAL, HTA and NHS EED)

Host: Wiley Online Library.

Data parameters: CENTRAL Issue 8 of 12, August 2014; HTA and NHS EED Issue 3 of 4 July 2014.

Date searched: 3 September 2014.

Volume: 174.

Search strategy

ID	Search	Hits
1	MeSH descriptor: [Kidney Transplantation] this term only	3298
2	(Kidney* near/2 transplant*)	5497
3	(Renal near/2 transplant*)	3841
4	((kidney or renal) near/2 (recipient* or dono* or donation* or replac*))	3399
5	((graft* or allograft* or homograft* or allogeneic) and (kidney* or renal))	4785
6	#1 or #2 or #3 or #4 or #5	8307
7	MeSH descriptor: [Renal Dialysis] this term only	3496
8	MeSH descriptor: [Peritoneal Dialysis] this term only	417
9	((kidney or renal or peritoneal) and (dialysis or dialyses))	8888
10	#7 or #8 or #9	8888
11	#6 or #10	15,502
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)	11,746
14	(sf10 or sf 10 or short form 10 or shortform 10 or sf ten or sften or shortform ten or short form ten)	12,533
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	22,511
26	#11 and #25	847

Notes: N/A.

File name: Cochrane.txt.

Resource: ScHARRHUD

URL: (http://update-sbs.update.co.uk/scharr11/index.php?recordsN1&m=search).

Date searched: 3 September 2014.

Volume: 9.

Search strategy

kidney* or renal or dialysis

Notes: N/A.

File name: N/A.

Resource: EuroQoL website

URL: www.euroqol.org/eq-5d-references/reference-search.html.

Date searched: 3 September 2014.

Volume: 24.

Search strategy

kidney or renal or dialysis

Notes: 5 out of 24 were unique when de-duplicated against the EMBASE search.

File name: N/A.

Resource: HERC database of mapping studies

URL: www.herc.ox.ac.uk/downloads/mappingdatabase.

Date searched: 3 September 2014.

Volume: 0.

Search strategy

A hand-search of the Excel database was performed.

Notes: Dakin H. 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). 2013. URL: www.herc.ox.ac.uk/downloads/mappingdatabase.

Appendix 2 Excluded studies

TABLE 135 Excluded studies

Study	Reason
Health Technology Assessment database. Immunosuppressive therapy for renal transplantation in children and adolescents. In NICE 2006. HTA database Accession Number: 32006000316	Abstract
Health Technology Assessment database. Belatacept for prophylaxis of organ rejection in renal transplantation. In National Horizon Scanning Centre 2008. HTA database Accession Number: 32010000604	Abstract
Health Technology Assessment database. Everolimus (Certican) for prophylaxis of organ rejection in renal or cardiac transplantation. In National Horizon Scanning Centre 2008. HTA database Accession Number: 32010000590	Abstract
Health Technology Assessment database. Rapid HTA on the use of everolimus to prevent renal transplant rejection. In Department of Science and Technology - Brazilian Health Technology Assessment General Coordination (DECIT-CGATS) 2009. HTA database Accession Number: 32011000271	Abstract
Health Technology Assessment database. Tacrolimus (Advagraf®) for the prophylaxis of transplantrejection in adult kidney or liver allograft recipients and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients. In All Wales Therapeutics and Toxicology Centre (AWTTC), secretariat of the All Wales Medicines Strategy Group (AWMSG) 2009. HTA database Accession Number: 32012000410	Abstract
Health Technology Assessment database. Tacrolimus (Advagraf®). In All Wales Therapeutics and Toxicology Centre (AWTTC) 2011. HTA database Accession Number: 32012000361	Abstract
Health Technology Assessment database. Belatacept (Nulojix®). In All Wales Therapeutics and Toxicology Centre (AWTTC) 2012. HTA database Accession Number: 32012000600)	Abstract
Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, *et al.* Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *Lancet* 2011;**377**:837–47. [Erratum published in *Lancet* 2012;**380**:1994.]	No data
Albano L, Banas B, Klempnauer JL, Glyda M, Viklicky O, Kamar N, Optimising immunoSuppression After Kidney transplantation with ADVAGRAF Study Group. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. *Transplantation* 2013;**96**:897–903 [Erratum published in *Transplantation* 2014;**97**:e38.]	No data
Silva AP, Tonato E, Durao Jr M, Requiao-Moura L, Arruda E, Chinen R, *et al.* A randomized clinical trial of early conversion from tacrolimus to everolimus in deceased donor kidney transplantation. *Transpl Int* 2013;26:277–78	Abstract
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). *Mol Immunol* 2003;**39**:1095–100	Population
Abou-Jaoude MM, Irani-Hakime N, Ghantous I, Najm R, Afif C, Almawi WY. Cyclosporine microemulsion (Neoral) versus tacrolimus (FK506) as maintenance therapy in kidney transplant patients. *Transplant Proc* 2003;**35**:2748–9	Study design
Abou-Jaoude MM, Najm R, Shaheen J, Nawfal N, Abboud S, Alhabash M, *et al.* Tacrolimus (FK506) versus cyclosporine microemulsion (neoral) as maintenance immunosuppression therapy in kidney transplant recipients. *Transplant Proc* 2005;**37**:3025–8	Study design
Abramowicz D, Del Carmen Rial M, Vitko S, del Castillo D, Manas D, Lao M, *et al.* Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen: results of a five-year, prospective, randomized study. *J Am Soc Nephrol* 2005;**16**:2234–40	Population
Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ* 2003;**326**:789	Study design
Agha IA, Brennan DC. BK virus and current immunosuppressive therapy. *Graft* 2002;**5**:S65–72	Study design

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Ahlenstiel-Grunow T, Koch A, Großhennig A, Frömke C, Sester M, Sester U, *et al.* A multicenter, randomized, open-labeled study to steer immunosuppressive and antiviral therapy by measurement of virus (CMV, ADV, HSV)-specific T cells in addition to determination of trough levels of immunosuppressants in pediatric kidney allograft recipients (IVIST01-trial): study protocol for a randomized controlled trial. *Trials* 2014;**15**:324	Study design
Ahsan N, Holman MJ, Jarowenko MV, Razzaque MS, Yang HC. Limited dose monoclonal IL-2R antibody induction protocol after primary kidney transplantation. *Am J Transplant* 2002;**2**:568–73	Intervention
Akalin E, Ames S, Sehgal V, Murphy B, Bromberg JS, Fotino M, Friedlander R. Intravenous immunoglobulin and thymoglobulin induction treatment in immunologically high-risk kidney transplant recipients. *Transplantation* 2005;**79**:742	Abstract
Al Najjar A, Etienne I, Le Pogamp P, Bridoux F, Le Meur Y, Toupance O, *et al.* Long-term results of monoclonal anti-Il2-receptor antibody versus polyclonal antilymphocyte antibodies as induction therapy in renal transplantation. *Transplant Proc* 2006;**38**:2298–9	Abstract
Al Najjar A, Etienne I, Toupance O, Westeel PF, Hurault De Ligny B, Rerolle JP, *et al.* Long term follow-up of a multicenter randomized trial comparing a CNI-free regimen with sirolimus (SRL) to a cyclosporine based regimen: the spiesser study. *Am J Transplant* 2010;**10**:505	Abstract
Albano L, Alamartine E, Toupance O, Moulin B, Merville P, Rerolle JP, *et al.* Conversion from everolimus with low-exposure cyclosporine to everolimus with mycophenolate sodium maintenance therapy in kidney transplant recipients: a randomized, open-label multicenter study. *Ann Transplant* 2012;**17**:58–67	Population
Albano L, Banas B, Kamar N. Safety and renal function in tacrolimus prolonged release vs tacrolimus immediate release-based therapy in renal transplantation – The OSAKA study. *Am J Transplant* 2011;**11**:125	Abstract
Albano L, Banas B, Kamar N. Outcomes with tacrolimus-based immunosuppression after kidney transplantation with standard-or extendedcriteria donor organsthe osaka study. *Transpl Int* 2013;**26**:59	Abstract
Albano L, Banas B, Rostaing L. Efficacy and optimised dosing in tacrolimus prolonged release vs tacrolimus immediate release-based therapy in renal transplantation – The OSAKA study. *Am J Transplant* 2011;**11**:125	Abstract
Albano L, Banas B, Klempnauer JL, Glyda M, Viklicky O, Kamar N, Optimising immunoSuppression After Kidney transplantation with ADVAGRAF Study Group. OSAKA trial: a randomized, controlled trial comparing tacrolimus QD and BD in kidney transplantation. *Transplantation* 2013;**96**:897–903	Population
Alberú J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M, *et al.* Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* 2011;**92**:303–10	Population
Alemi M, Samadzadeh B, Bardideh A, Heidarnejadiyan J, Torkaman Asadi F. The effect of preoperative induction therapy with mycophenolate mofetil in early outcomes of living-donor renal allograft transplantation. *Int J Urol* 2012;**19**:163	Abstract
Alloway R, Mulgaonkar S, Ueda K, Cohen D, Kaplan B. A Phase 2 randomized study of the pharmacokinetics, safety and efficacy of LCP-Tacro tablets once-a-day vs Prograf capsules twice-a-day in de novo kidney transplants. *Am J Transplant* 2011;**11**:355	Abstract
Alloway R, Steinberg S, Khalil K, Gourishankar S, Miller J, Norman D, *et al.* Conversion of stable kidney transplant recipients from a twice daily Prograf-based regimen to a once daily modified release tacrolimus-based regimen. *Transplant Proc* 2005;**37**:867–70	Study design
Alloway RR, Mulgaonkar S, Bowers VD, Stevenson KRU, Cohen DJ, Katz E, *et al.* A phase 2b, open-label, multi-center, prospective, randomized study to compare the pharmacokinetics and safety of lcp-tacro (TM) tablets once-a-day to prograf (R) capsules twice-a-day in de novo kidney transplant patients. *Am J Transplant* 2009;**9**:414	Abstract
Alloway RR, Sadaka B, Trofe-Clark J, Wiland A, Bloom RD. Pharmacokinetic comparison of generic tacrolimus (hecoria (TM)) versus prograf (R) in stable kidney transplant recipients: a randomized, crossover study. *Am J Transplant* 2012;**12**:406	Abstract
Alpay N. Conversion from calcineurin inhibitors to everolimus resulted in decrease of serum TGF-beta and urinary ngal in renal transplant recipients. *Nephrol Dial Transplant* 2013;**28**:i500–1	Abstract
Alvarado A, Chhabra D, Wang E, Najafian N, Friedewald J, Ho B, *et al.* Prospective randomized study to evaluate the feasability of CNI elimination with conversion to sirolimus in prednisone-free immunosuppressive regimen. *Am J Transplant* 2012;**12**:42	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Andrassy J, Hoffmann VS, Rentsch M, Stangl M, Habicht A, Meiser B, *et al.* Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? a systematic review and meta-analysis. *Transplantation* 2012;**94**:1208–17	Duplicate
Andres A, Bloom R, Bunnapradist S, Cassuto E, Chan L, Hart M, *et al.* Randomized, multicenter study on the safety and efficacy of enteric-coated mycophenolate sodium combined with basiliximab and low-or standard dose of tacrolimus in de novo renal transplant patients. *Transpl Int* 2007;**20**:217	Abstract
Andrés A, Budde K, Clavien PA, Becker T, Kessler M, Pisarski P, *et al.* A randomized trial comparing renal function in older kidney transplant patients following delayed versus immediate tacrolimus administration. *Transplantation* 2009;**88**:1101–8	Study design
Andres A, del Castillo D, Gainza FJ, Purroy A, Bustamante J, Rengel M, *et al.* Comparison of a secuential therapy with tacrolimus versusa standar triple therapy in aged kidney transplantation with aged donors: results of a multicenter, prospective and randomized trial (Estrella Study). *Am J Transplant* 2007;**7**:443	Abstract
Andrés A, Delgado-Arranz M, Morales E, Dipalma T, Polanco N, Gutierrez-Solis E, *et al.* Extended-release tacrolimus therapy in de novo kidney transplant recipients: single-center experience. *Transplant Proc* 2010;**42**:3034–7	Study design
Andres I, Font B, Mora S, Lahoz R, Ortega F. Quality of life of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant recipients with gastrointestinal tract complaints to mycophenolate mofetil (MMF)Myvida study. *Value Health* 2009;**12**:A311	Abstract
Anil Kumar MS, Heifets M, Fyfe B, Saaed MI, Moritz MJ, Parikh MH, Kumar A. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. *Transplantation* 2005;**80**:807–14	Population
Anil Kumar MS, Irfan Saeed M, Ranganna K, Malat G, Sustento-Reodica N, Kumar AM, Meyers WC. Comparison of four different immunosuppression protocols without long-term steroid therapy in kidney recipients monitored by surveillance biopsy: five-year outcomes. *Transpl Immunol* 2008;**20**:32–42	Population
Anonymous. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014;**349**:g7543	No data
Perez-Simon J, Sr., Martino R, Parody R, Cabrero M, Lopez-Corral L, Valcarcel D, *et al.* The combination of siromilus plus tacrolimus (SiTac) improves the results of cyclosporine plus mycophenolate mofetil (CsAMMF) after reduced intensity conditioning (RIC) unrelated donor allogeneic transplantation. *Blood* 2011;**118**:406–7	Abstract
Araki M, Flechner SM, Ismail HR, Flechner LM, Zhou L, Derweesh IH, *et al.* Posttransplant diabetes mellitus in kidney transplant recipients receiving calcineurin or mTOR inhibitor drugs. *Transplantation* 2006;**81**:335–41	Study design
Arns W, Breuer S, Choudhury S, Taccard G, Lee J, Binder V, *et al.* Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. *Clin Transplant* 2005;**19**:199–206	Outcome
Arns W, Neumayer HH, Lehner F, Witzke O, Sommerer C, Kliem V, *et al.* Herakles at month 24: follow-up results on efficacy and safety of three different treatment regimens in de novo renal transplant patients demonstrate options for individualized immunsosuppression. *Transpl Int* 2013;**26**:21	Abstract
Arns W, Sommerer C, Witzke O, Lehner F, Zeier M, Neumayer HH, *et al.* Efficacy and safety of three different treatment regimens in de novo renal transplant patients: results of the herakles trial. *Transplantation* 2012;**94**:995	Abstract
Arora S, Tangirala B, Osadchuk L, Sureshkumar KK. Belatacept : a new biological agent for maintenance immunosuppression in kidney transplantation. *Expert Opin Biol Ther* 2012;**12**:965–79	Study design
Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Hené RJ, *et al.* Randomized conversion from cyclosporine to tacrolimus in renal transplant patients: improved lipid profile and unchanged plasma homocysteine levels. *Transplant Proc* 2002;**34**:1793–4	Population
Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, *et al.* Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *J Am Soc Nephrol* 2003;**14**:1880–8	Population
Artz MA, Boots JM, Ligtenberg G, Roodnat JI, Christiaans MH, Vos PF, *et al.* Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. *Am J Transplant* 2004;**4**:937–45	Population

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Åsberg A, Apeland T, Reisaeter AV, Foss A, Leivestad T, Heldal K, *et al.* Long-term outcomes after cyclosporine or mycophenolate withdrawal in kidney transplantation - results from an aborted trial. *Clin Transpl* 2013;**27**:E151–6	Population
Asberg A, Midtvedt K, Line PD, Narverud J, Holdaas H, Jenssen T, *et al.* Calcineurin inhibitor avoidance with daclizumab, mycophenolate mofetil, and prednisolone in DR-matched de novo kidney transplant recipients. *Transplantation* 2006;**82**:62–8	Comparator
Baas MC, Gerdes VE, Ten Berge IJ, Heutinck KM, Florquin S, Meijers JC, Bemelman FJ. Treatment with everolimus is associated with a procoagulant state. *Thromb Res* 2013;**132**:307–11	Outcome
Baas MC, Kers J, Florquin S, de Fijter JW, van der Heide JJ, van den Bergh Weerman MA, *et al.* Cyclosporine versus everolimus: effects on the glomerulus. *Clin Transplant* 2013;**27**:535–40	Study design
Baas MC, Kers J, Florquin S, Van Den Bergh Weerman MA, Ten Berge IJM, Bemelman FF. Prolonged treatment with everolimus does not induce podocyte damage and leaves the glomerular basement membrane intact. *Am J Transplant* 2011;**11**:317	Abstract
Baboolal K, Zaiac M, Zamauskaite A, Newstead C. This multicentre, randomised study comparing conversion from calcineurin inhibitors (CNIs) to sirolimus versus standard therapy in renal allograft recipients showed a lower rate of development of subsequent malignant disease in the group receiving sirolimus. *Am J Transplant* 2009;**9**:238	Abstract
Baczkowska T, Perkowska-Ptasińska A, Sadowska A, Lewandowski Z, Nowacka-Cieciura E, Cieciura T, *et al.* Serum TGF-beta1 correlates with chronic histopathological lesions in protocol biopsies of kidney allograft recipients. *Transplant Proc* 2005;**37**:773–5	Intervention
Bakker RC, Hollander AA, Mallat MJ, Bruijn JA, Paul LC, de Fijter JW. Conversion from cyclosporine to azathioprine at three months reduces the incidence of chronic allograft nephropathy. *Kidney Int* 2003;**64**:1027–34	Intervention
Bakr MA, Gheith OA, Ismael AM, Baz ME, Shehab El-Dein AB, Ghoneim MA. Rescue immunosuppressive therapies in living-related renal allotransplant: a long-term prospective randomized evaluation. *Exp Clin Transplant* 2008;**6**:48–53	Population
Balbontin FG, Kiberd B, Belistky P, Singh D, Fraser A, Lawen JG. One year randomized study comparing cyclosporine microemulsion with C2 monitoring and tacrolimus in de novo kidney transplantation. *Am J Transplant* 2004;**4**:236–7	Abstract
Balbontin FG, Kiberd B, Belitsky P, Singh D, Fraser A, Lawen JG. Six month randomized study comparing cyclosporine microemulsion with C2 monitoring and tacrolimus in de novo kidney transplantation. *J Urol* 2004;**171**:515	Outcome
Banas B, Albano L, Cassuto E, Glyda M, Klempnauer J, Lehner F, *et al.* The impact of acute rejection on renal function-perspectives from the OSAKA study. *Transplantation* 2012;**94**:983	Abstract
Banas B, Boger CA, Lehner F. Efficacy, safety and optimised dosing in tacrolimus prolonged release vs tacrolimus immediate release-based therapy in renal transplantation-the Osaka study. *Transpl Int* 2011;**24**:35	Abstract
Banas B, Cassuto E, Glyda M, Kamar N, Klempnauer J, Lehner F, *et al.* Selection of appropriate composite endpoints is critical for assessing efficacy failure-perspectives from the OSAKA study. *Transplantation* 2012;**94**:3	Abstract
Banas B, Kamar N, Lehner F, Albano L, Glyda M, Viklicky O. Acute rejection in renal transplantation recipients treated with tacrolimus prolonged release-and immediate release-based therapy – The osaka study (optimizing immunosuppression after kidney transplantationwith advagraf). *Transpl Int* 2011;**24**:38–9	Abstract
Banas B, Kruger B, Viklicky O. Tacrolimus prolonged release optimises exposure during the immediate postoperative period. *Transplantation* 2012;**94**:81–2	Abstract
Bansal D, Yadav AK, Kumar V, Minz M, Sakhuja V, Jha V. Deferred pre-emptive switch from calcineurin inhibitor to sirolimus leads to improvement in GFR and expansion of T regulatory cell population: a randomized, controlled trial. *PLOS ONE* 2013;**8**:e75591	Study design
Barsoum RS, Morsey AA, Iskander IR, Morgan MM, Fayad TM, Atalla NT, *et al.* The Cairo kidney center protocol for rapamycin-based sequential immunosuppression in kidney transplant recipients: 2-year outcomes. *Exp Clin Transplant* 2007;**5**:649–57	Population
Bataille S, Moal V, Gaudart J, Indreies M, Purgus R, Dussol B, *et al.* Cytomegalovirus risk factors in renal transplantation with modern immunosuppression. *Transpl Infect Dis* 2010;**12**:480–8	Outcome

TABLE 135 Excluded studies (*continued*)

Study	Reason
Becker LE, Xue Y, Gross ML, Waldherr R, Schwenger V, Zeier M, *et al.* Evolution of allograft fibrosis and related markers in kidney transplant patients under treatment with cyclosporine and everolimus. *NDT Plus* 2010;**3**:iii527	Abstract
Bemelman FJ, de Maar EF, Press RR, van Kan HJ, ten Berge IJ, Homan van der Heide JJ, de Fijter HW. Minimization of maintenance immunosuppression early after renal transplantation: an interim analysis. *Transplantation* 2009;**88**:421–8	Population
Benfield MR, Tejani A, Harmon WE, McDonald R, Stablein DM, McIntosh M, Rose S, CCTPT Study Group. A randomized multicenter trial of OKT3 mAbs induction compared with intravenous cyclosporine in pediatric renal transplantation. *Pediatr Transplant* 2005;**9**:282–92	Study design
Bertoni E, Carta P, Salvadori M. Cyclosporine very low dose with everolimus high dose is associated with excellent outcomes in renal transplant patients. *Transpl Int* 2011;**24**:112	Abstract
Bertoni E, Larti A, Rosso G, Zanazzi M, Di Maria L, Salvadori M. Good outcomes with cyclosporine very low exposure with everolimus high exposure in renal transplant patients. *J Nephrol* 2011;**24**:613–8	Population
Birnbaum LM, Lipman M, Paraskevas S, Chaudhury P, Tchervenkov J, Baran D, *et al.* Management of chronic allograft nephropathy: a systematic review. *Clin J Am Soc Nephrol* 2009;**4**:860–5	Population
Blydt-Hansen TD, Gibson IW, Birk PE. Histological progression of chronic renal allograft injury comparing sirolimus and mycophenolate mofetil-based protocols. A single-center, prospective, randomized, controlled study. *Pediatr Transplant* 2010;**14**:909–18	No data
Boggi U, Danesi R, Vistoli F, Del Chiaro M, Signori S, Marchetti P, *et al.* A benefit-risk assessment of basiliximab in renal transplantation. *Drug Saf* 2004;**27**:91–106	Study design
Bolin P, Shihab FS, Mulloy L, Henning AK, Gao J, Bartucci M, *et al.* Optimizing tacrolimus therapy in the maintenance of renal allografts: 12-month results. *Transplantation* 2008;**86**:88–95	Study design
Borda B, Lengyel C, Várkonyi T, Kemény E, Ottlakán A, Kubik A, *et al.* Side effects of the calcineurin inhibitor, such as new-onset diabetes after kidney transplantation. *Acta Physiol Hung* 2014;**101**:388–94	Population
Bouwes Bavinck J. Prevention of skin cancer in organ transplant recipients. *Br J Dermatol* 2012;**167**:e2	Abstract
Bowman LJ, Edwards A, Brennan DC. The role of rabbit antithymocyte globulin in renal transplantation. *Exp Opin Orphan Drug* 2014;**2**:971–87	Study design
Brar JE, Nader ND. Immune minimization strategies in renal transplantation. *Immunol Invest* 2014;**43**:807–18	Study design
Brennan DC, Koch MJ. Is mycophenolate mofetil really necessary in renal transplantation? A review of the MYSS follow-up study. *Nat Clin Pract Nephrol* 2007;**3**:602–3	Abstract
Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, *et al.* Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005;**5**:582–94	Population
Brennan DC, Daller JA, Lake KD, Cibrik D, Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006;**355**:1967–77	Population
Bresnahan B, Vincenti F, Grinyo J, Charpentier B, Russo GD, Garg P, *et al.* Renal benefit of belatacept versus cyclosporine in kidney transplant patients is not impacted by acute rejection (BENEFIT study). *Am J Transplant* 2010;**10**:14	Abstract
Brian Stevens R, Skorupa JY, Rigley TH, Sandoz JP, Kellogg A, Miller N, *et al.* Calcineurin-inhibitor withdrawalvs. Minimization after kidney transplantation is safe but does not improve renalfunction; 5-year results of a prospective, randomized trial. *Am J Transplant* 2010;**10**:505	Abstract
Budde K, Arns W, Sommerer C, Reinke P, Eisenberger U, Fischer W, *et al.* Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 2 years follow-up of the zeus trial. *Am J Transplant*. 2010;**10**:503	Abstract
Budde K, Arns W, Sommerer C, Reinke P, Eisenberger U, Vogel EM, *et al.* Improved renal function of an Everolimus/Enteric-Coated Mycophenolate Sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 3 years follow-up of the ZEUS trial. *Am J Transplant* 2011;**11**:66	Abstract
Budde K, Arns W, Sommerer C, Lehner F, Zeier M, Neumayer H, *et al.* Superior renal function in an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus: follow-up of the herakles study at month 24. *Am J Transplant* 2013;**13**:310–1	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, *et al.* Analysis of renal function in everolimus/enteric-coated mycophenolate sodium treated de novo renal transplant recipients after calcineurin inhibitor withdrawal: the ZEUS study. *Am J Transplant* 2009;**9**:259	Abstract
Budde K, Becker T, Arns W, Sommerer C, Reinke P, Eisenberger U, *et al.* Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *Lancet* 2011;**377**:837–47	Population
Budde K, Bunnapradist S, Rostaing L. A phase III randomized trial of conversion to once-daily extended release meltdose tacrolimus tablets (LCP-tacro) from twice-daily tacrolimus capsules (prograf): efficacy results from an analysis of specific patient sub-populations. *Transplantation* 2012;**94**:984	Abstract
Budde K, Bunnapradist S, Grinyo JM, Ciechanowski K, Denny JE, Silva HT, Rostaing L, Envarsus study group. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of Phase III, double-blind, randomized trial. *Am J Transplant* 2014;**14**:2796–806	Population
Budde K, Curtis J, Knoll G, Chan L, Neumayer HH, Seifu Y, Hall M, ERL B302 Study Group. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. *Am J Transplant* 2004;**4**:237–43	Population
Budde K, Glander P, Diekmann F, Dragun D, Waiser J, Fritsche L, *et al.* Enteric-coated mycophenolate sodium: safe conversion from mycophenolate mofetil in maintenance renal transplant recipients. *Transpl Proc* 2004;**36**:524S–7S	Population
Budde K, Knoll G, Curtis J, Kahana L, Pohanka E, Seifu Y, Neumayer HH. Safety and efficacy after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium: results of a 1-year extension study. *Transplant Proc* 2005;**37**:912–5	Study design
Budde K, Knoll G, Curtis J, Chan L, Pohanka E, Gentil M, *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).] *Nieren- und Hochdruckkrankheiten* 2006;**35**:454–64	Study design
Budde K, Knoll G, Curtis J, Chan L, Pohanka E, Gentil M, *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). *Clin Nephrol* 2006;**66**:103–11	Language
Budde K, Lehner F, Arns W, Reinke P, Eisenberger U, Paulus EM, *et al.* Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 4 years follow-up of the zeus trial. *Am J Transplant* 2012;**12**:298	Abstract
Budde K, Lehner F, Sommerer C, Arns W, Reinke P, Eisenberger U, *et al.* Conversion from cyclosporine to everolimus at 4.5 months posttransplant: 3-year results from the randomized ZEUS study. *Am J Transplant* 2012;**12**:1528–40	Population
Budde K, Sommerer C, Haller H, Arns W, Kramer S, Vogel EM, *et al.* Renal function of an Everolimus based therapy after Calcineurin Inhibitor withdrawal in maintenance renal transplant recipients: 2 year data of the APOLLO trial. *Am J Transplant* 2011;**11**:411	Abstract
Budde K, Sommerer C, Haller H, Suwelack B, May C, Paulus EM, *et al.* Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 3 year data of the apollo trial. *Am J Transplant* 2012;**12**:298	Abstract
Budde K, Sommerer C, Reinke P, Haller H, Arns W, Witzke O, *et al.* Outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 4 year data of the apollo trial. *Am J Transplant* 2013;**13**:311–2	Abstract
Budde K, Witzke O, Sommerer C, Reinke P, Eisenberger U, Paulus E, *et al.* Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 5 years follow-up of the zeus trial. *Am J Transplant* 2013;**13**:35–6	Abstract
Budde K, Zeier M, Haller H, Arns W, Kramer S, E MV, *et al.* Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients. *Am J Transplant* 2010;**10**:504	Abstract
Büchler M, Caillard S, Barbier S, Thervet E, Toupance O, Mazouz H, *et al.* Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin, mycophenolate mofetil and a 6-month course of steroids. *Am J Transplant* 2007;**7**:2522–31	Population
Bunnapradist S, Danovitch GM. Minimizing ciclosporin in renal transplant recipients on daclizumab, mycophenolate and steroids. *Nat Clin Pract Nephrol* 2007;**3**:426–7	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Bunnapradist S, Ciechanowski K, West-Thielke P, Mulgaonkar S, Rostaing L, Vasudev B, Budde K, MELT investigators. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. *Am J Transplant* 2013;**13**:760–9	Population
Burke GW. Randomized Trial of 2 Antibody Induction Steroid Avoidance Protocols Accompanied by Maintenance Therapy with Prograf and Myfortic. URL: clinicaltrials.gov/ct2/show/NCT01172418 (accessed 25 July 2014)	Comparator
Burke GW, Ciancio C, Blomberg BB, Rosen A, Suzart K, Roth D, *et al.* Randomized trial of three different immunosuppressive regimens to prevent chronic renal allograft rejection. *Transplant Proc* 2002;**34**:1610–1	Comparator
Burkhalter F, Oettl T, Descoeudres B, Bachmann A, Guerke L, Mihatsch MJ, *et al.* High incidence of rejection episodes and poor tolerance of sirolimus in a protocol with early steroid withdrawal and calcineurin inhibitor-free maintenance therapy in renal transplantation: experiences of a randomized prospective single-center study. *Transpl Proc* 2012;**44**:2961–5	Study design
Busque S, Cantarovich M, Mulgaonkar S, Gaston R, Gaber AO, Mayo PR, *et al.* The PROMISE study: a phase 2b multicenter study of voclosporin (ISA247) versus tacrolimus in de novo kidney transplantation. *Am J Transplant* 2011;**11**:2675–84	Outcome
Cabello M, García P, González-Molina M, Díez de los Rios MJ, García-Sáiz M, Gutiérrez C, *et al.* Pharmacokinetics of once- versus twice-daily tacrolimus formulations in kidney transplant patients receiving expanded criteria deceased donor organs: a single-center, randomized study. *Transplant Proc* 2010;**42**:3038–40	Abstract
Cabello-Diaz M, Gutierrez-Vilchez E, Gonzalez-Molina M, Hidalgo-Guzman P, Diez-de los Rios MJ, Garcia-Saiz M, *et al.* Pharmacokinetics of the two tacrolimus formulations in older patients who receive a cadaveric kidney graft from an expanded criteria donor. Randomized single-centre study. *Basic Clinical Pharmacology and Toxicology* 2011;**109**:32	Population
Campbell S, Walker R, Pilmore H, Kanellis J, Russ G, Hutchison B. Wound healing events are dose related: a multicenter, Prospective study on everolimus in renal transplantation. *Immunol Cell Biol* 2011;**89**:A16–7	Abstract
Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transplant* 2012;**12**:1146–56	Population
Campistol JM, Holt DW, Epstein S, Gioud-Paquet M, Rutault K, Burke JT. Bone metabolism in renal transplant patients treated with cyclosporine or sirolimus. *Transpl Int* 2005;**18**:1028–35	Study design
Campos HH, Abbud Filho M, Brazilian Tacrolimus Study Group. One-year follow-up of a Brazilian randomized multicenter study comparing tacrolimus versus cyclosporine in kidney transplantation. *Transplant Proc* 2002;**34**:1656–8	Population
Cantarovich D, Rostaing L, Kamar N, Ducloux D, Saint-Hillier Y, Mourad G, *et al.* Early corticosteroid avoidance in kidney transplant recipients receiving ATG-F induction: 5-year actual results of a prospective and randomized study. *Am J Transplant* 2014;**14**:2556–64	Population
Cantarovich M, Durrbach A, Hiesse C, Ladouceur M, Benoit G, Charpentier B. 20-year follow-up results of a randomized controlled trial comparing antilymphocyte globulin induction to no induction in renal transplant patients. *Transplantation* 2008;**86**:1732–7	Study design
Cao X, Colombel JF. A systematic review of de novo IBD in solid organ transplant recipient. *J Gastroenterol Hepatol* 2013;**28**:590	Intervention
Carmellini M, Pattison J, Riad H, Yaqoob M, Vergara M, Witte S, *et al.* Renal function in renal transplant recipients after 24 months of immunosuppression with concentration-controlled everolimus plus reduced cyclosporine exposure: update from the A2309 study. *Transpl Int* 2011;**24**:57	Abstract
Carmellini M, Todeschini P, Manzia TM, Valerio F, Messina M, Sghirlanzoni MC, *et al.* Twelve-month outcomes from evidence trial (everolimus once-a-day regimen with cyclosporine versus corticosteroid elimination) in adult kidney transplant recipients. *Transpl Int* 2013;**26**:100	Abstract
Carmellini M, Yaqoob M, Pattison J, Riad H, Wang Z, Cornu-Artis HC, *et al.* Correlation of everolimus exposure with efficacy and safety outcomes in renal transplant recipients: 24-month update. *Transpl Int* 2011;**24**:248	Abstract
Carroll RP, Hester J, Wood KJ, Harden PN. Conversion to sirolimus in kidney transplant recipients with squamous cell cancer permits potential protective changes in immune phenotype. *Transplantation* 2012;**94**:167	Abstract

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Carroll RP, Hester J, Wood KJ, Harden PN. Conversion to sirolimus in kidney transplant recipients with squamous cell cancer and changes in immune phenotype. *Nephrol Dial Transplant* 2013;**28**:462–5	Population
Cataneo-Davila A, Zuniga-Varga J, Correa-Rotter R, Alberu J. Renal function outcomes in kidney transplant recipients after conversion to everolimus-based immunosuppression regimen with CNI reduction or elimination. *Transpl Proc* 2009;**41**:4138–46	Population
Cerezo O, Bravo MG, Jimenez Aranda P, Lemus EA. Clinical benefits of immunosuppression therapy in renal trasplant Patients. Systematic review and meta-analysis. *Value Health* 2013;**16**:A697	Abstract
Cerezo O, Bravo MG, Jimenez Aranda P, Lemus EA. Clinical benefits of immunosuppression therapy in renal trasplant Patients. Systematic review and meta-analysis. *Value Health* 2013;**16**:A697	Duplicate
Chadban S, Campbell S, Russ G, Walker R, Chapman J, Pussell B, *et al.* A one-year, randomised, open label, parallel group study to investigate the safety and efficacy of enteric-coated Mycophenolate sodium (EC-MPS) in combination with full dose or reduced dose cyclosporine microemulsion (CSA-ME), basiliximab and steroids in de novo kidney transplantation. *Immunol Cell Biol* 2006;**84**:A6–A	Abstract
Chadban S, Eris J, Pilmore H, Lee P, Woodcock C, Kurstjens N, *et al.* Socrates-steroid or cyclosporin removal after transplantation using everolimus: histological analysis. *Transplantation* 2012;**94**:977	Abstract
Chadban SJ, Eris JM, Kanellis J, Pilmore H, Lee PC, Lim SK, *et al.* A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. *Transpl Int* 2014;**27**:302–11	Population
Chan L, Greenstein S, Hardy MA, Hartmann E, Bunnapradist S, Cibrik D, *et al.* Multicenter, randomized study of the use of everolimus with tacrolimus after renal transplantation demonstrates its effectiveness. *Transplantation* 2008;**85**:821–6	Comparator
Charpentier B. A three arm study comparing immediate tacrolimus therapy with ATG induction therapy followed by either tacrolimus or cyclosporine in adult renal transplant recipients. *Transpl Proc* 2002;**34**:1625–6	Population
Charpentier B, Grinyo J, Medina Pestana JO, Vanrenterghem Y, Vincenti F, Dong Y, *et al.* 3-Year Safety profile of belatacept in kidney transplant recipients from the benefit and BENEFIT-EXT studies. *Transpl Int* 2011;**24**:68–9	Abstract
Charpentier B, Groth CG, Bäckman L, Morales JM, Calne R, Kreis H, *et al.* Bicêtre hospital experience with sirolimus-based therapy in human renal transplantation: the Sirolimus European Renal Transplant Study. *Transplant Proc* 2003;**35**(Suppl. 3):58–61	Population
Charpentier B, Medina Pestana JO, Del C Rial M, Rostaing L, Grinyó J, Vanrenterghem Y, *et al.* Long-term exposure to belatacept in recipients of extended criteria donor kidneys. *Am J Transplant* 2013;**13**:2884–91	Population
Charpentier B, Rostaing L, Berthoux F, Lang P, Civati G, Touraine JL, *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	Population
Charpentier B, Vincenti F, Rice K, Budde K, Campistol J, Duan T, *et al.* Three-year outcomes in patients with delayed graft function in phase iii studies of belatacept vs cyclosporine in kidney transplantation (benefit and benefit-ext). *Transplantation* 2012;**94**:996	Abstract
Chen KH, Tsai MK, Lai IR, Lin Wu FL, Hu RH, Lee PH. Favorable results of concomitant tacrolimus and sirolimus therapy in Taiwanese renal transplant recipients at 12 months. *J Formos Med Assoc* 2008;**107**:533–9	Population
Cheung CY, Chan HW, Liu YL, Chau KF, Li CS. Long-term graft function with tacrolimus and cyclosporine in renal transplantation: paired kidney analysis. *Nephrology* 2009;**14**:758–63	Study design
Cheung CY, Wong KM, Chan HW, Liu YL, Chan YH, Wong HS, *et al.* Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. *Transpl Int* 2006;**19**:657–66	Study design
Chhabra D, Alvarado A, Dalal P, Leventhal J, Wang C, Sustento-Reodica N, *et al.* Impact of calcineurin-inhibitor conversion to mTOR inhibitor on renal allograft function in a prednisone-free regimen. *Am J Transplant* 2013;**13**:2902–11	Population
Chhabra D, Skaro AI, Leventhal JR, Dalal P, Shah G, Wang E, Gallon L. Long-term kidney allograft function and survival in prednisone-free regimens: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. *Clin J Am Soc Nephrol* 2012;**7**:504–12	Population
Chisholm MA, Middleton MD. Modified-release tacrolimus. *Ann Pharmacother* 2006;**40**:270–5	Study design

TABLE 135 Excluded studies (*continued*)

Study	Reason
Christian M, Bjerre A, Wennberg L, Ettenger R, Pape L, Tonshoff B, *et al.* Design and baseline characteristics of CRADLE: a study evaluating the efficacy and safety of everolimus to reduce CNI exposure and to withdraw steroids in pediatric renal transplant recipients. *Pediatr Nephrol* 2014;**29**:1755	Abstract
Chun DXY, Alexandre H, Sandrine GS, Olivier T, Isabelle E, Christophe L, *et al.* The phenotype of tubular epithelial cells does not recover after a conversion from cyclosporine a to siroliumus. *Nephrol Dial Transpl* 2012;**27**:ii517	Abstract
Ciancio G, Burke GW, Gaynor JJ, Mattiazzi A, Roth D, Kupin W, *et al.* A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate mofetil versus cyclosporine (NEORAL)/sirolimus in renal transplantation. II. Survival, function, and protocol compliance at 1 year. *Transplantation* 2004;**77**:252–8	Study design
Ciancio G, Burke GW, Gaynor JJ, Mattiazzi A, Roth D, Kupin W, *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	Duplicate
Ciancio G, Burke GW, Gaynor JJ, Mattiazzi A, Roth D, Kupin W, *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	Duplicate
Ciancio G, Burke GW, Gaynor JJ, Mattiazzi A, Roth D, Kupin W, *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	Duplicate
Ciancio G, Burke GW, Gaynor JJ, Ruiz P, Roth D, Kupin W, *et al.* A randomized long-term trial of tacrolimus/sirolimus versus tacrolimums/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. *Transplantation* 2006;**81**:845–52	Population
Ciancio G, Burke GW, Gaynor JJ, Roth D, Sageshima J, Kupin W, *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**:67–74	Population
Ciancio G, Gaynor JJ, Guerra G, Sageshima J, Chen L, Mattiazzi A, *et al.* Randomized trial of three induction antibodies in kidney transplantation: long-term results. *Transplantation* 2014;**97**:1128–38	Population
Ciancio G, Gaynor JJ, Zarak A, Sageshima J, Guerra G, Roth D, *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**:1198–205	Population
Ciancio G, Miller J, Gonwa TA. Review of major clinical trials with mycophenolate mofetil in renal transplantation. *Transplantation* 2005;**80**(Suppl. 2):191–200	Study design
Cibrik D, Johnston T, Kim Y, Walker R, Zibari G, Cornu-Artis C, *et al.* Everolimus exposure and relationship to efficacy and safety: results from a multicenter study in renal transplantation using reduced CsA exposure. *Am J Transplant* 2010;**10**:567–8	Abstract
Cibrik D, Johnston T, Kim YS, Walker R, Zibari G, Mange K, *et al.* Everolimus allows for around 60% reduction in CsA exposure over 12 months: results from a multicenter, prospective study in renal transplantation. *Am J Transplant* 2010;**10**:511	Abstract
Cibrik D, Kim YS, Johnston T, Walker R, Zibari G, Mange K, *et al.* Benefits of everolimus with reduced CSA exposure on renal function: a multicenter, prospective study in renal transplantation. *Am J Transplant* 2010;**10**:151–2	Abstract
Cibrik D, Kim YS, Johnston T, Walker R, Zibari GB, Cornu-Artis C, *et al.* Renal function stability in renal transplant recipients receiving concentration-controlled everolimus with reduced cyclosporine exposure: 24 month results from the A2309 study. *Am J Transplant* 2011;**11**:406–7	Abstract
Cibrik D, Silva HT, Vathsala A, Lackova E, Cornu-Artis C, Walker RG, *et al.* Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. *Transplantation* 2013;**95**:933–42	Study design
Citterio F, Scatà MC, Romagnoli J, Pozzetto U, Nanni G, Castagneto M. Conversion to tacrolimus immunosuppression in renal transplant recipients: 12-month follow-up. *Transplant Proc* 2002;**34**:1685–6	Population

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Citterio F, Scolari MP, Salvadori M, Castagneto M, Rigotti P, Albertazzi A, *et al.* A randomized trial comparing standard everolimus plus cyclosporine with higher blood everolimus levels plus very low cyclosporine levels in renal transplant recipients: preliminary results of the everest study. *Transpl Int* 2007;**20**:124	Abstract
Claes K, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. *Nephrol Dial Transplant* 2012;**27**:850–7	Population
Clayton P, McDonald S, Chapman J, Chadban S. Mycophenolate vs azathioprine for kidney transplantation: 15 year follow-up of a randomized trial. *Nephrology* 2011;**16**:69	Abstract
Clayton PA, McDonald SP, Chapman JR, Chadban SJ. Mycophenolate versus azathioprine for kidney transplantation: a 15-year follow-up of a randomized trial. *Transplantation* 2012;**94**:152–8	Population
Cransberg K, Cornelissen M, Lilien M, Hoeck K, Davin JC, Nauta J. Maintenance immunosuppression with mycophenolate mofetil and corticosteroids in pediatric kidney transplantation: temporary benefit but not without risk. *Transplantation* 2007;**83**:1041–7	Population
Cristelli M, Felipe C, Oliveira N, Gusukuma L, Ferreira A, Sandes-Freitas T, *et al.* De novo everolimus (EVR) versus mycophenolate (MPA) in kidney transplant recipients receiving tacrolimus (TAC). *Transplantation* 2014;**98**:141	Abstract
Cruzado JM, Bestard O, Riera L, Torras J, Gil-Vernet S, Serón D, *et al.* Immunosuppression for dual kidney transplantation with marginal organs: the old is better yet. *Am J Transplant* 2007;**7**:639–44	Study design
Dalal P, Xu L, Joseph L, Shah G, Chhabra D, Wang E, *et al.* Prospective randomized study to evaluate the long term impact on graft survivaland function of two pred-free, cnibased maintenance immunosuppressions: FK/MMF vs. FK/SRL. *Am J Transplant* 2010;**10**:512	Abstract
Dantal J, Berthoux F, Moal MC, Rostaing L, Legendre C, Genin R, *et al.* 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. *Transpl Int* 2010;**23**:1084–93	Population
Dantal J, Berthoux F, Moal MC, Rostaing L, Legendre C, Genin R, *et al.* 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. *Transpl Int* 2010;**23**:1084–93 [Erratum published in *Transpl Int* 2012;**25**:138]	Duplicate
David-Neto E, Cocuzza CS, Pereira LM, de Castro MCR, Fadel LM, Prado ES, *et al.* A prospective, randomized, controlled study using oral GTT to diagnose impaired glucose metabolism in renal transplant patients under cyclosporin and tacrolimus. *Am J Transplant* 2005;**5**:408	Abstract
De Fijter JW, Ewe SH, Den Hartigh J, Ng ACT, Delgado V, Mallat MJK, *et al.* Beneficial effects of late concentration-controlled CNI withdrawal in renal transplant recipients. *Am J Transplant* 2011;**11**:406	Abstract
De Fijter JW, Hoogendijk-Van Den Akker JM, Harden PN, Hoitsma AJ, Proby C, Wolterbeek R, *et al.* Reduced cutaneous squamous cell carcinoma after conversion to sirolimus: a 2-year prospective open-label multicenter trial. *Am J Transplant* 2012;**12**:161	Abstract
De Simone P, Detry O, Kintmalm G, Goss J, McCormick P, Rossi M, *et al.* Superior renal function sustained for 24 months through early everolimus-facilitated reduction of tacrolimus versus standard tacrolimus in de novo liver transplant recipients: results of a randomized trial. *Am J Transplant* 2013;**13**:169–70	Abstract
Dean PG, Grande JP, Sethi S, Park WD, Griffin MD, Cosio FG, *et al.* Kidney transplant histology after one year of continuous therapy with sirolimus compared with tacrolimus. *Transplantation* 2008;**85**:1212–5	Study design
Dean PG, Lund WJ, Larson TS, Prieto M, Nyberg SL, Ishitani MB, *et al.* Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation* 2004;**77**:1555–61	Outcome
Del Castillo D, Franco A, Tabernero JM, Errasti P, Valdes F, Garcia C, *et al.* Prospective, multicenter, randomized, open-label study of myfortic (EC-MPS) with steroid withdrawal vs Myfortic (TM) (EC-MPS) with standard steroid regimen to prevent acute rejection in de novo kidney transplantation. *Am J Transplant* 2005;**5**:191	Abstract
Demirbas A, Hugo C, Grinyó J, Frei U, Gürkan A, Marcén R, *et al.* Low toxicity regimens in renal transplantation: a country subset analysis of the Symphony study. *Transpl Int* 2009;**22**:1172–81	Population
Dharnidharka VR, Fiorina P, Harmon WE. Kidney transplantation in children. *N Engl J Med* 2014;**371**:549–58	Study design

TABLE 135 Excluded studies (*continued*)

Study	Reason
Diekmann F, Gutiérrez-Dalmau A, López S, Cofán F, Esforzado N, Ricart MJ, *et al.* Influence of sirolimus on proteinuria in de novo kidney transplantation with expanded criteria donors: comparison of two CNI-free protocols. *Nephrol Dial Transplant* 2007;**22**:2316–21	Population
Dobbels F, Ruppar T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant* 2010;**14**:603–13	Study design
Dobbels F, Wong S, Joo S, Kalsekar A. Health-related quality of life after kidney transplantation: results from belatacept clinical trials. *Am J Transplant* 2011;**11**:352–3	Abstract
Dobbels F, Wong S, You M, Kalsekar A. Patient reports of immunosuppressant related side-effects after kidney transplantation: results from the belatacept phase III clinical trial (BENEFIT). *Am J Transplant* 2011;**11**:353	Abstract
Duboix-xu Y, Lebranchu Y, De Ligny BH, Thervet E, Mazouz H, Lepogamp P, *et al.* Conversion from cyclosporine to Sirolimus at M3 after renal transplantation does not reduce the score of epithelialto mesenchymaltransition at M12: ancillary study of the concept study. *Am J Transplant* 2010;**10**:510-1	Abstract
Dudley C, Pohanka E, Riad H, Dedochova J, Wijngaard P, Sutter C, Silva HT, Mycophenolate Mofetil Creeping Creatinine Study Group. Mycophenolate mofetil substitution for cyclosporine a in renal transplant recipients with chronic progressive allograft dysfunction: the "creeping creatinine" study. *Transplantation* 2005;**79**:466–75	Population
Duerr M, Naik M, Schmidt D, Neumayer H, Budde K. Higher rates of acute rejections despite enhanced rates of regulatory T cells under mtor inhibitor therapy in renal transplant patients. *Am J Transplant* 2012;**12**:301	Abstract
Duerr M, Nolting J, Naik M, Neumayer HH, Budde K. Higher frequency of regulatory T-cells after conversion from cyclosporine to everolimus in a prospective randomized trial in renal allograft recipients. *Am J Transplant* 2011;**11**:66	Abstract
Durlik M, Paczek L, Rutkowski B, Lewandowska D, Debska-Slizien A, Chamienia A, *et al.* The efficacy and safety of ciclosporin (Equoral®) capsules after renal transplantation: a multicentre, open-label, phase IV clinical trial. *Ann Transplant* 2010;**15**:51–9	Study design
Durrbach A, Florman S, Larsen C, Pestana JM, Vanrenterghem Y, Vincente F, *et al.* Primary outcomes from a randomized, phase III study of belatacept versus cyclosporine in ECD kidney transplants (BENEFIT-EXT study). *Am J Transplant* 2010;**10**:7	Abstract
Durrbach A, Florman S, Zhang R, Becker T, Grinyo J, Lang P, *et al.* Four-year outcomes by donor type from the long-term extension of the belatacept BENEFIT and BENEFIT-EXT studies. *Am J Transplant* 2012;**12**:407	Abstract
Durrbach A, Florman S, Zhang R, Lang P, Lehner F, Massari P, *et al.* Five-year outcomes by donor type from the long-term extension of the belatacept BENEFIT-EXT study. *Am J Transplant* 2013;**13**:311	Abstract
Durrbach A, Larsen C, Medina-Pestana JD, Vanrenterghem Y, Vincenti F, Florman S, *et al.* Primary outcomes from a randomized, Phase III study of belatacept vs cyclosporine in ECD kidney transplants (BENEFIT-EXT Study). *Am J Transplant* 2009;**9**:199	Abstract
Durrbach A, Larsen CP, Medina Pestana J, Vanrenterghem Y, Vincenti F, Florman S, *et al.* Belatacept vs cyclosporine in ECD kidney transplants: two-year outcomes from the BENEFIT-EXT study. *NDT Plus* 2010;**3**:iii262	Abstract
Durrbach A, Medina-Pestana JO, Rostaing L, Bresnahan B, Helderman JH, Rice K, *et al.* Improving or maintaining renal function with belatacept: 5-year benefit long-term extension results. *Transpl Int* 2013;**26**:92	Abstract
Durrbach A, Medina-Pestana JO, Vanrenterghem Y, Rial M, Charpentier B, Matas A, *et al.* Improving or maintaining renal function over 5 years with belatacept in recipients of extended-criteria donor kidneys. *Transpl Int* 2013;**26**:44	Abstract
Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, *et al.* A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transplant* 2010;**10**:547–57	Population
Durrbach A, Rostaing L, Tricot L, Ouali N, Wolf P, Pouteil-Noble C, *et al.* Prospective comparison of the use of sirolimus and cyclosporine in recipients of a kidney from an expanded criteria donor. *Transplantation* 2008;**85**:486–90	Population

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Ekberg H, Bernasconi C, Nöldeke J, Yussim A, Mjörnstedt L, Erken U, *et al.* Cyclosporine, tacrolimus and sirolimus retain their distinct toxicity profiles despite low doses in the Symphony study. *Nephrol Dial Transplant* 2010;**25**:2004–10	Population
Ekberg H, Grinyó J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, *et al.* Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. *Am J Transplant* 2007;**7**:560–70	Population
Ekberg H, Mamelok RD, Pearson TC, Vincenti F, Tedesco-Silva H, Daloze P. The challenge of achieving target drug concentrations in clinical trials: experience from the Symphony study. *Transplantation* 2009;**87**:1360–6	Population
Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Klempnauer J, Guerkan 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. *Transpl Int* 2007;**20**:2	Abstract
Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007;**357**:2562–75	Intervention
El-Agroudy AE, El-Dahshan KF, Wafa EW, Sheashaa HA, Gad ZA, Ismail AM, *et al.* Safe conversion of mycophenolate mofetil to azathioprine in kidney transplant recipients with sirolimus-based immunosuppression. *Nephrology* 2009;**14**:255–61	Population
El-Sabrout R, Delaney V, Qadir M, Butt F, Hanson P, Butt KMH. Sirolimus in combination with tacrolimus or mycophenolate mofetil for minimizing acute rejection risk in renal transplant recipients - A single center experience. *Transpl Proc* 2003;**35**:89S–94S	Study design
Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, *et al.* Sirolimus and secondary skin-cancer prevention in kidney transplantation. *N Engl J Med* 2012;**367**:329–39	Study design
Facundo C, Diaz JM, Guirado L, Duran F, Herreros MA, Diaz M, Sola R. Results of a triple induction regime with tacrolimus, mycophenolate mofetil, and prednisone in renal transplantation. *Transplant Proc* 2002;**34**:98	Study design
Favi E, Citterio F, Spagnoletti G, Gargiulo A, Delreno F, Romagnoli J, Castagneto M. 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. *Transplant Proc* 2009;**41**:1152–5	Study design
Favi E, Citterio F, Spagnoletti G, Gargiulo A, Romagnoli J, Castagneto M. A prospective clinical trial comparing tacrolimus-mmf to cyclosporine-everolimus in de novo renal transplant recipients: 2 years results. *Transpl Int* 2009;**22**:241	Abstract
Favi E, Silvestrini N, Pedroso J, Salerno M, Spagnoletti G, Bianchi V, *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. *Am J Transpl* 2013;**13**:316	Abstract
Favi E, Silvestrini N, Pedroso JA, Salerno MP, Spagnoletti G, Romagnoli J, *et al.* Er-tacrolimus plus everolimus vs ertacrolimus plus MMF in primary deceased donor kidney transplantation: 1-year results of single center, open label, prospective, randomized clinical trial. *Transpl Int* 2013;**26**:241	Abstract
Favi E, Silvestrini N, Salerno MP, Romagnoli J, Citterio F. Extended-release tacrolimus plus everolimus or micophenolate mofetil in deceased donor kidney transplant recipients: 6-month results of a prospective randomized clinical trial. *Am J Transpl* 2012;**12**:42–3	Abstract
Favi E, Silvestrini N, Spagnoletti G, Castagneto M, Citterio F. Thymoglobulin and basiliximab vs basiliximab as induction therapy in deceased donor kidney transplantation: 1-year results of a prospective clinical trial. *Am J Transpl* 2011;**11**:147	Abstract
Favi E, Silvestrini N, Valente I, Salerno MP, Castagneto M, Citterio F. Lower acute rejection with basiliximab and short course, low dose thymoglobulin vs basiliximab as induction therapy in deceased donor renal transplant recipients: 6-month results of a prospective clinical trial. *Am J Transpl* 2010;**10**:321	Abstract
Favi E, Spagnoletti G, Salerno MP, Pedroso JA, Romagnoli J, Citterio F. Tacrolimus plus mycophenolate mofetil vs. cyclosporine plus everolimus in deceased donor kidney transplant recipients: three-yr results of a single-center prospective clinical trial. *Clin Transpl* 2013;**27**:E359–67	Study design

TABLE 135 Excluded studies (*continued*)

Study	Reason
Favi E, Spagnoletti G, Silvestrini N, Salerno MP, Pedroso JA, Romagnoli J, *et al.* Thymoglobulin plus basiliximab versus basiliximab induction in deceased donor kidney transplant recipients treated with tacrolimus and MMF: 1-year results of a prospective clinical trial. *Transpl Int* 2013;**26**:83	Abstract
Favi E, Spagnoletti G, Silvestrini N, Salerno M, Pedroso J, Romagnoli J, *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. *Am J Transpl* 2013;**13**:426	Abstract
Felix M, Felipe C, Tedesco H, Medina-Pestana J. Safety profile after planned conversion from tacrolimus (TAC) to sirolimus (SRL) based immunosuppressive therapy in kidney transplant recipients (KTR). *Transplantation* 2014;**98**:544–5	Abstract
Fellstrom B, Holdas H, Holme I, Jardine A, Soveri I. Cardiovascular risk calculator for renal transplant recipients: applications to BENEFIT and BENEFIT-EXT trials. *Am J Transpl* 2012;**12**:409–10	Abstract
Feng XF, Min M, Zuo FJ, Zhou MS, Wang LM. Conversion from tacrolimus to cyclosporine A improves new-onset diabetes mellitus after transplantation. *Chinese Journal of Tissue Engineering Research* 2013;**17**:9176–81	Language
Ferguson R, Grinyó J, Vincenti F, Kaufman DB, Woodle ES, Marder BA, *et al.* Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant* 2011;**11**:66–76	Population
Ferguson R, Vincenti F, Kaufman DB, Woodle ES, Marder BA, Citterio F, *et al.* Immunosuppression with belatacept-based, CNI-avoiding and steroid-avoiding regimens vs a tacrolimus-based, steroid-avoiding regimen in kidney transplant patients: results of a 1-year, randomized study. *Am J Transpl* 2010;**10**:150	Abstract
Ferrer F, Machado S, Alves R, Macário F, Bastos C, Roseiro A, Mota A. Induction with basiliximab in renal transplantation. *Transplant Proc* 2010;**42**:467–70	Study design
Filipe R, Mota A, Alves R, Bastos C, Macário F, Figueiredo A, *et al.* Kidney transplantation with corticosteroid-free maintenance immunosuppression: a single center analysis of graft and patient survivals. *Transplant Proc* 2009;**41**:843–5	Study design
Filler G. Randomised clinical trial in paediatric renal transplantation: tacrolimus (tac) vs cyclosporine neoral (cya) - 3-year data [abstract]. *JASN* 2003;**14**:65a	Abstract
Filler G. Finding the optimal therapeutic window for tacrolimus. *Pediatr Transplant* 2014;**18**:783–5	Study design
Fisher G, Rocha V, dos Santos M, Devergie A, Robin M, de Latour RP, *et al.* Myeophenolate mofetil (MMF) with or without tracolimus (FK506) as a second line treatment for steroid-resistant acute graft-versus-host disease. The experience of Saint Louis Hospital. *Blood* 2006;**108**:819A–A	Abstract
Flechner S, Friend P, Campistol J, Weir M, Diekmann F, Russ G. De novo immunosuppression with mammalian target of rapamycin inhibitors and posttransplantation malignancy in focus. *Transplant Proc* 2009;**41**(Suppl. 6):42–4	Study design
Flechner S, Glyda M, Steinberg S, Harler MB, Invest OT. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with a tacrolimus (TAC) and mycophenolate mofetil (MMF) regimen in de novo renal allograft recipients: renal function results from the Orion study. *Transplant Int* 2007;**20**:25	Abstract
Flechner S, Glyda M, Steinberg S, Harler MB, Investigators OT. A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with a tacrolimus (TAC) and mycophenolate mofetil regimen (MMF) in De novo renal allograft recipients: acute rejection and graft survival results from the orion study. *Transplant Int* 2007;**20**:209–10	Abstract
Flechner SM, Cockfield S, Grinyo J, Russ G, Wissing KM, Legendre C, *et al.* A randomized, open-label study to compare the safety and efficacy of two different sirolimus (SRL) regimens with tacrolimus (TAC) plus mycophenolate mofetil (MMF) in De Novo renal allograft recipients: preliminary 2-year safety results from the ORION trial. *Am J Transplant* 2008;**8**:582	Abstract
Flechner SM, Glyda M, Tai SS. Delayed graft function (DGF) in two sirolimus (SRL)-based regimens compared with tacrolimus (TAC) and mycophenolate mofetil (MMF) in de novo renal allograft recipients. *Am J Transplant* 2009;**9**:277–8	Abstract
Flechner SM, Glyda M, Cockfield S, Grinyó J, Legendre Ch, Russ G, *et al.* The ORION study: comparison of two sirolimus-based regimens versus tacrolimus and mycophenolate mofetil in renal allograft recipients. *Am J Transplant* 2011;**11**:1633–44	Population

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Flechner SM, Goldfarb D, Modlin C, Feng JY, Krishnamurthi V, Mastroianni B, *et al.* Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporin. *Transplantation* 2002;**74**:1070–6	Population
Flechner SM, Goldfarb D, Solez K, Modlin CS, Mastroianni B, Savas K, *et al.* Kidney transplantation with sirolimus and mycophenolate mofetil-based immunosuppression: 5-year results of a randomized prospective trial compared to calcineurin inhibitor drugs. *Transplantation* 2007;**83**:883–92	Population
Flechner SM, Gurkan A, Hartmann A, Legendre CM, Russ GR, Campistol JM, *et al.* A randomized, open-label study of sirolimus versus cyclosporine in primary de novo renal allograft recipients. *Transplantation* 2013;**95**:1233–41	Population
Flechner SM, Gurkan A, Tai SS, Schulman SL. Incidence of delayed graft function (DGF) in a sirolimus (SRL)-based versus cyclosporine (CsA)-based regimen in de novo renal allograft recipients *Am J Transplant* 2009;**9**:278	Abstract
Flechner SM, Kurian SM, Solez K, Cook DJ, Burke JT, Rollin H, *et al.* De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *Am J Transplant* 2004;**4**:1776–85	Population
Florman S, Becker T, Bresnahan B, Chevaile-Ramos A, Carvalho D, Muehibacher F, *et al.* Three year outcomes by donor type in phase III studies of belatacept vs cyclosporine in kidney transplantation (benefit and benefit-EXT). *Transplant Int* 2011;**24**:51	Abstract
Florman S, Becker T, Bresnahan B, Chevaile-Ramos A, DeCarvalho D, Muehlbacher F, *et al.* Three-year outcomes by donor type in phase III studies of belatacept vs cyclosporine in kidney transplantation (BENEFIT & BENEFIT-EXT). *Am J Transplant* 2011;**11**:100	Abstract
Florman S, Bresnahan B, Chan L, Helderman H, Dong Y, Harler MB, *et al.* Three year outcomes in Black/African American kidney transplant recipients from the BENEFIT and BENEFIT-EXT studies. *Am J Transplant* 2011;**11**:350	Abstract
Florman S, Durrbach A, Grinyo J, Pestana JOM, Rial MDC, Vitko S, *et al.* 4-year results from the long-term extension of the belatacept BENEFIT-EXT study. *Am J Transplant* 2012;**12**:82	Abstract
Florman S, Durrbach A, Larsen C, Pestana JM, Vanrenterghem Y, Vincenti F, *et al.* Outcomes as a function of donor criteria from a phase III study of belatacept vs cyclosporine in kidney transplantation (benefitext). *Am J Transplant* 2010;**10**:150	Abstract
Florman S, Rice K, Chan L, Steinberg S, Pearson T, Duan T, *et al.* Four-year outcomes in black/African American kidney transplant recipients from the long-term extension of the belatacept BENEFIT and BENEFIT-EXT studies. *Am J Transplant* 2012;**12**:404	Abstract
Florman S, Rice K, Chan L, Zhang R, Abouljoud M, Steinberg S, *et al.* Outcomes at five years in black/African-American kidney transplant recipients from the long-term extension of the belatacept benefit and BENEFIT-EXT studies. *Am J Transplant* 2013;**13**:311	Abstract
Foroncewicz B, Mucha K, Ciszek M, Małkowski P, Durlik M, Szmidt J, *et al.* A comparison between two tacrolimus-based immunosuppression regimens in renal transplant recipients: 7-year follow-up. *Ann Transplant* 2013;**18**:384–92	Study design
Forsythe J. A phase II open label single centre randomized study of tacrolimus plus sirolimus and corticosteroids compared with tacrolimus plus azathioprine and corticosteroids in de novo renal allografts recipients. 2002. National Research Register, UK. URL: www.nrr.nhs.uk/ (accessed 25 July 2014)	Unobtainable
Franz S, Regeniter A, Hopfer H, Mihatsch M, Dickenmann M. Tubular toxicity in sirolimus- and cyclosporine-based transplant immunosuppression strategies: an ancillary study from a randomized controlled trial. *Am J Kidney Dis* 2010;**55**:335–43	Study design
Frei U, Daloze P, Vítko S, Klempnauer J, Reyes-Acevedo R, Titiz I, *et al.* Acute rejection in low-toxicity regimens: clinical impact and risk factors in the Symphony study. *Clin Transplant* 2010;**24**:500–9	Population
Friend PJ. 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. 2011. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/711/CN-00796711/frame.html (accessed 25 July 2014)	No data
Frimat L, Cassuto-Viguier E, Charpentier B, Noël C, Provôt F, Rostaing L, *et al.* Impact of cyclosporine reduction with MMF: a randomized trial in chronic allograft dysfunction. The 'reference' study. *Am J Transplant* 2006;**6**:2725–34	Population

TABLE 135 Excluded studies (*continued*)

Study	Reason
Frimat L, Cassuto-Viguier E, Provôt F, Rostaing L, Charpentier B, Akposso K, *et al.* Long-Term Impact of Cyclosporin Reduction with MMF Treatment in Chronic Allograft Dysfunction: REFERENECE Study 3-Year Follow Up. *J Transplant* 2010;**2010**:402750	Population
Gaber AO, Kahan BD, Van Buren C, Schulman SL, Scarola J, Neylan JF, Sirolimus High-Risk Study Group. Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. *Transplantation* 2008;**86**:1187–95	Population
Gallon L, Monica G, Friedewald J, Cabral B, Miller J, Najafaian N, *et al.* Prospective randomized study to evaluate feasibility of conversion of CNI to SRL in a pred-free immunosuppressive regimen. Impact on treg generation. *Am J Transplant* 2009;**9**:260	Abstract
Gallon L, Perico N, Dimitrov BD, Winoto J, Remuzzi G, Leventhal J, *et al.* Long-term renal allograft function on a tacrolimus-based, pred-free maintenance immunosuppression comparing sirolimus vs. MMF. *Am J Transplant* 2006;**6**:1617–23	Population
Gamboa O, Montero C, Mesa L, Benavides C, Reino A, Torres RE, Castillo JS. Cost-effectiveness analysis of the early conversion of tacrolimus to mammalian target of rapamycin inhibitors in patients with renal transplantation. *Transplant Proc* 2011;**43**:3367–76	Population
Martin Garcia D, Martin Gago J, Mendiluce A, Gordillo R, Bustamente J. Tacrolimus-Basiliximab versus Cyclosporine-Basiliximab in renal transplantation "de novo": acute rejection and complications. *Transplant Proc* 2003;**35**:1694–6	Study design
Garcia I, Spanish-Italian Tacrolimus Study Group. Efficacy and safety of dual versus triple tacrolimus-based therapy in kidney transplantation: two-year follow-up. *Transplant Proc* 2002;**34**:1638–9	Comparator
Garcia R, Machado PG, Felipe CR, Park SI, Spinelli GA, Franco MF, *et al.* Exploratory calcineurin inhibitor-free regimens in living-related kidney transplant recipients. *Braz J Med Biol Res* 2007;**40**:457–65	Study design
van Gelder T, Silva HT, de Fijter H, Budde K, Kuypers D, Mamelok RD, *et al.* How delayed graft function impacts exposure to mycophenolic acid in patients after renal transplantation. *Ther Drug Monit* 2011;**33**:155–64	Population
van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, *et al.* Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation* 2008;**86**:1043–51	Comparator
van Gelder T, Tedesco Silva H, de Fijter JW, Budde K, Kuypers D, Arns W, *et al.* Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. *Transplantation* 2010;**89**:595–9	Comparator
Gelder T, ter Meulen CG, Hené R, Weimar W, Hoitsma A. Oral ulcers in kidney transplant recipients treated with sirolimus and mycophenolate mofetil. *Transplantation* 2003;**75**:788–91	Study design
Gelens MA, Christiaans MH, van Heurn EL, van den Berg-Loonen EP, Peutz-Kootstra CJ, van Hooff JP. High rejection rate during calcineurin inhibitor-free and early steroid withdrawal immunosuppression in renal transplantation. *Transplantation* 2006;**82**:1221–3	Population
Gheith O, Al-Otaibi T, Mansour H. Next-generation calcineurin inhibitors in development for the prevention of organ rejection. *Transplant Research and Risk Management* 2014;**6**:23–30	Study design
Glotz D, Charpentier B, Abramovicz D, Lang P, Rostaing L, Rifle G, *et al.* 6 months preliminary results of a randomized trial comparing sirolimus (SRL) versus tacrolimus (FK) in 141 transplant patients receiving a cadaveric renal graft. *Am J Transplant* 2005;**5**:460	Study design
Glotz D, Charpentier B, Abramovicz D, Lang P, Rostaing L, Rifle G, *et al.* Thymoglobulin induction and sirolimus versus tacrolimus in kidney transplant recipients receiving mycophenolate mofetil and steroids. *Transplantation* 2010;**89**:1511–7	Abstract
Gonwa T, Johnson C, Ahsan N, Alfrey EJ, Halloran P, Stegall M, *et al.* Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine plus mycophenolate mofetill after cadaveric kidney transplantation: results at three years. *Transplantation* 2003;**75**:2048–53	Population
Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S, Prograf Study Group. Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. *Transplantation* 2003;**75**:1213–20	Population
Gonzalez F, Espinoza M, Herrera P, Rocca X, Reynolds E, Lorca E, *et al.* 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. *Transplant Proc* 2010;**42**:270–2	Study design

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Gonzalez Molina M, Morales JM, Marcen R, Campistol JM, Oppenheimer F, Serón D, *et al.* Renal function in patients with cadaveric kidney transplants treated with tacrolimus or cyclosporine. *Transplant Proc* 2007;**39**:2167–9	Study design
Graeme R, Mamta A, Thomas B, Bresnahan B, Campistol JM, Darji P, *et al.* Belatacept associated with preserved renal function and structure compared with cyclosporine (CSA) in kidney transplant patients. *Immunol Cell Biol* 2010;**88**(6):A11–12	Abstract
Graeme R, Steve C, Scott C, Brian H, John K, Philip O, *et al.* Everolimus plus reduced-dose cyclosporine: results from a randomized, phase iii study in 833 De-novo renal transplant recipients. *Immunol Cell Biol* 2010;**88**:A22	Study design
Grafals M. *Low Dose Thymoglobulin as Induction Agent on Prednisone-Free Regimens of Renal Transplant Recipients*. 2011. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/457/CN-00794457/frame.html (accessed 25 July 2014)	Comparator
Grannas G, Richter N, Klempnauer J, Lehner F. 10 years' experience with belatacept (nulojix). *Transplantation* 2012;**94**:964	Abstract
Grannas G, Schrem H, Klempnauer J, Lehner F. Ten years experience with belatacept-based immunosuppression after kidney transplantation. *J Clin Med Res* 2014;**6**:98–110	Study design
Gregoor P, De Sevaux RGL, Ligtenberg G, Hoitsma AJ, Hene RJ, Weimar W, *et al.* Withdrawal of cyclosporine or prednisone six months after kidney transplantation in patients on triple drug therapy: a randomized, prospective, multicenter study. *J Am Soc Nephrol* 2002;**13**:1365–73	Study design
Grinyo J, Abouljoud M, Germain M, Manfro R, Morales J, Legendre C, *et al.* Improving or sustaining renal function over 3 years with belatacept or cyclosporine a (CSA): insights from the benefit study. *Transplant Int* 2011;24:250	Abstract
Grinyo J, Abouljoud M, Germain M, Manfro R, Morales J, Legendre C, *et al.* Likelihood of improving or sustaining renal function over three years with belatacept or CsA: insights from the BENEFIT study. *Am J Transplant* 2011;**11**:349	Abstract
Grinyo J, Alberu J, Contieri FL, Manfro RC, Mondragon G, Nainan G, *et al.* Improvement in renal 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 Int* 2012;**25**:1059–64	Population
Grinyo J, Charpentier B, Medina Pestana J, Vanrenterghem Y, Vincenti F, Shi R, *et al.* Safety profile of belatacept in kidney transplant recipients from a pooled analysis of phase II and phase III studies. *NDT Plus* 2010;**3**:iii270	Abstract
Grinyo J, Durrbach A, Rostaing L, Bresnahan B, Helderman J, Rice K, *et al.* Likelihood of improving or maintaining renal function over five years with belatacept or CSA: insights from the benefit long-term extension study. *Am J Transplant* 2013;**13**:182	Abstract
Grinyo J, Florman S, Medina Pestana JO, Del Carmen Rial M, Muehlbacher F, Durrbach A, *et al.* Long-term extension of the belatacept BENEFIT-EXT study: results at month 48. *Transplantation* 2012;**94**:974	Abstract
Grinyo J, Nainan G, Del Carmen Rial M, Steinberg S, Vincenti F, Dong Y, *et al.* Renal function at 2 years in kidney transplant recipients switched from cyclcosporine or tacrolimus to belatacept: results from the long-term extension of a phase II study. *Transplant Int* 2011;**24**:70	Abstract
Grinyo J, Nainan G, Rial M, Steinberg S, Vincenti F, Dong Y, *et al.* Renal function at 2 years in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: results: from the long-term extension of a phase II study. *Am J Transplant* 2011;**11**:99	Abstract
Grinyo J, Pestana JM, Becker T, Rial MC, Dong Y, Block A, *et al.* Likelihood of improving or sustaining renal function over three years with belatacept or CsA: insights from the BENEFIT-EXT study. *Am J Transplant* 2012;**12**:82	Abstract
Grinyo J, Rial M, Alberu J, Steinberg S, Manfro R, Nainan G, *et al.* Outcomes of switching to belatacept from a calcineurin inhibitor in kidney transplant recipients: 3 year results from the long-term extension of a phase ii study. *Am J Transplant* 2013;**13**:182	Abstract
Grinyo J, Vanrenterghem Y, Durrbach A, Rial M, Charpentier B, Matas A, *et al.* Likelihood of improving or maintaining renal function in recipients of extended-criteria donor kidneys over five years with belatacept or CsA (benefit-ext long-term extension study). *Am J Transplant* 2013;**13**:310	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Grinyo JM, Campistol JM, Paul J, García-Martínez J, Morales JM, Prats D, *et al.* Pilot randomized study of early tacrolimus withdrawal from a regimen with sirolimus plus tacrolimus in kidney transplantation. *Am J Transplant* 2004;**4**:1308–14	Study design
Grinyo JM, Ekberg H, Mamelok RD, Oppenheimer F, Sanchez-Plumed J, Gentil MA, *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. *Nephrol Dial Transplant* 2009;**24**:2269–76	Population
Grinyo JM, Marks W, Vincenti F, Kaufman DB, Marder BA, Woodle S, *et al.* Immunosuppression with belatacept-based, CNI-free, steroid-avoiding regimens in kidney transplant recipients: 6 month, interim results. *Am J Transplant* 2009;**9**:382	Abstract
Grinyo JM, Mondragon-Ramirez G, Darji P, Bresnahan B, Pearson T, Di Russo GB, *et al.* Belatacept is associated with preservation of renal function and structure at 1 year compared to cyclosporine in kidney transplant patients (BENEFIT Study). *Am J Transplant* 2009;**9**:258–9	Abstract
Grinyo JM, Paul J, Novoa P, Errasti P, Franco A, Aldana G, *et al.* Better renal function in renal-transplant recipients treated with everolimus plus cyclosporine elimination compared with cyclosporine minimisation. *Am J Transplant* 2010;**10**:503	Abstract
Grushkin C, Mahan JD, Mange KC, Hexham JM, Ettenger R. De novo therapy with everolimus and reduced-exposure cyclosporine following pediatric kidney transplantation: a prospective, multicenter, 12-month study. *Pediatr Transplant* 2013;**17**:237–43	Population
Gu YH, Du JX, Ma ML. *Sirolimus and Non-melanoma Skin Cancer Prevention After Kidney Transplantation: A Meta-analysis (Provisional Abstract).* DARE; 2012. DARE Accession Number: 12013033631. URL: http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?AccessionNumber=12013033631&UserID=0 (accessed 25 July 2014)	Population
Gu YH, Du JX, Ma ML. Sirolimus and non-melanoma skin cancer prevention after kidney transplantation: a meta-analysis. *Asian Pac J Cancer Prev* 2012;**13**:4335–9	Population
Guba M, Pratschke J, Hugo C, Kraemer B, Burmeister D, Brockmann J, *et al.* A randomized multicenter trial of early conversion to sirolimus/mycophenolate/steroids versus cyclosporine/mycophenolate/steroids in renal transplantation: one-year analysis (SMART-study). *Am J Transplant* 2009;**9**:497	Abstract
Guba M, Pratschke J, Hugo C, Kraemer B, Nohr-Westphal C, Brockmann J, *et al.* Renal function, efficacy and safety of sirolimus and mycophenolat mofetil therapy after early calcineurin-inhibitor withdrawal in de novo renal transplant patients: one-year analysis of a randomized multicenter trial. *Transplant Int* 2009;**22**:78	Abstract
Guba M, Pratschke J, Hugo C, Krämer BK, Nohr-Westphal C, Brockmann J, *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**:175–83	Population
Guba M, Witzke O, Lehner F, Arns W, Sommerer C, Neumayer HH, *et al.* The herakles study at 24 month: superior renal function in an everolimus-based cnifree regimen. *Transplant Int* 2013;**26**:110	Abstract
Guerra G, Ciancio G, Gaynor JJ, Zarak A, Brown R, Hanson L, *et al.* Randomized trial of immunosuppressive regimens in renal transplantation. *JASN* 2011;**22**:1758–68	Study design
Guerra G, Gaynor JJ, Ciancio G, Zarak A, Sageshima J, Roth D, *et al.* Randomized trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate versus cyclosporine (neoral (r))/sirolimus in renal transplantation: seven year results. *Am J Transplant* 2009;**9**:325	Abstract
Gupta D. Design of a randomized study evaluating everolimus in pediatric renal transplant recipients. *Transplant Int* 2013;**26**:328	Abstract
Gürkan A, Kaçar S, Erdogdu U, Varilsüha C, Kandemir G, Karaca C, *et al.* The effect of sirolimus in the development of chronic allograft nephropathy. *Transplant Proc* 2008;**40**:114–6	Population
Hakemi M, Shahebrahimi K, Ganji MR, Najafi I, Broumand B. Side effects of mycophenolate mofetil versus azathioprine in iranian renal transplant recipients (single-center experience). *Transplant Proc* 2002;**34**:2091–2	Study design
Hamdy AF, Bakr MA, Ghoneim MA. Long-term efficacy and safety of a calcineurin inhibitor-free regimen in live-donor renal transplant recipients. *J Am Soc Nephrol* 2008;**19**:1225–32	Population

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Hamdy AF, Bakr MA, Ghoneim MA. Proteinuria among primarily sirolimus treated live-donor renal transplant recipients' long-term experience. *Exp Clin Transplant* 2010;**8**:283–91	Population
Hamdy AF, El-Agroudy AE, Bakr MA, Mostafa A, El-Baz M, El-Shahawy el-M, Ghoneim MA. Comparison of sirolimus with low-dose tacrolimus versus sirolimus-based calcineurin inhibitor-free regimen in live donor renal transplantation. *Am J Transplant* 2005;**5**:2531–8	Population
Han D, Kim Y-S, Park KT, Kim S-J, Ha J-W, Kim H-C, *et al.* A Phase III, Randomized, open-label, comparative, multicenter study to assess the safety and efficacy of prograf (R) (tacrolimus) and extended release (XL) Tacrolimus in asian de novo kidney transplants from living donors: 6 month results. *Am J Transplant* 2009;**9**:413	Abstract
Han DJ, Park JB, Kim YS, Kim SJ, Ha J, Kim HC, *et al.* 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. *Transplant Proc* 2012;**44**:115–7	Study design
Han F, Wu J, Huang H, Zhang X, He Q, Wang Y, *et al.* Conversion from cyclosporine to sirolimus in chronic renal allograft dysfunction: a 4-year prospective study. *Exp Clin Transplant* 2011;**9**:42–9	Population
Hanaway M, Woodle ES, Mulgaonkar S, Peddi R, Harrison G, Vandeputte K, *et al.* 12 month results of a multicenter, randomized trial comparing three induction agents (alemtuzumab, thymoglobulin and basiliximab) with tacrolimus, mycophenolate mofetil and a rapid steroid withdrawal in renal transplantation. *Am J Transplant* 2008;**8**:215	Abstract
Hardinger KL, Bohl DL, Schnitzler MA, Lockwood M, Storch GA, Brennan DC. A randomized, prospective, pharmacoeconomic trial of tacrolimus versus cyclosporine in combination with thymoglobulin in renal transplant recipients. *Transplantation* 2005;**80**:41–6	Population
Harold Y. A phase III, randomized, open-label, comparative, multi-center study to assess the safety and efficacy of Prograf (R) (Tacrolimus)/MMF, extended release (XL) Tacrolimus/MMF and Neoral (R) (Cyclosporine)/MMF in de novo kidney transplant recipients: 2 year results. *Am J Transplant* 2007;**7**:183	Abstract
Havenith SH, Yong SL, Donselaar-van der Pant KA, Lier RA, Berge IJ, Bemelman FJ. Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. *Transplantation* 2013;**95**:184–91	Study design
Hazzan M, Buob D, Labalette M, Provot F, Glowacki F, Hoffmann M, *et al.* Assessment of the risk of chronic allograft dysfunction after renal transplantation in a randomized cyclosporine withdrawal trial. *Transplantation* 2006;**82**:657–62	Outcome
Hazzan M, Labalette M, Copin MC, Glowacki F, Provôt F, Pruv FR, Noël C. Predictive factors of acute rejection after early cyclosporine withdrawal in renal transplant recipients who receive mycophenolate mofetil: results from a prospective, randomized trial. *J Am Soc Nephrol* 2005;**16**:2509–16	Outcome
Heilman RL, Cortese C, Geiger XJ, Younan K, Wadei HM, Mai ML, *et al.* Impact of early conversion from tacrolimus to sirolimus on chronic allograft changes in kidney recipients on rapid steroid withdrawal. *Transplantation* 2012;**93**:47–53	Population
Heilman RL, Younan K, Wadei HM, Mai ML, Reddy KS, Chakkera HA, Gonwa TA. Results of a prospective randomized trial of sirolimus conversion in kidney transplant recipients on early corticosteroid withdrawal. *Transplantation* 2011;**92**:767–73	Population
Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004;**4**:583–95	Population
Heller T, Gelder T, Budde K, Fijter JW, Kuypers D, Arns W, *et al.* Plasma concentrations of mycophenolic acid acyl glucuronide are not associated with diarrhea in renal transplant recipients. *Am J Transplant* 2007;**7**:1822–31	Outcome
Hernández D, Miquel R, Porrini E, Fernández A, González-Posada JM, Hortal L, *et al.* Randomized controlled study comparing reduced calcineurin inhibitors exposure versus standard cyclosporine-based immunosuppression. *Transplantation* 2007;**84**:706–14	Population
Hertig A, Kamar N, Anglicheau D, Moulin B, Hazzan M, Hurault De Ligny B, *et al.* Epithelial to mesenchymal transition markers in kidney transplant recipients: the certitem trial. *Transplant Int* 2013;**26**:2	Abstract
Hest RM, Gelder T, Vulto AG, Mathot RA. Population pharmacokinetics of mycophenolic acid in renal transplant recipients. *Clin Pharmacokinet* 2005;**44**:1083–96	Study design

TABLE 135 Excluded studies (*continued*)

Study	Reason
Hirsch HH, Vincenti F, Friman S, Wiecek A, Pescovitz MD, Jenssen T, *et al.* Prospective study of polyomavirus BK viruria and viremia in De Novo renal transplantation comparing cyclosporine and tacrolimus: a multivariate analysis. *Am J Transplant* 2009;**9**:337	Abstract
Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, *et al.* Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. *Am J Transplant* 2013;**13**:136–45	Outcome
Ho ETL, Wong G, Chapman JR, Craig J. Once daily extended release versus twice daily standard release tacrolimus in kidney transplant recipients: a systematic review. *Transplantation* 2012;**94**:989	Abstract
Hoerning A, Köhler S, Jun C, Lu J, Fu J, Tebbe B, *et al.* Cyclosporin but not everolimus inhibits chemokine receptor expression on CD4+ T cell subsets circulating in the peripheral blood of renal transplant recipients. *Clin Exp Immunol* 2012;**168**:251–9	Outcome
Holdaas H, Rostaing L, Serón D, Cole E, Chapman J, Fellstrøm B, *et al.* Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 2011;**92**:410–8	Duplicate
Holdaas H, Rostaing L, Serón D, Cole E, Chapman J, Fellstrøm B, *et al.* Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 2011;**92**:410–8	Duplicate
Holdaas H, Rostaing L, Serón D, Cole E, Chapman J, Fellstrøm B, *et al.* Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 2011;**92**:410–8	Population
Holdaas H, Rostaing L, Serón D, Cole E, Chapman J, Fellstrøm B, *et al.* Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. *Transplantation* 2011;**92**:410–8	Duplicate
Homan Van Der Heide JJ, De Fijter JW, Ten Berge I, De Maar EF, Bemelman FJ. Mecano: mycophenolate sodium vs everolimus or ciclosporin with allograft nephropathy as outcome study: clinical results. *Transplant Int* 2011;**24**:85	Abstract
Hooff J, Walt I, Kallmeyer J, Miller D, Dawood S, Moosa MR, *et al.* Pharmacokinetics in stable kidney transplant recipients after conversion from twice-daily to once-daily tacrolimus formulations. *Therapeutic Drug Monitoring* 2012;**34**:46–52	Study design
van Hooff JP, Squifflet JP, Vanrenterghem Y. Benelux experience with a combination of tacrolimus and mycophenolate mofetil: 4-year results. *Transplant Proc* 2002;**34**:1591–3	Comparator
Hooff JP, Squifflet JP, Wlodarczyk Z, Vanrenterghem Y, Paczek L. A prospective randomized multicenter study of tacrolimus in combination with sirolimus in renal-transplant recipients. *Transplantation* 2003;**75**:1934–9	Comparator
Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, Proby CM, Wolterbeek R, Bouwes Bavinck JN, de Fijter JW. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus. *J Clin Oncol* 2013;**31**:1317–23	Study design
Howell M, Yeo R, Tong A, Craig JC, Howard K, Wong G. Adverse events of maintenance immunosuppression following kidney transplantation reported in randomised controlled trials: a systematic review. URL: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/360/CN-01009360/frame.html (accessed 25 July 2014)	Abstract
Huang HF, Yao X, Chen Y, Xie WQ, Shen-Tu JZ, Chen JH. 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. *Int J Clin Pract Suppl* 2014;**68**:4–9	Outcome
Huh W, Lee K, Lee K, Kim S, Joh J, Oh H. Randomized trial of tacrolimus versus cyclosporine in steroid withdrawal regimen after living kidney transplantation. *Clin Pharmacol Ther* 2003;**73**:P26	Abstract
Iaria G, Pisani F, Iorio B, Lucchesi C, De Luca L, Ielpo B, *et al.* Long-term results of kidney transplantation with cyclosporine- and everolimus-based immunosuppression. *Transplant Proc* 2006;**38**:1018–9	Study design
Ibrahim H, Issa N, Spong R, Kukla A, Kandaswamy R, Dunn T, *et al.* CNI reduction vs. mTOR based immunosuppression after prednisone discontinuation: four year preliminary results from a large randomized trial. *Am J Transplant* 2012;**12**:302	Abstract

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Ireland R. Transplantation: early switch from calcineurin inhibitors to mTOR inhibitors leads to improved renal graft function. *Nat Rev Nephrol* 2011;**7**:243	Study design
Nicholson M. A prospective randomised trial of the use of cellcept to allow early tacrolimus withdrawal in live donor kidney transplantation. ISRCTN. URL: www.controlled-trials.com/ISRCTN63298320 (accessed 25 July 2014)	No data
Hammad A. 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. ISRCTN. URL: www.controlled-trials.com/ISRCTN74336394 (accessed 25 July 2014)	No data
Jarzembowski T, Panaro F, Raofi V, Dong G, Testa G, Sankary H, Benedetti E. Long-term results of a prospective randomized trial comparing tacrolimus versus cyclosporine in African-American recipients of primary cadaver renal transplant. *Transpl Int* 2005;**18**:419–22	Population
Jesky MD, Sharif A, Borrows RJ. Does conversion from cyclosporine to tacrolimus as secondary prevention provide better outcomes in renal allograft recipients? A meta-analysis. *Am J Transplant* 2011;**11**:410	Abstract
Jevnikar A, Arlen D, Barrett B, Boucher A, Cardella C, Cockfield SM, *et al.* Five-year study of tacrolimus as secondary intervention versus continuation of cyclosporine in renal transplant patients at risk for chronic renal allograft failure. *Transplantation* 2008;**86**:953–60	Population
Joannides R, Etienne I, Iacob M, Hurault de Ligny B, Barbier S, Bellien J, *et al.* Comparative effects of sirolimus and cyclosporin on conduit arteries endothelial function in kidney recipients. *Transpl Int* 2010;**23**:1135–43	Population
Joannidès R, Monteil C, de Ligny BH, Westeel PF, Iacob M, Thervet E, *et al.* Immunosuppressant regimen based on sirolimus decreases aortic stiffness in renal transplant recipients in comparison to cyclosporine. *Am J Transplant* 2011;**11**:2414–22	Population
Johari Y, Bryson D, Nicholson M. A randomised controlled trial comparing switching to rapamune based immunosuppression with tacrolimus minimisation for renal transplantation. *Br J Surg* 2010;**97**:68–9	Abstract
Johari Y, Bryson D, Barlow A, Nicholson M. Cyclosporine micro-emulsion versus tacrolimus for renal transplantation: 10-year follow-up for single centre randomised controlled trial. *Br J Surg* 2010;**97**:32–3	Abstract
Johari Y, Bryson D, Medcalf J, Nicholson M. Cyclosporine versus tacrolimus for renal transplantation: 10 year follow up of a randomised controlled trial. *Br J Surg* 2010;**97**:37	Abstract
Jose M, Caring for Australians with Renal Impairment (CARI). The CARI guidelines. Calcineurin inhibitors in renal transplantation: adverse effects. *Nephrology* 2007;**12**(Suppl. 1):66–74	Study design
Joss N, Rodger RS, McMillan MA, Junor BJ. Randomized study comparing cyclosporine with azathioprine one year after renal transplantation-15-year outcome data. *Transplantation* 2007;**83**:582–7	Population
Junge G, De Simone P, Fung J, Kohler S, Saliba F. Urinary protein excretion in non-renal transplant patients-does mTOR-inhibitor treatment matter? *Am J Transplant* 2013;**13**:531–2	Abstract
Junge G, Tufveson G, Riad H, Cibrik D, Tedesco H, Schwende H, *et al.* Better renal allograft function with everolimus facilitated CNI reduction - Graft type, donor criteria and gender analysis. *NDT Plus* 2010;**3**:iii540	Abstract
Jungraithmayr TC, Wiesmayr S, Staskewitz A, Kirste G, Bulla M, Fehrenbach H, *et al.* Five-year outcome in pediatric patients with mycophenolate mofetil-based renal transplantation. *Transplantation* 2007;**83**:900–5	Study design
Jurewicz WA. Tacrolimus versus ciclosporin immunosuppression: long-term outcome in renal transplantation. *Nephrol Dial Transplant* 2003;**18**:i7–i11	Population
Kaabak M, Babenko N, Zokoyev A, Schekaturov S, Sandrikov V. Eculizumab for prevention and treatment of kidney graft reperfusion injury, preliminary results of RCT. *Transplantation* 2014;**98**:257–8	Abstract
Kahan BD. Two-year results of multicenter phase III trials on the effect of the addition of sirolimus to cyclosporine-based immunosuppressive regimens in renal transplantation. *Transplant Proc* 2003; **35**(Suppl. 3):37–51	Population
Kalil AC, Florescu DF, Sun J. Induction immunosuppression: what is the difference in the risk of serious infections between interleukin-2RA and polyclonal antibodies? *Am J Transplant* 2009;**9**:283	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Kalil AC, Florescu MC, Grant W, Miles C, Morris M, Stevens RB, *et al.* Risk of serious opportunistic infections after solid organ transplantation: interleukin-2 receptor antagonists versus polyclonal antibodies. A meta-analysis. *Expert Rev Anti Infect Ther* 2014;**12**:881–96	Study design
Kamar N, Allard J, Ribes D, Durand D, Ader JL, Rostaing L. Assessment of glomerular and tubular functions in renal transplant patients receiving cyclosporine A in combination with either sirolimus or everolimus. *Clin Nephrol* 2005;**63**:80–6	Study design
Kamar N, Lehner F, Banas B, Viklicky O, Albano L, Glyda M. Efficacy and safety of tacrolimus prolonged release and immediate release in de novo renal transplantation – the osaka study (optimizing immunosuppression after kidney transplantation with advagraf). *Transplant Int* 2011;**24**:39	Abstract
Kamar N, Rial M, Alberu J, Steinberg SM, Manfro R, Nainan G, *et al.* 3-year outcomes after switching to belatacept from a calcineurin inhibitor in stable kidney transplant recipients. *Transplant Int* 2013;**26**:44	Abstract
Kamar N, Rial M, Alberu J, Steinberg S, Manfro R, Nainan G, *et al.* Three-years outcomes after switching to belatacept from calcineurin inhibitor in stable kidney transplant recipients. *Transplant Int* 2013;**26**:22	Abstract
Kamar N, Rostaing L, Cassuto E, Villemain F, Moal MC, Ladrière M, *et al.* A multicenter, randomized trial of increased mycophenolic acid dose using enteric-coated mycophenolate sodium with reduced tacrolimus exposure in maintenance kidney transplant recipients. *Clin Nephrol* 2012;**77**:126–36	Population
Kandaswamy R, Melancon JK, Dunn T, Tan M, Casingal V, Humar A, *et al.* A prospective randomized trial of steroid-free maintenance regimens in kidney transplant recipients – an interim analysis. *Am J Transplant* 2005;**5**:1529–36	Population
Kang MH, Kim HJ, Ko RK, Ko SK. A systematic review of immunosuppressive regimens in lower immunological risk renal transplant recipients. *Value Health* 2010;**13**:A473–4	Abstract
Kang MH, Kim HJ, Ko RK, Ko SK. A systematic review of immunosuppressive regimens in lower immunological risk renal transplant recipients. *Value Health* 2010;**13**:A473–4	Duplicate
Karpe Krishna M, Talaulikar Girish S, Walters G. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients. *Cochrane Database System Rev* 2007;**4**:CD006750	Study design
Kasiske BL, de Mattos A, Flechner SM, Gallon L, Meier-Kriesche HU, Weir MR, Wilkinson A. Mammalian target of rapamycin inhibitor dyslipidemia in kidney transplant recipients. *Am J Transplant* 2008;**8**:1384–92	Study design
Keown P, Balshaw R, Khorasheh S, Chong M, Marra C, Kalo Z, Korn A. Meta-analysis of basiliximab for immunoprophylaxis in renal transplantation. *BioDrugs* 2003;**17**:271–9	Population
Ke-Pu L, Xiao-Min Y, Shuai-Jun M, Zhi-Bin L, Geng Z, Jian-Lin Y. Effects of tacrolimus and cyclosporine A on inflammatory cytokines and blood lipid after renal transplantation. *Journal of Clinical Rehabilitative Tissue Engineering Research* 2011;**15**:5769–72	Language
Keven K, Sahin M, Kutlay S, Sengul S, Erturk S, Ersoz S, Erbay B. Immunoglobulin deficiency in kidney allograft recipients: comparative effects of mycophenolate mofetil and azathioprine. *Transpl Infect Dis* 2003;**5**:181–6	Outcome
Khosroshahi HT, Tubbs RS, Shoja MM, Ghafari A, Noshad H, Ardalan MR. Effect of prophylaxis with low-dose anti-thymocyte globulin on prevention of acute kidney allograft rejection. *Transplant Proc* 2008;**40**:137–9	Population
Khwaja K, Asolati M, Harmon J, Melancon JK, Dunn T, Gillingham K, *et al.* Outcome at 3 years with a prednisone-free maintenance regimen: a single-center experience with 349 kidney transplant recipients. *Am J Transplant* 2004;**4**:980–7	Study design
Kihm LP, Hinkel UP, Michael K, Sommerer C, Seckinger J, Morath C, *et al.* Contrast enhanced sonography shows superior microvascular renal allograft perfusion in patients switched from cyclosporine A to everolimus. *Transplantation* 2009;**88**:261–5	Population
Knight SR, Morris PJ. Does the evidence support the use of mycophenolate mofetil therapeutic drug monitoring in clinical practice? A systematic review. *Transplantation* 2008;**85**:1675–85	Study design
Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, *et al.* Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014;**349**:g6679	Duplicate
Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, *et al.* Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014;**349**:g6679	Study design

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Kobashigawa J, Ross H, Kfoury AG, Van Bakel A, Ewald G, Burton J, *et al.* CMV infections are less frequent in de novo heart transplant recipients receiving immunosuppression with everolimus plus reduced CsA compared to MMF and standard CsA. *Am J Transplant* 2011;**11**:131–2	Abstract
Koch M, Becker T, Lueck R, Neipp M, Klempnauer J, Nashan B. Basiliximab induction therapy in kidney transplantation: benefits for long term allograft function after 10 years? *Biologics* 2009;**3**:51–6	Study design
Koukoulaki M, Grispou U, Pistolas D, Balaska K, Apostolou T, Anagnostopoulou M, *et al.* Monitoring of BK polyoma virus in renal transplant recipients. Preliminary results of a prospective study. *Nephrol Dial Transplant* 2005;**20**:V177–V	Abstract
Kovac D, Kotnik V, Kandus A. Basiliximab and mycophenolate mofetil in combination with low-dose cyclosporine and methylprednisolone effectively prevent acute rejection in kidney transplant recipients. *Transplant Proc* 2005;**37**:4230–4	Study design
Kramer B. Significantly better freedom from acute rejection with tacrolimus vs. cyclosporine-based immunosuppression in renal transplant recipients at 7-year follow-up. *Am J Transplant* 2010;**10**:568	Abstract
Kramer B, Kruger B, Banas B, Tomlinson P. Early post-transplant blood levels in de novo renal recipients on tacrolimus prolonged release (TACQD) versus tacrolimus immediate release (TACBD) in A phase III double-blind double-dummy study. *Transplant Int* 2011;**24**:54	Abstract
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	Abstract
Krämer BK, Böger C, Krüger B, Marienhagen J, Pietrzyk M, Obed A, *et al.* Cardiovascular risk estimates and risk factors in renal transplant recipients. *Transplant Proc* 2005;**37**:1868–70	Population
Krämer BK, Del Castillo D, Margreiter R, Sperschneider H, Olbricht CJ, Ortuño J, *et al.* Efficacy and safety of tacrolimus compared with ciclosporin A in renal transplantation: three-year observational results. *Nephrol Dial Transplant* 2008;**23**:2386–92	Population
Krämer BK, Charpentier B, Bäckman L, Silva HT, Mondragon-Ramirez G, Cassuto-Viguier E, *et al.* Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. *Am J Transplant* 2010;**10**:2632–43	Population
Krämer BK, Klinger M, Vítko Š, Glyda M, Midtvedt K, Stefoni S, *et al.* Tacrolimus-based, steroid-free regimens in renal transplantation: 3-year follow-up of the ATLAS trial. *Transplantation* 2012;**94**:492–8	Comparator
Krämer BK, Klinger M, Wlodarczyk Z, Ostrowski M, Midvedt K, Stefoni S, *et al.* Tacrolimus combined with two different corticosteroid-free regimens compared with a standard triple regimen in renal transplantation: one year observational results. *Clin Transplant* 2010;**24**:E1–9	Study design
Krämer BK, Montagnino G, Castillo D, Margreiter R, Sperschneider H, Olbricht CJ, *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**:968–73	Study design
Kramer BK, Zulke C, Kammerl MC, Schmidt C, Hengstenberg C, Fischereder M, *et al.* Cardiovascular risk factors and estimated risk for CAD in a randomized trial comparing calcineurin inhibitors in renal transplantation. *Am J Transplant* 2003;**3**:982–7	Outcome
Kreis H. Worse renal transplant outcomes with sirolimus-mycophenolate than with calcineurin inhibitor regimens. *Nat Clin Pract Nephrol* 2007;**3**:424–5	Study design
Krischock L, Marks SD. Induction therapy: why, when, and which agent? *Pediatr Transplant* 2010;**14**:298–313	Study design
Kumar A, Zaman W, Chaurasia D, Gupta A, Sharma RK, Gulati S. Prospective randomized trial to evaluate the efficacy of single low dose ATG induction in renal transplant recipient with spousal kidney. *Indian J Urol* 2002;**19**:58–62	Study design
Kumar N, Manimaran R, Williams C, Ravanan R. Tacrolimus preserves renal function better than cyclosporin at 10 years – long term results of a randomised controlled trial. *Am J Transplant* 2009;**9**:200	Abstract
Kwon O, Cho JH, Choi JY, Park SH, Kim YL, Kim HK, *et al.* Long-term outcome of azathioprine versus mycophenolate mofetil in cyclosporine-based immunosuppression in kidney transplantation: 10 years of experience at a single center. *Transplant Proc* 2013;**45**:1487–90	Study design
Kyllönen LE, Eklund BH, Pesonen EJ, Salmela KT. Single bolus antithymocyte globulin versus basiliximab induction in kidney transplantation with cyclosporine triple immunosuppression: efficacy and safety. *Transplantation* 2007;**84**:75–82	Population

TABLE 135 Excluded studies (*continued*)

Study	Reason
Langer RM, Hené R, Vitko S, Christiaans M, Tedesco-Silva H, Ciechanowski K, *et al.* Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation. *Transpl Int* 2012;**25**:592–602	Study design
Langer RM, Pape L, Tonshoff B, Dello Strologo L, Ettenger R, Niaudet P, *et al.* Evaluation of safety and efficacy of everolimus with reduced tacrolimus: design of a randomized, multicenter, open-label study in pediatric renal transplant recipients. *Pediatr Transplant* 2013;**17**:80	Abstract
Langone AJ, Chan L, Bolin P, Cooper M. Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study. *Transplantation* 2011;**91**:470–8	Population
Larsen C, Alberu J, Massari P, Acevedo RR, Kamar N, Lin CS, *et al.* 4-Year results from the long-term extension of the belatacept BENEFIT study. *Am J Transplant* 2012;**12**:82	Abstract
Larsen C, Vincenti F, Grinyo J, Rice K, Steinberg S, Gaite L, *et al.* Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension (LTE) of the belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression trial (benefit) study. *Am J Transplant* 2013;**13**:312	Abstract
Larsen C, Vincenti F, Grinyo JM, Charpentier B, Di Russo GB, Garg P, *et al.* Renal benefit of belatacept vs cyclosporine in kidney transplant patients is not impacted by acute rejection (BENEFIT Study). *Am J Transplant* 2009;**9**:220	Abstract
Larsen CP, Bray R, Gebel H, Ganguly B, Kulbokas E, Brickman D, *et al.* Evaluation of donor-specific antibodies in kidney transplant patients treated with belatacept-or cyclosporine-based immunosuppression in benefit and BENEFIT-EXT. *Transplant Internat* 2011;**24**:69	Abstract
Larsen CP, Grinyo J, Charpentier B, Medina Pestana J, Kamar N, Vanrenterghem Y, *et al.* Belatacept vs cyclosporine in kidney transplant recipients: two-year outcomes from the benefit study. *NDT Plus* 2010;**3**:iii262	Abstract
Larsen CP, Grinyó J, Medina-Pestana J, Vanrenterghem Y, Vincenti F, Breshahan B, *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**:1528–35	Population
Larson TS, Dean PG, Stegall MD, Griffin MD, Textor SC, Schwab TR, *et al.* Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. *Am J Transplant* 2006;**6**:514–22	Population
Lawen JG, Davies EA, Mourad G, Oppenheimer F, Molina MG, Rostaing L, *et al.* Randomized double-blind study of immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. *Transplantation* 2003;**75**:37–43	Population
Lebranchu Y, Bridoux F, Büchler M, Le Meur Y, Etienne I, Toupance O, *et al.* Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. *Am J Transplant* 2002;**2**:48–56	Population
Lebranchu Y, Buchler M, Etienne I, Toupance O, Westel PF, Legendre C, *et al.* 12 month results of a randomized trial comparing sirolimus (SRL) versus cyclosporine (CsA) in 150 transplant patients receiving a cadaveric renal graft. *Am J Transplant* 2005;**5**:540	Abstract
Lebranchu Y, Etienne I, Toupance O, Westeel PF, de Ligny BH, Rerolle JP, *et al.* Cni avoidance and steroid withdrawal in renal transplantation. Results at three years of a prospective multicenter randomized trial comparing sirolimus (srl) and cyclosporine (csa): the spiesser study. *Transplant Internat* 2009;**22**:244	Abstract
Lebranchu Y, Legendre C, Merville P, Durrbach A, Rostaing L, Thibault G, *et al.* Comparison of interleukin-2 (Il-2) Blockade in kidney transplant patients randomized to 40mg or 80mg basiliximab (BSX) with cyclosporine (CsA) or 80mg BSX with everolimus (EVR). *Transplantation* 2014;**98**:581	Abstract
Lebranchu Y, Snanoudj R, Toupance O, Weestel PF, Hurault de Ligny B, Buchler M, *et al.* Five-year results of a randomized trial comparing de novo sirolimus and cyclosporine in renal transplantation: the SPIESSER study. *Am J Transplant* 2012;**12**:1801–10	Population
Lebranchu Y, Thierry A, Thervet E, Büchler M, Etienne I, Westeel PF, *et al.* Efficacy and safety of early cyclosporine conversion to sirolimus with continued MMF-four-year results of the Postconcept study. *Am J Transplant* 2011;**11**:1665–75	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Lebranchu Y, Thierry A, Toupance O, Westeel PF, Etienne I, Thervet E, *et al.* Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. *Am J Transplant* 2009;**9**:1115–23	Population
Lebranchu Y, Touchard G, Buchler M, Thervet E, Etienne I, Westeel PF, *et al.* Efficacy and safety of early cyclosporine (CSA) conversion to sirolimus (SRL) with mycophenolate mofetil (MMF): 5-year results of the post-concept study. *Transplant Internat* 2011;**24**:57	Population
Lebranchu Y, Toupance O, Touchard G, Thervet E, Etienne I, Mazouz H, *et al.* Impact on renal function of early conversion at 3 months from cyclosporine (CsA) to sirolimus (SRL) in association with mycophenolate mofetil (MMF) in kidney transplantation: 30-months follow up of a multicenter randomized controlled trial: the concept study. *Am J Transplant* 2009;**9**:260	Abstract
Lebranchu Y, Toupance O, Touchard G, Thervet E, Etienne I, Westeel PF, *et al.* Impact of early conversion at 3 months from cyclosporine (CSA) to sirolimus (SRL) in association with mycophenolate mofetil (MMF) on renal function – "Results at 48 months of follow up of a multicenter randomized controlled trial: the concept study". *Am J Transplant* 2010;**10**:151	Abstract
Lee YJ, Kim B, Lee JE, Kim YG, Kim DJ, Kim SJ, *et al.* Randomized trial of cyclosporine and tacrolimus therapy with steroid withdrawal in living-donor renal transplantation: 5-year follow-up. *Transpl Int* 2010;**23**:147–54	Population
Legendre C, Campistol JM, Squifflet JP, Burke JT, Sirolimus European Renal Transplant Study Group. Cardiovascular risk factors of sirolimus compared with cyclosporine: early experience from two randomized trials in renal transplantation. *Transplant Proc* 2003;**35**(Suppl. 3):151–3	Study design
Legendre C, Srinivas TR, Pascual J, Chadban S, Citterio F, Henry M, *et al.* The transform trial design: a large randomized, multicenter, open-label study of everolimus with reduced calcineurin inhibitors in de novo renal transplantation. *Transplant Internat* 2013;**26**:23–4	Abstract
Lehner F, Banas B. Influence of donor related factors on outcomes with tacrolimus-based immunosuppression after kidney transplantation – the Osaka study. *Transplant Internat* 2011;**24**:21	Abstract
Lehner F, Anns W, Witzke O, Budde K, Sommerer C, Eisenber-Ger U, *et al.* Three years follow-up of the zeus trial: maintained better renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients. *Transplant Internat* 2011;**24**:50	Abstract
Lehner F, Arns W, Reinke P, Eisenberger U, Paulus EM, Scheidl S, *et al.* Renal function in everolimus/enteric-coated mycophenolate sodium treated de novo living renal transplant recipients after calcineurin inhibitor withdrawal: subgroup analysis of the zeus study. *Transplant Internat* 2011;**24**:50–1	Abstract
Lehner F, Banas B, Kamar N, Glyda M, Viklicky O, Albano L. Influence of donor related factors on outcomes with tacrolimus-based immunosuppression after kidney transplantation – the osaka study (optimizing immunosuppression after kidney transplantationwith Advagraf). *Transplant Internat* 2011;**24**:164-5	Abstract
Lehner F, Budde K, Arns W, Sommerer C, Reinke P, Eisenberger U, *et al.* Improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients: 3 year follow-up of the zeus trial. *Transplant Internat* 2011;**24**:57	Abstract
Lehner F, Guba M, Arns W, Sommerer C, Neumayer HH, Jacobi J, *et al.* Follow-up data from herakles study at month 24: maintained superior renal function in patients on an everolimus-based calcineurin inhibitor free regimen compared to standard cyclosporine/mycophenolate and low cyclosporine/everolimus. *Transplant Internat* 2013;**26**:28	Abstract
Lehner F, Sommerer C, Arns W, Eisenberger U, Reinke P, Pressmar K, *et al.* A post hoc analysis of 2 prospective, open-label, multicenter, randomized trials: onset and progression of diabetes in kidney transplant patients receiving everolimus or cyclosporine. Results from ZEUS and HERAKLES. *Transplant Internat* 2013;**26**:21	Abstract
Lehner F, Sommerer C, Arns W, Reinke P, Eisenberger U, Wuthrich RP, *et al.* Post HOC subgroup analysis from ZEUS: outcome on renal function, efficacy and safety in livingdonor kidney transplant recipients after conversion from a calcineurin inhibitor to an everolimus based regimen. *Transplant Internat* 2013;**26**:8	Abstract
Lehner F, Sommerer C, Reinke P, Arns W, Eisenberger U, Paulus EM, *et al.* 5-year follow-up on the ZEUS KTX trial: everolimus conversion after CNI withdrawal. *Transplant Internat* 2013;**26**:81	Abstract
Lehner F, Sommerer C, Witzke O, Arns W, Kliem V, Neumayer HH, *et al.* Herakles at month 24: efficacy and safety of 3 different regimens in de novo renal transplant patients. *Transplant Internat* 2013;**26**:82	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Lezaic VD, Marinkovic J, Ristic S, Dokic ZM, Basta Jovanovic G, Radivojevic DM, *et al.* Conversion of azathioprine to mycophenolate mofetil and chronic graft failure progression. *Transplant Proc* 2005;**37**:734–6	Population
Libetta C, Canevari M, Margiotta E, Martinelli C, Borettaz I, Esposito P, *et al.* Preliminary data of controlled randomized study (ever twist) on tolerance induction. *Transplant Internat* 2013;**26**:20	Abstract
Libetta C, Margiotta E, Borettaz I, Canevari M, Martinelli C, Lainu E, *et al.* Everolimus and lowdose of tacrolimus combined with thymoglobulin induction induces regulatory t cells expansion in de novo kidney transplant recipients: preliminary data of controlled randomized study (ever twist). *Nephrol Dial Transplant* 2013;**28**:i277	Abstract
Liefeldt L, Brakemeier S, Glander P, Waiser J, Lachmann N, Schönemann C, *et al.* Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. *Am J Transplant* 2012;**12**:1192–8	Population
Lim W, Eris J, Kanellis J, Pussell B, Wiid Z, Witcombe D, *et al.* Conversion from calcineurin-inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients: a systematic review and meta-analysis of randomised trials. *Nephrology* 2013;**18**:44–5	Abstract
Lim W, Eris J, Kanellis J, Pussell B, Wiid Z, Witcombe D, *et al.* Conversion from calcineurin-inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients: a systematic review and meta-analysis of randomised trials. *Nephrology* 2013;**18**:44–5	Duplicate
Lim WH, Eris J, Kanellis J, Pussell B, Wiid Z, Witcombe D, *et al.* A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. *Am J Transplant* 2014;**14**:2106–19	Population
Lin CC, Chuang FR, Lee CH, Wang CC, Chen YS, Liu YW, *et al.* The renal-sparing efficacy of basiliximab in adult living donor liver transplantation. *Liver Transpl* 2005;**11**:1258–64	Study design
Liu B, Lin ZB, Ming CS, Zhang WJ, Chen ZS, Sha B, *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. *Transplant Proc* 2003;**35**:87–8	Study design
Liu M, Zhang W, Gu M, Yin C, Zhang WY, Lv Q, Xu D. Protective effects of sirolimus by attenuating connective tissue growth factor expression in human chronic allograft nephropathy. *Transplant Proc* 2007;**39**:1410–5	Outcome
Liu Y, Yang MS, Yuan JY. Immunosuppressant utilization and cardiovascular complications among Chinese patients after kidney transplantation: a systematic review and analysis. *Int Urol Nephrol* 2013;**45**:885–92	Study design
Liu Y, Yang MS, Yuan JY. Immunosuppressant utilization and cardiovascular complications among Chinese patients after kidney transplantation: a systematic review and analysis. *Int Urol Nephrol* 2013;**45**:885–92	Duplicate
Liu Y, Zhou P, Han M, Xue CB, Hu XP, Li C. Basiliximab or antithymocyte globulin for induction therapy in kidney transplantation: a meta-analysis. *Transplant Proc* 2010;**42**:1667–70	Study design
Ljuca F, Imamović S, Mesić D, Hasukić SH, Omerović S, Bazardzanović M, Iljazagić-Halilović F. Micophenolat Mofetil versus Azathioprine: effects on renal graft function in early posttransplant period. *Bosn J Basic Med Sci* 2009;**9**:156–60	Study design
Lo A, Egidi MF, Gaber LW, Amiri HS, Vera S, Nezakatgoo N, Gaber AO. Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 2004;**77**:1228–35	Study design
Lorber MI, Mulgaonkar S, Butt KM, Elkhammas E, Mendez R, Rajagopalan PR, *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**:244–52	Population
Loriga G, Ciccarese M, Pala PG, Satta RP, Fanelli V, Manca ML, *et al.* De novo everolimus-based therapy in renal transplant recipients: effect on proteinuria and renal prognosis. *Transplant Proc* 2010;**42**:1297–302	Population
Lou HX, Vathsala A. Conversion from mycophenolate mofetil to azathioprine in high-risk renal allograft recipients on cyclosporine-based immunosuppression. *Transplant Proc* 2004;**36**:2090–1	Population

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Luan FL, Zhang H, Schaubel DE, Miles CD, Cibrik D, Norman S, Ojo AO. Comparative risk of impaired glucose metabolism associated with cyclosporine versus tacrolimus in the late posttransplant period. *Am J Transplant* 2008;**8**:1871–7	Outcome
Maamoun H, Khashab S, Belal D, Soliman AR. Azathioprine increases cyclosporine-induced hyperuricemia in renal transplant recipient. *Transplantation* 2012;**94**:969	Abstract
Machado PG, Felipe CR, Hanzawa NM, Park SI, Garcia R, Alfieri F, *et al.* An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone combination. *Clin Transplant* 2004;**18**:28–38	Population
Maiorano A, Stallone G, Schena A, Infante B, Pontrelli P, Schena FP, Grandaliano G. Sirolimus interferes with iron homeostasis in renal transplant recipients. *Transplantation* 2006;**82**:908–12	Population
Marchetti P, Vincenti F, Friman S, Scheuermann E, Grp DS. New-onset diabetes impaired fasting glucose after renal transplantation: results of a prospective, randomised trial comparing cyclosporine versus tacrolimus. *Diabetologia* 2006;**49**:500–1	Abstract
Margreiter R, European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. *Lancet* 2002;**359**:741–6	Population
Margreiter R. Tacrolimus vs ciclosporin microemulsion in renal transplantation. A randomized multicentre study. *Chirurgische Praxis*. 2002;**60**:611–2	Abstract
Margreiter R, Pohanka E, Sparacino V, Sperschneider H, Kunzendorf U, Huber W, *et al.* Open prospective multicenter study of conversion to tacrolimus therapy in renal transplant patients experiencing ciclosporin-related side-effects. *Transpl Int* 2005;**18**:816–23	Study design
Marks WH, Ilsley JN, Dharnidharka VR. Posttransplantation lymphoproliferative disorder in kidney and heart transplant recipients receiving thymoglobulin: a systematic review. *Transplant Proc* 2011;**43**:1395–404	Study design
Martínez-Castelao A, Sarrias X, Bestard O, Gil-Vernet S, Serón D, Cruzado JM, *et al.* Arterial elasticity measurement in renal transplant patients under anticalcineurin immunosuppression. *Transplant Proc* 2005;**37**:3788–90	Population
Mas V, Maluf D, Scian M, Chalasani G, Sustento-Reodica N, Leventhal J, *et al.* Differential impact of calcineurin and mammalian target of rapamycin inhibition on immune, inflammation and antigen presentation genes expression in renal allograft biopsies. *Am J Transplant* 2012;**12**:40	Abstract
Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev* 2014;**11**:CD010699	Duplicate
Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev* 2014;**11**:CD010699	Study design
Masson P, Henderson LK, Craig J, Webster AC. Belatacept for kidney transplant recipients: a systematic review and meta-analysis. *Transplantation* 2012;**94**:968–9	Abstract
Masson P, Henderson LK, Craig J, Webster AC. Belatacept for kidney transplant recipients: a systematic review and meta-analysis. *Transplantation* 2012;**94**:968–9	Duplicate
Matas A, Gillingham K. Prospective randomized study of low level CNI vs SRL @ 6 mos posttx, while pred (P)-free. *Transplantation* 2014;**98**:542	Abstract
Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant* 2004;**18**:446–9	Study design
Mayer AD. Chronic rejection and graft half-life: five-year follow-up of the European Tacrolimus Multicenter Renal Study. *Transplant Proc* 2002;**34**:1491–2	Population
Medina Pestana J, Grinyo J, Vanrenterghem Y, Becker T, Florman S, Lang P, *et al.* Belatacept compared with cyclosporine in renal allograft recipients of extended criteria donor kidneys: 3-year outcomes from the phase III benefit-EXT trial. *Transplant Int* 2011;**24**:51	Abstract
Medina-Pestana JO, Garcia VD, David-Neto E, Carvalho DBM, Contieri F, Abbud-Filho M, *et al.* Conversion from tacrolimus to sirolimus-based immunosuppressive regimen in kidney transplant recipients. Preliminary results. *Am J Transplant* 2011;**11**:462	Abstract
Meier M, Bode W, Nitschke M, Wong W, Kramer J, Lehnert H, *et al.* Low dose tacrolimus versus mycophenolate-mofetil in 'old for old' kidney transplantation: a one year prospective multicenter randomized controlled trial. *Am J Transplant* 2009;**9**:498	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Meier M, Nitschke M, Weidtmann B, Jabs WJ, Wong W, Suefke S, *et al.* Slowing the progression of chronic allograft nephropathy by conversion from cyclosporine to tacrolimus: a randomized controlled trial. *Transplantation* 2006;**81**:1035–40	Population
Meier-Kriesche HU, Davies NM, Grinyó J, Heading R, Mamelok R, Wijngaard P, *et al.* Mycophenolate sodium does not reduce the incidence of GI adverse events compared with mycophenolate mofetil. *Am J Transplant* 2005;**5**:1164	Study design
Mendez R, Gonwa T, Yang HC, Weinstein S, Jensik S, Steinberg S. A prospective, randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 1 year. *Transplantation* 2005;**80**:303–9	Population
Merville P, Bergé F, Deminière C, Morel D, Chong G, Durand D, *et al.* Lower incidence of chronic allograft nephropathy at 1 year post-transplantation in patients treated with mycophenolate mofetil. *Am J Transplant* 2004;**4**:1769–75	Population
Metcalfe MS, Jain S, Waller JR, Saunders RN, Bicknell GR, Nicholson ML. A randomized trial of mycophenolate mofetil versus azathioprine as calcineurin inhibitor sparing agents in the treatment of chronic allograft nephropathy. *Transplant Proc* 2002;**34**:1812–4	Population
Mjornstedt L, Schwartz Sorensen S, Von Zur Muhlen B, Jespersen B, Hansen JM, Bistrup C, *et al.* Renal function three years after early conversion from a calcineurin inhibitor to everolimus: results from a randomized trial in kidney transplantation. *Transplant Int* 2014;**28**:42–51	Population
Mjornstedt L, Sorensen SS, Von Zur Muhlen B, Jespersen B, Hansen JM, Bistrup C, *et al.* Improved renal function by overnight switch from cyclosporine to everolimus at week 7 after renal transplantation. One year results from a randomized, controlled trial. *Transplant Int* 2011;**24**:94	Abstract
Mjörnstedt L, Sørensen SS, Zur Mühlen B, Jespersen B, Hansen JM, Bistrup C, *et al.* Improved renal function after early conversion from a calcineurin inhibitor to everolimus: a randomized trial in kidney transplantation. *Am J Transplant* 2012;**12**:2744–53	Population
Monaco AP, Morris PJ. Everolimus and long-term outcomes in renal transplantation: seeking an optimal strategy for immunosuppression. *Transplantation* 2011;**92**(Suppl. 3):1–2	Study design
Montagnino G, Krämer BK, Arias M, European Tacrolimus vs Cyclosporin Microemulsion Renal Transplantation Study Group. Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in kidney transplantation: twelve-month follow-up. *Transplant Proc* 2002;**34**:1635–7	Abstract
Montagnino G, Sandrini S, Casciani C, Schena FP, Carmellini M, Civati G, *et al.* A randomized trial of steroid avoidance in renal transplant patients treated with everolimus and cyclosporine. *Transplant Proc* 2005;**37**:788–90	Comparator
Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. *Diabetes Care* 2002;**25**:583–92	Population
Moore R. New-onset diabetes after renal transplantation: comparing ciclosporin and tacrolimus. *Nature Clinical Practice Nephrology* 2008;**4**:20–1	Comparator
Morales JM, Andrés A, Dominguez-Gil B, Arriola M, Gutiérrez MJ, Hernández E, *et al.* Ten years of treatment with tacrolimus is related to an excellent renal function, allowing monotherapy in a large proportion of cases: unicentric results of the tacrolimus versus cyclosporine: a European multicentric study in kidney transplant patients. *Transplant Proc* 2005;**37**:3738-42	Study design
Morales JM, Campistol JM, Kreis H, Mourad G, Eris J, Schena FP, *et al.* Sirolimus-based therapy with or without cyclosporine: long-term follow-up in renal transplant patients. *Transplant Proc* 2005; **37**:693–6	Language
Morales JM, Grinyó JM, Campistol JM, García-Martínez J, Arias M, Paul J, *et al.* Improved renal function, with similar proteinuria, after two years of early tacrolimus withdrawal from a regimen of sirolimus plus tacrolimus. *Transplantation* 2008;**86**:620–2	Study design
Morales JM, Hartmann A, Walker R, Arns W, Senatorski G, Grinyó JM, *et al.* Similar lipid profile but improved long-term outcomes with sirolimus after cyclosporine withdrawal compared to sirolimus with continuous cyclosporine. *Transplant Proc* 2009;**41**:2339–44	Outcome
Morales JM, Tedesco-Silva H, Peddi VR, Russ GR, Marder BA, Hahn CM, *et al.* Planned transition from tacrolimus to sirolimus versus continued tacrolimus in renal allograft patients. *Transplant Int* 2013;**26**:81	Abstract
Moscarelli L, Caroti L, Antognoli G, Zanazzi M, Di Maria L, Carta P, Minetti E. Everolimus leads to a lower risk of BKV viremia than mycophenolic acid in de novo renal transplantation patients: a single-center experience. *Clin Transplant* 2013;**27**:546–54	Study design

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Mourad G, Rostaing L, Legendre C, Garrigue V, Thervet E, Durand D. Sequential protocols using basiliximab versus antithymocyte globulins in renal-transplant patients receiving mycophenolate mofetil and steroids. *Transplantation* 2004;**78**:584–90	Population
Mourer JS, Hartigh J, Zwet EW, Mallat MJ, Dubbeld J, Fijter JW. Randomized trial comparing late concentration-controlled calcineurin inhibitor or mycophenolate mofetil withdrawal. *Transplantation* 2012;**93**:887–94	Study design
Mucha K, Foroncewicz B, Durlik M, Chmura A, Szmidt J, Paczek L. Seven-year follow-up of 77 renal transplant reciepients (RTRs) treated with tacrolimus-based immunosuppression (IS). *NDT Plus* 2010;**3**:iii 268–9	Abstract
Mucha K, Foroncewicz B, Paczek L, Pazik J, Lewandowska D, Krawczyk A, *et al.* 36-month follow-up of 75 renal allograft recipients treated with steroids, tacrolimus, and azathioprine or mycophenolate mofetil. *Transplant Proc* 2003;**35**:2176–8	Abstract
Muehlbacher F, Becker T, Campistol JM, Carvalho DBM, Florman S, Lang P, *et al.* Donor sub-type analysis of three-year outcomes from a phase iii study of belatacept in recipients of extended criteria donor kidneys (benefit-ext trial). *Transplant Int* 2011;**24**:221–2	Abstract
Muhlbacher F, Florman S, Zhang R, Lang P, Lehner F, Massari P, *et al.* 5-year outcomes by donor type from the longterm extension of the belatacept benefit-ext study. *Transplant Int* 2013;**26**:92	Abstract
Mühlbacher F, Neumayer HH, del Castillo D, Stefoni S, Zygmunt AJ, Budde K, European Rapamune Cyclosporine Minimization Study Group. The efficacy and safety of cyclosporine reduction in de novo renal allograft patients receiving sirolimus and corticosteroids: results from an open-label comparative study. *Transpl Int* 2014;**27**:176–86	Population
Mulay AV, Cockfield S, Stryker R, Fergusson D, Knoll GA. Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. *Transplantation* 2006;**82**:1153–62	Population
Mulay AV, Hussain N, Fergusson D, Knoll GA. Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials. *Am J Transplant* 2005;**5**:1748–56	Duplicate
Mulay AV, Hussain N, Fergusson D, Knoll GA. Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials. *Am J Transplant* 2005;**5**:1748–56	Population
Murakami N, Riella LV, Funakoshi T. Risk of metabolic complications in kidney transplantation after conversion to mTOR inhibitor: a systematic review and meta-analysis. *Am J Transplant* 2014;**14**:2317–27	Population
Murbraech K, Holdaas H, Massey R, Undset LH, Aakhus S. Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients: an echocardiographic substudy of the randomized controlled CENTRAL trial. *Transplantation* 2014;**97**:184–8	Outcome
Murphy GJ, Waller JR, Sandford R, Nicholson ML. De novo tacrolimus-based immunosuppression reduces renal allograft fibrosis compared to neoral: a prospective randomized clinical trial. *Br J Surg* 2002;**89**:7	Outcome
Murphy GJ, Waller JR, Sandford RS, Furness PN, Nicholson ML. Randomized clinical trial of the effect of microemulsion cyclosporin and tacrolimus on renal allograft fibrosis. *Br J Surg* 2003;**90**:680–6	Population
Nafar M, Alipour B, Ahmadpoor P, Pour-Reza-Gholi F, Samadian F, Samavat S, Farhangi S. Sirolimus versus calcineurin inhibitor-based immunosuppressive therapy in kidney transplantation: a 4-year follow-up. *Iran J Kidney Dis* 2012;**6**:300–6	Population
Nashan B, Ivens K, Suwelack B, Arns W, Abbud Filho M, myPROMS DE02 Study Group. Conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in maintenance renal transplant patients: preliminary results from the myfortic prospective multicenter study. *Transplant Proc* 2004;**36**(Suppl. 2):521–3	Population
NCT. *A Randomized, Open-Label, Comparative Evaluation of Conversion from Calcineurin Inhibitors to Sirolimus Versus Continued Use of Calcineurin Inhibitors in Renal Allograft Recipients*. URL: www.clinicaltrials.gov/ct/show/NCT00038948 (accessed 25 July 2014)	No data
NCT. *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.* URL: www.clinicaltrials.gov/ct2/show/NCT00035555 (accessed 25 July 2014)	No data
NCT. *A Multi-Centre, Randomised, Open-Label Study to Compare Conversion from Cyclosporin to Rapamune (Sirolimus) Versus Standard Therapy in Established Renal Allograft Recipients on Maintenance Therapy with Mild to Moderate Renal Insufficiency (UK-RAP-09*). URL: www.clinicaltrials.gov/ct2/show/NCT00273871 (accessed 25 July 2014)	No data

TABLE 135 Excluded studies (*continued*)

Study	Reason
NCT. *A Phase III, Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Prograf (tacrolimus)/MMF, Modified Release (MR) Tacrolimus/MMF and Neoral (cyclosporine)/MMF in de novo Kidney Transplant Recipients*. URL: www.clinicaltrials.gov/ct2/show/NCT00064701 (accessed 25 July 2014)	No data
NCT. *An Open-Label, Concentration Controlled, Randomized, 12 Month Study of Prograf + Rapamune + Cor [Study Evaluating Sirolimus in End Stage Renal Disease in High Risk Kidney Transplant Recipients].* URL: www.clinicaltrials.gov/ct2/show/NCT00044720 (accessed 25 July 2014)	Study design
Nguyen C, Shapiro R. New immunosuppressive agents in pediatric transplantation. *Clinics* 2014;**69**(Suppl. 1):8–16	Study design
Nichelle L, Canet S, Garrigue V, Chong G, Mourad G. Arterial hypertension in renal transplant recipients treated with tacrolimus or cyclosporine-Neoral. *Transplant Proc* 2002;**34**:2824–5	Intervention
Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, *et al.* Interventions for enhancing medication adherence. *Cochrane Database of Syst Rev* 2014:CD000011	Population
Novoa PA, Grinyó JM, Ramos FJ, Errasti P, Franco A, Aldana G, *et al.* De novo use of everolimus with elimination or minimization of cyclosporine in renal transplant recipients. *Transplant Proc* 2011;**43**:3331–9	Comparator
Noyola-Villalobos H, Martinez-Calva I, Gomez Vazquez A, Mendiola Fernandez R, Jimenez Chavarria E, Rendon Dosal H, *et al.* Randomized controlled trial of early conversion from calcineurin inhibitor to everolimus in adult renal allograft patients at a single transplant center in Mexico. *Transplantation* 2012;**94**:910.	Abstract
Oberbauer R. Calcineurin inhibitor withdrawal from sirolimus-based therapy in kidney transplantation: a systematic review of randomized trials. *Am J Transplant* 2005;**5**:3023	Outcome
Oberbauer R, Hutchison B, Eris J, Arias M, Claesson K, Mota A, *et al.* 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* 2003;**75**:1277–85	Comparator
Oberbauer R, Segoloni G, Campistol JM, Kreis H, Mota A, Lawen J, *et al.* Early cyclosporine withdrawal from a sirolimus-based regimen results in better renal allograft survival and renal function at 48 months after transplantation. *Transpl Int* 2005;**18**:22–8	Study design
O'Connell P, Fassett R, Pilmore H, Chapman J, Hutchison B, Russ G, *et al.* Long-term post transplantation switch to an everolimus-based therapy with cni elimination/minimization does not overall impact graft function: the ascertain study. *Immunol Cell Biol* 2011;**89**:A5	Abstract
O'Connell P, Fassett R, Pilmore H, Chapman J, Hutchison B, Russ G, *et al.* Post-HOC analysis of the ascertain trial: everolimus based therapy with CNI elimination improves renal function in select populations. *Immunol Cell Biol* 2011;**89**:A5	Abstract
Oh C, Huh K, Lee J, Lee J, Cho H, Kim Y. Multicenter randomized clinical investigation for the safety and efficacy of advagraf (R) (extended-release tacrolimus) vs. prograf (R) (twice-daily tacrolimus) in de novo korean adult kidney recipients. *Am J Transplant* 2013;**13**:317	Abstract
Oh CK, Huh KH, Ha J, Kim YH, Kim YL, Kim YS. Safety and efficacy of the early introduction of everolimus with reduced-exposure cyclosporine a in de novo kidney recipients. *Transplantation* 2015;**99**:180–6	Population
Oppenheimer F, Rebollo P, Grinyo JM, Ortega F, Sanchez-Plumed J, Gonzalez-Molina M, *et al.* Health-related quality of life of patients receiving low-toxicity immunosuppressive regimens: a substudy of the Symphony Study. *Transplantation* 2009;**87**:1210–3	Intervention
Ortega F, Sanchez-Fructuoso A, Cruzado JM, Gomez-Alamillo JC, Alarcon A, Pallardo M, *et al.* Quality of life and tolerability of enteric-coated mycophenolate sodium (EC-MPS) in renal transplant recipients with gastrointestinal tract complaints to mycophenolate mofetil (MMF): a multicenter, randomized, open-label, controlled trial. *Am J Transplant* 2009;**9**:408–9	Abstract
Ortega F, Sanchez-Fructuoso A, Cruzado JM, Gomez-Alamillo JC, Alarcon A, Pallardo L, *et al.* The use of higher doses of mycophenolic acid (MPA) is not associated with worse gastrointestinaltolerability in renal transplant patients converted from mycophenolate mofetil (MMF) to enteric-coated mycophenolate sodium (EC-MPS). *Am J Transplant* 2010;**10**:512	Abstract
Ortega F, Sanchez-Fructuoso A, Cruzado JM, Gomez-Alamillo JC, Alarcon A, Pallardo LL, *et al.* A high glomerular filtration rate (GFR) and the use of an enteric-coated formulation of mycophenolic acid predict less gastrointestinal complaints in renal transplant patients. *Transplant Int* 2011;**24**:220	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Ortega F, Sánchez-Fructuoso A, Cruzado JM, Gómez-Alamillo JC, Alarcón A, Pallardó L, *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**:426–32	Outcome
Otukesh H. Basiliximab induction therapy in pediatric renal transplantation, a double blind clinical trial. *Pediatr Nephrol* 2013;**28**:1533	Abstract
Özdemir BH, Özdemir AA, Erdal R, Özdemir FN, Haberal M. Rapamycin prevents interstitial fibrosis in renal allografts through decreasing angiogenesis and inflammation. *Transplant Proc* 2011;**43**:524–6	Study design
Painter PL, Topp KS, Krasnoff JB, Adey D, Strasner A, Tomlanovich S, Stock P. Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. *Kidney Int* 2003;**63**:2309–16	Comparator
Pankewycz O, Leca N, Kohli R, Weber-Shrikant E, Said M, Alnimri M, *et al.* Conversion to low-dose tacrolimus or rapamycin 3 months after kidney transplantation: a prospective, protocol biopsy-guided study. *Transplant Proc* 2011;**43**:519–23	Abstract
Pankewycz O, Leca N, Said M, Feng L, Patel S, Alnimri M, *et al.* Tacrolimus minimization or sirolimus conversion at 3 months provides equivalent 1 year renal allograft function and histology in low-risk patients with normal protocol biopsies. *Am J Transplant* 2011;**11**:408	Abstract
Pankewycz O, Leca N, Said M, Feng L, Patel S, Kohli R, *et al.* A protocol biopsy directed randomized trial comparing tacrolimus minimization to sirolimus conversion at 3 months results in an equivalent degree of histological injury at 1 year and equivalent renal function at 2 years. *Am J Transplant* 2012;**12**:304	Abstract
Pankewycz O, Leca N, Said M, Feng L, Patel S, Kohli R, *et al.* A protocol biopsy directed randomized trial comparing tacrolimus minimization to sirolimus conversion at 3 months results in an equivalent degree of histological injury at 1 year yet equivalent renal function at 2 years. *Transplantation* 2012;**94**:967	Abstract
Pankewycz O, Leca N, Wallace P, Said M, Feng L, Patel S, *et al.* Rabbit anti-thymocyte globulin (rATG) induction therapy followed by tacrolimus conversion to sirolimus at 3 months does not expand treg cells. *Transplantation* 2012;**94**:771	Abstract
Pankewycz O, Leca N, Wallace P, Said M, Feng L, Patel S, *et al.* Rabbit anti-thymocyte globulin (rATG) induction therapy followed by tacrolimus conversion to sirolimus at 3 months does not increase treg cells. *Am J Transplant* 2012;**12**:448	Abstract
Pankewycz O, Said M, Feng L, Patel S, Alnimri M, Kohli R, *et al.* Conversion to low dose tacrolimus or rapamycin 3 months after kidney transplant: a prospective, protocolbiopsy guided study. *Am J Transplant* 2010;**10**:509	Abstract
Pankewycz OG, Wallace PK, Said M, Leca N, Feng L, Patel S, *et al.* Low dose rabbit anti-thymocyte globulin induction therapy selectively depletes blood lymphocytes but does not promote Treg expansion. *Am J Transplant* 2011;**11**:177–8	Abstract
Paoletti E, Marsano L, Bellino D, Cassottana P, Cannella G. Effect of everolimus on left ventricular hypertrophy of de novo kidney transplant recipients: a 1 year, randomized, controlled trial. *Transplantation* 2012;**93**:503–8	Study design
Paoletti E, Marsano L, Bellino D, Cassottana P, Rolla D, Di Maio G. Everolimus for regression of left ventricular hypertrophy of renal transplant recipients: a randomized controlled trial. *Am J Transplant* 2012;**12**:31	Abstract
Park JB, Kim SJ, Oh HY, Han YS, Kim DJ, Park JW, *et al.* Steroid withdrawal in living donor renal transplant recipients using tacrolimus and cyclosporine: a randomized prospective study. *Transplant Int* 2006;**19**:478–84	Population
Parrott NR, Hammad AQ, Watson CJ, Lodge JP, Andrews CD. Multicenter, randomized study of the effectiveness of basiliximab in avoiding addition of steroids to cyclosporine a monotherapy in renal transplant recipients. *Transplantation* 2005;**79**:344–8	Comparator
Pascual J, Ortuño J, Spanish and Italian Tacrolimus Study Group. Simple tacrolimus-based immunosuppressive regimens following renal transplantation: a large multicenter comparison between double and triple therapy. *Transplant Proc* 2002;**34**:89–91	Study design
Pascual J, Del Castillo D, Cabello M, Pallardo L, Grinyo JM, Fernandez AM, *et al.* Tacrolimus (Tac)-Everolimus (EVL) combination for kidney transplantation (KT): a phase II dose comparison randomized pharmacokinetic (PK). *Am J Transplant* 2008;**8**:585	Abstract
Pascual J, Galeano C, Royuela A, Zamora J. A systematic review on steroid withdrawal between 3 and 6 months after kidney transplantation. *Transplantation* 2010;**90**:343–9	Comparator

TABLE 135 Excluded studies (*continued*)

Study	Reason
Pascual J, Hene R, Langer R, Christiaans M, Ciechanowski K, Vilatoba M, *et al.* Preservation of renal function with everolimus and very low tacrolimus exposure in de novo renal transplant recipients (RTXR) at 12 months: the asset study. *Am J Transplant* 2010;**10**:502	Abstract
Pascual J, Hooff JP, Salmela K, Lang P, Rigotti P, Budde K. Three-year observational follow-up of a multicenter, randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplant. *Transplantation* 2006;**82**:55–61	Study design
Pascual J, Segoloni G, Gonzalez Molina M, Castillo D, Capdevila L, Arias M, *et al.* 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. *Transplant Proc* 2003;**35**:1701–3	Population
Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009;**1**:CD005632	Study design
Pavlakis M. Mycophenolate mofetil versus sirolimus as an adjunct to calcineurin inhibition after renal transplantation. *Nat Clin Pract Nephrol* 2006;**2**:558–9	Outcome
Pearson T, Vincenti F, Grinyo J, Charpentier B, Pestana JM, Rostaing L, *et al.* Primary outcomes from a randomized, phase III study of belatacept versus cyclosporine in kidney transplant recipients (BENEFIT study). *Am J Transplant* 2010;**10**:6	Abstract
Peddi R, Hanaway M, Woodle S, Mulgaonkar S, Harrison G, Vandeputte K, *et al.* Final 36 month results of a randomized trial comparing three induction agents (Alemtuzumab, Thymoglobulin and Basiliximab) with tacrolimus, mycophenolate mofetil and rapid steroid withdrawal in renal transplantation. *Am J Transplant* 2010;**10**:49	Abstract
Perkins J, Alsina M, Anasetti C, Ayala E, Fernandez HF, Kharfan-Dabaja M, *et al.* A randomized, controlled trial of graft-versus-host disease (GVHD) prophylaxis comparing tacrolimus and mycophenolate mofetil to tacrolimus and methotrexate: analysis of GVHD, relapse and survival. *Blood* 2008;**112**:779	Abstract
Pescovitz MD, El-Shahawy M, Vincenti F. Incidence of glucose metabolism disorders at six months after kidney transplantation in non-white patients randomized to cyclosporine or tacrolimus: results of a multicenter study. *Am J Transplant* 2008;**8**:525	Abstract
Pescovitz MD, Vincenti F, Hart M, Melton L, Whelchel J, Mulgaonkar S, *et al.* Pharmacokinetics, safety, and efficacy of mycophenolate mofetil in combination with sirolimus or ciclosporin in renal transplant patients. *Br J Clin Pharmacol* 2007;**64**:758–71	Intervention
Pestana JO, Grinyo JM, Vanrenterghem Y, Becker T, Campistol JM, Florman S, *et al.* Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. *Am J Transplant* 2012;**12**:630–9	Population
Picard N. Does tacrolimus, in comparison with sirolimus, increase mycophenolic acid exposure in kidney transplant recipients? *Clin Pharmacol Ther* 2010;**87**:650–1	Study design
Pietruck F, Budde K, Salvadori M, Sollinger H, Bourbigot B, Gentil MA, Oppenheimer F. Efficacy and safety of enteric-coated mycophenolate sodium in renal transplant patients with diabetes mellitus: post hoc analyses from three clinical trials. *Clin Transplant* 2007;**21**:117–25	Study design
Pilch NA, Taber DJ, Moussa O, Thomas B, Denmark S, Meadows HB, *et al.* Prospective randomized controlled trial of rabbit antithymocyte globulin compared with IL-2 receptor antagonist induction therapy in kidney transplantation. *Ann Surg* 2014;**259**:888–93	Study design
Plischke M, Riegersperger M, Steiner S, Seidinger D, Winkelmayer WC, Sunder-Plassmann G. Short-term renal function in long-term kidney transplant recipients after conversion from cyclosporine a to tacrolimus. A randomized controlled trial. *Am J Transplant* 2012;**12**:204	Abstract
Pliszczynski J, Kahan BD. 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. *Transplant Proc* 2011;**43**:3657–68	Population
Pliszczynski J, Abraham JBA, Schoenberg L, Kahan BD. Fullor 80% reduced cyclosporine (CSA) exposure improves 1 but not 10 or 5 year renal transplant outcomes with sirolimus (SRL) base therapy. *Am J Transplant* 2010;**10**:507	Abstract
Polvino WJ, Melkus TC, Nigro V. Reduction in tacrolimus c-max by conversion from twice-daily tacrolimus capsules (prograf (R)) to once-daily extended release meltdose (R) tacrolimus tablets (LCP-Tacro (TM)): phase ii randomized trial in stable kidney transplant patients. *Am J Transplant* 2012;**12**:407–8	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Ponticelli C. The pros and the cons of mTOR inhibitors in kidney transplantation. *Expert Rev Clin Immunol* 2014;**10**:295–305	Study design
Ponticelli C, Salvadori M, Scolari MP, Citterio F, Rigotti P, Veneziano A, Bartezaghi M, EVEREST Study. Everolimus and minimization of cyclosporine in renal transplantation: 24-month follow-up of the EVEREST study. *Transplantation* 2011;**91**:e72–3	Comparator
Prokopenko E, Scherbakova E, Vatazin A, Pasov S, Budnikova N, Agafonova S. Does mycophenolate mofetil increase the incidence of infections in renal transplant recipients? *Drugs Exp Clin Res* 2005;**31**:199–205	Study design
Pussell B, Russ G, Walker R, Campbell S, O'Connell P, Kanellis J, *et al.* Conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: 18-month efficacy and safety results from a large, randomized, open-label, comparative trial. *Immunol Cell Biol* 2006;**84**:A19–20	Abstract
Reinke P, Haller H, Rath T, Arns W, Paulus EM, Scheidf S, *et al.* Two year data of the apollo trial: renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients. *Transplant Int* 2011;**24**:50	Abstract
Reinke P, Lehner F, Witzke O, Sommerer C, Eisenberger U, Arns W, *et al.* 5 Years follow-up on renal function-ZEUS trial: improved renal function of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in de novo renal transplant patients. *Transplant Int* 2013;**26**:21	Abstract
Remuzzi G, Cravedi P, Costantini M, Lesti M, Ganeva M, Gherardi G, *et al.* Mycophenolate mofetil versus azathioprine for prevention of chronic allograft dysfunction in renal transplantation: the MYSS follow-up randomized, controlled clinical trial. *J Am Soc Nephrol* 2007;**18**:1973–85	Population
Remuzzi G, Lesti M, Gotti E, Ganeva M, Dimitrov BD, Ene-Iordache B, *et al.* Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial. *Lancet* 2004;**364**:503–12	Population
Renner FC, Dietrich H, Bulut N, Celik D, Gaertner ND, Karoui S, *et al.* The development of BK viremia after renal transplantation is associated with a reduced CD8 cell IL-2 response. *Transplant Int* 2011;**24**:56	Abstract
Renner FC, Dietrich H, Bulut N, Celik D, Freitag E, Gaertner N, *et al.* The risk of polyomavirus-associated graft nephropathy is increased by a combined suppression of CD8 and CD4 cell-dependent immune effects. *Transplant Proc* 2013;**45**:1608–10	No data
Rhat T, Sommerer C, Haller H, Reinke P, Witzke O, Suwelack B, *et al.* Outcome on renal function of everolimus conversion in maintenance KTX patients: 4 years apollo trial. *Transplant Int* 2013;**26**:240	Abstract
Rice K, Vanrenterghem Y, Merville P, Muehlbacher F, Zhang R, Duan T, *et al.* Three-year outcomes in elderly kidney transplant recipients treated with belatacept vs cyclosporine in BENEFIT-EXT. *Am J Transplant* 2012;**12**:403	Abstract
Richard MG, Angela W, Ruster Lorenn P, Matheson Sandra L, Higgins Gail Y, Willis Narelle S, *et al.* Interleukin-2 receptor antagonists versus atg for kidney transplant recipients: an updated cochrane review. *Immunol Cell Biol* 2010;**88**:A21	Abstract
Riegersperger M, Plischke M, Sengoelge G, Steiner S, Seidinger D, Winkelmayer WC, *et al.* Effect of conversion from cyclosporine to tacrolimus on endothelial progenitor cells in stable long-term kidney transplant recipients A Randomized Controlled Trial. *Am J Transplant* 2012;**12**:203	Population
Riegersperger M, Plischke M, Steiner S, Seidinger D, Sengoelge G, Winkelmayer WC, Sunder-Plassmann G. Effect of conversion from ciclosporin to tacrolimus on endothelial progenitor cells in stable long-term kidney transplant recipients. *Transplantation* 2013;**95**:1338–45	Abstract
Roodnat J, Hilbrands LB, Hene RJ, De Sevaux RGL, Gregoor PJHS, Van Gestel JAK, *et al.* 15 year follow-up of a multicentre, randomised, calcineurin inhibitor (CNI) withdrawal study in kidney transplantation. *Transplant Int* 2013;**26**:83–4	Abstract
Roodnat JI, Hilbrands LB, Hené RJ, de Sévaux RG, Smak Gregoor PJ, Kal-van Gestel JA, *et al.* 15-year follow-up of a multicenter, randomized, calcineurin inhibitor withdrawal study in kidney transplantation. *Transplantation* 2014;**98**:47–53	Population
Rostaing L, Budde K, Bunnapradist S. A phase 3, double-blind, multi-center, non-inferiority, randomized study to examine the efficacy and safety of lcp-tacro (TM) tablets, once daily, compared to prograf (R) capsules, twice daily, in combination with mycophenolate mofetil in de novo adult kidney transplantation: baseline characteristics. *Am J Transplant* 2013;**13**:339	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Rostaing L, Budde K, Ciechanowski K, Bunnapradist S, Silva H, Grinyi JM. Once-daily LCP-tacro demonstrates comparable efficacy and safety to twice daily prograf: a phase 3 study for prevention of acute allograft rejection in de novo adult kidney transplant recipients. *Transplant Int* 2013;**26**:171	Abstract
Rostaing L, Ciechanowski K, Bunnapradist S, Mulgaonkar S. Conversion from tacrolimus capsules twice daily to tacrolimus tablets once daily in stable kidney transplant patients: efficacy results from a phase iii, open-label, multicenter, prospective, randomized study. *Transplant Int* 2011;**24**:227	Abstract
Rostaing L, Fassett R, Dantal J, Binet I, O'Connell P, MacHein U, *et al.* Risk factor analysis for renal function outcome in maintenance renal transplant recipients from the ASCERTAIN study. *Am J Transplant* 2011;**11**:44–5	Abstract
Rostaing L, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, del Carmen Rial M, *et al.* Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. *Clin J Am Soc Nephrol* 2011;**6**:430–9	Population
Rostaing L, Mourad G, Legendre C. Sustainable tolerability effects of myfortic (R) in combination with Neoral (R) and steroids at 12 months, in de novo kidney transplantation: a randomized, multicentre, open, prospective controlled study. *Am J Transplant* 2005;**5**:190	Abstract
Rostaing L, Nainan G, Del Carmen Rial M, Steinberg S, Vincenti F, Shi R, *et al.* Switch from a CNI-to a belatacept-based immunosuppressive regimen in kidney transplant recipients is safe and results in better renal function: 12 month results from a phase II study. *NDT Plus* 2010;**3**:iii285	Abstract
Rostaing L, Neumayer HH, Reyes-Acevedo R, Bresnahan B, Florman S, Vitko S, *et al.* Belatacept-versus cyclosporine-based immunosuppression in renal transplant recipients with pre-existing diabetes. *Clin J Am Soc Nephrol* 2011;**6**:2696–704	Population
Rostaing L, Reyes-Acevedo R, Neumayer HH, Vitko S, Xing J, Thomas D, *et al.* Outcomes at 3 years in kidney transplant recipients with pre-transplant diabetes from two phase 3 belatacept studies. *Transplant Int* 2011;**24**:69	Abstract
Rostaing L, Vincenti F, Grinyó J, Rice KM, Bresnahan B, Steinberg S, *et al.* Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. *Am J Transplant* 2013;**13**:2875–83	Population
Ruggenenti P, Codreanu I, Cravedi P, Perna A, Gotti E, Remuzzi G. 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. *Clin J Am Soc Nephrol* 2006;**1**:546–54	Comparator
Ruggenenti P, Perico N, Gotti E, Cravedi P, D'Agati V, Gagliardini 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**:956–64	Population
Ruiz JC, Alonso A, Arias M, Campistol JM, González Molina M, González Posada JM, *et al.* Conversion to sirolimus. *Nefrologia* 2006;**26**(Suppl. 2):52–63	Study design
Ruiz JC, Campistol JM, Sanchez-Fructuoso A, Mota A, Grinyo JM, Paul J, *et al.* Early sirolimus use with cyclosporine elimination does not induce progressive proteinuria. *Transplant Proc*. 2007;**39**:2151–2	Abstract
Ruiz JC, Sanchez Fructuoso A, Hernandez D, Sanchez Plumed J, Fernandez A, Pastor Rodriguez A, *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 Int* 2011;**24**:112	Abstract
Ruiz JC, Sanchez Fructuoso A, Hernandez D, Sanchez Plumed J, Fernandez A, Pastor Rodriguez A, *et al.* Better renal function with early everolimus introduction and calcineurin inhibitor withdrawal at third month in kidney recipients at month 12: results of the the ERIC study. *Am J Transplant* 2011;**11**:407	Abstract
Rush DN, Cockfield SM, Nickerson PW, Arlen DJ, Boucher A, Busque S, *et al.* Factors associated with progression of interstitial fibrosis in renal transplant patients receiving tacrolimus and mycophenolate mofetil. *Transplantation* 2009;**88**:897–903	Study design
Russ G, Durrbach A, Larsen CP, Medina Pestana J, Vanrenterghem Y, Vincenti F, *et al.* Benefit-ext study two year outcomes: belatacept vs cyclosporine (CSA) in extended criteria donor (ECD) kidney transplants. *Immunol Cell Biol* 2011;**89**:A2	Abstract
Russ G, Eris J, Kanellis J, Hutchison B, Hibberd A, Pilmore H, *et al.* Multicentre rct of early switch to everolimus plus steroids or everolimus plus csa versus csa, mpa and steroids in de novo kidney transplant recipients: 12 month analysis. *Immunol Cell Biol* 2012;**90**:A30–A	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Russ G, Jamieson N, Oberbauer R, Arias M, Murgia MG, Blancho G, *et al.* Three-year health-related quality-of-life outcomes for sirolimus-treated kidney transplant patients after elimination of cyclosporine. *Transpl Int* 2007;**20**:875–83	Study design
Russ G, Segoloni G, Oberbauer R, Legendre C, Mota A, Eris J, *et al.* Superior outcomes in renal transplantation after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function. *Transplantation* 2005;**80**:1204–11	Comparator
Russ G, Walker R, Pilmore H, Kanellis J, Hutchison B, Chadban S, *et al.* Lower incidence of cytomegalovirus and BK virus with everolimus versus mycophenolate in DE novo renal transplant patients: results from a multicenter, prospective study. *Immunol Cell Biol* 2011;**89**:A23–4	Abstract
Russ G, Walker R, PilmoreH, Kanellis J, Hutchison B, Chadban S, *et al.* Everolimus plus reduced csa exposure: efficacy results from a multicenter, randomized prospective study in renal transplantation. *Immunol Cell Biol* 2011;**89**:A1–2	Study design
Saddadi F, Sedghipour M, Tabatabaei A, Kamal Hedaiat D, Alatab S. Comparison of the effects of sirolimus and cyclosporine on left ventricular hypertrophy in kidney transplant recipients, a 1-year single center prospective cohort study in Dr. Shariati hospital Tehran, Iran. *Iranian J Kidney Dis* 2011;**5**:62–3	Abstract
Sadek S, Medina J, Arias M, Sennesael J, Squifflet JP, Vogt B, Neo Int-05 Study group. Short-term combination of mycophenolate mofetil with cyclosporine as a therapeutic option for renal transplant recipients: a prospective, multicenter, randomized study. *Transplantation* 2002;**74**:511–7	Population
Saito K, Uchida K, Takahara S, Yoshimura N, Teraoka S, Cornu-Artis C, *et al.* Efficacy of everolimus with reduced cyclosporine in japanese de novo renal transplant recipients: 24-month, randomized, multicenter study. *Am J Transplant* 2013;**13**:314	Abstract
Salmela K, Vitko S, Wlodarczyk Z, Czajkowski Z, Margreiter R, Grp TS. Tacrolimus with MMF or two different doses of sirolimus in kidney transplantation: a large randomised multicentre study. *Am J Transplant* 2005;**5**:571	Abstract
Salvadori M, Holzer H, Civati G, Sollinger H, Lien B, Tomlanovich S, *et al.* Long-term administration of enteric-coated mycophenolate sodium (EC-MPS; myfortic) is safe in kidney transplant patients. *Clin Nephrol* 2006;**66**:112–9	Study design
Salvadori M, Holzer H, De Mattos A, Sollinger H, Arns W, Oppenheimer F, *et al.* Enteric-coated mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2004;**4**:231–6	Population
Salvadori M, Scolari MP, Bertoni E, Citterio F, Rigotti P, Cossu M, *et al.* Everolimus with very low-exposure cyclosporine a in de novo kidney transplantation: a multicenter, randomized, controlled trial. *Transplantation* 2009;**88**:1194–202	Study design
Samadzadeh B, Alemi M, Heidarnejadiyan J, Torkamanasadi F. Prophylactic effect of mycophenolate mofetil on early outcomes of living donor kidney transplantation. *Iran J Kidney Dis* 2012;**6**:63–8	Population
Sampaio EL, Pinheiro-Machado PG, Garcia R, Felipe CR, Park SI, Casarini DE, *et al.* Mycophenolate mofetil vs. sirolimus in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen. *Clin Transplant* 2008;**22**:141–9	Population
Samsel R, Pliszczyński J, Chmura A, Korczak G, Włodarczyk Z, Cieciura T, *et al.* Safety and efficacy of high dose ATG bolus administration on rewascularization in kidney graft patients – long term results. *Ann Transplant* 2008;**13**:32–9	Population
Sanchez-Fructuoso A, Ruiz JC, Hernandez D, Sanchez-Plumed J, Fernandez A, Pastor Rodriguez A, *et al.* Early everolimus introduction and calcineurin inhibitor withdrawal in renal transplant patients: a multicenter, randomized, open-label study (the eric study). *Am J Transplant* 2010;**10**:506	Abstract
Sánchez-Fructuoso AI. Everolimus: an update on the mechanism of action, pharmacokinetics and recent clinical trials. *Expert Opin Drug Metab Toxicol* 2008;**4**:807–19	Comparator
Sandes Freitas TV, Harada KM, Felipe CR, Galante NZ, Sampaio EL, Ikehara E, *et al.* Steroid or tacrolimus withdrawal in renal transplant recipients using sirolimus. *Int Urol Nephrol* 2011;**43**:1221–8	Abstract
Sandes-Freitas T, Felipe C, Campos E, Soares M, Tedesco H, Franco M, *et al.* Incidence of subclinical rejection and de novo donor specific antibodies in calcineurin sparing regimens. *Am J Transplant* 2013;**13**:35	Study design
Sarvary E, Wagner L, Telkes G, Gaman G, Varga M, Gaal I, *et al.* De novo Prograf versus de novo Advagraf: are trough level profile curves similar? *Transplant Proc* 2014;**46**:2164–7	Population

TABLE 135 Excluded studies (*continued*)

Study	Reason
Saturnino Luciana TM, Ceccato Maria GB, Cherchiglia Mariangela L, Andrade Eli Iola G, Giordano Luiz Flavio C, Acurcio Francisco A. Target of rapamycin inhibitors (TORi) as maintenance immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2012;**3**:CD009637	Study design
Schaefer HM, Kizilisik AT, Feurer I, Nylander WA, Langone AJ, Helderman JH, Shaffer D. Short-term results under three different immunosuppressive regimens at one center. *Transplant Proc* 2006;**38**:3466–7	Population
Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, *et al.* Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. *Transplantation* 2009;**87**:233–42	Population
Schena FP, Wali RK, Pascoe MD, Alberu J, Rial MD, Sirolimus Renal Conversion Trial S. A randomized, open-label, comparative evaluation of conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients. *Am J Transplant* 2005;**5**:413	Abstract
Schnuelle P, van der Heide JH, Tegzess A, Verburgh CA, Paul LC, van der Woude FJ, de Fijter JW. Open randomized trial comparing early withdrawal of either cyclosporine or mycophenolate mofetil in stable renal transplant recipients initially treated with a triple drug regimen. *J Am Soc Nephrol* 2002;**13**:536–43	Study design
Schwarz C, Mayerhoffer S, Berlakovich G, Steininger R, Soliman T, Watschinger B, *et al.* Belatacept in de novo kidney transplant recipients-10-year experience in a single center. *European Surgery – Acta Chirurgica Austriaca* 2011;**43**:12–13	Abstract
Sellarés J, Moreso F, Ruiz JC, Seron D. Mean glomerular volume after renal transplantation in patients receiving sirolimus and cyclosporine a compared with elimination of cyclosporine a at 3 months. *Transplantation* 2011;**91**:e5–6	Comparator
Sellars D. A *phase 4, randomised open-label, controlled, single centre study of induction with basiliximab, mycophenolate mofetil and tacrolimus with rapid steriod withdrawal and randomisation to either continuation with mycophenolate mofetil and tacromlimus or switch to sirolimus and mycophenolate mofetil maintenance in renal transplant recipeints*. 2004. National Research Register, UK. URL: www.nrr.nhs.uk (accessed 25 July 2014)	Unobtainable
Servais A, Meas-Yedid V, Toupance O, Lebranchu Y, Thierry A, Moulin B, *et al.* Interstitial fibrosis quantification in renal transplant recipients randomized to continue cyclosporine or convert to sirolimus. *Am J Transplant* 2009;**9**:2552–60	Population
Shah G, Xu L, Dalal P, Chhabra D, Friedewald J, Ho B, *et al.* Conversion from CNI to SRL in a pred-free immunosuppressive regimen: interim report of a prospective randomized study. *Am J Transplant* 2010;**10**:504	Abstract
Shamseddin MK, Gupta A. Sirolimus: not so sparing in the Spare-the-Nephron trial. *Kidney Int* 2011;**79**:1379	Language
Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R. Meta-analysis of calcineurin-inhibitor-sparing regimens in kidney transplantation. *J Am Soc Nephrol* 2011;**22**:2107–18	Study design
Sheashaa HA, Bakr MA, Ismail AM, Gheith OE, El-dahshan KF, Sobh MA, Ghoneim MA. Long-term evaluation of basiliximab induction therapy in live donor kidney transplantation: a five-year prospective randomized study. *Am J Nephrol* 2005;**25**:221–5	Population
Sheashaa HA, Bakr MA, Ismail AM, Mahmoud KM, Sobh MA, Ghoneim MA. Basiliximab induction therapy for live donor kidney transplantation: a long-term follow-up of prospective randomized controlled study. *Clin Exper Nephrol* 2008;**12**:376–81	Population
Sheashaa HA, Bakr MA, Ismail AM, Sobh MA, Ghoneim MA. Basiliximab reduces the incidence of acute cellular rejection in live-related-donor kidney transplantation: a three-year prospective randomized trial. *J Nephrol* 2003;**16**:393–8	Population
Sheashaa HA, Bakr MA, Rashad RH, Ismail AM, Sobh MA, Ghoneim MA. Ten-year follow-up of basiliximab induction therapy for live-donor kidney transplant: a prospective randomized controlled study. *Exp Clin Transplant* 2011;**9**:247–51	Population
Sheashaa HA, Hamdy AF, Bakr MA, Abdelbaset SF, Ghoneim MA. Long-term evaluation of single bolus high dose ATG induction therapy for prophylaxis of rejection in live donor kidney transplantation. *Int Urol Nephrol* 2008;**40**:515–20	Population
Shehata M, Bhandari S, Venkat-Raman G, Moore R, D'Souza R, Riad H, *et al.* Effect of conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium on maximum tolerated dose and gastrointestinal symptoms following kidney transplantation. *Transpl Int* 2009;**22**:821–30	Study design

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Shehata M, Bhandari S, Venkat-Raman G, Moore R, D'Souza R. Health-related quality of life maintained despite increase in mycophenolic acid (mpa) dose following conversion from mycophenolate mofetil (mmf) to enteric-coated mycophenolate sodium (ec-mps): a randomized, multicenter trial in kidney transplant recipients. *Transplant Int* 2009;**22**:110	Abstract
Shihab F, Christians U, Smith L, Wellen JR, Kaplan B. Focus on mTOR inhibitors and tacrolimus in renal transplantation: pharmacokinetics, exposure-response relationships, and clinical outcomes. *Transpl Immunol* 2014;**31**:22–32	Study design
Shihab F, Tedesco-Silva H, Johnston T, Kim YS, Zibari GB, Walker R, *et al.* Lower incidence of cytomegalovirus and BK virus adverse events with everolimus versus mycophenolate was maintained over 24 months in de novo renal transplant recipients. *Am J Transplant* 2011;**11**:45	Abstract
Shihab FS, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, *et al.* Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. *Clin Transplant* 2013;**27**:217–26	Study design
Shihab FS, Waid TH, Conti DJ, Yang H, Holman MJ, Mulloy LC, *et al.* Conversion from cyclosporine to tacrolimus in patients at risk for chronic renal allograft failure: 60-month results of the CRAF Study. *Transplantation* 2008;**85**:1261–9	Population
Shun CS, Hao JW, Sun J, Yang DA. A comparison between the therapeutic effects of mycophenolate mofetil and azathioprine in the management of patients after renal transplantation. *Herald of Medicine* 2002;**21**:544–6	Language
Sidhu M, Odeyemi AO, Hart WM, Dada BR. Belatacept versus tacrolimus: results of an indirect analysis from a systematic review of immunosuppressive therapies for kidney transplant recipients. *Value Health* 2011;**14**:A330	Abstract
Sid Sidhu M, Odeyemi AO, Hart WM, Dada BR. Belatacept versus tacrolimus: results of an indirect analysis from a systematic review of immunosuppressive therapies for kidney transplant recipients. *Value Health* 2011;**14**:A330	Dupliocate
Silva H. A phase III, randomized, open-label, comparative, multi-center study to assess the safety and efficacy of Prograf (Tacrolimus)/MMF, modified release (MR) Tacrolimus/MMF and Neoral (Cyclosporine)/MMF in de novo kidney transplant recipients: 12 month results. *Am J Transplant* 2006;**6**(Suppl. 2):318	Abstract
Silva HT, Yang HC, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, *et al.* One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *Am J Transplant* 2007;**7**:595–608	Population
Silva HT, Yang HC, Meier-Kriesche HU, Croy R, Holman J, Fitzsimmons WE, First MR. 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* 2014;**97**:636–41	Population
Silva HT, Felipe CR, Garcia VD, Neto ED, Filho MA, Contieri FL, *et al.* Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. *Am J Transplant* 2013;**13**:3155–63	Population
Smith MP, Newstead CG, Ahmad N, Lewington AJ, Tibble S, Lodge JP, *et al.* Poor tolerance of sirolimus in a steroid avoidance regimen for renal transplantation. *Transplantation* 2008;**85**:636–9	Study design
Sola R, Diaz JM, Guirado L, Sainz Z, Gich I, Picazo M, *et al.* Tacrolimus in induction immunosuppressive treatment in renal transplantation: comparison with cyclosporine. *Transplant Proc* 2003;**35**:1699–700	Study design
Soleimani AR, Kamkar I, Nikoueinejad H, Moraweji AR. Comparison of cyclosporine and sirolimus effects on serum creatinine level over five years after kidney transplantation. *Transplant Proc* 2013;**45**:1644–7	Population
Sollinger H. Enteric-coated mycophenolate sodium: therapeutic equivalence to mycophenolate mofetil in de novo renal transplant patients. *Transplant Proc* 2004;36:517S–20S	Comparator
Sommerer C, Budde K, Becker T, Arns W, Reinke P, Eisenberger U, *et al.* New onset diabetes after transplantation and mTOR inhibitors: results of the ZEUS trial. *Am J Transplant* 2011;**11**:412–13	Abstract
Sommerer C, Rath T, Budde K, Haller H, Arns W, Scheidl S, *et al.* Renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients: 2 year follow-up data of the apollo trial. *Transplant Int* 2011;**24**:180	Abstract
Sommerer C, Rath T, Haller H, Arns W, Suwelack B, Reinke P, *et al.* 4 Year data of the apollo trial: outcome on renal function of an everolimus based therapy after calcineurin inhibitor withdrawal in maintenance renal transplant recipients. *Transplant Int* 2013;**26**:21	Abstract

TABLE 135 Excluded studies (*continued*)

Study	Reason
Squifflet JP, Vanrenterghem Y, Hooff JP, Salmela K, Rigotti P. Safe withdrawal of corticosteroids or mycophenolate mofetil: results of a large, prospective, multicenter, randomized study. *Transplant Proc* 2002;**34**:1584–6	Study design
SRCTN. *Mycophenolate sodium versus Everolimus or Cyclosporine with Allograft Nephropathy as Outcome*. URL: www.controlled-trials.com/ISRCTN69188731 (accessed 25 July 2014)	No data
Stallone G, Di Paolo S, Schena A, Infante B, Battaglia M, Ditonno P, *et al.* Addition of sirolimus to cyclosporine delays the recovery from delayed graft function but does not affect 1-year graft function. *J Am Soc Nephrol* 2004;**15**:228–33	Population
Stallone G, Infante B, Schena A, Battaglia M, Ditonno P, Loverre A, *et al.* Rapamycin for treatment of chronic allograft nephropathy in renal transplant patients. *JASN* 2005;**16**:3755–62	Population
Stegall MD, Larson TS, Prieto M, Gloor J, Textor S, Nyberg S, *et al.* Kidney transplantation without calcineurin inhibitors using sirolimus. *Transplant Proc* 2003;**35**:125S–7S	Population
Stevens RB, Foster KW, Lane JT, Miles CD, Kalil AC, Sandoz JP, *et al.* Significantly reduced renal allograft histopathology after single-dose rATG induction and calcineurin-inhibitor withdrawal vs. minimization: final report from a prospective, randomized clinical trial. *Am J Transplant* 2011;**11**:209–10	Abstract
Stoves J, Newstead CG, Baczkowski AJ, Owens G, Paraoan M, Hammad AQ. A randomized controlled trial of immunosuppression conversion for the treatment of chronic allograft nephropathy. *Nephrol Dial Transplant* 2004;**19**:2113–20	Population
Strologo LD, Tonshoff B, Pape L, Ettenger R, Niaudet P, Martzloff ED, *et al.* Rationale and design of a study evaluating the efficacy and safety of early conversion of calcineurin inhibitor to everolimus in paediatric renal transplant recipients. *Pediatr Nephrol* 2012;**27**:1816	Abstract
Su L, Tam N, Deng R, Chen P, Li H, Wu L. Everolimus-based calcineurin-inhibitor sparing regimens for kidney transplant recipients: a systematic review and meta-analysis. *Int Urol Nephrol* 2014;**46**:2035–44	Population
Sułowicz W, Bachleda P, Rydzewski A, Rutkowski B, Szakály P, Asztalos L, *et al.* Discontinuation of mycophenolate mofetil from a tacrolimus-based triple regimen 2 months after renal transplantation: a comparative randomized, multicentre study. *Transpl Int* 2007;**20**:230–7	Population
Suszynski TM, Gillingham KJ, Rizzari MD, Dunn TB, Payne WD, Chinnakotla S, *et al.* Prospective randomized trial of maintenance immunosuppression with rapid discontinuation of prednisone in adult kidney transplantation. *Am J Transplant* 2013;**13**:961–70	Population
Suwelack B, Gerhardt U, Kobelt V, Hillebrand U, Matzkies F, Hohage H. 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. *Transplant Proc* 2002;**34**:1803–5	Study design
Taber D, Bratton C, Al Manasra A, Pilch N, Meadows H, McGillicuddy J, *et al.* The impact of induction therapy on clinical outcomes and quality of life in aged kidney transplant recipients. *Am J Transplant* 2013;**13**:429	Abstract
Taber DJ, Pilch NA, Meadows HB, Denmark S, McGillicuddy JW, Bratton CF, *et al.* Prospective comparative efficacy of induction therapy in a high-risk kidney transplant (KTX) population. *Am J Transplant* 2012;**12**:57	Abstract
Takahara S, Uchida K, Yoshimura N, Teraoka S, Kobayashi E, Teshima R, *et al.* Efficacy and safety of concentration controlled everolimus with reduced dose cyclosporine in japanese adult de-novo renal transplant patients: 12 month results. *Am J Transplant* 2012;**12**:300	Abstract
Takahashi K, Uchida K, Yoshimura N, Takahara S, Teraoka S, Teshima R, *et al.* Efficacy and safety of concentration-controlled everolimus with reduced-dose cyclosporine in Japanese de novo renal transplant patients: 12-month results. *Transplant Res* 2013;**2**:14	Population
Tan J, Yang S, Wu W. Basiliximab (Simulect) reduces acute rejection among sensitized kidney allograft recipients. *Transplant Proc* 2005;**37**:903–5	Comparator
Tanabe K, Tsuchiya T, Ishida H, Tanabe T, Shimizu T, Omoto K, *et al.* An open label, prospective randomized controlled study comparing tacrolimus once-daily and twice-daily in de novo kidney transplantation: pharmacokinetics and pathological analysis by protocol biopsy. *Am J Transplant* 2012;**12**:55	Abstract
Tang SC, Chan KW, Tang CS, Lam MF, Leung CY, Tse KC, *et al.* Conversion of ciclosporin A to tacrolimus in kidney transplant recipients with chronic allograft nephropathy. *Nephrol Dial Transplant* 2006;**21**:3243–51	Study design

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Tedesco H. *Efficacy and Safety of Induction Strategies Combined with Low Tacrolimus Exposure in Kidney Transplant Recipients Receiving Everolimus or Sodium Mycophenolate*. 2011. URL: www.clinicaltrials.gov/ct2/show/NCT01354301 (accessed 25 July 2014)	No data
Tedesco H, Felipe C, Franco M, Sandes T, Campos E, Pestana JOM. High incidence of subclinical acute rejection in low risk kidney transplant recipients on tacrolimus-based immunosuppressive regime. *Transplantation* 2012;**94**:329	Abstract
Tedesco H, Felipe C, Sandes T, Cristelli M, Rodrigues C, Pestana JOM. A prospective randomized trial aimed to reduce the incidence of cytomegalovirus (CMV) infection in kidney transplant recipients. *Transplantation* 2012;**94**:4	Abstract
Tedesco H, Felipe C, Wang L, Rodrigues C, Sandes T, Cristelli M, *et al.* A prospective randomized trial aimed to reduce the incidence of cytomegalovirus (CMV) infection in kidney transplant (KT) recipients. *Am J Transplant* 2013;**13**:56	Abstract
Tedesco H, Garcia V, David-Neto E, Contieri F, Carvalho D, Abbud M, *et al.* Conversion from tacrolimus (TAC) to sirolimus (SRL)-based immunosuppressive regimen in kidney transplant recipients: 1 year results. *Am J Transplant* 2012;**12**:299	Abstract
Tedesco H, Kim YS, Lackova E, Johnston T, Zibari G, Panis C, *et al.* Everolimus with reduced-dose cyclosporine as a strategy for optimizing long-term renal function: results from a randomized study in 833 de-novo renal-transplant recipients. *Transplant Int* 2009;**22**:186–7	Abstract
Tedesco H, Neto E, Garcia V, Continieri F, Carvalho D, Abbud M, *et al.* Conversion from tacrolimus (TAC) to sirolimus (SRL)-based immunosuppressive regimen in kidney transplant recipients: 2 years results. *Am J Transplant* 2013;**13**:313	Abstract
Tedesco Silva H, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, *et al.* Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant* 2010;**10**:1401–13	Study design
Tedesco-Silva H, Bernhardt P, Dong G, Escrig C. Search for new endpoints for clinical trials of immunosuppressive drugs in kidney transplantation. *Transplant Int* 2013;**26**:248	Abstract
Tedesco-Silva H, Kim YS, Johnston T, Walker R, Zibari GB, Cornu-Artis C, *et al.* Concentration-controlled everolimus with reduced cyclosporine concentration in de novo renal transplant recipients: efficacy results at 24 months. *Am J Transplant* 2011;**11**:46	Abstract
Tedesco-Silva H, Peddi R, Russ G, Marder B, Hahn C, Li H, *et al.* Open-label study of planned transition from tacrolimus to sirolimus vs continued tacrolimus in renal allograft recipients: demographics and interim safety results. *Am J Transplant* 2013;**13**:337	Abstract
Tedesco-Silva H, Peddi VR, Sanchez-Fructoso A, Russ G, Marder B, Hahn C, *et al.* Interim results from an open-label study of planned transition from tacrolimus to sirolimus vs continued tacrolimus in renal allograft recipients: cardiovascular safety. *Transplantation* 2012;**94**:142	Abstract
Tedesco-Silva H, Vitko S, Pascual J, Eris J, Magee JC, Whelchel J, *et al.* 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in de novo renal transplant recipients. *Transpl Int* 2007;**20**:27–36	Comparator
Teh LK, Dom SHM, Zakaria ZA, Salleh MZ. A systematic review of the adverse effects of tacrolimus in organ transplant patients. *African J Pharmacy Pharmacol* 2011;**5**:764–71	Population
Thervet E, Durrbach A, Rostaing L, Ouali N, Wolf P, Pouteil-Noble C, *et al.* Use of sirolimus as initial therapy after renal transplantation: preliminary results of a randomized pilot study in patient receiving marginal kidneys. *Am J Transplant* 2004;**4**(Suppl. 8):345	Abstract
Thierry A, Pourreau F, Jollet I, Abou-Ayache R, Bridoux F, Touchard G. Minimization of immunosuppression: long-term impact on HLA allo-immunisation and graft outcome. *Am J Transplant* 2012;**12**:302	Abstract
Thurston S, Kalsekar A, G.J LI, Sennfalt K. Mixed treatment comparisons of immunosuppressants following renal transplant. *Value Health* 2011;**14**:A331	Abstract
Thurston S, Kalsekar A, G.J LI, Sennfalt K. Mixed treatment comparisons of immunosuppressants following renal transplant. *Value Health* 2011;**14**:A331	Duplicate
Tian JH, Wang X, Yang KH, Liu AP, Luo XF, Zhang J. Induction with and without antithymocyte globulin combined with cyclosporine/tacrolimus-based immunosuppression in renal transplantation: a meta-analysis of randomized controlled trials. *Transplant Proc* 2009;**41**:3671–6	Population

TABLE 135 Excluded studies (*continued*)

Study	Reason
Tischer SM, Pilch NA, Taber DJ, Krisl JC, Meadows HB, Byrns JS, *et al.* Does RATG induction therapy increase the risk of severe infection in kidney transplant recipients? *Am J Transplant* 2012;**12**:317	Abstract
Tischer SM, Taber DJ, Pilch NA, Krisl JC, Meadows HB, McGillicuddy JW, *et al.* Critical analysis of BK infection in kidney transplant recipients with modern immunosuppression. *Am J Transplant* 2012;**12**:346	Abstract
Toenshoff B, Weber L, Hoecker B. Prospective randomized multicenter trial on withdrawal of steroids in pediatric renal transplant recipients with stable graft function on cyclosporin a (CsA) and mycophe-nolate mofetil (MMF). *Pediatr Nephrol* 2007;**22**:1429	Abstract
Tonshoff B, Pape L, Ettenger R, Dello Strologo L, Niaudet P, Martzloff D, *et al.* Early conversion of calcineurin inhibitor to everolimus in de novo paediatric renal transplant recipients and its impact on efficacy and renal function; design of an open-label, randomised, multi-centre study. *Transplantation* 2012;**94**:1208	Abstract
Tonshoff B, Pape L, Strologo LD, Ettenger R, Niaudet P, Martzloff ED, *et al.* Design of crad001a2314: a randomised study evaluating everolimus in paediatric renal transplantation. *Transplant Int* 2013;**26**:328	Abstract
Touchard G, Mourad G, Lebranchu Y, Rostaing L, Villemain F, Heng A-E, *et al.* Intensified dose of enteric-coated mycophenolate sodium (EC-MPS) for steroids avoidance, in combination with ciclosporine micro-emulsion (CSA-ME): multicenter, randomized, open label, comparative study in de novo kidney transplantation (DOMINOS). *Transplant Int* 2009;**22**:232–3	Abstract
Touchard G, Mourad G, Lebranchu Y, Rostaing L, Villemain F. Multicenter, randomized, comparative, open-labelstudy to evaluate efficacy and safety a combination of anti-IL2R, intensified dose of enteric-coated mycophenolate sodium (EC-MPS) for 6 weeks, ciclosporine micro-emulsion (CSA-ME), with or without steroids, in adult kidney de novo transplant recipients (TxR). *Am J Transplant* 2010;**10**:515	Abstract
Töz H, Sen S, Sezi M, Duman S, Ozkahya M, Ozbek S, *et al.* Comparison of tacrolimus and cyclosporin in renal transplantation by the protocol biopsies. *Transplant Proc* 2004;**36**:134–6	Population
Trofe-Clark J, Goral S, Shaw L, Figurski M, Abt PL, Bloom RD. Comparative study of gastrointestinal(GI) events in african american kidney transplant recipients treated with mycophenolate mofetil (MMF) versus enteric coated mycophenolate sodium (ECMS). *Am J Transplant* 2010;**10**:470	Abstract
Trompeter R, Filler G, Webb NJA, Watson AR, Milford DV, Tyden G, *et al.* Randomized trial of tracolimus versus cyclosporin microemulsion in renal transplantation. *Pediatr Nephrol* 2002;**17**:141–9	Duplicate
Tsuchiya T, Ishida H, Tanabe T, Shimizu T, Honda K, Omoto K, Tanabe K. 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**:198–204	Population
Tullius SG, Pratschke J, Strobelt V, Kahl A, Reinke P, May G, *et al.* ATG versus basiliximab induction therapy in renal allograft recipients receiving a dual immunosuppressive regimen: one-year results. *Transplant Proc* 2003;**35**:2100–1	Abstract
Turconi A, Rilo LR, Goldberg J, de Boccardo G, Garsd A, Otero A. 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. *Transplant Proc* 2005;**37**:672–4	No data
Urbizu JM, Amenabar JJ, Gomez-Ullate P, Zarraga S, Lampreabe I. Immunosuppression using tacrolimus/mycophenolate versus neoral/mycophenolate following kidney transplantation: a single-center experience. *Transplant Proc* 2002;**34**:87–8	Study design
Vacher-Coponat H, Brunet C, Moal V, Loundou A, Bonnet E, Lyonnet L, *et al.* Tacrolimus/mycophenolate mofetil improved natural killer lymphocyte reconstitution one year after kidney transplant by reference to cyclosporine/azathioprine. *Transplantation* 2006;**82**:558–66	Outcome
Vacher-Coponat H, Moal V, Indreies M, Purgus R, Loundou A, Burtey S, *et al.* A randomized trial with steroids and antithymocyte globulins comparing cyclosporine/azathioprine versus tacrolimus/ mycophenolate mofetil (CATM2) in renal transplantation. *Transplantation* 2012;**93**:437–43	Population
Van Der Giet M, Brakemeier S, Liefeldt L, Glander P, Diekmann F, Hohne M, *et al.* The impact of everolimus versus CNI-based immuno suppression on cardiovascular function and stiffness after renal transplantation. *Am J Transplan*. 2010;**10**:506	Abstract
Van Der Heide JJH, De Fijter JW, De Maar EF, Ten Berge I, Bemelman FJ. Low acute rejection rate and superior renal function 2 years after early CsA with drawal and overnight switch to everolimus. *Am J Transplant* 2010;**10**:508	Abstract

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Van Doesum W, Gard L, Van Son WJ, Sanders JSF, Riezebos A, Niesters BGM, *et al.* Incidence and outcome of BK infection in a randomized controlled multicenter study with renal transplant patients receiving duo-therapy. *Transplant Int* 2013;**26**:166	Abstract
Van Gurp E, Bustamante J, Franco A, Rostaing L, Becker T, Rondeau E, *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. *J Transplant* 2010;**2010**:731426	Population
Vanrenterghem Y, Bresnahan B, Campistol J, Durrbach A, Grinyó J, Neumayer HH, *et al.* Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation* 2011;**91**:976–83	Outcome
Vanrenterghem Y, Hooff JP, Squifflet JP, Salmela K, Rigotti P, Jindal RM, *et al.* Minimization of immunosuppressive therapy after renal transplantation: results of a randomized controlled trial. *Am J Transplant* 2005;**5**:87–95	Study design
Vathsala A, Schena FP, Wali RK, Pascoe MD, Alberu J, Del Carmen Rial M, *et al.* Conversion from calcineurin inhibitors to sirolimus versus continued use of calcineurin inhibitors in renal allograft recipients: a randomized, open-label, comparative trial. *Nephrology* 2005;**10**:A217–A	Abstract
Vester U, Kranz B, Wehr S, Boger R, Hoyer PF, RAD B 351 Study Group. Everolimus (Certican) in combination with neoral in pediatric renal transplant recipients: interim analysis after 3 months. *Transplant Proc* 2002;**34**:2209–10	Study design
Vincenti F, Blancho G, Durrbach A, Friend P, Grinyo J, Halloran PF, *et al.* Five-year safety and efficacy of belatacept in renal transplantation. *J Am Soc Nephrol* 2010;**21**:1587–96	Population
Vincenti F, Charpentier B, Rostaing L, Reyes-Acevedo R, Massari P, Vitko S, *et al.* Long-term extension of the belatacept benefit study: result's at month 48. *Transplantation* 2012;**94**:958	Abstract
Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, *et al.* A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010;**10**:535–46	Population
Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, *et al.* Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 2007;**7**:1506–14	Study design
Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, *et al.* DIRECT (diabetes incidence after renal transplantation: neoral (R) C2 monitoring versus tacrolimus) investigators (2007) results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus (vol 7, pg 1506, 2007). *Am J Transplant* 2008;**8**:908	Study design
Vincenti F, Grinyo JM, Charpentier B, Medina-Pestana JD, Rostaing L, Vanrenterghem Y, *et al.* Primary outcomes from a randomized, Phase III study of belatacept vs cyclosporine in kidney transplant recipients (BENEFIT Study). *Am J Transplant* 2009;**9**:191–2	Abstract
Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation* 2002;**73**:775–82	Population
Vincenti F, Larsen C, Alberu J, Garcia V, Rostaing L, Rice K, *et al.* Three-year outcomes from benefit: a phase III-study of belatacept vs cyclosporine in kidney transplant recipients. *Transplant Int* 2011;**24**:21	Abstract
Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G, *et al.* Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005;**353**:770–81	Population
Vincenti F, Larsen CP, Alberu J, Bresnahan B, Garcia VD, Kothari J, *et al.* Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. *Am J Transplant* 2012;**12**:210–7	Population
Vincenti F, Pescovitz MD, El-Shahawy M. Glucose metabolism disorders in non-white renal transplant patients receiving cyclosporine or tacrolimus in an international, randomized trial. *Transplant Int* 2007;**20**:115	Abstract
Vincenti F, Rostaing L, DIRECT (Diabetes Incidence after REnal Transplantation: Neoral C2 monitoring versus Tacrolimus) investigators. Rationale and design of the DIRECT study: a comparative assessment of the hyperglycemic effects of tacrolimus and cyclosporine following renal transplantation. *Contemp Clin Trials* 2005;**26**:17–24	No data

TABLE 135 Excluded studies (*continued*)

Study	Reason
Vincenti F, Tuncer M, Castagneto M, Klinger M, Friman S, Scheuermann EH, *et al.* 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. *Transplant Proc* 2005;**37**:1001–4	Duplicate
Vítko S, Klinger M, Salmela K, Wlodarczyk Z, Tydèn G, Senatorski G, *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**:1734–41	Comparator
Vítko S, Klinger M, Salmela K, Wlodarczyk Z, Tydèn G, Senatorski G, *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**:1734–41	Study design
Vítko S, Margreiter R, Weimar W, Dantal J, Viljoen HG, Li Y, *et al.* Everolimus (Certican) 12-month safety and efficacy versus mycophenolate mofetil in de novo renal transplant recipients. *Transplantation* 2004;**78**:1532–40	Population
Vítko S, Margreiter R, Weimar W, Dantal J, Kuypers D, Winkler M, *et al.* Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in de novo renal transplant patients. *Am J Transplant* 2005;**5**:2521–30	Population
Vondrak K, Grenda R, Watson A, Janda J, Simkova E, Seeman T, *et al.* Immunosupression with triple combination with tacrolimus with or without monoclonal antibody induction: a multicentric randomized study in children after kidney transplantation. *Kidney Blood Press Res* 2006;**29**:381	Abstract
Vondrak K, Grenda R, Watson AR, Webb NJA, Beattie J, Pediat Tacrolimus Study G. Tacrolimus triple therapy with or without monoclonal antibody administration: a multicentre, randomized study in pediatric kidney transplantation. *Am J Transplant* 2005;**5**:401–2	Abstract
Wagner M, Balk EM, Webster AC, et al. Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2009;**2**:CD007746	No data
Waid T. Tacrolimus as secondary intervention vs. cyclosporine continuation in patients at risk for chronic renal allograft failure. *Clin Transplant* 2005;**19**:573–80	Intervention
Walker R, Vathsala A, Zibari GB, Kim YS, Cibrik D, Johnston T, *et al.* Class related adverse events in renal transplant recipients treated with everolimus: 24 month results from the A2309 study. *Am J Transplant* 2011;**11**:407	Abstract
Walker RG, Cottrell S, Sharp K, Tripodi R, Nicholls KM, Fraser I, *et al.* 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* 2007;**12**:607–14	Outcome
Walker RG, Rostaing L, Nainan G, Del CRM, Steinberg S, Vincenti F, *et al.* A switch to belatacept-based immunosuppresive regimen in kidney transplant recipients from calcineurin inhibitors (CNI) has a favourable safety profile and results in improved renal function: 12-month results from a phase II study. *Immunol Cell Biol* 2011;**89**:A3	Abstract
Waller JR, Murphy GJ, Metcalfe MS, Sandford RM, Pattenden CJ, Nicholson ML. Primary immunosuppression with tacrolimus is associated with a reduction in renal allograft fibrosis compared with neoral therapy. *Transplant Proc* 2002;**34**:1587–8	Population
Wang K, Zhang H, Li Y, Wei Q, Li H, Yang Y, Lu Y. Efficacy of mycophenolate mofetil versus azathioprine after renal transplantation: a systematic review. *Transplant Proc* 2004;**36**:2071–2	Population
Wang K, Zhang H, Li Y, Wei Q, Li H, Yang Y, Lu Y. Safety of mycophenolate mofetil versus azathioprine in renal transplantation: a systematic review. *Transplant Proc* 2004;**36**:2068–70	Population
Wang R, Xu Y, Wu J, Wang Y, He Q, Chen J. Reduced-dose cyclosporine with mycophenolate mofetil and prednisone significantly improves the long-term glomerular filtration rate and graft survival. *Intern Med* 2013;**52**:947–53	Study design
Warejko JK, Hmiel SP. Single-center experience in pediatric renal transplantation using thymoglobulin induction and steroid minimization. *Pediatr Transplant* 2014;**18**:816–21	Study design
Watorek E, Szymczak M, Boratynska M, Patrzalek D, Klinger M. Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. *Transplant Proc* 2011;**43**:2967–9	Comparator

continued

TABLE 135 Excluded studies (*continued*)

Study	Reason
Watorek E, Szymczak M, Boratynska M, Patrzalek D, Klinger M. Cardiovascular risk in kidney transplant recipients receiving mTOR inhibitors. *Transplant Int* 2011;**24**:118	Abstract
Watson AR, Grenda R, Vondrak K, European Multicentre Tacrolimus S. A multicentre, randomised trial of tacrolimus triple therapy with or without basiliximab in paediatric kidney transplantation. *Pediatr Transplant* 2005;**9**:56	Abstract
Watson CJ, Firth J, Williams PF, Bradley JR, Pritchard N, Chaudhry A, *et al.* A randomized controlled trial of late conversion from CNI-based to sirolimus-based immunosuppression following renal transplantation. *Am J Transplant* 2005;**5**:2496–503	Population
Weimer R, Süsal C, Yildiz S, Streller S, Pelzl S, Staak A, *et al.* sCD30 and neopterin as risk factors of chronic renal transplant rejection: impact of cyclosporine A, tacrolimus, and mycophenolate mofetil. *Transplant Proc* 2005;**37**:1776–8	Population
Weimer R, Süsal C, Yildiz S, Staak A, Pelzl S, Renner F, *et al.* Post-transplant sCD30 and neopterin as predictors of chronic allograft nephropathy: impact of different immunosuppressive regimens. *Am J Transplant* 2006;**6**:1865–74	Population
Weir M. Long-term assessment of function in patients completing the spare-the-nephron study with a functioning graft. *Am J Transplant* 2013;**13**:36	Abstract
Weir M, Mulgaonkar S, Pearson T, Patel A, Patel D, Shidban H, *et al.* Mycophenolate Mofetil/Sirolimus maintenance therapy after calcineurin inhibitor withdrawal in renal transplant recipients: 2-Year Outcomes of the spare-the-nephron (STN) Trial. *Am J Transplant* 2009;**9**:200–1	Abstract
Weir MR, Mulgaonkar S, Chan L, Shidban H, Waid TH, Preston D, *et al.* Mycophenolate mofetil-based immunosuppression with sirolimus in renal transplantation: a randomized, controlled Spare-the-Nephron trial. *Kidney Int* 2011;**79**:897–907	Abstract
Welberry Smith MP, Cherukuri A, Newstead CG, Lewington AJ, Ahmad N, Menon K, *et al.* Alemtuzumab induction in renal transplantation permits safe steroid avoidance with tacrolimus monotherapy: a randomized controlled trial. *Transplantation* 2013;**96**:1082–8	Population
West-Thielke PM, Bodziak KA, Cohen DJ. Conversion to once-daily extended release meltdose (R) tacrolimus tablets (lcp-tacro (TM)) from twice-daily tacrolimus capsules (prograf (R)) is safe and efficacious in african american kidney transplant recipients: results from a phase iii randomized trial. *Am J Transplant* 2012;**12**:405–6	Abstract
Williams P. An open label randomised study of sirolimus in patients with impaired renal function following renal transplantation. National Research Register, UK. URL: www.nrr.nhs.uk/ (accessed 25 July 2014)	Unobtainable
Wiseman AC, McCague K, Kim Y, Geissler F, Cooper M. The effect of everolimus versus mycophenolate upon proteinuria following kidney transplant and relationship to graft outcomes. *Am J Transplant* 2013;**13**:442–9	Outcome
Wissing KM, Pipeleers L. Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: prevention and treatment. *Transplant Rev* 2014;**28**:37–46	Study design
Wissing KM, Fomegné G, Broeders N, Ghisdal L, Hoang AD, Mikhalski D, *et al.* HLA mismatches remain risk factors for acute kidney allograft rejection in patients receiving quadruple immunosuppression with anti-interleukin-2 receptor antibodies. *Transplantation* 2008;**85**:411–6	Study design
Wissing KM, Kuypers D, Abramowicz D, Weekers L, Budde KMD, Rath T, *et al.* Conversion from tacrolimus to cyclosporine a improves glucose metabolism in patients with new onset diabetes after renal transplantation: interim analysis of a prospective and randomized study. *Transplant Int* 2013;**26**:37	Abstract
Wlodarczyk Z, Ostrowski M, Mourad M, Krämer BK, Abramowicz D, Oppenheimer F, *et al.* Tacrolimus pharmacokinetics of once- versus twice-daily formulations in de novo kidney transplantation: a substudy of a randomized phase III trial. *Ther Drug Monit* 2012;**34**:143–7	Population
Wlodarczyk Z, Squifflet JP, Ostrowski M, Rigotti P, Stefoni S, Citterio F, *et al.* Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial. *Am J Transplant* 2009;**9**:2505–13	Population
Włodarczyk Z, Wałaszewski J, Perner F, Vitko S, Ostrowski M, Bachleda P, *et al.* Freedom from rejection and stable kidney function are excellent criteria for steroid withdrawal in tacrolimus-treated kidney transplant recipients. *Ann Transplant* 2002;**7**:28–31	Population

TABLE 135 Excluded studies (*continued*)

Study	Reason
Wlodarczyk Z, Walaszewski J, Perner F, Vitko S, Ostrowski M, Bachleda P, *et al.* Steroid withdrawal at 3 months after kidney transplantation: a comparison of two tacrolimus-based regimens. *Transpl Int* 2005;**18**:157–62	Population
Woestenburg AT, Peeters P, Sennesael J, Abramowicz D, Wissing KM, Geers C, *et al.* Interstitial fibrosis and fibrous intimal thickening in de novo renal allografts under sirolimus or cyclosporine: results of a randomised, controlled trial (FIBRASIC). *Transplant Int* 2009;**22**:79	Abstract
Wohlfahrtova M, Viklicky O. Recent trials in immunosuppression and their consequences for current therapy. *Curr Opin Organ Transplant* 2014;**19**:387–94	Study design
Woodle ES, Grp TS. A randomized, prospective, multicenter study of thymoglobulin in renal transplantation for induction and minimization of steroids (TRIMS). *Am J Transplant* 2005;**5**:571	Abstract
Woodside KJ, Thomas PG, Lappin JA, Vaidya S, Rajaraman S, Gugliuzza KK. An open label, randomized, controlled trial of a tolerogenic induction protocol using alemtuzumab (Campath 1H) and tacrolimus monotherapy versus thymoglobulin induction with triple drug therapy in high immunological risk renal transplantation. *Am J Transplant* 2007;**7**:522	Abstract
Wu B, Wu FB, Yu L, Li TP, Tang Y. Effectiveness and safety of calcineurin inhibitor withdrawal from target-of-rapamycin-inhibitor-based immunosuppression in kidney transplantation: a meta analysis (Provisional abstract). *Chinese Journal of Evidence-Based Medicine* 2010;**10**:33–9	Study design
Wu FL, Tsai MK, Chen RR, Sun SW, Huang JD, Hu RH, *et al.* Effects of calcineurin inhibitors on sirolimus pharmacokinetics during staggered administration in renal transplant recipients. *Pharmacotherapy* 2005;**25**:646–53	Study design
Wyrley-Birch H, Kanwar A, Vijayanand D, Navarro A, Reddy M, Wilson C, *et al.* A prospective randomised paired trial of sirolimus versus tacrolimus as primary immunosuppression following non heart beating donor kidney transplantation after anti-il2 monoclonal antibody induction. *Transplant Int* 2010;**23**:16	Abstract
Xue W, Zhang Q, Xu Y, Wang W, Zhang X, Hu X. Effects of tacrolimus and cyclosporine treatment on metabolic syndrome and cardiovascular risk factors after renal transplantation: a meta-analysis. *Chin Med J* 2014;**127**:2376–81	Population
Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.* A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. *Health Technol Assess* 2006;**10**(49)	Duplicate
Yaqoob M, Pattison J, Riad H, Cornu-Artis C, Wang Z, Shihab F. Cytomegalovirus and BK virus infections are less frequent with everolimus versus mycophenolate immunosuppression: 24-month update from the 2309 study in de novo renal transplant recipients. *Transplant Int* 2011;**24**:40–1	Unobtainable
Yaqoob M, Riad H, Pattison J, Cornu-Artis C, Wang Z, Tedesco Silva H. Efficacy and safety of 24 months immunosuppression with concentration-controlled everolimus and reduced cyclosporine in de novo renal transplant recipients. *Transplant Int* 2011;**24**:39	Abstract
Yoshimura N, Uchida K, Takahara S, Teraoka S, Kobayashi E, Teshima R, *et al.* Concentration-controlled everolimus with reduced cyclosporine concentration in Japanese de novo renal transplant recipients: efficacy and safety results at 12 months: Japanese multicenter study. *Transplantation* 2012;**94**:990	Abstract
Zachariah M, Nader ND, Brar J, Singh N, Venuto R, Patel S, *et al.* Alemtuzumab and minimization immunotherapy in kidney transplantation: long-term results of comparison with rabbit anti-thymocyte globulin and standard triple maintenance therapy. *Transplant Proc* 2014;**46**:94–100	Study design
Zadrazil J, Horak P, Strebl P, Krejci K, Kajabova M, Schneiderka 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. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2012;**156**:14–20	Population
Zeier M, Budde K, Arns W, Guba M, Sommerer C, Neumayer H, *et al.* Efficacy and safety of three different treatment regimens in de novo renal transplant patients: follow-up results of the herakles trial at month 24. *Am J Transplant* 2013;**13**:183	Abstract

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TABLE 135 Excluded studies (*continued*)

Study	Reason
Zhang YG, Teng DH, Wang L, *et al.* Effectiveness and safety of rapamycin-based immunosuppression regimen with or without CsA in renal transplantation: a systematic review. *Chinese Journal of Evidence-Based Medicine* 2006;**6**:94–106	Study design
Zhong J-y, Qu L-x, Zhang M, Jiao Z, Lu F-m. Application of basiliximab in prevention of acute allograft rejection in kidney transplantation recipients. *Zhongguo Xinyao yu Linchuang Zazhi* 2005;**24**:468–71	Language
Zhu QG, Zhao YK, Liu W, Luo H, Qiu Y, Gao ZZ. Two-year observation of a randomized trial on tacrolimus-based therapy with withdrawal of steroids or mycophenolate mofetil after renal transplantation. *Chinese Med Sci J* 2008;**23**:244–8	Study design

TABLE 136 Mixed-population RCTs

Study	Treatment comparisons (number of participants in each arm)	Eligibility criteria	Age mean (SD), median [range] (years)
Ciancio G, Burke GW, Gaynor JJ, Mattiazzi A, Roth D, Kupin W, *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**:244–251	TAC + SRL (50) vs. TAC + MMF (50) vs. CSA + SRL (50)	≥ 13 years	50 (13) vs. 47 (16) vs. 44 (16)
Flechner SM, Gurkan A, Hartmann A, Legendre CM, Russ GR, Campistol JM, *et al.* A randomized, open-label study of sirolimus versus cyclosporine in primary de novo renal allograft recipients. *Transplantation* 2013;**95**:1233–41	SRL (314) vs. CSA (161)	≥ 13 years	42.9 (SE 0.8) vs. 42.7 (SE 1.1)
Gaber AO, Kahan BD, Buren C, Schulman SL, Scarola J, Neylan JF. Comparison of sirolimus plus tacrolimus versus sirolimus plus cyclosporine in high-risk renal allograft recipients: results from an open-label, randomized trial. *Transplantation* 2008;**86**:1187–95	TAC (224) vs. CSA (224)	≥ 13 years	46.4 [15–73] vs. 44.4 [15–80]
Kahan BD for The Rapamune US Study Group. Efficacy of sirolimus compared with azathoprine for reduction of acute renal allograft rejection: a randomised multicentre study. *Lancet* 2000;**356**:194–202[a]	SRL 2 mg (284) vs. SRL 5 mg (274) vs. AZA (161)	≥ 13 years[b]	44.9 (13.6) vs. 46.8 (13.0) vs. 45.6 (13.0)
MacDonald AS for The Rapamune US Study Group. A worldwide, phase III ranomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001;**71**:271–80[a]	SRL 2 mg (227) vs. SRL 5 mg (219) vs. PBO (130)	Included participants aged 15–71 years[c]	45.6 (12.3) [15–71] vs. 45.1 (12.2) [17–68] vs. 46 (13.1) [16–72]
Lee YJ, Kim B, Lee JE, Kim YG, Kim DJ, Kim SJ, *et al.* Randomized trial of cyclosporine and tacrolimus therapy with steroid withdrawal in living-donor renal transplantation: 5-year follow-up. *Transplant Int* 2010;**23**:147–54	CSA (55) vs. TAC (62)	> 15 years	38.5 (9.5) vs. 38.8 (9.2)

TABLE 136 Mixed-population RCTs (*continued*)

Study	Treatment comparisons (number of participants in each arm)	Eligibility criteria	Age mean (SD), median [range] (years)
Machado PG, Felipe CR, Hanzawa NM, Park SI, Garcia R, Alfieri F, *et al.* An open-label randomized trial of the safety and efficacy of sirolimus vs. azathioprine in living related renal allograft recipients receiving cyclosporine and prednisone combination. *Clin Transplant* 2004;**18**:28–38	SRL (35) vs. AZA (35)	≥ 13 years	35.8 (10.5) vs. 32.7 (10.4)
Wu FL, Tsai MK, Chen RR, Sun SW, Huang JD, Hu RH, *et al.* Effects of calcineurin inhibitors on sirolimus pharmacokinetics during staggered administration in renal transplant recipients. *Pharmacotherapy* 2005;**25**:646–53	TAC (11) vs. CSA (10)	13–65 years[d]	40.4 (10.4) vs. 36.9 (8.1)
Silva HT Jr, Yang HC, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, *et al.* One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *Am J Transplant* 2007;**7**:595–608[e]	TAC PR (214) vs. TAC (212) vs. CSA (212)	≥ 12 years	47.8 (13), 48 [17–77] vs. 48.6 (12.9), 50.5 [19–74] vs. 47.6 (13), 48.5 [17–77]

a Identified from Kahan *et al.*[259]
b Yao *et al.*[2] states: 'participants between 12–18 years were assigned as 6 vs. 3 vs. 3'.
c Yao *et al.*[2] states: 'participants under 18 years were assigned as 1 vs. 1 vs. 1'.
d This is unclear as the paper also states: 'study recruited 22 adults'.
e The 4-year follow-up data can be found in Silva HT Jr, Yang HC, Meier-Kriesche HU, Croy R, Holman J, Fitzsimmons WE, *et al.* 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* 2014;**97**:636–41

Appendix 3 Systematic reviews

TABLE 137 Included systematic reviews

Trial	Aim	Identified RCTs	Identified non-RCTs
Almeida *et al.* 2013[260]	To evaluate the safety of the most commonly used immunosuppressive regimens	0	0
Andrassy *et al.* 2012[261]	To summarise clinical trials after solid organ transplantation and describe potential mechanisms involved in the antiCMV effect of mTOR-inhibitors	0	0
Brooks *et al.* 2010[262]	To evaluate the quality of reporting of transplantation trials in children published in contemporary biomedical literature	2	0
Ho *et al.* 2013[263]	To evaluate the benefits and harms of sustained-release daily dosing formulation compared with standard twice daily TAC in KTRs	0	0
Kasiske *et al.* 2008[264]	To conduct a systematic review of RCTs to critically examine the incidence and type of dyslipidemia associated with mTOR-Is	0	0
Knight *et al.* 2009[265]	To identify whether or not MMF improves outcomes compared with AZA in renal transplant recipients, particularly in incidence of acute rejection, patient and graft survival, and toxicity	0	0
Liu *et al.* 2010[266]	To compare the efficacy and safety of BAS with antithymocyte globulin for induction therapy	0	0
Masson *et al.* 2014[267]	To synthesise data from RCTs that compared belatacept with other primary maintenance immunosuppression regimens	0	0
Moore *et al.* 2009[268]	To assess transplant outcomes after CNI sparing with mycophenolate as sole adjunctive immunosuppression	0	0
Mulay *et al.* 2006[269]	To systematically review all clinical studies that evaluated CNI conversion to SRL in patients with chronic nephropathy	0	0
Peddi *et al.* 2013[270]	To evaluate the efficacy and safety of immunosuppressive regimens containing a mTOR-I with TAC minimisation therapy in solid organ transplant recipients	0	0
Pengel *et al.* 2011[271]	To evaluate the occurrence of wound complications and lymphoceles in solid organ transplant recipients receiving mTOR-Is from the time of transplantation compared with patients not receiving mTOR-I	0	0
Su *et al.* 2011[272]	To evaluate clinical consequences of and MMF dose reduction in renal transplant recipients on TAC based regimens	0	0
Webster *et al.* 2004[273]	To systematically identify and summarise the effects of IL-2Ra as induction agents, as an addition to standard therapy, or as an alternative to other antibody therapies in common use (antithymocyte globulins, antilymphocyte globulins, monomurab-CD3)	0	0
Webster *et al.* 2004[274]	To systematically identify and summarise the effects of using an IL2Ra, as an addition to standard therapy, or as an alternative to other antibody therapy	0	0
Webster *et al.* 2005[207]	To systematically review randomised controlled trials in which TAC had been compared with ciclosporin as initial immunosuppressive therapy in the treatment of KTRs	0	0

continued

TABLE 137 Included systematic reviews (*continued*)

Trial	Aim	Identified RCTs	Identified non-RCTs
Webster *et al.* 2005[275]	To compare the effects of TAC with ciclosporin as primary therapy for KTRs	0	0
Webster *et al.* 2006[156]	To identify systematically and summarise the current available evidence of the short- and long-term benefits and harms of SRL and everolimus when used in primary immunosuppressive regimens for KTRs	0	0
Webster *et al.* 2006[276]	To investigate the benefits and harms of immunosuppressive regimens containing TOR-I when compared with other regimens as initial therapy for KTRs	0	0
Webster *et al.* 2010[277] (update of Webster *et al.* 2004[274])	To systematically identify and summarise the effects of using an IL2Ra, as an addition to standard therapy, or as an alternative to another immunosuppressive induction strategy	0	0
Woodroffe *et al.* 2005[255]	To examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: BAS, daclizumab, TAC, mycophenolate (mofetil and sodium) and SRL	1	0
Yan *et al.* 2014[278]	To evaluate the efficacy and safety of CNI avoidance, CNI withdrawal, and CNI regimens on postoperative patient and graft survival, acute rejection, renal function and adverse events	0	0
Yao *et al.* 2006[2]	To establish the clinical effectiveness (harms and benefits) and cost-effectiveness of four of the newer immunosuppressive drugs for renal transplantation, namely BAS, daclizumab, TAC and MMF and sodium) and of SRL in children	2	4

Appendix 4 Ongoing trials

TABLE 138 Ongoing trials

Study	Sponsor/collaborators	Trial name	*n*	Status	Included in PenTAG (reason)
NCT01791491	Bristol-Myers Squibb	Phase II Pharmacokinetics, Efficacy, and Safety of Belatacept in Paediatric Renal Transplant Recipients	54	Recruiting	N/A
NCT01544491 A2314; Gupta *et al.* 2013,[86] Langer *et al.* 2013,[87] Tonshoff *et al.* 2012[89] and Tonshoff *et al.* 2013[88]	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	N/A
NCT01550445 Oh *et al.* 2012[279]	Ajou University School of Medicine	Steroid Withdrawal Immunosuppression After Renal Transplantation	30	Unknown	Not included (design)
NCT00023244, Study 315 (mentioned in Yao *et al.* 2006[2] as ongoing; Benfield *et al.* 2010[280])	National Institute of Allergy and Infectious Diseases (NIAID), Cooperative Clinical Trials in Paediatric Transplantation; Pfizer (formerly Wyeth)	Steroid Withdrawal in Pediatric Kidney Transplant Recipients	274	Terminated	Not included (steroid withdrawal)
NCT00137345 Flechner *et al.* 2013[281]	Pfizer (formerly Wyeth)	Study Comparing Sirolimus With Cyclosporine in a Calcineurin Inhibitor (CNI)-Free Regimen in Kidney Transplant Recipients	500	Terminated	Not included (population)
NCT00005113 (included in Yao *et al.* 2006[2]; 0468E1–217-US)	Children's Hospital Boston; Pfizer (formerly Wyeth)	A Study to Compare Treatment With Sirolimus Versus Standard Treatment in Patients Who Have Received a Kidney Transplant	213	Terminated	Not included (no data available and population)
NCT00228020 Offner *et al.* 2008[73]	Novartis	Study of Safety and Efficacy of a Basiliximab, Mycophenolate Mofetil, Cyclosporine Microemulsion and Prednisone Combination Treatment Regimen in Pediatric Renal Allograft Recipients	212	Completed	Included
NCT00141037 Sarwal *et al.* 2012[282]	National Institute of Allergy and Infectious Diseases (NIAID) Astellas Pharma Inc. Hoffmann-La Roche	Steroid-Free Versus Steroid-Based Immunosuppression in Pediatric Renal (Kidney) Transplantation	130	Completed	Not included

continued

TABLE 138 Ongoing trials (*continued*)

Study	Sponsor/collaborators	Trial name	*n*	Status	Included in PenTAG (reason)
NCT00296348	Astellas Pharma Inc.	Comparing Efficacy and Safety of Steroid Withdrawal With Tacrolimus and MMF With Induction in Children After Kidney Transplantation (TWIST)	198	Completed	Not included
NCT00166244 van Gelder *et al.* 2008[283]	Erasmus Medical Hoffmann-La Roche Center	Fixed Dose MMF vs. Concentration Controlled MMF After Renal Transplantation	901	Completed	Not included (population)
ISRCTN89278733 Cransberg *et al.* 2007[284]	Erasmus Medical Center	Safety and efficacy of mycophenolate mofetil in pediatric renal transplantation	44	Completed	Not included (design)

Appendix 5 Clinical effectiveness: additional information

TABLE 139 TA99: included adult RCTs

Study	Multiple publications	Treatments	Included in PenTAG (reason)
Vincenti *et al.* 1998[285]	Vincenti *et al.* 1998[286] Hengster *et al.* 1999[287] Bumgarden *et al.* 2001[288]	DAC vs. PBO	No (treatment)
Bingyi *et al.* 2003[104]	N/A	BAS vs. PBO	Yes
Ponticelli *et al.* 2001[102]	Ponticelli *et al.* 2001[289]	BAS vs. PBO	Yes
Sheashaa *et al.* 2003[99]	N/A	BAS vs. NI	Yes
Folkmane *et al.* 2001[290]	Folkmane *et al.* 2002[291] (a)	BAS vs. NI and MMF vs AZA	No (design)
Shapiro *et al.* 1991[292]	N/A	TAC vs. CSA	No (design)
Mayer *et al.* 1997[107]	Mayer *et al.* 1999[293] Mayer *et al.* 2002[294] Mayer *et al.* 2002[295] European Tacrolimus Multicentre Renal Study	TAC vs. CSA	Yes
Radermacher *et al.* 1998[124]	N/A	TAC vs. CSA	No (design)
Van Duijnhoven *et al.* 2002[123]	N/A	TAC vs. CSA	Yes
Jurewicz *et al.* 1999[296]	Baboolal *et al.* 2002[121] Jurewicz *et al.* 2003[297] Welsh Transplant Research group	TAC vs. CSA	Yes
Sperschneider *et al.* 2001[298]	Krämer *et al.* 2003[299] Dietl *et al.* 2002[300] Margreiter *et al.* 2002[110]	TAC vs. CSA	Yes
Töz *et al.* 2004[301]	N/A	TAC vs. CSA	Yes
Campost *et al.* 2003[109]	Brazilian TAC study	TAC vs. CSA	Yes
Murphy *et al.* 2003[302]	N/A	TAC vs. CSA	Yes
Mathew *et al.* 1998[303]	Tricontinental Mycophenolate Mofetil Renal Transplantation Study 1996	MMF vs. AZA	Yes
Miladipour *et al.* 2002[304]	N/A	MMF vs. AZA	No (design)
Sadek *et al.* 2002[116]	N/A	MMF vs. AZA	Yes
Tuncer *et al.* 2002[118]	N/A	MMF vs. AZA	Yes
Sollinger *et al.* 1995[120]	MMF Acute Renal transplantation Study Group 1996	MMF vs. AZA	Yes
Baltar *et al.* 2002[305]	N/A	MMF vs. AZA	No (language)
Salvadori *et al.* 2004[306]	N/A	MPS vs. MMF	Yes
Kahan 2000[257]	Rapamune US study	SRL vs. AZA	No (design)
Machado *et al.* 2004[258]	N/A	SRL vs. AZA	No (design)
Groth *et al.* 1999[206]	Sirolimus European Renal transplantation Study group	SRL vs. CSA	Yes
Johnson *et al.* 2001[307]	Rapamune Maintenance Regimen (RMR) study	Addition of SRL and CSA removal	No (design)

N/A, not applicable; NI, no induction.

TABLE 140 Adverse events, long-term follow-up: Staskewitz *et al.*[83]

AE	Follow-up	CSA + MMF + CCS		
		n *events*	n *participants*	%
Respiratory infections	1 year	24	69	35
	1–2 years	6	57	11
	2–3 years	4	44	9
UTIs	1 year	14	69	20
	1–2 years	6	57	11
	2–3 years	4	44	9
CMV infections	1 year	11	69	16
	1–2 years	2	57	4
	2–3 years	0	44	0
	3–5 years	2	44	5
EBV infections	1 year	2	69	3
	1–2 years	8	57	14
	2–3 years	2	44	5
	3–5 years	3	78	4
Solid tumour	1 year	0	69	0
	1–2 years	0	57	0
	2–3 years	1	44	2
	3–5 years	0	78	0
PTLD	1 year	1	69	1
	1–2 years	0	57	0
	2–3 years	0	44	0
	3–5 years	0	78	0
Herpes simplex	1 year	11	69	16
	1–2 years	4	57	7
	2–3 years	0	44	0
	3–5 years	8	78	10
HPV6	1 year	1	69	1
	1–2 years	2	57	4
	2–3 years	1	44	2
	3–5 years	3	78	4
Oral thrush	1 year	3	69	4
	1–2 years	2	57	4
	2–3 years	0	44	0

TABLE 140 Adverse events, long-term follow-up: Staskewitz *et al.*[83] (*continued*)

AE	Follow-up	CSA + MMF + CCS		
Diarrhoea	1 year	37	69	54
	1–2 years	9	57	16
	2–3 years	3	44	7
Abdominal pain/nausea	1 year	12	69	17
	1–2 years	5	57	9
	2–3 years	3	44	7

HPV6, human papillomavirus type 6.
Note
Staskewitz *et al.*[83] did not report any AE for the historic control AZA group; only AE for MMF group were reported. All ORs were calculated by PenTAG.

Appendix 6 Astellas' submission

TABLE 141 Astellas' trials included in submission

Study	Arm 1	Arm 2	Arm 3	Arm 4	Parallel Adult HTA (reason)
Ekberg *et al.* 2007[127]	CSA + MMF + CCS	DAC + LOW CSA + MMF + CCS	DAC + LOW TAC + MMF + CCS	DAC + LOW SRL + MMF + CCS	Included
Abou-Jaoude *et al.* 2003[308]	DAC/r-ATG/NON + TAC + AZA + CCS	DAC/r-ATG/NON + CSA + AZA + CCS	N/A	N/A	Excluded (study design)
Abou-Jaoude *et al.* 2005[309]	DAC/ZENA/NONE + TAC + AZA/MMF + CCS	DAC/ZENA/NONE + CSA + AZA/MMF + CCS	N/A	N/A	Excluded (study design)
Busque *et al.* 2001[310]	TAC + MMF + CCS	TAC + AZA + CCS	CSA + MMF + CCS	N/A	Excluded (study design)
Campos *et al.* 2002[109]	TAC + AZA + CCS	CSA + AZA + CCS	N/A	N/A	Included
Hardinger *et al.* 2005[113]	r-ATG + TAC + AZA + CCS	r-ATG + CSA + AZA + CCS	N/A	N/A	Included
Johnson *et al.* 2000[311]	TAC + AZA + CCS	CSA + MMF + CCS	TAC + MMF + CCS	N/A	Excluded (population)
Margreiter *et al.* 2002[110]	TAC + AZA + CCS	CSA + AZA + CCS	N/A	N/A	Included
Garcia *et al.* 2003[312]	CSA + CCS	BAS + CSA + CCS	BAS + TAC + CCS	N/A	Excluded (study design)
Morris-Stiff *et al.* 2000[313]	TAC + AZA + CCS	CSA + AZA + CCS	N/A	N/A	Excluded (population)
Murphy *et al.* 2003[302]	TAC + AZA + CCS	CSA + AZA + CCS	N/A	N/A	Included
Raofi *et al.* 1999[195]	OKT3 + TAC + CCS	OKT3 + CSA + CCS	N/A	N/A	Included
Silva *et al.* 2007[152]	BAS + TAC PR + MMF + CCS	BAS + TAC + MMF + CS	BAS + CSA + MMF + CCS	N/A	Excluded (population)
Toz *et al.* 2004[301]	TAC + AZA + CCS	CSA + AZA + CCS	N/A	N/A	Included
Vincenti *et al.* 2007[314]	BAS + TAC + MMF/MPS + CCS	BAS + CSA + MMF/MPS + CCS	N/A	N/A	Excluded (intervention)
Wang *et al.* 2000[315]	TAC + MMF + CCS	CSA + MMF + CCS	N/A	N/A	Excluded (abstract)

Study	Arm 1	Arm 2	Arm 3	Arm 4	Parallel Adult HTA (reason)
White *et al.* 2000[316]	TAC + CCS	CSA + CCS	N/A	N/A	Excluded (abstract)
Williams *et al.* 1999[317]	TAC + CCS	CSA + CCS	N/A	N/A	Excluded (abstract)
Yang *et al.* 1999[125]	TAC + MMF + CCS	CSA + MMF + CCS	N/A	N/A	Included
Flechner *et al.* 2011[318]	DAC + TAC + SRL + CCS	DAC + MMF + SRL + CCS	N/A	N/A	Included
Glotz *et al.* 2010[128]	TAC + MMF + CCS	r-ATG + SRL + MMF + CCS	N/A	N/A	Excluded (intervention)
Larson *et al.* 2006[319]	r-ATG + TAC + MMF + CCS	r-ATG + SRL + MMF + CCS	N/A	N/A	Included
Vincenti *et al.* 2010[198]	BAS + BEL LOW + MMF + CCS	BAS + BEL HIGH + MMF + CCS	BAS + CSA + MMF + CCS	N/A	Included
Durrbach *et al.* 2010[199]	BAS + BEL LOW + MMF + CCS	BAS + BEL HIGH + MMF + CCS	BAS + CSA + MMF + CCS	N/A	Included
Bertoni *et al.* 2011[320]	BAS + EVL + CSA + CCS	BAS + MPS + CSA + CCS	N/A	N/A	Included
Tedesco Silva *et al.* 2010[191]	BAS + EVL LOW + CSA + CCS	BAS + EVL HIGH + CSA + CCS	BAS + MPA + CSA + CCS	N/A	Included
Albano *et al.* 2013[97]	TAC + MMF + CCS	TAC(0.2 MG) + MMF + CCS	TAC PR (0.3 MG) + MMF + CCS	BAS + TAC PR + MMF + CCS	Included
Krämer *et al.* 2010[139]	TAC + MMF + CCS	TAC + MMF + CCS	N/A	N/A	Included
Ciancio *et al.* 2004[321]	SRL + TAC + CCS	MMF + TAC + CCS	SRL + CSA + CCS	N/A	Excluded (population)
Gonwa *et al.* 2003[193]	SRL + TAC + CCS	MMF + TAC + CCS	N/A	N/A	Included
Mendez *et al.* 2005[322]	SRL + TAC + CCS	MMF + TAC + CCS	N/A	N/A	Included

N/A, not applicable.

Appendix 7 Summary of model parameters

Parameter	Value	PSA distribution
Study characteristics (clinical effectiveness estimates from adult RCTs)		
Patient age (years)	10	Not varied
Patient weight (kg)	31.8	Not varied
Proportion male	0.598	Not varied
Donor type (first graft)		
DBD	0.645	Not varied
Living related	0.355	Not varied
Donor type (subsequent grafts)		
DBD	0.833	Not varied
Living related	0.167	Not varied
***Study characteristics (Trompeter* et al.[77])**		
Patient age (years)	10.3	Normal(10.31, 0.325)
Patient weight (kg)	32.6	Normal(32.58, 1.159)
Proportion male	0.612	Beta(120, 76)
***Study characteristics (Grenda* et al.[75])**		
Patient age (years)	11.4	Normal(11.40, 0.292)
Proportion male	0.620	Beta(119, 73)
***Study characteristics (Offner* et al.[73])**		
Patient age (years)	10.7	Normal(10.75, 0.342)
Proportion male	0.615	Beta(118, 74)
Surrogate relationships		
Graft survival (censored for DWFG)		
AR	1.60	Log-normal(0.47, 0.037)
NODAT	1.12	Log-normal(0.113, 0.061)
eGFR (ml/minute/1.73 m^2)		
≥ 80	1	Not varied
45–80	1.59	Log-normal(0.463, 0.571)
< 45	55.9	Log-normal(4.024, 1.203)
DWFG		
NODAT	1.41	Log-normal(0.113, 0.061)
Sex = female	0.865	Log-normal(–0.145, 0.036)
Donor type		
DBD	1	Not varied
Living related	0.551	Log-normal(–0.595, 0.071)

Parameter	Value	PSA distribution
Age (years)		
0–17	0.377	Log-normal(–0.975, 0.186)
18–30	0.369	Log-normal(–0.996, 0.117)
31–40	0.712	Log-normal(–0.339, 0.091)
41–50	1	Not varied
51–60	2.140	Log-normal(0.761, 0.059)
61–70	4.128	Log-normal(1.418, 0.053)
Effectiveness estimates from adult RCTs		
Mortality within 12 months [ln(OR)]		
Induction agents (vs. no induction)		Multivariate normal
BAS	–0.117	
R-ATG	–0.461	
Maintenance regimens (vs. CSA + AZA)		Multivariate normal
TAC + AZA	0.323	
CSA + MMF	–0.057	
TAC + MMF	0.422	
BEL + MMF	–0.763	
CSA + EVL	0.333	
TAC + SRL	0.325	
SRL + MMF	0.542	
Head to head		
MPS vs. MMF	–0.435	Normal(–0.435, 1.231)
TAC-PR vs. TAC	0.245	Normal(0.245, 0.481)
Graft loss within 12 months [ln(OR)]		
Induction agents (vs. no induction)		Multivariate normal
BAS	–0.171	
R-ATG	–0.253	
Maintenance regimens (vs. CSA + AZA)		Multivariate normal
TAC + AZA	0.135	
CSA + MMF	–0.297	
TAC + MMF	–0.379	
BEL + MMF	–0.492	
CSA + EVL	–0.484	
TAC + SRL	0.159	
SRL + MMF	0.032	
Head to head		
MPS vs. MMF	–0.148	Normal(–0.148, 0.524)
TAC-PR vs. TAC	0.183	Normal(0.183, 0.290)

Parameter	Value	PSA distribution
BPAR within 12 months [ln(OR)]		
Baseline (BAS + TAC + AZA)	0.192	Beta(19, 80)
Induction agents (vs. no induction)		Multivariate normal
BAS	–0.688	
R-ATG	–1.041	
Maintenance regimens (vs. CSA + AZA)		Multivariate normal
TAC + AZA	–0.548	
CSA + MMF	–0.752	
TAC + MMF	–0.921	
BEL + MMF	–0.216	
CSA + EVL	–0.784	
TAC + SRL	–0.957	
SRL + MMF	–0.828	
Head to head		
MPS vs. MMF	0.396	Normal(0.396, 0.678)
TAC-PR vs. TAC	–0.025	Normal(–0.025, 0.383)
Graft function at 12 months [mean difference (ml/minute/1.73 m^2)]		
Baseline (BAS + TAC + AZA)	82 (SD 27)	Not varied
Induction agents (vs. no induction)		Multivariate normal
BAS	2.615	
R-ATG	0.752	
Maintenance regimens (vs. CSA + AZA)		Multivariate normal
TAC + AZA	9.304	
CSA + MMF	1.609	
TAC + MMF	6.531	
BEL + MMF	10.550	
CSA + EVL	4.863	
TAC + SRL	–0.352	
SRL + MMF	3.846	
Head to head		
MPS vs. MMF	3.9	Normal(3.9, 2.9)
TAC-PR vs. TAC	–0.211	Normal(–0.211, 1.302)

Parameter	Value	PSA distribution
***Effectiveness estimates (Trompeter* et al.[77])**		
Mortality within 4 years		
TAC + AZA	0.06	Beta(6, 97)
CSA + AZA	0.08	Beta(7, 86)
Graft loss (excluding DWFG) within 4 years		
TAC + AZA	0.046	Beta(5, 98)
CSA + AZA	0.208	Beta(19, 74)
AR within 12 months		
TAC + AZA	0.43	Beta(44, 58)
CSA + AZA	0.62	Beta(58, 35)
eGFR at 12 months (ml/minute/1.73 m^2)		
TAC + AZA	64.9	Normal(64.9, 2.17)
CSA + AZA	57.8	Normal(57.8, 2.27)
***Effectiveness estimates (Grenda* et al.[75])**		
Mortality within 48 months		
TAC + AZA	0.011	Beta(1.5, 92.5)
BAS + TAC + AZA	0.000	Beta(0.5, 99.5)
Graft loss (excluding DWFG) within 48 months		
TAC + AZA	0.104	Beta(10.2, 83.8)
BAS + TAC + AZA	0.051	Beta(5.5, 94.5)
AR within 12 months		
TAC + AZA	0.26	Beta(24, 69)
BAS + TAC + AZA	0.24	Beta(23.5, 75.5)
eGFR at 12 months (ml/minute/1.73 m^2)		
TAC + AZA	74.9	Normal(74.9, 2.04)
BAS + TAC + AZA	74.0	Normal(74.0, 1.98)
***Effectiveness estimates (Offner* et al.[73])**		
Mortality within 48 months		
BAS + CSA + MMF	0.028	Beta(3.3, 97.7)
CSA + MMF	0.000	Beta(0.5, 92.5)
Graft loss (excluding DWFG) within 48 months		
BAS + CSA + MMF	0.019	Beta(1.9, 98.1)
CSA + MMF	0.011	Beta(1.0, 91.0)
AR within 12 months		
BAS + CSA + MMF	0.13	Beta(13, 87)
CSA + MMF	0.23	Beta(21, 71)
eGFR at 12 months (ml/minute/1.73 m^2)		
BAS + CSA + MMF	79	Normal(79, 2.3)
CSA + MMF	82	Normal(82, 2.5)

Parameter	Value	PSA distribution
NODAT within 12 months		
Based on adult evidence		
Baseline	0.040	Beta(4, 95)
Maintenance agents (vs. TAC) [ln(OR)]		Multivariate normal
TAC-PR	0.169	
CSA	–0.816	
BEL	–1.671	
SRL	–0.234	
Maintenance agents (vs. MMF) [ln(OR)]		Multivariate normal
MPS	–0.070	
SRL	0.474	
EVL	–0.052	
Trompeter *et al.*[77]		
TAC + AZA	0.019	Beta(2,101)
CSA + AZA	0.011	Beta(1, 92)
Grenda *et al.*[75]		
TAC + AZA	0.011	Beta(1, 92)
BAS + TAC + AZA	0.040	Beta(4, 95)
Offner *et al.*[73]		
BAS + CSA + MMF	0.0	Beta(0.5, 100.5)
CSA + MMF	0.0	Beta(0.5, 92.5)
AEs		
CMV		
Based on adult evidence		
Baseline	0.258	Beta(41, 118)
Maintenance agents (vs. no mTOR-I) [ln(OR)]		Multivariate normal
mTOR-I replacing CNI	–0.798	
mTOR-I replacing antimetabolite	–1.153	
Grenda *et al.*[75]		
TAC + AZA	0.022	Beta(2, 91)
BAS + TAC + AZA	0.071	Beta(7, 92)
Offner *et al.*[73]		
BAS + CSA + MMF	0.128	Beta(14, 95)
CSA + MMF	0.086	Beta(8, 85)
Dyslipidaemia		
Based on adult evidence		
Baseline	0.555	Beta(313, 251)
Maintenance agents (vs. no mTOR-I) [ln(OR)]		
mTOR-I	0.557	Normal(0.557, 0.100)

Parameter	Value	PSA distribution
PTLD		
Trompeter *et al.*[77]		
TAC + AZA	0.029	Beta(3, 100)
CSA + AZA	0.032	Beta(3, 90)
Grenda *et al.*[75]		
TAC + AZA	0.022	Beta(2, 91)
BAS + TAC + AZA	0.010	Beta(1, 98)
Offner *et al.*[73]		
BAS + CSA + MMF	0.028	Beta(3, 106)
CSA + MMF	0.054	Beta(5, 88)
Toxic nephropathy		
Grenda *et al.*[75]		
TAC + AZA	0.043	Beta(4, 89)
BAS + TAC + AZA	0.141	Beta(14, 85)
Abdominal pain		
Grenda *et al.*[75]		
TAC + AZA	0.022	Beta(2, 91)
BAS + TAC + AZA	0.111	Beta(11, 88)
DGF		
Grenda *et al.*[75]		
TAC + AZA	0.054	Beta(5, 88)
BAS + TAC + AZA	0.111	Beta(11, 88)
Hypertension		
Trompeter *et al.*[77]		
TAC + AZA	0.883	Beta(91, 12)
CSA + AZA	0.871	Beta(81, 12)
Hypomagnesaemia		
Trompeter *et al.*[77]		
TAC + AZA	0.408	Beta(42, 61)
CSA + AZA	0.226	Beta(21, 72)
Anaemia		
Based on adult evidence	0.052	Beta(207, 3762)
Retransplantation		
Probability of pre-emptive retransplantation on loss of first graft	0.2	Beta(3, 12)
Rate of retransplantation (by age)		
< 18 years (HR)	3.422	Normal(3.422, 0.397)
18–64 years	0.104	Normal(0.104, 0.0023)
(Rate declines after 65 years)		
Baseline rate of DWFG (subsequent grafts)	0.0078	Log-normal(–4.853, 0.472)
Baseline rate of graft loss (subsequent grafts)	0.0359	Log-normal(–3.327, 0.084)

Parameter	Value	PSA distribution
Mortality		
Rate of death on dialysis following graft loss (by age in years)		
0–17	0.034	Normal(0.034, 0.010)
18–24	0.010	Normal(0.010, 0.003)
25–29	0.012	Normal(0.012, 0.003)
30–34	0.009	Normal(0.009, 0.002)
35–39	0.015	Normal(0.015, 0.002)
40–44	0.021	Normal(0.021, 0.002)
45–49	0.027	Normal(0.027, 0.002)
50–54	0.041	Normal(0.041, 0.003)
55–59	0.053	Normal(0.053, 0.003)
60–64	0.079	Normal(0.079, 0.004)
65–69	0.107	Normal(0.107, 0.005)
Other natural history parameters		
Probability of PNF		
DBD	0.014	Beta(21, 1456)
Living related	0.019	Beta(15, 755)
Proportion of NODAT in first 6 months	0.75	Beta(75, 25)
Risk stratification for CMV infection		Dirichlet(54, 84, 71)
High risk (D+/R–)	0.258	
Intermediate risk (D±/R+)	0.402	
Low risk (D–/R–)	0.340	
Risk stratification for EBV infection		Dirichlet(28, 48, 6)
High risk (D+/R–)	0.341	
Intermediate risk (D±/R+)	0.585	
Low risk (D–/R–)	0.073	
Utilities		
Baseline utility		Multivariate normal
Constant	0.9679812	
Coefficient for age	–0.001807	
Coefficient for age^2	–0.00000971	
Coefficient for sex (male)	0.0232887	
Disutilities		
Functioning graft	0.053	Gamma(1.179, 0.045)
Haemodialysis	0.277	Gamma(66.90, 0.004)
Peritoneal dialysis	0.264	Gamma(35.73, 0.007)

Parameter	Value	PSA distribution
Resource use		
Induction therapy		
BAS (10 mg if weight < 35 kg; 20 mg if weight ≥ 35 kg)	1.964	1 + beta(95, 4)
R-ATG drug acquisition (mg/kg)	6.5	Normal(6.5, 0.126)
R-ATG i.v. administration	4.525	Normal(4.525, 0.079)
Maintenance therapy		
See *Table 87*		Unless SE reported or could be calculated, a log-normal distribution was fitted using the method of moments and assuming coefficient of variation of 10% with following exceptions: coefficient of variation = 50% for TAC-PR vs. TAC resource use coefficient of variation = 2% for BEL resource use
Trompeter *et al.*[77]		
TAC (with AZA) (mg/m²/day)		X1 ~ normal(8.80, 0.240) X2 ~ normal(6.33, 0.292) X3 ~ normal(4.89, 0.329)
0–6 months	7.565	(X1 +X2)/2
6–12 months	5.610	(X2 +X3)/2
Thereafter	4.890	X3
CSA (with AZA) (mg/m²/day)		X1 ~ normal(299.4, 10.4) X2 ~ normal(203.3, 5.1) X3 ~ normal(180.0, 6.6)
0–6 months	251.35	(X1 +X2)/2
6–12 months	191.65	(X2 +X3)/2
Thereafter	180.00	X3
AZA (mg/kg/day)	1.80	Normal(1.80, 0.04)
Prednisolone (mg/kg/day)		X1 ~ normal(3.9, 0.19) X2 ~ normal(4.5, 0.37) X3 ~ normal(0.3, 0.02)
0–6 months (with TAC)	2.1	(X1 +X3)/2
0–6 months (with CSA)	2.4	(X2 +X3)/2
Thereafter (with TAC or CSA)	0.3	X3
Grenda *et al.*[75]		
TAC (with MMF) (mg/kg/day)		
Throughout (prepubertal)	0.180	Normal(0.180, 0.014)
Throughout (pubertal)	0.130	Normal(0.130, 0.010)

Parameter	Value	PSA distribution
MMF (with TAC) (g/m^2/day)		
Throughout (prepubertal)	0.54	Normal(0.54, 0.002)
Throughout (pubertal)	0.60	Normal(0.60, 0.003)
Offner *et al.*[73]		
CSA (with BAS+MMF) (mg/kg/day)		
0–3 months	7.80	Normal(7.80, 0.34)
3–6 months	7.15	Normal(7.15, 0.33)
6–12 months	6.65	Normal(6.65, 0.29)
Thereafter	6.20	Normal(6.20, 0.27)
CSA (with MMF) (mg/kg/day)		
0–3 months	7.67	Normal(7.67, 0.34)
3–6 months	6.85	Normal(6.85, 0.30)
6–12 months	6.20	Normal(6.20, 0.28)
Thereafter	5.90	Normal(5.90, 0.26)
MMF (with BAS+CSA) (g/m^2/day)		X1 ~ normal(1.06, 0.03)
		X2 ~ normal(1.06, 0.03)
		X3 ~ normal(0.96, 0.04)
		X4 ~ normal(0.93, 0.04)
0–3 months	1.06	(X1 + 2×X2)/3
3–6 months	1.01	(X2 +X3)/2
6–12 months	0.95	(X3 +X4)/2
Thereafter	0.93	X4
MMF (with CSA) (g/m^2/day)		X1 ~ normal(1.11, 0.03)
		X2 ~ normal(1.00, 0.04)
		X3 ~ normal(0.85, 0.04)
		X4 ~ normal(0.82, 0.04)
0–3 months	1.04	(X1 + 2×X2)/3
3–6 months	0.93	(X2 +X3)/2
6–12 months	0.83	(X3 +X4)/2
Thereafter	0.82	X4

Parameter	Value	PSA distribution
Graft loss		
Proportion of failed grafts explanted by time since transplantation		
0–3 months	0.41	Beta(1.95, 2.81)
3–12 months	0.23	Beta(2.85, 9.54)
12–24 months	0.09	Beta(3.55, 35.9)
24+ months	0.04	Beta(3.80, 91.2)
Proportion of failed grafts explanted (subsequent grafts)	0.056	Linear combination of above
Subsequent transplantation		
Workup for retransplantation	1.44	Normal(3423, 58.5)/2370
Living donor costs	0.349	Beta(826, 1544)
Deceased donor costs	0.651	1 minus above
Maintenance immunosuppression		
TAC (mg/kg/day)	0.1	Log-normal(–2.31, 0.1)
MMF (g/day)	2	Log-normal(0.688, 0.1)
Prednisolone (mg/day)	16.3	Log-normal(2.79, 0.1)
Infection prophylaxis		
Co-trimoxazole (PJP and UTI prophylaxis): Septrin (480-mg tablets in first three months)	90	Log-normal(4.49, 0.1)
Valganciclovir (CMV prophylaxis) (proportion of affected patients multiplied by time)		
Full dose 0–3 months	1	Not varied
Half dose 3–6 months	0.3	Beta(3, 7)
Full dose 3–6 months	0.16	Beta(1.6, 8.4)
Valganciclovir dosage according to target dose	(Daily only/alternate days allowed)	
0–337.5	450/225	
337.5–675	450/450	
675+	900/900	
GFR for target dose calculation	80	Normal(80, 2)
AR		
Expected number of AREs per patient experiencing 1 + ARE	1.193	Normal(136, 11.7)/114
CMV infection treatment		
Expected number of CMV infections per patient experiencing 1 + CMV infection	1	Not varied
Diabetes mellitus		
Antidiabetic medication: metformin 500-mg tablets per 3 months	273.9	Log-normal(5.61, 0.1)
Complications (inpatient)	0.25	Not varied
Complications (non-inpatient)	0.25	Not varied

Parameter	Value	PSA distribution
Dyslipidaemia		
Statins (mg per cycle per affected patient)		
Fluvastatin	2191	Log-normal(7.66, 0.25)
Pravastatin	548	Log-normal(6.28, 0.25)
Simvastatin	91	Log-normal(4.48, 0.25)
Medical management (attendances per cycle per affected patient)		
Dietetics outpatients	0.25	Log-normal(–1.42, 0.25)
GP	0.25	Log-normal(–1.42, 0.25)
Anaemia		
Proportion requiring ESA treatment	0.052	Beta(207, 3762)
Mean weekly dose	5.832	Normal(5.832, 0.067)
Monitoring		
Clinics (first 3 months)	26.1	Log-normal(3.26, 0.05)
Blood tests (first 3 months)	26.1	Log-normal(3.26, 0.05)
Clinics + bloods (per cycle)		
3–6 months	6.5	Log-normal(1.87, 0.1)
6–12 months	3	Log-normal(1.09, 0.1)
12–24 months	3	Log-normal(1.09, 0.1)
24–36 months	2	Log-normal(0.69, 0.1)
36 + months	1	Log-normal(1.87, 0.1)
Subsequent grafts	3	Log-normal(1.07, 0.25)
Viral PCR		
0–3 months (CMV) (if no r-ATG)	6.02	Log-normal(1.76, 0.25)
0–3 months (CMV) (with r-ATG)	1.98	Log-normal(0.65, 0.25)
3–6 months (CMV)	0.26	Log-normal(–1.38, 0.25)
0–6 months (BKV)	1	Log-normal(–0.03, 0.25)
6–12 months (BKV)	0.5	Log-normal(–0.72, 0.25)
0–6 months (EBV)	1.02	Log-normal(–0.01, 0.25)
6–12 months (EBV)	0.34	Log-normal(–1.10, 0.25)
Viral serology (per cycle)		
0–3 months (CMV)	0.26	Log-normal(–1.38, 0.25)
At 12 and 24 months (CMV)	0.60	Log-normal(–0.54, 0.25)
At 36, 48 and 60 months (CMV)	0.34	Log-normal(–1.11, 0.25)

Parameter	Value	PSA distribution
Dialysis		
Proportion of dialysis patients receiving haemodialysis (by age in years)		
0–1	0.455	Beta(10, 12)
2–3	0.464	Beta(13, 15)
4–7	0.556	Beta(15, 12)
8–11	0.645	Beta(20, 11)
12–15	0.705	Beta(31, 13)
16–17	0.625	Beta(15, 9)
18–24	0.791	Beta(276, 73)
25–34	0.804	Beta(913, 223)
35–44	0.845	Beta(1853, 340)
45–54	0.843	Beta(3358, 624)
55–64	0.852	Beta(4408, 768)
65–74	0.858	Beta(5824, 967)
75–84	0.890	Beta(5533, 681)
85 +	0.915	Beta(1246, 116)
Access surgery		
Temporary access (for HD)	1	Not varied
Long-term access (for HD)	1	Not varied
Long-term access (for PD)	1	Not varied
Unit costs *Dialysis*		
Access surgery		
Long-term access for HD	£1946	Normal(1946, 98)
Temporary access for HD (years)		
< 19	£1747	Normal(1747, 113)
≥ 19	£823	Normal(823, 40)
Long-term access for PD	£1101	Normal(1101, 120)
Ongoing costs (per cycle)		
Haemodialysis		
< 19	£20,278	Normal(20,278, 3134)
≥ 19	£6093	Normal(6093, 164)
Peritoneal dialysis		
< 19	£10,515	Normal(10,515, 881)
≥ 19	£6000	Normal(6000, 183)
Induction agents		
BAS and r-ATG	See *Table 96*	Not varied

Parameter	Value	PSA distribution
Maintenance agents		
TAC-PR, MPS, SRL, EVL and BEL	See *Table 96*	Not varied
TAC-IR, CSA, MMF, AZA and prednisolone	See *Table 97*	Mixture models
AR treatment		
AR (per episode)	£3557	Log-normal(8.15, 0.25)
Spontaneously resolving	£145	Log-normal(4.97, 0.1)
Steroid sensitive	£1274	Log-normal(7.14, 0.1)
Steroid resistant (medical management)	£3456	Log-normal(8.12, 0.25)
Steroid resistant (drug acquisition per kg)	£44.46	Log-normal(0.64, 0.25)
Infection prophylaxis		
Septrin (per 480-mg tablet)	£0.16	Not varied
Valcyte (per 450-mg tablet)	£18.02	Not varied
Infection treatment		
CMV infection	£3,009	Log-normal(7.98, 0.25)
Anaemia		
Binocrit (per 1000 IU)	£4.33	Not varied
Diabetes mellitus		
Metformin (per 500-mg tablet)	£0.0054	Normal(0.0054, 0.00001)
Complications (annual cost)		
Inpatient	1389	Normal(1389, 99)
Non-inpatient	695	Normal(695, 19)
Dyslipidaemia		
Statins (per mg)		
Fluvastatin	£0.0022	Mixture model
Pravastatin	£0.0026	Mixture model
Simvastatin	£0.0003	Mixture model
Medical management		
Dietetics	£62.70	Normal(62.70, 2.76)
GP	£50.82	Normal(50.82, 5.38)
PTLD		
MabThera (per mg)	£1.75	Not varied
Hypertension		
Amlodipine (per mg)	£0.0071	Not varied
Bendroflumethiazide (per 2.5-mg tablet)	£0.0344	Not varied
Captopril (per mg)	£0.0035	Not varied
Hypomagnesaemia		
Magnaspartate (per sachet)	£0.80	Not varied

APPENDIX 7

Parameter	Value	PSA distribution
Drug administration		
i.v. infusion (first)	£228.95	Normal(228.95, 15.54)
i.v. infusion (subsequent)	£325.59	Normal(325.59, 45.74)
Monitoring		
Clinic	£145	Log-normal(4.97, 0.1)
Viral PCR (CMV, EBV, BKV)	£46.75	Log-normal(3.81, 0.25)
CMV serology	£18.29	Log-normal(2.88, 0.25)
Therapeutic drug monitoring (CSA, TAC, SRL, EVL)	£26.71	Log-normal(3.25, 0.25)
Full blood count	£5.05	Log-normal(1.62, 0.1)
Renal profile	£4.54	Log-normal(1.51, 0.1)
Liver profile	£4.64	Log-normal(1.53, 0.1)
Explant		
< 19	£4829	Normal(4829, 483)
≥ 19	£4966	Normal(4966, 497)
Subsequent retransplantation		
Recipient workup		
< 19	£505	Normal(505, 50)
≥ 19	£849	Normal(849, 84)
Living donor costs	£8914	Normal(8914, 891)
Deceased donor costs	£10,142	Normal(10142, 1014)
Transplant surgery		
< 19	£20,913	Normal(20913, 2091)
≥ 19	£16,030	Normal(16030, 1603)

ARE, acute rejection episode; D–/R–, donor is seronegative, recipient is seronegative; D+/R–, donor is seropositive, recipient is seronegative; D±/R+, donor is seropositive/seronegative, recipient is seropositive; HD, haemodialysis; PD, peritoneal dialysis.

Note

Normal distributions are reported as mean (SD) and beta distributions are reported as beta(α, β).

Appendix 8 Comparison of the Peninsula Technology Assessment Group, Astellas and previous Assessment Group's model-based analyses

TABLE 142 Major cost elements in the different analyses

Cost parameter	Previous Assessment Group model[2] (£)	PenTAG[a] (£)	Astellas[b] (£)
TAC therapy (per year)	(£1.70/mg) 3909	With MMF • 1114 (first year) • 1234–1527 (second year to age 17 years) • 959 (age 18+ years) With AZA • 1376 (first year) • 1115–1579 (second year to age 17 years) • 959 (age 18+ years) With SRL • Year 1: £610 • Year 2 to age 17 years (average cost per year): £664 • Age 18 years onwards: £839	1559 (first year) 1366 (second year)
TAC administration	0	1031 (first year) 321 (second year) 214 (third year) 107 (fourth year +)	0
MMF therapy (per year)	2737	With TAC • 82–141 (first year to age 17 years) • 203 (age 18+ years) With CSA • 138 (first year) • 135–191 (second year to age 17 years) • 230 (age 18+ years)	1326
CSA therapy (per year)	1368	With MMF • 1317 (first year) • 1281–2194 (second year to age 17 years) • 1071 (age 18+ years) With AZA • 1466 (first year) • 1299–1841 (second year to age 17 years) • 1078 (age 18+ years)	N/A

continued

TABLE 142 Major cost elements in the different analyses (*continued*)

Cost parameter	Previous Assessment Group model[2] (£)	PenTAG[a] (£)	Astellas[b] (£)
CSA administration	0	1031 (first year) 321 (second year) 214 (third year) 107 (fourth year+)	N/A[c]
BEL (per year)	N/A	7276 (first year) 4624 (thereafter for weight ≤ 50 kg) 9249 (thereafter for weight > 50 kg)	4018 (first year) 2374 (second year+)
BEL administration	N/A	4632 (first year) 4247 (thereafter)	0
CCSs	0	46 (first year) 13–20 (thereafter)	176 (first year) 139 (second year+)
AR (event)	4644	3557 (4244 per patient experiencing AR)	2536 (first year) 2522 (second year+)
Dialysis (per year)	21,060	< 19 years • 81,112 (HD) • 42,058 (PD) ≥ 19 years • 24,372 (HD) • 24,000 (PD)	0
Retransplantation	N/A	< 19 years • 20,913 (procedure only) ≥ 19 years • 16,030 (procedure only)	5086
Retransplantation: organ procurement	N/A	9714	0

HD, haemodialysis; PD, peritoneal dialysis.
a The values are based on applying adult weight-based doses to children and adolescents.
b Adopted a 31.5 kg weight for representative patient in the model
c Astellas does not evaluate CSA as a comparator in their submission. However, the model spreadsheets include information where the annual costs of CSA are calculated based on market shares to be £3731 for the first and £3514 for subsequent years.

TABLE 143 Key effectiveness assumptions and outcomes in economic models compared

Effectiveness parameter	Previous Assessment Group model[2]	PenTAG	Astellas
Time to graft failure (median)	NR	(To nearest 0.25 years, excluding DWFG) CSA + MMF: 14.00 TAC + MMF: 17.50 CSA + AZA: 12.00 TAC + AZA: 18.75 CSA + EVL: 16.25 TAC + SRL: 12.75 TAC-PR + MMF: 17.25 BAS + CSA + MMF: 16.50 BAS + TAC + MMF: 21.00 BAS + CSA + AZA: 14.50 BAS + TAC + AZA: 22.75 BAS + SRL + MMF: 18.00 BAS + BEL + MMF: 24.25 BAS + CSA + MPS: 19.25 r-ATG + CSA + MMF: 15.75 r-ATG + TAC + MMF: 19.50 r-ATG + CSA + AZA: 13.75 r-ATG + TAC + AZA: 21.50	Time to 15% failure (median not achieved within model horizon) Without BCAR at 12 months: 7 years With BCAR at 12 months: 6 years[a]
Time to transplantation from graft failure (mean unless otherwise stated)	NR	Mean time to transplantation or death following failure of initial graft: 4.86 years (range 4.39–5.17 years)	3.5 years (median)
Annual change in GFR	N/A	N/A	N/A
Utility of functioning graft – first transplant	0.84 (NR, assumed is same as Woodroffe *et al.*[255])	0.909 (age 10 years) 0.888 (age 20 years) 0.866 (age 30 years) 0.841 (age 40 years) 0.815 (age 50 years) 0.786 (age 60 years)	0.712

continued

TABLE 143 Key effectiveness assumptions and outcomes in economic models compared (*continued*)

Effectiveness parameter	Previous Assessment Group model[2]	PenTAG	Astellas
Utility of functioning graft –second + transplants	0.84 (NR, assumed is same as Woodroffe *et al.*[255])	As first	0.712
Utility of dialysis state	0.65 (NR, assumed is same as Woodroffe *et al.*[255])	0.691 (age 10 years) 0.668 (age 20 years) 0.645 (age 30 years) 0.619 (age 40 years) 0.592 (age 50 years) 0.564 (age 60 years)	0.483

N/A, not applicable.
a Model was driven by surrogate marker of AR.

TABLE 144 Results of the Astellas and PenTAG model-based analyses compared

Model	Regimens compared	Functioning first graft (years)	Functioning graft (years)	Years with graft loss/dialysis	Life-years	QALYs[a]	Costs (£)[a]	ICER incremental cost per QALY
Astellas	TAC (+ MMF + CCS)	NR	NR	NR	9.472	5.569	58,471	TAC TD vs. SRL I: £1,576,937 (other options are dominated by TAC TD)
	SRL I (+ MMF + CCS)				9.468	5.565	52,339	
	EVL (+ MMF + CCS)				9.467	5.564	90,168	
	SRL II (+ MMF + CCS)				9.456	5.553	61,490	
	BEL (+ MMF + CCS)				9.455	5.551	75,726	
Assessment Group (PenTAG)	TAC TD[b] (+ MMF + CCS)	NR	NR	NR	9.472	5.569	58,471	TAC OD dominates
	TAC OD[b] (+ MMF + CCS)				9.502	5.604	53,395	
	TAC (+ MMF)	19.94	35.35	8.14	43.49	18.21	182,163	CSA vs. TAC: TAC dominates
	TAC (+ BAS + MMF)	22.45	36.29	7.46	43.75	18.36	170,915	AZA vs. MMF: AZA dominates (with TAC) MMF dominates (with CSA)
	SRL I (+ BAS + MMF)	20.38	35.53	8.00	43.53	18.24	199,144	
	BEL (+ BAS + MMF)	24.62	37.24	6.89	44.12	18.59	324,708	SRL vs. TAC: TAC dominates
	CSA (+ AZA)	14.80	33.67	9.46	43.13	17.98	212,626	BEL vs. TAC: £667,031
	CSA (+ MMF)	16.79	34.32	9.01	43.33	18.10	202,424	
	TAC (+ AZA)	20.91	35.77	7.82	43.59	18.27	177,360	
	TAC-PR (+ MMF)	19.68	35.21	8.17	43.38	18.15	198,433	

OD, once daily (prolonged release); TD, twice daily (immediate release); NR, not reported.
SRL I is a CNI minimisation strategy (using SRL) as used in Astellas' submission.
SRL II is a CNI avoidance strategy (using SRL) as used in Astellas' submission.
a Discounted at 3.5% per year.
b Model adjusted for compliance; this analysis is not comparable with the above Astellas analyses.

Appendix 9 Additional results from the Peninsula Technology Assessment Group model

TABLE 145 Disaggregated discounted costs (clinical effectiveness estimates from adult RCTs)

Regimen	Induction (first graft)	Maintenance immunosuppression (first graft)	AR (first graft)	Graft loss (first graft)	Infection prophylaxis (first graft)	CMV infection (first graft)	Monitoring (first graft)
CSA + MMF	£0	£17,911	£1128	£164	£550	£760	£17,101
TAC + MMF	£0	£16,460	£994	£146	£550	£760	£18,176
CSA + AZA	£0	£14,302	£1834	£189	£547	£760	£16,307
TAC + AZA	£0	£15,517	£1302	£170	£546	£760	£18,335
CSA + EVL	£0	£88,084	£1102	£147	£551	£291	£20,309
TAC + SRL	£0	£28,250	£967	£195	£545	£291	£18,809
TAC-PR + MMF	£0	£31,223	£976	£155	£549	£760	£18,032
BAS + CSA + MMF	£2019	£19,892	£675	£147	£551	£760	£17,845
BAS + TAC + MMF	£2019	£17,594	£585	£129	£552	£760	£18,902
BAS + CSA + AZA	£2019	£15,552	£1211	£168	£549	£760	£17,118
BAS + TAC + AZA	£2019	£16,586	£798	£148	£548	£760	£19,132
BAS + SRL + MMF	£2019	£34,225	£633	£155	£548	£399	£18,141
BAS + BEL + MMF	£2019	£155,131	£1034	£117	£553	£760	£16,891
BAS + CSA + MPS	£2019	£39,558	£930	£132	£552	£760	£18,595
r-ATG + CSA + MMF	£2676	£17,820	£494	£158	£1194	£760	£16,579
r-ATG + TAC + MMF	£2676	£15,744	£425	£142	£1194	£760	£17,584
r-ATG + CSA + AZA	£2676	£13,952	£925	£178	£1190	£760	£15,948
r-ATG + TAC + AZA	£2676	£15,045	£590	£159	£1187	£760	£17,863

TABLE 146 Disaggregated discounted costs (based on adult effectiveness estimates)

Regimen	Retransplantation	Immunosuppression (subsequent grafts)	Monitoring (subsequent grafts)	Graft loss (subsequent grafts)	Dialysis	NODAT	Anaemia	Dyslipidaemia
CSA + MMF	£16,885	£9842	£14,995	£68	£116,778	£813	£1238	£1677
TAC + MMF	£14,706	£8493	£12,939	£59	£101,680	£1802	£1272	£1681
CSA + AZA	£18,376	£10,766	£16,414	£75	£126,832	£810	£1214	£1671
TAC + AZA	£14,305	£8235	£12,570	£57	£98,419	£1805	£1283	£1683
CSA + EVL	£15,418	£8936	£13,610	£62	£106,710	£774	£1260	£2074
TAC + SRL	£17,837	£10,414	£15,887	£72	£122,944	£2806	£1221	£2061
TAC-PR + MMF	£14,882	£8597	£13,105	£60	£102,768	£2115	£1267	£1677
BAS + CSA + MMF	£15,467	£8966	£13,654	£62	£107,059	£816	£1261	£1682
BAS + TAC + MMF	£13,324	£7653	£11,656	£53	£92,165	£1808	£1296	£1686
BAS + CSA + AZA	£16,827	£9803	£14,939	£68	£116,300	£813	£1239	£1677
BAS + TAC + AZA	£12,804	£7330	£11,186	£51	£88,144	£1811	£1310	£1689
BAS + SRL + MMF	£14,707	£8490	£12,944	£59	£101,528	£1437	£1272	£2074
BAS + BEL + MMF	£12,101	£6918	£10,537	£48	£83,688	£354	£1325	£1698
BAS + CSA + MPS	£14,072	£8111	£12,350	£56	£97,426	£765	£1287	£1690
r-ATG + CSA + MMF	£17,617	£10,307	£15,694	£71	£122,014	£812	£1225	£1675
r-ATG + TAC + MMF	£15,581	£9037	£13,758	£63	£107,937	£1801	£1256	£1679
r-ATG + CSA + AZA	£18,810	£11,048	£16,833	£77	£130,031	£810	£1206	£1670
r-ATG + TAC + AZA	£14,966	£8646	£13,182	£60	£103,299	£1804	£1270	£1682

TABLE 147 Health outcomes for different regimens (based on adult effectiveness estimates)

Regimen	Life expectancy	Undiscounted life-years with functioning graft	Undiscounted life-years on dialysis	AR within 12 months	NODAT within 12 months	Proportion receiving second transplant	Proportion receiving third transplant	Proportion receiving fourth transplant
CSA + MMF	43.37	34.44	8.93	0.271	0.018	0.780	0.326	0.081
TAC + MMF	43.55	35.50	8.05	0.239	0.040	0.715	0.284	0.069
CSA + AZA	43.17	33.78	9.39	0.441	0.018	0.812	0.352	0.090
TAC + AZA	43.65	35.92	7.72	0.313	0.040	0.691	0.274	0.067
CSA + EVL	43.50	35.12	8.38	0.265	0.017	0.739	0.299	0.073
TAC + SRL	43.14	33.98	9.16	0.232	0.063	0.797	0.341	0.087
TAC-PR + MMF	43.45	35.37	8.08	0.235	0.048	0.717	0.287	0.070
BAS + CSA + MMF	43.57	35.16	8.41	0.162	0.018	0.741	0.300	0.073
BAS + TAC + MMF	43.75	36.29	7.46	0.141	0.040	0.669	0.258	0.062
BAS + CSA + AZA	43.38	34.49	8.89	0.291	0.018	0.777	0.324	0.081
BAS + TAC + AZA	43.86	36.78	7.07	0.192	0.040	0.638	0.245	0.059
BAS + SRL + MMF	43.53	35.53	8.00	0.152	0.032	0.711	0.283	0.069
BAS + BEL + MMF	44.12	37.24	6.89	0.249	0.008	0.623	0.234	0.055
BAS + CSA + MPS	43.81	35.98	7.83	0.224	0.017	0.698	0.273	0.066
r-ATG + CSA + MMF	43.29	34.06	9.24	0.119	0.018	0.801	0.341	0.086
r-ATG + TAC + MMF	43.47	34.99	8.47	0.102	0.040	0.746	0.302	0.074
r-ATG + CSA + AZA	43.14	33.56	9.58	0.222	0.018	0.824	0.361	0.093
r-ATG + TAC + AZA	43.58	35.47	8.11	0.142	0.040	0.720	0.288	0.071

TABLE 148 Total discounted costs and QALYs for scenario analyses

	Total discounted costs			Total discounted QALYs		
Regimen	Base case	Scenario 1	Scenario 2	Base case	Scenario 1	Scenario 2
CSA + MMF	£199,910	£197,252	£195,685	18.1269	18.1554	18.1269
TAC + MMF	£179,719	£178,138	£175,974	18.2398	18.2569	18.2398
CSA + AZA	£210,097	£202,041	£206,583	18.0031	18.0868	18.0031
TAC + AZA	£174,989	£171,128	£171,604	18.2970	18.3387	18.2970
CSA + EVL	£259,327	£258,260	£242,849	18.2209	18.2474	18.2209
TAC + SRL	£222,300	£221,113	£215,947	17.9553	17.9696	17.9553
TAC-PR + MMF	£196,165	£194,866	£189,774	18.1854	18.2008	18.1854
BAS + CSA + MMF	£190,856	£191,872	£186,442	18.2468	18.2358	18.2468
BAS + TAC + MMF	£170,182	£171,903	£166,389	18.3596	18.3407	18.3596
BAS + CSA + AZA	£199,042	£195,682	£195,463	18.1308	18.1663	18.1308
BAS + TAC + AZA	£164,316	£164,316	£160,885	18.4259	18.4259	18.4259
BAS + SRL + MMF	£198,631	£199,792	£191,707	18.2423	18.2277	18.2423
BAS + BEL + MMF	£293,175	£292,935	£283,749	18.5901	18.6097	18.5901
BAS + CSA + MPS	£198,303	£197,393	£190,327	18.3907	18.4023	18.3907
r-ATG + CSA + MMF	£209,097	£211,660	£204,555	18.0702	18.0432	18.0702
r-ATG + TAC + MMF	£189,637	£192,841	£185,673	18.1763	18.1422	18.1763
r-ATG + CSA + AZA	£216,114	£215,070	£212,374	17.9721	17.9827	17.9721
r-ATG + TAC + AZA	£183,191	£184,933	£179,583	18.2468	18.2283	18.2468

Notes
Scenario 1: surrogate relationship between AR and graft survival is removed.
Scenario 2: body weight follows ninth centile for age (instead of median).

Appendix 10 UK Transplant Registry standard national organ transplant data set

The UK Transplant Registry maintains a standard data set, which is available on request without the need for prior approval (URL: www.odt.nhs.uk/uk-transplant-registry/data/; Cathy Hopkinson, Statistics and Clinical Studies, NHSBT, 15 October 2014, personal communication). The data set contains details of all solid organ transplants (kidney, liver, pancreas, intestine, heart, lung and multiorgan) between 1995 and 2012. The data set contains limited information about the donor, recipient and match between them.

Key variables in the data set which have been used in analyses supporting the economic modelling:

- RECIP_ID – allows subsequent retransplantations to be identified and graft number to be estimated
- DTYPE (DBD; DCD; living related; living unrelated; domino; living – relationship unspecified; living unrelated – pooled; living unrelated – altruistic) – classification of donor type (it was assumed that relationships from domino onwards are living unrelated)
- RAGE_GRP (< 18; 18–30; 31–50; 51–60; 61–70; > 70) – recipient age group
- RSEX (male; female) – recipient sex
- TY_YR (1995; 1996; . . .; 2012) – transplant year
- TX_TYPE (kidney only; . . .) – used to restrict to kidney-only transplants
- KID_GSURV – kidney (graft) survival (days since transplantation)
- KID_GCENS – 0 if graft survival was censored; 1 if graft failed
- KID_PSURV – patient survival following kidney transplant (days since transplantation)
- KID_PCENS – 0 if patient survival was censored; 1 if patient died.

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