Health Technology Assessment 2005; Vol. 9: No. 21

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study

R Woodroffe, GL Yao, C Meads, S Bayliss,
A Ready, J Raftery and RS Taylor

May 2005

Health Technology Assessment
NHS R&D HTA Programme

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study

R Woodroffe,[1] GL Yao,[2] C Meads,[1] S Bayliss,[1] A Ready,[3] J Raftery[2] and RS Taylor[1*]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK
[2] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK
[3] Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK

*Corresponding author

Declared competing interests of authors: RS Taylor has undertaken paid educational presentation for Roche (2000). Otherwise no members of the review team or the units to which they belong at the University of Birmingham have any pecuniary relationship with sponsors, specific or non-specific. A Ready has received funding (direct and indirect) from Fujisawa, Novartis Roche and Wyeth.

Published May 2005

This report should be referenced as follows:

Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. *Health Technol Assess* 2005;**9**(21).

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

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/59/01. 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 referees 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.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study

R Woodroffe,[1] GL Yao,[2] C Meads,[1] S Bayliss,[1] A Ready,[3] J Raftery[2] and RS Taylor[1*]

[1] Department of Public Health and Epidemiology, University of Birmingham, UK

[2] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK

[3] Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK

*Corresponding author

Objectives: To examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus.

Data sources: Electronic databases. Industry submissions. Current Clinical Trials register. Cochrane Collaboration Renal Disease Group.

Review methods: The review followed the InterTASC standards. Each of the five company submissions to the National Institute for Clinical Excellence (NICE) contained cost-effectiveness models, which were evaluated by using a critique covering (1) model checking, (2) a detailed model description and (3) model rerunning.

Results: For induction therapy, three randomised controlled trials (RCTs) found that daclizumab significantly reduced the incidence of biopsy-confirmed acute rejection and patient survival at 6 months/1 year compared with placebo, but not compared with the monoclonal antibody OKT3. There was no significant gain in patient survival or graft loss at 3 years. The incidence of side-effects with daclizumab reduced compared to OKT3. Eight RCTs found that basiliximab significantly improved 6-month/1-year biopsy-confirmed acute rejection compared to placebo, but not compared to either ATG or OKT3. There was no significant gain in either 1-year patient survival or graft loss. The incidence of side-effects with basiliximab was not significantly different compared to OKT3/ATG. For initial/maintenance therapy, 13 RCTs found that tacrolimus reduced the 6-month/1-year incidence of biopsy-proven acute rejection compared to ciclosporin. There was no significant improvement in either 1-year or long-term (up to 5 years) graft loss or patient survival. The acute rejection benefit of tacrolimus over ciclosporin appeared to be equivalent for Sandimmun and Neoral. There were important differences in the side-effect profile of tacrolimus and ciclosporin. Seven RCTs found that mycophenolate mofetil (MMF) reduced the incidence of acute rejection. There was no significant difference in patient survival or graft loss at 1-year or 3-year follow-up. There appeared to be differences in the side-effect profiles of MMF and azathioprine (AZA). No RCTs comparing MMF with AZA were identified. One RCT compared mycophenolate sodium (MPS) to MMF and reported no difference between the two drugs in 1-year acute rejection rate, graft survival, patient survival or side-effect profile. Two RCTs suggest that addition of sirolimus to a ciclosporin-based initial/maintenance therapy reduces 1-year acute rejections in comparison to a ciclosporin (Neoral) dual therapy alone and substituting azathioprine with sirolimus in initial/maintenance therapy reduces the incidence of acute rejection. Graft and patient survival were not significantly different with either sirolimus regimen. Adding sirolimus increases the incidence of side-effects. The side-effect profiles of azathioprine and sirolimus appear to be different. For the treatment of acute rejection, three RCTs suggested that both tacrolimus and MMF reduce the incidence of subsequent acute rejection and the need for additional drug therapy. Only one RCT and one subgroup analysis in children (<18 years) were identified comparing ciclosporin to tacrolimus and sirolimus, respectively.

Conclusions: The newer immunosuppressant drugs (basiliximab, daclizumab, tacrolimus and MMF) consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy. The independent use of basiliximab, daclizumab, tacrolimus and MMF was

associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%). However, the effects of these drugs did not appear to be additive (e.g. benefit of tacrolimus with adjuvant MMF was 5% reduction in acute rejection rate compared with 15% reduction with adjuvant AZA). Thus, the addition of one of these drugs to a baseline immunosuppressant regimen was likely to affect adversely the incremental cost-effectiveness of the addition of another. The trials did not assess how the improvement in short-term outcomes (e.g. acute rejection rate or measures of graft function), together with the side-effect profile associated with each drug, translated into changes in patient-related quality of life. Moreover, given the relatively short duration of trials, the impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain. The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost-effectiveness on the newer immunosuppressants contingent on modelling based on extrapolations from short-term trial outcomes. The choice of the most appropriate short-term outcome (e.g. acute rejection rate or measures of graft function) for such modelling remains a matter of clinical and scientific debate. The decision to use acute rejection in the meta-model in this report was based on the findings of a systematic review of the literature of predictors of long-term graft outcome. Only a very small proportion of the RCTs identified in this review assessed patient-focused outcomes such as quality of life. Since immunosuppressive drugs have both clinical benefits and specific side-effects, the balance of these harms and benefits could best be quantified through future trials using quality of life measures. The design of future trials should be considered with a view to the impact of drugs on particular renal transplant groups, particularly higher risk individuals and children. Finally, there is a need for improved reporting of methodological details of future trials, such as the method of randomisation and allocation concealment. A number of issues exist around registry data, for example the use of multiple drug regimens and the need to assess the long-term outcomes. An option is the use of observational registry data including, if possible, prospective data on all consecutive UK renal transplant patients. Data capture for each patient should include immunosuppressant regimens, clinical and patient-related outcomes and patient demographics.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Antibodies Substances produced by white blood cells in response to foreign antigens such as infections and foreign cells such as kidney transplants. After a transplant, antibodies can attack the new kidney and cause rejection. Antibodies can also cause renal disease such as glomerulonephritis.

Antigen Any substance that can stimulate the production of antibodies.

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

Cold ischaemia time Period during which a donated kidney is transported in ice from donor to recipient. Duration is related to the extent of kidney damage.

Creatinine clearance A test for measuring renal, dialysis or transplant function. The normal level for the kidney(s) is about 1200 litres per week (120 ml min^{-1}); for patients on continuous ambulatory peritoneal dialysis it is 50 litres per week, on continuous cycling peritoneal dialysis 65 litres per week and on haemodialysis 100 litres per week.

Cross-match Blood test to check whether a patient has antibodies to the donor kidney.

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

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

Donor kidney A kidney that has been donated.

Glomerulus One of the filtering units inside the kidney (plural glomeruli).

Graft or allograft Transplanted kidney.

1-Haplotype identical HLA are inherited as a set called a haplotype from one or both parents. 1-Haplotype identical is not a perfect HLA match; 2-haplotype identical is a perfect HLA match.

Heart-beating donor A donor kidney where the heart is still beating in the donor after brain death has occurred. Most, but not all, cadaveric transplants come from heart-beating donors.

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.

Nephritis A general term for inflammation of the kidneys. Also used as an abbreviation for glomerulonephritis.

Nephron Small filtering unit in the kidney, made up of glomeruli and tubules.

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.

continued

Glossary *continued*

Tissue type A set of inherited characteristics on the surface of cells. Each person's tissue type has six components (three from each parent). Although there are only three main sorts of tissue type characteristic (called A, B and DR), each of these comes in 20 or more different versions.

Transplant A term used to mean either a transplant kidney or the transplant operation.

Transplantation The addition of or replacement of an organ in the body by a recipient's organ.

Transplant kidney A kidney moved from the donor to the recipient; can be in cadaveric, living related or living unrelated transplant.

List of abbreviations

ALG	antilymphocyte globulin
AR	acute rejection
ARR	acute rejection rate
ATG	antithymocyte globulin
AZA	azathioprine
BNF	British National Formulary
BPAR	biopsy-proven acute rejection
BTS	British Transplantation Society
C_2	ciclosporin blood concentration measured 2 hours after administration
CAN	chronic allograft nephropathy
CAPD	continuous ambulatory peritoneal dialysis
CI	confidence interval
CMV	cytomegalovirus
CsA	ciclosporin A
DARE	Database of Abstracts of Reviews of Effectiveness
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQol 5 Dimensions
ESRD	end-stage renal disease
ESRF	end-stage renal failure
FK506	tacrolimus
GFR	glomerular filtration rate
GSCE	graft survival cost-effectiveness
HB_sAg	hepatitis B surface antigen
HEED	Health Economic Evaluation Database
HLA	human leucocyte antigen
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IL-2	interleukin-2
ITT	intention to treat
IV	intravenous
IVS	intravenous steroids
mAB	monoclonal antibody
MI	myocardial infarction
MMF	mycophenolate mofetil
MMRRR	Mycophenolate Mofetil Acute Renal Rejection Group
MPS	mycophenolate sodium
MRC	Medical Research Council
NA	not applicable
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NR	not reported

continued

List of abbreviations *continued*

NRR	National Research Register
ns	not significant
OKT3	orthoclone K T-cell receptor 3 antibody
OR	odds ratio
p.a.	per annum
PRA	panel-reactive antibodies
PTDM	post-transplant diabetes mellitus
PTLD	post-transplant lymphoproliferative disease
QALY	quality-adjusted life-year
QE	Queen Elizabeth Hospital, Birmingham
RCT	randomised controlled trial
RMR	Repamune Maintenance Regimen (trial)
RRT	renal replacement therapy
ScHARR	School of Health and Related Research
SCr	serum creatinine concentration
SF-36	Short Form 36
TOR	target of rapamycin
TTO	time trade-off
UHW	University Hospital Wales
UKTSSA	United Kingdom Transplant Support Service Authority

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Kidney transplantation is the treatment of choice for end-stage renal disease because, if successful, it achieves better quality and duration of life than with long-term dialysis. Approximately 1400 renal transplants are performed in England and Wales each year (1700 in the UK). A variety of immunosuppressive drugs is used in the management of renal transplants in the UK.

Objective

The aim of this study was to examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus.

Methods

The clinical effectiveness review followed the explicit Quality Standards agreed by InterTASC. A search for reviews and primary studies was undertaken using a variety of sources. Studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken.

Each of the five company submissions to the National Institute for Clinical Excellence (NICE) contained cost-effectiveness models. Given both the breadth of this review and details of these submitted models, rather than develop a *de novo* model, a three-stage critique of the company models was undertaken. This included (1) model checking (technical checking and quality assessment), (2) a detailed model description (assumptions, model parameters, sources and values) and (3) model rerunning.

Number and quality of studies, and direction of evidence

Induction therapy

Daclizumab: three randomised controlled trials (RCTs) were found comparing daclizumab to either placebo or another induction agent (OKT3). Daclizumab significantly reduced the incidence of biopsy-confirmed acute rejection and patient survival at 6 months/1 year compared with placebo, but not compared with OKT3. There was no significant gain in patient survival or graft loss at 3 years. The incidence of side-effects with daclizumab reduced compared to OKT3. No RCTs in children were found.

Basiliximab: eight RCTs compared basiliximab to placebo/no therapy or other induction agents (either ATG or OKT3). Basiliximab significantly improved 6-month/1-year biopsy-confirmed acute rejection compared to placebo, but not compared to either ATG or OKT3. There was no significant gain in either 1-year patient survival or graft loss. The incidence of side-effects with basiliximab was similar compared to OKT3/ATG. Although one RCT included children, results in this group were not reported.

Initial/maintenance therapy

Tacrolimus: 13 RCTs compared tacrolimus to ciclosporin (either Sandimmun® or Neoral®). Tacrolimus reduced the 6-month/1-year incidence of biopsy-proven acute rejection compared to ciclosporin. There was no significant improvement in either 1-year or long-term (up to 5 years) graft loss or patient survival. The magnitude of the acute rejection benefit of tacrolimus over ciclosporin appeared to be equivalent for Sandimmun and Neoral. There were important differences in the side-effect profile of tacrolimus and ciclosporin. One paediatric RCT reported a reduction in rejection rate and improvement in graft survival with tacrolimus compared to ciclosporin at 1 year.

Mycophenolate mofetil (MMF): seven RCTs compared MMF to azathioprine (AZA). MMF reduced the incidence of acute rejection. There was no significant difference in patient survival or graft loss at 1-year or 3-year follow-up. There appeared to be differences in the side-effect profiles of MMF and AZA. No RCTs comparing MMF with azathioprine were identified.

Mycophenolate sodium (MPS): one RCT compared MPS to MMF and reported no

difference between the two drugs in 1-year acute rejection rate, graft survival, patient survival or side-effect profile. No RCTs in children were found.

Sirolimus: two RCTs were included. The results suggest, first, that the addition of sirolimus to a ciclosporin-based initial/maintenance therapy reduces 1-year acute rejections in comparison to a ciclosporin (Neoral) dual therapy alone and, second, that substituting azathioprine with sirolimus in initial/maintenance therapy reduces the incidence of acute rejection. Graft and patient survival were not significantly different with either sirolimus regimen. The addition of sirolimus increases the incidence of side-effects. The side-effect profiles of AZA and sirolimus appear to be different. A small subgroup analysis of one RCT indicated the benefits of sirolimus in children to be similar to those in adults.

Treatment of acute rejection

Three RCTs were found that assessed the use of either tacrolimus or MMF in the treatment of acute rejection. Tacrolimus was compared to ciclosporin and MMF compared to either AZA or high-dose steroids. The results suggested that both tacrolimus and MMF reduce the incidence of subsequent acute rejection and the need for additional drug therapy.

Costs/cost-effectiveness

Induction therapy

Daclizumab: one cost-effectiveness study compared daclizumab to placebo. Combining costs and graft survival, the results of this US study suggested that daclizumab is cost-effective at 10 years, but not at 1 year.

Basiliximab: two cost-effectiveness analyses compared basiliximab to placebo. A US study reported basiliximab to have superior 1-year and 10-year graft survival cost-effectiveness to placebo. A Canadian study found basiliximab to have a similar gain in quality-adjusted life-years (QALY) to ATG at 1 year, but lower costs.

Initial/maintenance therapy

Tacrolimus: three cost-effectiveness analyses compared tacrolimus to ciclosporin (either Sandimmun or Neoral). Two modelling studies, undertaken from a UK perspective, demonstrated that the 1-year cost-effectiveness of tacrolimus relative to ciclosporin was unattractive (£120,000 vs £220,000/QALY or £30,000 per additional graft saved or patient death avoided). A more recent European-based retrospective cost-effectiveness analysis using 6-month RCT data concluded that, compared to ciclosporin, tacrolimus both improved clinical outcomes and reduced overall health service costs.

MMF: three cost-effectiveness analyses compared MMF to azathioprine. Results consistently demonstrated that at 1 year post-transplant, MMF may be a cost-effective substitute for azathioprine in initial and maintenance immunosuppressant renal transplant therapy (e.g. incremental cost of Can$14,268 per graft-year gained and incremental cost of Can$50,717 per QALY).

MPS: no cost-effectiveness studies for MPS were found.

Sirolimus: no cost-effectiveness studies for sirolimus were found.

Treatment of acute rejection

Only one cost-effectiveness analysis of the use of newer immunosupressants in acute rejection treatment was found. This study estimated a cost saving per graft of US$12,400 with MMF compared to muromonab CD3 in patients with intractable acute rejection.

Conclusions

The newer immunosuppressant drugs (basiliximab, daclizumab, tacrolimus and MMF) consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy. The independent use of basiliximab, daclizumab, tacrolimus and MMF was associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%). However, the effects of these drugs did not appear to be additive (e.g. benefit of tacrolimus with adjuvant MMF was 5% reduction in acute rejection rate compared with 15% reduction with adjuvant AZA). Thus, the addition of one of these drugs to a baseline immunosuppressant regimen was likely to affect adversely the incremental cost-effectiveness of the addition of another.

The trials did not assess how the improvement in short-term outcomes (e.g. acute rejection rate or measures of graft function), together with the side-effect profile associated with each drug, translated into changes in patient-related quality of life. Moreover, given the relatively short duration of

trials, the impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain.

Five industry submissions included models assessing the cost-effectiveness of basiliximab and daclizumab as induction therapies and tacrolimus, MMF, MPS and sirolimus as initial/maintenance therapies. The differences in unit cost for the same drugs between models, along with wide variations in the ratios between the unit costs of drugs in the same regimen and differences in the range of other costs considered, mean that cost-effectiveness comparisons between the models must be treated with caution. The cost-effectiveness results of the meta-model analysis conducted in this report support this conclusion.

Limitations of the calculations

The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost-effectiveness on the newer immunosuppressants contingent on modelling based on extrapolations from short-term trial outcomes. The choice of the most appropriate short-term outcome (e.g. acute rejection rate or measures of graft function) for such modelling remains a matter of clinical and scientific debate. The decision to use acute rejection in the meta-model in this report was based on the findings of a systematic review of the literature of predictors of long-term graft outcome.

Recommendations for research

The majority of trials to date have been designed solely with drug licensing in mind and are powered to examine short-term changes in clinical outcome (e.g. acute rejection rate). Future trials need to include quality of life measures, examine effects in high-risk patients and children, and improve their reporting. It is recognised that a number of the issues in this area make RCTs potentially difficult to design and undertake (e.g. comparisons of multiple therapies, collection of long-term outcomes). Consideration should therefore also be given to the collection of prospective observational outcome data on immunosuppressant regimens and the potential to do this within the context of a national registry.

Chapter 1

Aim of the review

Over the past three decades renal transplantation has become established as the optimum treatment for end-stage renal failure (ESRF). This has been supported by a number of developments, advances in immunosuppression being arguably one of the most significant.

The principal aim of immunosuppression is to promote graft survival through the prevention of acute rejection, which is a natural consequence of the transplantation of tissues from one individual to another. However, immunosuppressive agents are powerful drugs and to optimise the results of transplantation their efficacy must be balanced against safety. Hence, any toxicity to the recipient or graft, or both, must be minimised, as must their potential to add to the already significant co-morbidity risks of patients in renal failure.

From an era when the choice of immunosuppressive agents was limited, there has now emerged a number of agents. The aim of this review is to examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus.

Chapter 2
Background

Description of underlying health problem

Renal failure and reasons for transplantation

ESRF occurs when the kidneys are no longer able to function so that the patient would die unless given dialysis or renal transplantation. This is a permanent state that necessitates lifelong and/or life-saving intervention in the form of dialysis or kidney transplantation.[1]

Although not suitable for all patients, kidney transplantation is the treatment of choice for ESRF because, if successful, quality and duration of life are better than achieved with long-term dialysis.[2] However, successful kidney transplantation is reliant on the use of immunosuppressant agents. The regimen and dose of these agents must be tailored to the needs of each individual to achieve the best possible patient outcomes.[3]

In 1992 the cost of transplantation was calculated to be £11,600 for the transplant procedure, with each subsequent year of a successful transplant costing £4000 per annum.[4] In contrast to 1992, the cost per annum for dialysis was calculated to be £21,000 in the recent National Institute for Clinical Excellence (NICE) appraisal of home versus hospital haemodialysis (£21,000 and £22,000 for haemodialysis in a satellite unit and hospital, respectively).[5]

Renal transplantation procedures

Although renal transplantation has clear advantages over alternative modalities of care, many patients in ESRF are prevented from receiving a transplant owing to the limited supply of donor organs. In the UK, kidneys for transplantation have principally come from dead (cadaveric) donors. In general, these donors have sustained catastrophic head injury or other intracranial event (e.g. stroke) and have been treated on an intensive care unit (ICU), ultimately being diagnosed as having reached brainstem death, although as the heart still beats and artificial ventilation continues the organs are well maintained. Following the granting of permission by relatives the kidneys are removed, usually as part of a multiorgan retrieval. The kidneys are then allocated to suitable recipients using a nationwide scheme (maintained by UK Transplant in Bristol) based on tissue type compatibility. Once allocated, organs are 'shipped' to the recipient, who may be in a part of the country distant from the place of retrieval.

As a result of a number of healthcare measures, increased road safety and improved neurosurgical techniques the number of cadaveric donors has been dropping over the past decade, threatening to limit the benefits of renal transplantation to a fortunate few patients. A number of initiatives have been commenced to address this. Pre-eminent in this is the increased use of living donor organs in the UK. In these circumstances the donor kidney is usually obtained, after a stringent review process, from a close blood relative or spouse. The donor and recipient operations occur in the same hospital, usually sequentially, usually with excellent outcomes. Donor and recipient operations often occur in different hospitals where the recipient is a child and is in a children's hospital. The number of living donor transplants has increased steadily in the UK and has supported the fall in cadaveric donor organs, although there is not yet clear evidence that the overall number of transplants performed has increased.[6]

A further initiative to increase the number of kidneys available for transplantation has been the use of 'non-heart-beating donors'. In these situations kidneys are removed from patients soon after the confirmation of death, in the absence of brainstem death criteria and after cardiac arrest. These procedures usually occur on neurosurgical ICUs or in accident and emergency units. By virtue of the need for rapid removal of organs after death the retrieval process is technically and ethically complex and very resource dependent. Furthermore, the kidneys obtained are subject to variable lengths of ischaemia during the process, leading to an increased rate of delayed function, non-function and postoperative dialysis requirements. Accordingly, non-heart-beating donation has not achieved widespread introduction in the UK. However, an increasing number of reports indicate that kidneys from this source can function

adequately and they will probably play an increasing role in the future.

It is evident from the above that the process of obtaining kidneys for transplantation is complex, with many steps, each requiring close attention to detail if optimum results are to be attained. Hence, surgical trauma must be avoided, while adequate perfusion and cooling of the kidneys at the time of retrieval are of paramount importance since delays can reduce graft viability (warm ischaemia).[7,8] Similarly, the time between retrieval of kidneys and transplantation should be minimised since viability is also reduced as the length of cold storage (cold ischaemia time) increases so that prolonged cold ischaemia is associated with reduced 5-year graft survival.[9,10]

Rejection of transplanted organs

The continued imbalance between the limited supply of kidneys for transplantation and the increasing demand for them indicates that kidneys that have been transplanted are precious, both to individual recipients and as a national resource. Accordingly, there is a clear obligation on the part of those looking after these patients to ensure the continued survival and function of these grafts for as long as possible.

Renal transplants are lost for a number of reasons, including technical failures, death (of the recipient) with a functioning graft, recurrence of original renal disease in the allograft, chronic allograft nephropathy (formerly called chronic rejection) and acute rejection. Although few grafts are now lost to acute rejection, owing to developments in immunosuppression, the ubiquitous nature of the rejection response means that it is an ever-present threat, hence the pre-eminence of immunosuppression in the management of renal transplant recipients.[11]

Acute rejection is most frequent during the first few weeks after a transplant, but can occur at any time if the level of immunosuppression becomes inadequate.[12] The response is cell mediated and leads to injury to or destruction of the functioning cellular structures of the transplanted organ. Occasionally, the response may be more aggressive and include an antibody-mediated vascular component.

Clinically, acute rejection tends to occur as acute episodes heralded by a reduction in graft function (seen on biochemistry), and clinical features such as fluid retention and occasionally graft tenderness and fever. Episodes are usually managed by an intensive, short-term course of corticosteroids, which in most instances restores graft stability. In a small percentage of grafts, rejection persists requiring additional 'rescue therapy' to 'salvage' the graft.

The importance of acute rejection is not only the risk of acute graft loss, but also that it may be more likely that a patient will subsequently lose the graft through chronic dysfunction (chronic rejection). The concept of chronic rejection has been revised over the past few years.[13] Initially, the slow, progressive decline in function exhibited by many grafts was considered to be evidence of a slowly progressive immunological process. However, it is now recognised that the end stage of this progression, in which the functional units of the graft are largely replaced by fibrous tissue, is the result of a number of possible insults, including repeated immunological attack, hypertension, hyperlipidaemia, diabetes mellitus and the nephrotoxic actions of a number of immunosuppressive agents. Accordingly, the process has been renamed chronic allograft nephropathy (CAN).[14]

CAN tends to be a gradual process, although both the time of onset and the rate of progression vary. It may develop as early as within a few months of the transplant or emerge after several years. The course is generally unremitting and ultimately leads to total loss of graft function, necessitating a return to dialysis or retransplantation. The poorly understood nature of the condition and the absence of any realistic models for study have limited the treatment available to the more than 30% of renal transplant patients who experience this process. However, the strategy of reduction or elimination of nephrotoxic immunosuppressive agents in such situations has been increasingly adopted. Despite such interventions, CAN remains one of the greatest challenges facing renal transplantation. In an era when graft losses due to acute rejection are very low and the majority of patients are dialysis independent at 1 year (initially a time-point that was difficult to achieve), many patients still lose their graft, prematurely, owing to the development of CAN. Although all of the aetiological factors are important, it is critical that any contribution from immunosuppression is recognised.

A more detailed discussion of the individual side-effect profiles of specific immunosuppressive agents will be undertaken in the main body of the report. However, the side-effects of immunosuppressive drugs can be defined as either

the general effects of suppression of the immune system, irrespective of the agents used, or those effects that are specific to individual drugs.

Complications of immunosuppression include an increased risk of developing infections, including viral infections such as cytomegalovirus (CMV), herpes simplex, herpes zoster and Epstein–Barr virus, and opportunistic protozoal, fungal and bacterial infections.[15] As immunosuppression is at its highest level in the first 6 months post-transplant, this is also the peak period for infections in these patients. Although modern immunosuppressive agents are becoming more specific, directing their activity principally towards the components of the rejection response, recipients are at higher risk for infections than the general population throughout their post-transplant life.[16]

Suppression of the immune system is also associated with an increase in the development of cancers, especially lymphoproliferative disorders, which appears to be directly related to the total exposure to immunosuppression.

Individual side-effects may include exacerbation of hypertension, hirsutism or alopecia, tremors, mood swings, weight gain, diabetes mellitus, gastrointestinal intolerance, hyperlipidaemia, bone-marrow suppression and nephrotoxicity.[17] Some side-effects are temporary and resolve as the body adjusts to the medication, whereas some will continue for as long as the medication is taken.[17]

Some of these effects compromise the graft, some compromise the well-being of patients who are already overburdened with co-morbidity and some reduce their quality of life. Some also have a major effect on compliance, which is a major issue in graft survival. It is vitally important to match individual patients to the regimen that not only is efficacious, but also provides the lowest level of side-effects.

One-year graft survival has steadily improved over the past two decades and is now over 90% in low-risk patients. However, for transplant patients who survive beyond the first year, improvements in the rate of graft failure have been more modest. In the long term, approximately 50% of grafts are still functioning at the death of transplant patients, the most common cause of death in these patients being cardiovascular complications.[10]

Epidemiology

ESRF can occur in people of any age and ethnic background, and for a variety of different reasons. Forty-seven per cent of people receiving renal replacement therapy (RRT) were over 65 years old in 1999. Around 130 children under the age of 18 years receive a new kidney in the UK each year.[18] The age distribution of recipients is shown in *Table 1*.[11]

Kidney transplants are performed in the UK at 23 centres and alliances. Approximately 1400 renal transplants are performed in England and Wales each year (1700 in the UK), with about 10% of organs coming from live donors (see *Table 2*).[18]

During 1999 approximately 25,900 patients in England and 1716 in Wales were receiving immunosuppression following kidney transplantation. Because of the increasing incidence, which has exceeded the death rate, the

TABLE 1 *Age distribution of renal graft recipients*

	Age (years)							
	0–5	**6–11**	**12–17**	**18–34**	**35–49**	**50–59**	**60–64**	**65+**
% of recipients	1	1.9	4.8	19.8	34.1	23.5	7.4	7.5
No. of recipients	13	25	64	263	453	312	99	100

TABLE 2 *Kidney transplantation, 1990–1998*

	1990–1992	**1993–1995**	**1996–1998**	**Total**
Adult: cadaveric	5,022	4,722	4,357	14,101
Paediatric: cadaveric	369	345	279	993
Adult: living	224	322	467	1,013
Paediatric: living	26	46	58	130
Total	5,641	5,435	5,161	16,237

prevalence rates have increased over time, with an increase in prevalence of 6500 patients in England and 300 in Wales since 1993.[18]

Sixty-one per cent of transplant recipients in the UK are men.[18] Black people are three times as likely as the general population to develop renal failure and more than one in nine renal transplants were in ethnic minority recipients.[18]

There is a 7–10% annual increase in the UK dialysis population. As the uptake rate of kidney transplantation has increased over time, the median age of patients and the number of co-morbidities that they suffer have also increased.[19] The number of people needing a transplant is expected to rise steeply over the next decade owing to an ageing population, an increase in renal failure, return of patients with a failed graft and scientific advances resulting in more people being suitable for a transplant.[11]

Living donor renal transplants have increased by 3% and now represent about one in ten of all renal transplants, the remainder being cadaveric transplants.[18] Nine per cent of living donor renal transplant recipients were under 18 years and 4% were aged 60 or over.[11] Adult and paediatric kidney transplants reported to UK Transplant between 1 January 1990 and 31 December 1998 are summarised in *Table 2*.

Current service provision

Categories of immunosuppressive therapy

Although there is no standard immunosuppressive drug for renal transplantation in the UK, several immunosuppressive drugs have been traditionally used (see section 'Current service delivery', p. 7).[20] Immunosuppression treatment following kidney transplantation can be categorised into prevention of graft rejection (induction, initial, maintenance therapy) and the treatment of established acute allograft rejection.

Induction therapy

This may be used as a short course of intensive immunosuppression immediately postoperatively, with the aim of 'switching off' the immune system for approximately 2 weeks post-transplant to reduce the likelihood of accelerated rejection and acute rejection. Traditionally, the term induction therapy has been linked with the use of three principal agents: the polyclonal antibodies antithymocyte immunoglobulin (ATG) and antilymphocyte immunoglobulin (ALG) and the monoclonal antibody OKT3 (muromonab CD3).[21] Induction therapy with these agents has been used extensively in the USA, whereas its use has been more limited in the UK. More recently, induction therapy using the newer CD25 monoclonal antibodies (basiliximab and daclizumab) has become more established.[22]

Initial therapy

This is given to all recipients, except where the donor is an identical twin, at the outset of treatment. Various definitions of the duration of initial therapy are used, for example at 0–14 days post-transplantation or 0–3 months post-transplantation. Therapy is usually triple therapy, using one specific calcineurin inhibitor (i.e. ciclosporin or tacrolimus) in combination with a steroid (e.g. prednisolone) and azathioprine. Occasionally, dual therapy (primary agent plus a steroid) or even monotherapy (primary agent alone) can be used.[23] Increasingly, stratification of initial therapy is being made on the basis of the perceived risk of acute rejection for each individual graft–recipient combination. Those patients considered at high risk of rejection will, in most units, receive additional levels of immunosuppression using various combinations of the available agents. Risk factors for acute rejection include poor human leucocyte antigen (HLA) matching, high levels of antibody sensitisation, prolonged graft cold ischaemia times, black recipients and unrelated living donor recipients.

Maintenance therapy

This is the immunosuppression on which patients are maintained long term, essentially the entire duration of the survival of the kidney graft. Often maintenance therapy is identical to initial therapy, but at a reduced dosage since the transplanted kidney becomes immunologically more stable with increasing time.[24] However, it is also not uncommon for agents used in maintenance therapy to be altered in response to side-effects or the development of acute rejection or chronic allograft nephropathy. Compliance with drugs is another reason for change, since certain cosmetic effects such as obesity, acne and hirsutism (or hypertrichosis) may have a major psychological impact, particularly in adolescent recipients.[25]

Acute rejection therapy

Short courses of therapy, usually in the form of high-dose steroids, are given as necessary to treat episodes of acute rejection. Steroid-resistant rejection is variably defined. One definition is acute rejection that does not resolve after two courses of steroids.[26] In the USA, UK and Europe,

steroid-resistant acute rejection was often treated with the polyclonal antibodies ALG or ATG or the monoclonal antibody OKT3. However, it has become more usual to adopt an adjunctive strategy of switching ciclosporin for another calcineurin inhibitor, such as tacrolimus.[27] However, there comes a point where the complications of excessive immunosuppression outweigh the benefits of keeping a kidney with persistent untreatable acute rejection. The graft is unsalvageable and ensuring that the patient comes to no additional harm is more important.[28]

Children and immunosuppression

The pharmacokinetics of many of the immunosuppressive drugs in young children differ from those of older children and adults, with poorer bioavailability and a higher rate of drug clearance.[29] However, dosages for children are based on the same principles for adults (usually milligrams of drug per kilogram of body weight). The appropriateness of this system is under question.[27] Growth retardation often occurs in children and adolescents with chronic renal insufficiency, and the use of steroids in children may also retard growth.[30] The long-term goal for immunosuppressive protocols in children is steroid-free regimens. There is also an increase in lymphoproliferative disease in paediatric recipients post-transplantation and this may be related to induction drugs.[31]

Description of new intervention

Description of newer immunosuppressive drugs

The newer immunosuppressant drugs for renal transplantation to be reviewed in this report are as follows.

Daclizumab

This CD25 monoclonal antibody is used as an induction agent in the prophylaxis of acute rejection. It binds to the CD25 antigen, part of the interleukin-2 (IL-2) receptor on T lymphocytes, causing a rapid reduction in T cells expressing the CD25 antigen. Side-effects include hyperglycaemia, hypertension, impaired wound healing, nausea, vomiting and abdominal pain.[32]

Basiliximab

This is another CD25 monoclonal antibody used as an induction agent. Side-effects include hyperglycaemia, hypertension, hyperkalaemia, hypokalaemia, hyperuricaemia, neurotoxicity, anaemia, nausea, vomiting, abdominal pain, weight gain and impaired wound healing.[32]

Tacrolimus

Tacrolimus, like ciclosporin, is a calcineurin inhibitor and is used in initial and maintenance therapy. Oral administration achieves adequate absorption, but may be highly variable. Close monitoring may be required at initial dosing. Side-effects include nephrotoxicity, hyperglycaemia, hyperkalaemia, neurotoxicity, anorexia and mood disturbances. Tacrolimus has been used as an adjunctive therapy in the treatment of acute rejection.[33]

Mycophenolate mofetil and mycophenolate sodium

Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS), like azathioprine, inhibit DNA proliferation, and are used in the initial and maintenance therapy. MMF is a prodrug that is converted to its active metabolite in the gastrointestinal tract. Side-effects include leucopenia, thrombocytopenia, anaemia, diarrhoea, abdominal pain, nausea, vomiting and secondary infections. MPS is an enteric-coated drug with a similar mechanism of action to MMF. MMF has been used as an adjunctive therapy in the treatment of acute rejection.[33]

Sirolimus

Sirolimus has a different mechanism of action to other immunosuppressants and potentially can act synergistically when administered with ciclosporin. It can therefore be used during initial and maintenance therapy. Sirolimus is reported to be non-nephrotoxic, but its principal side-effect is hyperlipidaemia. Other side-effects include thrombocytopenia, leucopenia, anaemia, abdominal liver function tests, rashes and mouth ulcers.[33]

The indications and costs of the immunosuppressive drugs used in renal transplantation are summarised in *Table 3*.

Current service delivery

The British Transplantation Society (BTS) recently requested unit policies on their immunosuppressive protocols. They compiled the results in order to assess the variability of regimens used in UK renal transplantation. A questionnaire was sent to all clinicians in renal transplant units around the UK. Seventy-six responses from 37 units were received.[35]

The proportion of patients estimated to receive 'high-risk' immunosuppressive regimens varied from 5 to 75%. Respondents were also asked what immunosuppressive regimen they used in high-

TABLE 3 *Immunosuppressive therapy: indications and costs (assuming a 70-kg individual)*[34]

Trade name	Generic name	Manufacturer	Type	Licensed indication	Cost per dose
Simulect®	Basiliximab	Novartis	Monoclonal antibody	Prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation in adult and paediatric patients. To be used concomitantly with ciclosporin microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies <80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil	20-mg vial (with water for injections), net price = £842.38 Dose: 20 mg within 2 hours before transplant surgery and a further 20 mg 4 days after surgery £824.38 per dose
Zenapax®	Daclizumab	Roche	Monoclonal antibody	Prophylaxis of acute organ rejection in *de novo* allogeneic adult and paediatric renal transplantation. To be used concomitantly with an immunosuppressive regimen including ciclosporin and corticosteroids in patients who are not highly immunised	5-ml vial with 5 mg ml^{-1}, net price = £240.52 Dose: 1 mg kg^{-1} within the 24-hour period before transplantation, then 1 mg kg^{-1} every 14 days for a total of five doses £721.56 per dose
Orthoclone®	OKT3, muronomab CD3	Johnson & Johnson	Monoclonal antibody	Named patient basis only	Price from QE pharmacy 5-ml ampoule with 1 mg ml^{-1}, £465.30 Dose 5 mg day^{-1} (induction and rejection), 2 mg day^{-1} (low-dose induction) £465.30 per day
Ahlbulin®[a]	ALG	Mitsubishi Pharma	Polyclonal antibody	Named patient basis only	Price from QE pharmacy 100-mg vial, £72.26 Dose: 5–10 mg kg^{-1} £289.04–502.82 per day
ATGAM®[a] (horse)	ATG	Pharmacia-Upjohn	Polyclonal antibody	Named patient basis only	Price from QE pharmacy 5-ml vial with 50 mg ml^{-1}, £205.50 Dose: 15–30 mg kg^{-1} daily £1027.50–£1849.50 per day

continued

TABLE 3 *Immunosuppressive therapy: indications and costs (assuming a 70-kg individual)*[34] *(cont'd)*

Trade name	Generic name	Manufacturer	Type	Licensed indication	Cost per dose
Thymoglobulin®[a] (rabbit)		Sangstat	Polyclonal antibody	Named patient basis only	Price from QE pharmacy 25-mg vial, £82.83 Dose: 1.5 mg kg^{-1} per daily £414.15 per day
Neoral®	Ciclosporin microemulsion	Novartis	Calcineurin inhibitor	Prevention of graft rejection following adult and paediatric kidney, liver, heart, combined heart–lung, lung or pancreas transplantation. Treatment of transplant rejection in patients previously receiving other immunosuppressive agents	100 mg ml^{-1} oral solution, net price 50 ml = £114.38 Dose: 10–15 mg kg^{-1} by mouth 4–12 hours before transplantation, followed by 10–15 mg kg^{-1} daily for 1–2 weeks postoperatively, then reduced gradually to 2–6 mg kg^{-1} daily for maintenance Initial cost £15.96–24.02 per day Maintenance cost £3.20–9.60 per day
SangCya®	Ciclosporin microemulsion	Sangstat	Calcineurin inhibitor	Prevention of graft rejection following adult and paediatric kidney, liver, heart, combined heart–lung, lung or pancreas transplantation. Treatment of transplant rejection in patients previously receiving other immunosuppressive agents	100 mg ml^{-1} oral solution, net price 50 ml = £94.36 Dose: 10–15 mg kg^{-1} by mouth 4–12 hours before transplantation, followed by 10–15 mg kg^{-1} daily for 1–2 weeks postoperatively, then reduced gradually to 2–6 mg kg^{-1} daily for maintenance Initial cost £13.21–19.82 per day Maintenance cost £2.64–7.93 per day
Sandimmun®	Ciclosporin	Novartis	Calcineurin inhibitor	Prevention of graft rejection following kidney, liver, heart, combined heart–lung, lung or pancreas transplantation. Treatment of transplant rejection in patients previously receiving other immunosuppressive agents[b]	Assuming price similar to Neoral tablets, 30-capsule packs of 10 mg = £8.22, 25 mg = £20.54, 50 mg = £40.22, 100 mg = £76.33 Dose: 10–15 mg kg^{-1} by mouth 4–12 hours before transplantation, followed by 10–15 mg kg^{-1} daily for 1–2 weeks postoperatively, then reduced gradually to 2–6 mg kg^{-1} daily for maintenance Initial cost £18.90–28.30 per day Maintenance cost £3.78–11.34 per day

continued

TABLE 3 *Immunosuppressive therapy: indications and costs (assuming a 70-kg individual)[34] (cont'd)*

Trade name	Generic name	Manufacturer	Type	Licensed indication	Cost per dose
Numerous, including Imurane®, Immunopurine®, Osprisine® and Azamine®	Azathioprine	Non-proprietary	Antimetabolite	Given in combination with corticosteroids and/or other immunosuppressive agents and procedures, to enhance the survival of organ transplants, such as renal transplants, and to reduce the corticosteroid requirements of renal transplant recipients	25 mg, 28-tablet pack, net price = £9.28; 50-mg, 56-tablet pack = £9.97 Dose: 5 mg kg^{-1} then 1–4 mg kg^{-1} daily according to response Initial cost £1.25 per day Maintenance cost £0.51–1.22 per day
Medrone®	Methylprednisolone	Pharmacia	Steroid	Indicated for suppression of inflammatory and allergic disorders and immunosuppression	30-tablet packs of 2 mg = £2.57, 4 mg = £4.93, 16 mg = 13.67; 20-tablet packs of 100 mg = £38.46 Dose: 2–40 mg daily £0.08–1.24 per day
Deltacortril® enteric	Prednisolone	Non-proprietary	Steroid	Indicated for suppression of inflammatory and allergic disorders and immunosuppression	30-tablet packs (enteric coated) 2.5 mg = £0.26, 5 mg = £0.43 Initial dose 10–20 mg daily Maintenance dose 2.5–15 mg daily Initial cost £0.03–0.06 per day Maintenance cost £0.01–0.04 per day
Prograf®	Tacrolimus	Fujisawa	Calcineurin inhibitor	Primary immunosuppression in liver and kidney allograft adult and paediatric recipients, and liver and kidney allograft rejection resistant to conventional immunosuppressive regimens. Prograf is not licensed for use with Cellcept or Simulect	50-capsule pack, 500 mg net price = £71.56, 1 mg = £92.93, 5 mg = £343.34 Dose: 150–300 mg kg^{-1} per daily £16.31–31.61 per day
Cellcept®	MMF	Roche	Antimetabolite	Indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult and paediatric (>2 years old) patients receiving allogeneic renal, cardiac or hepatic transplants. Cellcept is not licensed for use with Prograf	500-mg tablets, 50-tablet pack net price = £113.41 Dose: 2 g daily £9.07 per day

continued

TABLE 3 *Immunosuppressive therapy: indications and costs (assuming a 70-kg individual)[34] (cont'd)*

Trade name	Generic name	Manufacturer	Type	Licensed indication	Cost per dose
Myfortic®[a] (currently under regulatory review in Europe)	MPS (enteric coated)	Novartis	Antimetabolite	Indicated in combination with ciclosporin microemulsion and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal transplants. Adults only (provisional)	£9.05 per day[c]
Rapamune®	Sirolimus	Wyeth	Proliferation signal inhibitor	Adults only. Indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. Recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2–3 months, then may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued	Oral solution 1 mg ml^{-1}, 60 ml net price = £148.20 Dose: 6 mg after surgery, then 2 mg daily Initially cost £14.82 per day Maintenance cost £4.94 per day

[a] Not in British National Formulary (BNF).
[b] Now only available as intravenous (IV) drug.
[c] From industry submission.
QE, Queen Elizabeth Hospital, Birmingham, UK.

TABLE 4 *Immunosuppressive regimens offered by UK renal transplant units, July 2002*

No. of units providing drug regimen	**4**	**4**	**4**	**2**	**1**	**1**	**1**	**1**	**1**	**1**
Prednisolone	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ciclosporin	×	×	×	×	✓	✓	×	×	✓	✓
Azathioprine	×	×	✓	✓	×	×	×	✓	✓	×
Tacrolimus	✓	✓	×		×	×		✓	×	×
MMF	✓	✓	×	×	✓	✓	×	×	×	✓
IL-2 receptor blocker (basiliximab/ daclizumab)	✓	×	✓	✓	✓	×	✓	×	×	×
ATG/ALG	×	×	×	×	×	×	×	×	×	✓

✓, drug used; ×, drug not used.

risk patients, and whether this differed from that used in standard-risk patients. Replies to this question varied widely, with some units reporting a single high-risk regimen and others stratifying the regimen according to medium, high or very high risk. Most reported that they adopt a different strategy for patients with delayed graft function or recipients of non-heart-beating or live donor kidneys. To illustrate the degree of variability, the initial immunosuppressive strategy adopted for 20 units where it is perceived that there is a high immunological risk in an adult recipient is shown in *Table 4*.

With the exception of steroid (prednisolone) usage, there appears to be great variation in the choice of immunosuppressive drugs across units.[35]

Questions to be addressed in this review

This review will address the following specific questions related to the use of the newer immunosuppressive drugs in renal transplantation.

- The clinical and cost-effectiveness of daciluzimab and basiliximab as induction therapies.
- The clinical and cost-effectiveness of tacrolimus compared with ciclosporin (Sandimmun or Neoral) as an initial and a maintenance therapy.
- The clinical and cost-effectiveness of mycophenolate (mofetil and sodium) compared with azathioprine as an initial and a maintenance therapy.
- The clinical and cost-effectiveness of sirolimus as an initial and a maintenance therapy.
- The clinical and cost-effectiveness of daclizumab, basiliximab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus as treatments for acute rejection.

Where possible, each of these questions will be explored with specific consideration of children (i.e. <18 years) and high-risk patient groups (e.g. unrelated living graft recipients, poor HLA matching).

Chapter 3
Methods

Methods for reviewing clinical effectiveness

The clinical effectiveness review followed the explicit Quality Standards agreed by InterTASC.

Search strategy

A search for reviews and primary studies was undertaken using a variety of sources:

- bibliographic databases: Cochrane Library, Issue 3 2002, MEDLINE (Ovid) 1966 to July 2002 and EMBASE (Ovid) 1980 to July 2002. The National Research Register (NRR), Issue 2 2002, was searched to identify ongoing and unpublished research; details of specific search strategies are given in Appendix 1
- citation lists of relevant papers (including reviews identified at the scoping stage)
- Internet searches using Alta Vista, Dogpile and OMNI, website searching on UK, European and USA registries; UK Transplant, BTS, Renal National Service Framework, National Kidney Research Fund and British Renal Society
- handsearches of the most recent issues of the following journals: *Transplantation*, *Nephrology Dialysis and Transplantation*, *Transplantation Proceedings*, *Clinical Transplantation*, *Kidney International*, *American Journal of Kidney Disease*, *Journal of the American Society of Nephrology*, *Pediatric Nephrology* and *Pediatric Transplantation* (up to October 2002)
- contact with the Cochrane Collaboration Renal Disease Group based in Sydney, Australia
- citations in the industry submissions to NICE
- contact with clinical experts and with authors of papers where there were any queries
- Current Clinical Trials register [includes number of individual trials registers, such as the UK NRR and Medical Research Council (MRC) Clinical Trials Register], for information on registered trials that are currently underway

No language or age restrictions were applied to the searches. All references were exported to Reference Manager version 9.5 (ISI ResearchSoft, Carlsbad, CA, USA).

Inclusion and exclusion criteria

Two reviewers (RW and RT or RW and CM) independently scanned all the titles and abstracts and identified the potentially relevant articles to be retrieved. Where there was uncertainty, full text copies of papers were obtained. Studies were considered eligible if they met the following criteria (see Appendix 2 for the inclusion/exclusion criteria form).

Study design

Randomised controlled trials (RCTs) that include comparison of included drugs (see below) and any or all of the listed outcomes were assessed. RCTs were excluded where the trial had not finished recruiting, or if trial baseline characteristics or follow-up results for only a small proportion of the trial participants were reported.

Participants

The review assessed trials on adults or children (<18 years) who had received a kidney transplant from a live donor, a cadaveric or an asystolic donor. Trials including only patients with concomitant other organ transplants were excluded.

Outcomes

Data on the following outcome measures were sought:

- patient survival
- graft survival
- acute rejection episodes
- quality of life
- graft functioning [e.g. serum creatinine, glomerular filtration rate (GFR)]
- adverse events and side-effects (e.g. cardiovascular complications, malignancies, diabetes, infections and nephrotoxicity)
- growth (in children)
- patient-related quality of life.

Interventions

Drug comparisons were included according to three categories of immunosuppression: induction therapy, initial/maintenance treatment or treatment of acute rejection (rescue therapy). The immunosuppressive drugs assessed in each of these categories are summarised in *Table 5*.

Any comparisons that were identified and were not currently licensed in the UK were also included for comprehensiveness. Given the scope of this review,

TABLE 5 *Included comparisons of renal immunosuppression drugs*

	Intervention	Comparator
Induction therapy	Any combinations which include daclizumab or basiliximab	Either (1) triple combination therapy with ciclosporin, a corticosteroid and azathioprine or (2) dual combination therapy with ciclosporin and a corticosteroid alone or with any of ALG, ATG and OKT3
Initial/maintenance therapy	Any combinations of any of mycophenolate (mofetil or sodium), sirolimus, tacrolimus, daclizumab or basiliximab only	Either (1) triple combination therapy with ciclosporin, a corticosteroid and azathioprine or (2) dual combination therapy with ciclosporin and a corticosteroid
Treatment of acute rejection (rescue therapy)	Any combinations of mycophenolate (mofetil or sodium), sirolimus, tacrolimus, daclizumab or basiliximab (following initial high-dose steroids)	ALG, ATG and OKT3 (following initial high-dose steroids) or any other combinations of drugs

Adapted from NICE (2002).[36]

RCTs that examined the effectiveness of a strategy of drug tapering or drug switching were excluded.

Reviewers' inclusion and exclusion decisions were checked for agreement and any differences were discussed and resolved with a third reviewer. Given the large volume of material a good level of agreement was obtained between reviewers [weighted kappa: RW versus CM/RT: 0.70, 95% confidence interval (CI): 0.66 to 0.73].

Data extraction and quality

Data extraction was performed by three reviewers (RW, CM and RT). One reviewer independently extracted the effectiveness and quality assessment data from all included studies. The data were checked by a second reviewer.

Three reviewers (RW, CM and RT) independently evaluated the included RCTs for methodological quality using a modified version of the Jadad scale[37] (Appendix 3).

Data synthesis and analysis

A detailed tabular summary of the characteristics (i.e. patients, intervention, comparator and outcomes) and methodological quality of all included studies was undertaken.

Any information specified by companies as 'commercial in confidence' was underlined in one version of the draft report and omitted from the other.

Where appropriate, meta-analysis was undertaken using a fixed effects model, except in those situations where there was evidence of statistical heterogeneity, where a random effects model was used instead.

Binary outcomes are calculated as odds ratios (ORs) and reported as means and 95% CI. The results are taken forward for cost-effectiveness analysis as absolute risk reductions. All analyses were undertaken using RevMan version 4.1 and Stata version 6 (StataCorp LP, College Station, TX, USA).

Methods for reviewing cost-effectiveness

Search strategy

To identify relevant cost studies, economic evaluations and quality of life studies the following sources were searched:

- bibliographic databases: Cochrane Library [NHS Economic Evaluation Database (EED) and Database of Abstracts of Reviews of Effectiveness (DARE)], Issue 3 2002, MEDLINE (Ovid) 1966 to August 2002 and EMBASE (Ovid) 1980 to August 2002. The Health Economic Evaluations Database (HEED, September 2002 update) was also searched. Details of search strategies are given in Appendix 1
- Internet sites of national economic units
- citation lists of relevant papers (including reviews identified during a scoping search)
- citations in industry submissions to NICE.

No language or age restrictions were applied to the searches. All references were exported to Reference Manager version 9.5.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were applied as for the clinical effectiveness section of this review. In addition, to be included, studies must assess either resource implications or costs, or both.

No language restriction was applied. Study selection was carried out independently by three reviewers (RW and CM or RW and RT) using the same inclusion and exclusion form that was used for clinical effectiveness.

Data extraction, quality assessment and data handling

Data extraction was performed by three reviewers (RW, CM and RT). One reviewer independently extracted the effectiveness and quality assessment data from all included studies. These data were then checked by a second reviewer.

The methodological quality and results of all included studies were assessed according to the headings adapted from the BMJ Guidelines for authors and peer reviewers of economic submissions.[38] Quality assessment was performed by a single reviewer (RW, CM or RT) and checked by another.

Any information specified by companies as 'commercial in confidence' was underlined in one version of the draft report and omitted from the other.

Methods for economic modelling

Each of the five company submissions to NICE contained cost-effectiveness models. Given both the breadth of this review and details of these submitted models, rather than develop a *de novo* model, a three-stage critique of the company models was undertaken.[39] This included (1) model checking (technical checking and quality assessment), (2) a detailed model description (assumptions, model parameters, sources and values) and (3) model rerunning.

Model checking

The model architecture (logic and structure) was assessed in detail by two members of the review team (LY and JR).

Model description

A detailed summary of each of the models was undertaken (RW, JR, LY and RT). This included a summary of the principal model assumption, model parameters (values and sources) and model results.

Model reanalysis

After any adjustment for any logic errors detected in the first stage, each of the models was rerun using alternative parameter values and cost-effectiveness values were recalculated. Preferred parameter values were applied to each model. These parameter values were sourced from the systematic review and company submissions. The process of handling and synthesising the industry models will be discussed in more detail later in the report.

Chapter 4

Results

Format for reporting of results

Given the breadth of this review, it was decided that the most efficient way to present the evidence was according to each of the three key stages of immunosuppression therapy after renal transplant, namely, induction, initial/maintenance and rescue therapy. Within each therapy stage, the clinical effectiveness and cost-effectiveness evidence of a number of newer immunosuppression drugs was assessed. The report will present the clinical and cost-effectiveness evidence for each drug separately according to each therapy stage:

- induction therapy
  - daclizumab
  - basiliximab
- initial and maintenance therapy
  - tacrolimus
  - mycophenolate (mofetil or sodium)
  - sirolimus
- treatment of acute rejection
  - tacrolimus
  - mycophenolate (mofetil or sodium)
  - sirolimus
  - daclizumab
  - basiliximab.

Quantity of evidence

The identification, selection and exclusion process for clinical studies is summarised in *Figure 1*. A list of all included RCTs and associated papers is provided in Appendix 4. Details of ongoing trials in the UK as reported in the NRR are shown in Appendix 21.

Induction agents

Daclizumab versus placebo or another induction agent

Previous reviews and systematic reviews

The Daclizumab Study Group reported the pooled results of two large placebo-controlled RCTs: the double- and triple-therapy trials.[40–42] There was one review of the use of daclizumab in renal transplantation.[43]

Quantity of evidence

Three RCTs of the use of daclizumab in renal immunosuppression met the inclusion criteria of the review. Two of the trials were large multicentre trials (the Daclizumab Double Therapy Study Group; 275 patients[44,45] and the Daclizumab Triple Therapy Study Group; 260 patients),[46,47] whereas the third[48,49] was much smaller (28 patients). One of the trials included UK-based centres. The details of these trials are presented in Appendix 7.

Characteristics and quality of evidence

The two large trials[44–47] compared the efficacy of daclizumab to placebo, while a smaller third trial[48,49] compared daclizumab to OKT3. Daclizumab was given either in the 24 hours pretransplant or perioperatively, and then up to 8 weeks post-transplant daclizumab was added to either ciclosporin-based dual or triple therapy (azathioprine and MMF adjuvant therapy).

Although no details of randomisation or allocation concealment were reported, both large trials used double blinding and analysed by intention to treat (ITT). Lacha and colleagues[48,49] provided no methodological details. The two large trials provide follow-up data at 12 and 36 months, whereas only 6-month data are available for Lacha.[48,49] The median Jadad score across the three RCTs was 3 (range 1–3).

Results

Given the similarities in renal transplant populations and drug regimens across trials, all-cause mortality, graft loss and incidence of acute rejection were pooled across the two large placebo trials. Given the lack of heterogeneity ($p < 0.10$), fixed effect meta-analyses were undertaken.

However, owing to variation across trials in the side-effects collected and the definition of these side-effects, it was decided not to pool these results. For example, some studies measured the incidence of post-transplant diabetes mellitus (PTDM) on the basis of blood glucose levels, while others used insulin levels. The side-effects are therefore summarised by vote counting; trials were classified according to whether they reported a statistically

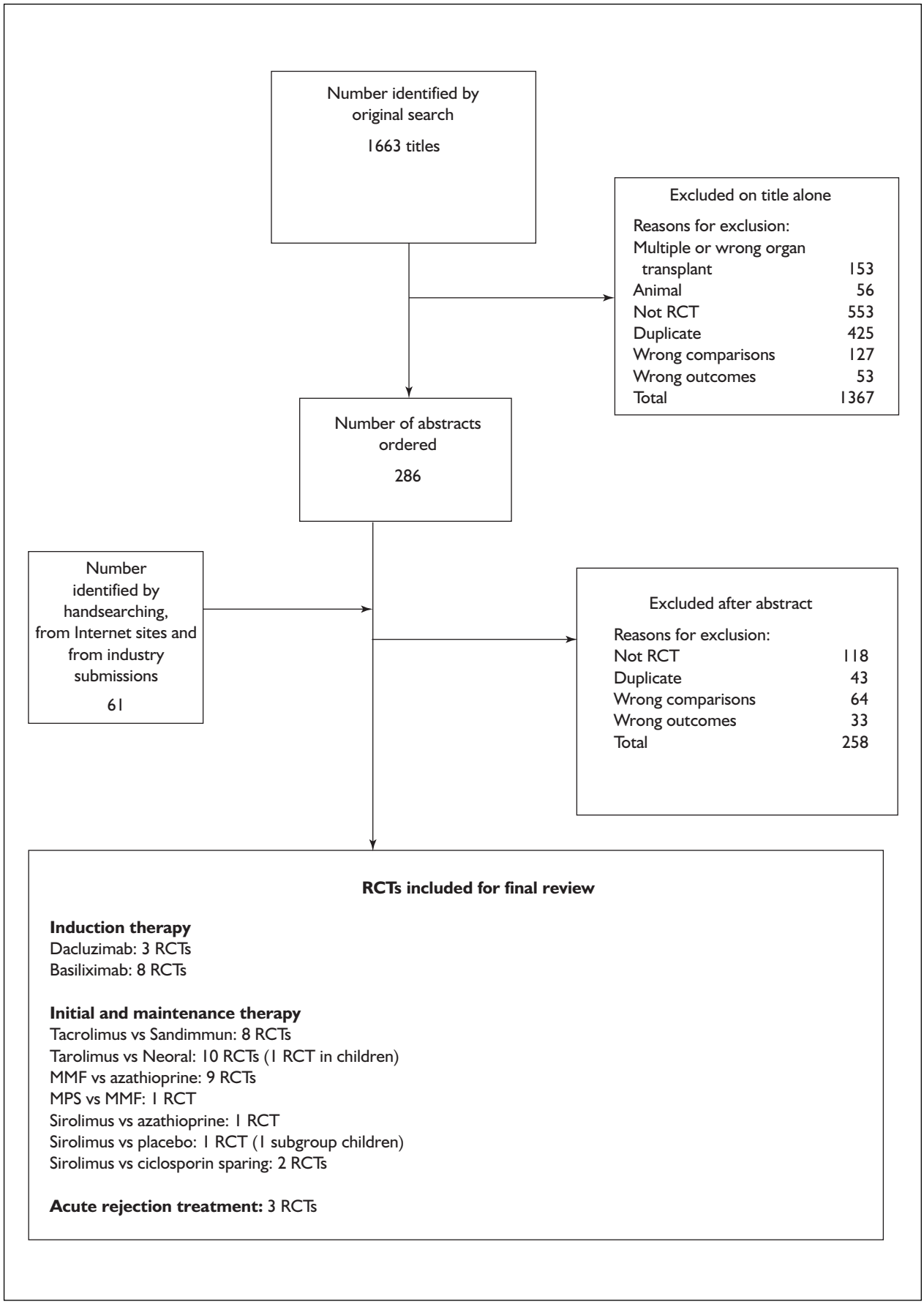

FIGURE 1 *Clinical effectiveness quantity of evidence*

significant increase, a statistically significant decrease or no statistical difference in a side-effect.

Short-term outcomes

There was evidence of an improvement in 6- or 12-month pooled all-cause mortality (OR: 0.30, 95% CI 0.10 to 0.93) and incidence of biopsy-proven acute rejection (BPAR) (OR: 0.47, 95% CI 0.32 to 0.67) with daclizumab compared to placebo *(Table 6)*. There was no significant improvement in graft loss. Compared to OKT3, there was no improvement in 6-month BPAR rate (OR: 1.35, 95% CI 0.29 to 6.18); graft loss was the same in both groups and all-cause mortality was similar.

No increase was observed in the most frequently reported adverse events in daclizumab-treated patients. Infusion-related adverse events were more common in placebo-treated patients. Reactions typically seen with OKT3, such as dyspnoea, oedema or fever, occurred at the time of infusion. The incidence of specific infections was comparable in daclizumab-treated and placebo-treated patients. The incidence of CMV infection was comparable in daclizumab-treated and placebo-treated patients. Vincenti and colleagues[44,45] reported a higher incidence of post-transplant lymphoproliferative disease (PTLD) in patients treated with daclizumab (1.6%, $n = 126$) compared with placebo (0.7%, $n = 134$). The incidence of malignancy was not reported. In contrast, Nashan and colleagues[46] reported no PTLD in the daclizumab-treated patients (0%, $n = 141$) and only one case (0.8%) in the placebo group ($n = 134$), potentially related to the use of OKT3. There was no difference in serum creatinine at follow-up between daclizumab and placebo. No malignant disease was reported for either group.

Long-term outcomes

There was no significant difference between daclizumab and OKT3. At the 3-year follow-up, there was no significant difference in graft loss (OR: 0.59, 95% CI 0.34 to 1.03) or all-cause mortality (OR: 0.67, 95% CI 0.17 to 2.69) between daclizumab and placebo.

TABLE 6 *Daclizumab versus placebo: pooled analysis at 12-month follow-up*

	No. of trials	OR (95% CI)
All-cause mortality	2	0.22 (0.06 to 0.79)
Graft loss	2	0.59 (0.34 to 1.03)
BPAR	2	0.47 (0.32 to 0.67)

Subgroup analysis

None of the daclizumab trials reported that they undertook subgroup analyses.

Children

No RCTs of the use of daclizumab in children were identified.

Summary

- Three RCTs were identified. Two large RCTs compared daclizumab to placebo and one small trial compared daclizumab to OKT3.[44–49]
- The level of trial reporting was generally poor, making an assessment of the methodological quality of these trials difficult. However, the two large trials were double blind and all three appeared to analyse their results by ITT.
- At 6 months or 1 year post-transplant, compared with placebo there was a significant reduction in all-cause mortality and BPAR rate with basiliximab. At 3 years, there was no improvement in patient or graft loss with daclizumab.
- Compared with another induction agent (OKT3), there was no significant improvement in 6-month BPAR, all-cause mortality or graft loss.
- The incidence of adverse events with daclizumab appeared to be low and comparable to that in placebo-treated patients. OKT3 appeared to be associated with increased infusion-related adverse events, such as dyspnoea, oedema and fever.
- None of the RCTs collected health-related quality of life data.
- None of the RCTs undertook subgroup analyses.
- No RCTs of the use of daclizumab in children were identified.

Basiliximab versus placebo or another induction agent

Previous systematic reviews and meta-analyses

Two previous pooled analyses were identified[50,51] which combined the results of two RCTs.[52,53] One previous review of the role of basiliximab in renal transplantation was found.[54]

Quantity of evidence

Eight basiliximab RCTs met the inclusion criteria of this review.[52,53,55–60] Five of these trials randomised over 100 patients each and four were multicentre, including centres in North America, Europe, South America and Asia. The two European multicentre trials included centres in the UK. The details of these trials are presented in Appendix 8.

Characteristics and quality of evidence

Six trials compared basiliximab to placebo or no

therapy, two trials compared basiliximab to another induction agent (either ATG or OKT3) and one trial compared basiliximab to both no therapy and OKT3. All the studies reported outcomes at 6- or 12-month follow-up. Kahan included a 5-year follow up.[53] Patient, graft loss, acute rejection episodes and side-effects were consistently reported across trials. There was evidence that a number of trials included higher risk patients, with kidney mismatches, living donors or second transplants.

The quality of trials was variable. Two trials[52,55] reported their methods of randomisation and allocation concealment, were placebo controlled, reported small losses to follow-up (<10%) and undertook ITT analysis (achieving a maximum Jadad score of 5). However, the remaining trials reported few methodological details. The median Jadad score across all eight RCTs was 2 (range 1–5).

Results

Given that all-cause mortality, graft loss and acute rejection episodes were reported across trials, it was decided to pool these studies. Trials were pooled according to whether they compared basiliximab to placebo (or no therapy) (seven trials) or to another induction agent (two trials).

Short-term outcomes

Compared to both placebo or no therapy and other induction agents, basiliximab did not improve either all-cause mortality or graft loss at 6- or 12-month follow-up (*Table 7*). However, compared to placebo or no therapy, basiliximab markedly reduced the relative risk of 6- or 12-month BPAR rate (OR: 0.57, 95% CI 0.45 to 0.72). No significant difference in BPAR was observed when comparing basiliximab to other induction agents (OR: 1.17, 95% CI 0.54 to 2.55). Comparing basiliximab to placebo, there was no evidence of a difference in the rate of CMV infection or serum creatinine levels at follow-up.

Subgroup analysis

Kahan and colleagues compared the acute rejection rates (ARRs) with basiliximab treatment in a number of subgroups, comparing gender (males versus females), age (>50 versus <50 years) and ethnic group (black versus other).[53] They found that ARRs were higher in blacks. However, despite this increased risk, basiliximab was equally effective in blacks and non-blacks in preventing acute rejection. Ponticelli and colleagues found the reduction in ARR in second transplants to be higher than for the trial.[55] Finally, Thistlewaite and colleagues in a pooled analysis of the placebo-controlled trials of Kahan and Nashan, compared the outcomes of diabetics to non-diabetics.[50,52,55] They found no significant difference between the two groups in terms of ARR, but there was a significant reduction in graft loss in diabetics.

TABLE 7 *Basiliximab trials: pooled analysis at 6- or 12-month follow-up*

	No. of trials	OR (95% CI)
Versus placebo or no therapy		
All-cause mortality	7	1.09 (0.57 to 2.10)
Graft loss	7	0.86 (0.59 to 1.24)
BPAR	7	0.57 (0.45 to 0.72)
Versus other induction agent		
All-cause mortality	2	1.70 (0.35 to 8.19)
Graft loss	2	4.26 (0.71 to 25.54)
BPAR	2	1.17 (0.54 to 2.55)

Children

No RCTs of the use of basiliximab therapy in children (<18 years) were identified. One of the adult trials recruited a proportion of patients of 15 years or older.[56] However, this trial did not state the proportion of patients recruited to this age group or report outcomes specifically in this younger group.

Summary

- Eight RCTs were identified that assessed the impact of basiliximab in renal transplantation. Several of these studies were large, multicentre trials.[52,53,55–60]
- Six RCTs compared basiliximab to either no therapy or placebo. Two RCTs have compared the addition of basiliximab to another induction agent (either ATG or OKT3).
- Although some of the larger trials appeared to be well conducted, the quality of the smaller trials was not well reported.
- Trials of basiliximab tended to recruit higher risk patients (non-matched donors or second transplants).
- Compared to placebo, basiliximab improved the 6- or 12-month incidence of BPAR. There were no significant improvements in either all-cause mortality or graft loss with basiliximab.
- Compared to another induction agent, there was no improvement in 6- or 12-month BPAR, all-cause mortality or graft loss.
- No RCTs reported the impact of basiliximab on patient-related quality of life.
- The impact of basiliximab on the ARR appears to be equivalent across subgroups.
- There appears to be little increase in side-effects with basiliximab.

- There is a small body of RCT evidence that has assessed the use of basiliximab in children.
- No RCTs directly comparing daclizumab and basiliximab were identified.

Initial and maintenance immunosuppressive therapy

Tacrolimus versus ciclosporin (Sandimmun)

Previous reviews and systematic reviews

A systematic review of Sandimmun versus ciclosporin by Knoll and Bell was published in 1999.[61] This review included a meta-analysis of the 1-year all-cause mortality, graft loss and acute rejection across four RCTs and 937 patients. This paper reported no difference in either the patient (OR: 1.07, 95% CI 0.47 to 2.49) or graft loss (OR: 0.95, 95% CI 0.65 to 1.40), although there was a significant reduction overall of ARR (OR: 0.52, 95% CI 0.36 to 0.61). The authors also reported a significant increase in the incidence of PTDM with tacrolimus (OR: 5.03, 95% CI 2.04 to 12.36). Six other systematic reviews were identified but these either referred to the Knoll and Bell review or included a subset of trials.[61–67]

Quantity of evidence

Six RCTs comparing tacrolimus to Sandimmun met the inclusion criteria of the review.[68–89] The details of these trials are presented in Appendix 9.

Characteristics and quality of evidence

Two RCTs compared tacrolimus to Sandimmun in the presence of an induction agent and three RCTs without an induction agent. In one trial the adjuvant drug was not reported. The doses of tacrolimus and Sandimmun appeared to be very similar across the trials, although the trough levels sought varied. For tacrolimus the dose varied from 0.2 to 0.3 mg kg^{-1} per day and the desired trough level from 7 to 20 ng ml^{-1}. For ciclosporin the dose varied from 8 to 10 mg kg^{-1} per day and the desired trough level from 100 to 300 ng ml^{-1}. The majority of patients recruited to the trials were adults (≥ 18 years), receiving first time cadaveric renal transplants. Two US trials included other racial groups[69,73] and Shapiro included a proportion of living donors.[83]

All of the trials were 'open label'. Few reported details of randomisation and allocation concealment. However, loss to follow-up appeared to be consistently low, and although not always stated, most, if not all, trials undertook ITT analysis. The median Jadad score was 2 (range 1–3). All of the trials provided follow-up data at 12 months. Only the two large RCTs provided data at 5 years.

Results

Given the similarities in renal transplant populations and drug regimens across trials, all-cause mortality, graft loss and incidence of biopsy-confirmed acute rejection, and the lack of heterogeneity ($p < 0.10$), fixed effect meta-analyses were undertaken. Owing to variation across trials in the side-effects collected and the definition of these side-effects, it was not possible to pool results. For example, some studies gave the incidence of PTDM on the basis of blood glucose levels, whereas others used insulin usage levels. The side-effects are therefore summarised by vote counting: trials were classified according to whether they reported a statistically significant increase, a statistically significant decrease or no statistical difference in a side-effect.

Short-term outcomes

No evidence was found of a significant difference in either pooled all-cause mortality or graft loss at 12 months. There was a significant decrease in the 12-month BPAR rate (OR: 0.46, 95% CI 0.35 to 0.61) with tacrolimus (*Table 8*).

Only the US multicentre trial collected health-related quality of life, using a generic [Short Form 36 (SF-36)] and a disease-specific measure (Bergner Appearance Scale).[78] No statistically significant difference in SF-36 was reported between tacrolimus and Sandimmun groups. However, results on the Bergner scale were significantly better for tacrolimus.
Across the trials there was evidence of an increase in the incidence of tremor, serum creatinine levels and PTDM with tacrolimus. There was no difference in CMV infection rates. Conversely, there appeared to be an increase in hirsutism, hyperlipidaemia and gingivitis with Sandimmun.

Long-term outcomes

In the two trials that reported long-term outcomes, there was no significant difference in the pooled

TABLE 8 *Tacrolimus versus Sandimmun: pooled analysis at 12-month follow-up*

	No. of trials	OR (95% CI)
All-cause mortality	5	1.26 (0.68 to 3.32)
Graft loss	4	0.93 (0.64 to 1.36)
BPAR	3	0.46 (0.35 to 0.61)

5-year all-cause mortality (OR: 1.17, 95% CI 0.81 to 1.68) or graft loss (OR: 0.90, 95% CI 0.67 to 1.20). Moreover, the significant increase in PTDM with tacrolimus and increase in hyperlipidaemia with Sandimmun were maintained.

Subgroup analysis

Two different subgroup analyses were undertaken at 1-year follow-up by each of the two large trials. The US multicentre study compared the treatment effect in Caucasians versus African–Americans. The European multicentre study compared the treatment effect in high- versus low-risk renal transplant patients. No significant difference was observed in either subgroup analysis.

Children

No RCTs were found that recruited children exclusively. The US multicentre trial recruited patients aged 6 years or older.[73] However, neither the proportion of young patients nor the treatment results specifically for this group were reported. Thus, there is no RCT evidence available on the relative effectiveness of tacrolimus and Sandimmun in children.

Tacrolimus versus ciclosporin (Neoral)

Previous reviews and systematic reviews

No previous systematic review or meta-analysis was found comparing tacrolimus to the Neoral formulation of ciclosporin.

Quantity of evidence

Seven RCTs comparing tacrolimus to Neoral in adults and one RCT in children met the inclusion criteria of this review.[90–108] The details of these trials are presented in Appendices 10 and 20.

Characteristics and quality of evidence

With the exception of one trial,[105] all trials compared Neoral versus tacrolimus in an induction-free regimen. Three RCTs used azathioprine, three RCTs used MMF and one RCT used neither.

Doses of tacrolimus and Neoral were similar across trials. The dose of tacrolimus ranged from 0.1 to 0.3 mg kg^{-1} per day (the European multicentre trial having the highest dose),[97] with a desired trough level of 5–15 mg dl^{-1}. For Neoral the dose ranged from 7 to 15 mg kg^{-1} per day, with a desired trough level of 100–400 mg dl^{-1}.

The majority of trials were conducted with individuals with first time cadaveric renal transplants, although three trials also included living and asystolic donors. Three trials included a proportion of patients with a non-Caucasian ethnic background.

All trials were open label and therefore there was no blinding of patients, clinicians or outcome assessment. None provided sufficient details on which to judge the appropriateness of the method of randomisation or allocation concealment. However, loss to follow-up appeared to be consistently low, and although not always stated, most, if not all, trials undertook ITT analysis. The median Jadad score was 2 (range 1–2).

Results

The results for patient mortality, graft loss and ARR of the Neoral versus tacrolimus trials were pooled overall as well as separately by azathioprine and MMF therapy.

Short-term outcomes

The 6- and 12-month pooled results are summarised in *Table 9*. There was no significant difference in either all-cause mortality or graft loss at 12 months (OR: 1.33, 95% CI 0.60 to 2.94; OR: 0.80, 95% CI 0.51 to 1.40). There was evidence of a marked reduction in the 12-month BPAR rate (OR: 0.44, 95% CI 0.33 to 0.58).

There was consistent evidence of an increase in the incidence of tremor, but no difference in PTDM in tacrolimus-treated patients compared to Neoral-treated patients. Neoral appeared to increase the incidence of hyperlipidaemia, hirsutism and gingivitis. There appeared to be a lower serum creatinine in Neoral-treated patients. There was

TABLE 9 *Tacrolimus versus Neoral: pooled analysis at 6- or 12-month follow-up*

	No. of trials	OR (95% CI)
Azathioprine adjuvant therapy		
All-cause mortality	2	2.97 (0.60 to 10.02)
Graft loss	2	0.71 (0.37 to 1.36)
BPAR	3	0.39 (0.28 to 0.54)
MMF adjuvant therapy		
All-cause mortality	3	1.03 (0.39 to 2.78)
Graft loss	3	0.83 (0.37 to 1.88)
BPAR	3	0.64 (0.33 to 1.33)
All trials		
All-cause mortality	5	1.33 (0.60 to 2.94)
Graft loss	5	0.77 (0.46 to 1.29)
BPAR	7[a]	0.44 (0.33 to 0.58)

[a] Includes one trial with neither MMF nor azathioprine.

no difference in the rates of CMV infection. None of the trials reported quality of life data.

Long-term outcomes

Only two trials performed follow-up beyond 1 year. Morris-Stiff and Johnson reported outcomes at 3 and 2 years, respectively.[96,103] Pooling of these two trials revealed no significant difference in either all-cause mortality (OR: 0.46, 95% CI 0.20 to 1.16) or graft loss (OR: 0.57, 95% CI 0.32 to 1.01). Neither of these trials with longer term follow-up reported the incidence of side-effects.

Subgroup analysis

Johnson and colleagues[103] found no difference in the reduction in acute rejection with tacrolimus in the subgroup of African–Americans compared to the overall trial population results.

Children

Although the trial of Johnson and colleagues included patients aged 12 years and older, no separate report of the treatment effect in this group was reported.[103]

One recent moderately sized RCT by Trompeter and colleagues[107,108] compared Neoral and tacrolimus solely in transplant recipients below the age of 18 years (see Appendix 20). This trial was well conducted with a Jadad score of 4. The trial collected outcomes at 6, 12 and 24 months. There was no significant evidence of an advantage with either drug in overall survival (OR 0.90, 95% CI 0.18 to 4.57) or graft loss (OR: 0.56, 95% CI 0.24 to 1.31) at 6 months. At 24 months the improvement in graft loss with tacrolimus reached statistical significance (OR: 0.42, 95% CI 0.18 to 0.95). In addition, there was a significant reduction in the incidence of both BPAR (OR: 0.33, 95% CI.0.17 to 0.65) and steroid-resistant acute rejection (OR: 0.23, 95% CI 0.09 to 0.59) with tacrolimus at 6 months. There were some significant differences in the pattern of side-effects between the two drugs. There were no significant differences in either PTDM or hypercholesterolaemia.

Neoral versus Sandimmun

Two previous systematic reviews of Neoral compared to Sandimmun were identified.[109,110] The review by Shah and colleagues was the most comprehensive and also conducted meta-analyses.[109] The results of this review for renal transplantation were rather contradictory: there were no differences in adverse events, acute rejections, graft loss or all-cause mortality for all studies, but when looking at RCTs only (although not stratified by renal and hepatic) there was evidence of a statistical difference in favour of Neoral for acute rejections and adverse events. To assess the relative effectiveness of Neoral and Sandimmun, it was decided to update and reanalyse the trials from these previous reviews (see Appendix 1 for the search strategy and Appendix 11 for trial details).

Given that this review was beyond the initial scope of this report, the reviewers limited the degree of data extraction and focused only on acute rejection episodes (either all or biopsy confirmed).

Five trials were identified.[111–115] Although not stated in all trials, the additional drugs appeared to be azathioprine and a steroid. The trial by Hricik[114] also included induction therapy. The follow-up period of the trials was 24 months, with the exception of the trials by Niese, in which it was 12 months.[113]

There was evidence of a non-significant reduction in the pooled ARR (OR: 0.75, 95% CI 0.55 to 1.03, heterogeneity p-value = 0.249) across the five trials.

Summary

- Thirteen RCTs were included that compared tacrolimus to ciclosporin. Of these, six and seven used the Sandimmun and Neoral formulations of ciclosporin, respectively.[90–107] Only one RCT was identified that was conducted exclusively in children.[107]
- All the RCTs were open label and few provided details of the methods of randomisation or allocation concealment. However, most were analysed by ITT.
- Tacrolimus significantly reduced the incidence of BPAR episodes compared to ciclosporin. However, there was no significant improvement in either short- or long-term (>1 year) graft loss.
- The improvement in BPAR with tacrolimus was equivalent for the Sandimmun and Neoral comparisons.
- There were important differences in the side-effect profile of tacrolimus and ciclosporin. Tacrolimus was associated with an increase in the incidence of tremor and PTDM compared to Sandimmun. Compared to Neoral, there was no difference in PTDM. Both Sandimmun and Neoral were associated with an increase in the incidence of hirsutism, gingivitis and hyperlipidaemia. It was not possible to assess the global impact on patients of these side-effects owing to the lack of quality of life data.

- The one paediatric RCT comparing tacrolimus and Neoral reported a lower ARR in the tacrolimus group. At 2-year follow-up there was evidence of an improvement in graft loss with tacrolimus.
- There has been considerable discussion in the literature about the relative benefits of Neoral over Sandimmun in terms of the achievement of ciclosporin levels at a lower dose. All trials identified in this review appeared to review trough monitoring. The doses of ciclosporin and trough levels were found to be comparable between Neoral and Sandimmun trials.

MMF versus azathioprine

Previous systematic reviews and meta-analysis

Several previous reviews of the use of MMF in renal transplantation were identified. Chilcott and colleagues,[63] in their HTA report, identified three large multicentre RCTs (the European MMF, US MMF and Tricontinental MMF trials),[116–118] two of which compared MMF to azathioprine and one compared MMF to placebo. Both Carl and colleagues[119] and Halloran and colleagues[120] undertook pooled analyses of these three trials. Behrend[121] and Young and Plosker[122] both undertook reviews which focused on the above three large trials comparing MMF and azathioprine. The European MMF trial was excluded from this section as it compared MMF to placebo and not azathioprine.[116]

Quantity of evidence

In this review seven RCTs were identified comparing MMF to azathioprine in either a ciclosporin-based or tacrolimus immunosuppression regimen in adults. Although MMF is not currently licensed in combination with tacrolimus, these trials are reviewed in this report for comprehensiveness. The two groups of MMF trials are described separately. The details of these trials are presented in Appendices 12 and 13.

Five RCTs compared MMF to azathioprine in a ciclosporin-based regimen in adults[117,118,123–125] and two RCTs compared MMF to azathioprine in a tacrolimus-based regimen.[103,126] One study investigated MMF in children.[127]

Characteristics and quality of evidence

Ciclosporin-based therapy

All trials included an MMF dose of 2 g per day, while the US MMF and Tricontinental MMF trials also included 3 g per day. Two trials included a triple-therapy comparator (ciclosporin, azathioprine and steroid) and two trials quadruple therapy (ATG, ciclosporin, azathioprine and steroid). Trials used either the Sandimmun or Neoral formulation of ciclosporin and all recruited adult (>18 years) patients with first time cadaveric transplants. The outcomes collected included all-cause mortality, graft loss, ARRs and side-effects.

The US and Tricontinental trials were well conducted. Both the method of randomisation and allocation were reported, they were double blind and their analysis was undertaken by ITT. However, the level of patient dropout at 12 months in both trials exceeded 20%.[117,118] The other two trials were not blinded and provided few details about their methodological quality.[123,124]

Tacrolimus-based therapy

The FK506/MMF Dose-Ranging Study Group study compared 1 g and 2 g per day MMF to azathioprine (1.5 mg kg^{-1} per day) in first cadaveric transplant patients receiving tacrolimus 5–15 μg, corticosteroids and induction therapy (OKT3).[103] Busque and colleagues compared 2 mg MMF to azathioprine (1.5–2 mg kg^{-1}) in a tacrolimus and steroid-based regimen.[106] Both trials recruited first time renal cadaveric transplant recipients.

Both trials were open label and provided no details of randomisation and allocation concealment or dropouts. However, both trials appeared to report their results by ITT analysis.[103,106]

Results

Given the common principal comparison across the five trials (i.e. MMF compared to azathioprine) and the similarity of patient populations, it was decided to pool all-cause mortality, graft loss and ARR results. The ciclosporin-based regimen and tacrolimus regimen trials were pooled separately. Where trials included more than one dose of MMF, only the licensed dose of MMF (i.e. 2 g per day) was used in this pooling. Owing to the variation in assessment and reporting of side-effects, it was not possible to pool these outcomes. Instead, side-effect results across trials are qualitatively summarised.

Short-term outcomes

There was no evidence of significant differences in either all-cause mortality or graft loss at 12 months (OR: 1.26, 95% CI 0.69 to 2.27; OR: 0.76, 95% CI 0.49 to 1.18, respectively). MMF significantly reduced the incidence of BPAR at 6 and 12 months (OR: 0.42, 95% CI 0.32 to 0.55) (*Table 10*).

There was an increase in the level of side-effects with both MMF and azathioprine therapy. The

TABLE 10 *MMF (2 g per day) versus azathioprine: pooled analysis at 6- or 12-month follow-up*

	No. of trials	OR (95% CI)
Ciclosporin adjuvant regimen		
All-cause mortality	4	1.12 (0.56 to 2.24)
Graft loss	4	0.66 (0.40 to 1.09)
BPAR	3	0.45 (0.34 to 0.59)
Tacrolimus adjuvant regimen		
All-cause mortality	2	1.71 (0.50 to 5.37)
Graft loss	2	0.69 (0.27 to 1.72)
BPAR	2	0.43 (0.10 to 1.84)[a]
All trials		
All-cause mortality	6	1.26 (0.69 to 2.27)
Graft loss	5	0.66 (0.43 to 1.04)
BPAR	5	0.42 (0.32 to 0.55)

[a] Random effects model: statistically significant heterogeneity.

TABLE 11 *MMF (2 g per day) versus azathioprine: pooled analysis at 3-year follow-up*

	No. of trials	OR (95% CI)
All-cause mortality	3[a]	0.77 (0.47 to 1.26)
Graft loss	4	0.81 (0.57 to 1.15)

[a] Tuncer[125] excluded: Kaplan–Meier estimates (actual number of deaths is lower than at 1 year).

pattern of side-effects appeared to be different across the two drugs. With azathioprine, there was an increase in the rate of nausea, thrombocytopenia and jaundice. Compared with azathioprine, with MMF there appeared to be an increase in both gastrointestinal problems (diarrhoea and gastrointestinal bleeding) and CMV infection, and a reduction in PTDM. None of the trials reported quality of life data.

Long-term outcomes

Four MMF trials undertook long-term follow-up to 3 years. There was no significant difference in all-cause mortality and graft loss with MMF at 3 years (*Table 11*).

The gastrointestinal and CMV infection side-effect profile of MMF, and the thrombocytopenia and hyperbilirubaemia side-effect profile of azathioprine appeared to be sustained in the long term.

Subgroups

No subgroups were identified.

MMF versus MPS

Previous systematic reviews and meta-analyses

No previous reviews of MPS were identified.

Quantity of evidence

Only two RCTs of the use of MPS in renal transplantation were found. The first trial (study 301) was a 12-month follow-up trial comparing MPS to MMF in *de novo* renal transplant patients. The details of study B301 and the interim 6-month follow-up results have been published.[128]

The unpublished 12-month trial results of study 301 were presented in the Novartis submission to NICE. Study 302 is an unpublished trial comparing patients randomised at 6 months post-transplant to either MMF or MPS. Study 302 failed to meet the inclusion criteria of this review and was therefore excluded.

Characteristics and quality of evidence

Study B301 is a large double-dummy trial where adult *de novo* cadaveric transplant patients were randomised to either MPS (213 patients) or MMF (210 patients). The trial was conducted in centres in Europe (including the UK), the USA and Canada. This study was described as an equivalence study, and powered as such on the primary efficacy end-point of the incidence of a composite outcome variable (i.e. BPAR, graft loss, death or loss to follow-up within 6 months of initial treatment with the study medication). Patients who met inclusion/exclusion criteria were to be randomised within 48 hours of transplantation to either MMF (2 g per day) or MPS (1.44 g per day) as part of a triple immunosuppressive therapy using Neoral and steroid.[128]

No details of the methods of trial randomisation or concealment of allocation were provided. Outcome assessment appeared to be blinded. At 12 months there was a high level of dropout in both groups (MPS: 29.1%; MMF: 24.8%). Trial results were analysed by ITT.

Results

There was no significant difference between MPS and MMF in all-cause mortality, graft loss or BPAR episodes (*Table 12*). The proportion of patients discontinuing for safety events (adverse event, abnormal laboratory finding, death or graft loss) was similar for the MPS group (20%) and the MMF group (19%). The most common primary reason for discontinuation of study medication was adverse events in both groups. The most frequent adverse events leading to discontinuation of study medication were gastrointestinal disorders, and no

TABLE 12 *Results of B301 study of MMF (2 g per day) versus MPS (1.44 g per day) at 12-month follow-up*

	OR (95% CI)
All-cause mortality	0.39 (0.07 to 2.06)
Graft loss	0.87 (0.32 to 2.30)
BPAR	0.91 (0.58 to 1.42)

clinically meaningful between-group differences were observed.

No report of patient-related quality of life was provided.

Subgroup analysis

No trial subgroup analyses were reported.

Children

The B301 study excluded children. No other RCTs of the use of MPS in children with renal transplantation were found.

Summary

- Seven RCTs comparing MMF to azathioprine in either an initial/maintenance ciclosporin- or tacrolimus-based immunosuppressant regimen for renal transplants were included.
- One RCT was identified that compared MMF to MPS in an initial/maintenance ciclosporin-based regimen.
- Some of the trials were large, multicentre, double-blind RCTs. However, the majority of RCTs provided no details of the methods of randomisation or concealment of allocation. Most trials appeared to undertake their analysis of results by ITT. The median Jadad score was 2 (range 1–3).
- MMF reduced the 6- and 12-month incidence of BPAR. There was no significant improvement in all-cause mortality or graft loss. This pattern of results appeared to be consistent across both ciclosporin- and tacrolimus-based regimens. At 3 years there was no significant difference in all-cause mortality or graft loss.
- The pattern of side-effects appeared to be different for MMF and azathioprine.
- There was no significant difference in MMF and MPS in terms of all-cause mortality, graft loss, ARR or side-effect profile in this single trial. Further RCTs are needed to confirm that MPS is clinically equivalent to MMF.
- There is no randomised evidence for MMF compared to azathioprine in children.
- There was an absence of trial-based patient-related quality of life data.
- No trials reported health-related quality of life.

Sirolimus

A number of recent reviews concluded that the precise role of sirolimus in current renal immunosuppression therapy is unclear. This is reflected in the variety of ways in which sirolimus has been assessed in clinical trials,[129] and probably reflects the fact that sirolimus has only recently been licensed (2001).[130] To rationalise this review of sirolimus, it was decided to focus on the licensed use of sirolimus:

> "It is recommended that Rapamune (sirolimus) be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued" (BNF).

Therefore, the review only included trials that examined the use of the sirolimus in a ciclosporin-based therapy regimen and where sirolimus was given at the recommended dose of 2 mg per day. The following questions were specifically addressed: (1) How effective is adding sirolimus to a ciclosporin dual-based therapy in initial treatment? (2) How effective is substituting AZA or MMF with sirolimus in a ciclosporin-based triple therapy in initial and maintenance treatment?

From discussion with the review clinicians and with reference to the current licence for sirolimus, it was clear that there was an additional issue within question (1) to be addressed: (3) What is the impact of removing (or reducing the dose of) ciclosporin from an initial treatment strategy that consists of sirolimus and ciclosporin?

Previous systematic reviews and meta-analyses

Two previous reviews of sirolimus were identified, although it was uncertain whether either was a systematic review.[129,130]

Quantity of evidence

Substitution of azathioprine or MMF with sirolimus in initial and maintenance therapy

Three RCTs were identified that examined sirolimus substitution in a ciclosporin-based initial therapy regimen. Two trials examined the issue of substitution of azathioprine with sirolimus. The first of these studies was a large multicentre trial by the Rapamune US Study Group[131,132] and the second was a single-centre ongoing trial.[133] As the second trial only provided a partial report of the trial results (36 of the 70 patients at 24 weeks with a 1-year planned follow-up) it was excluded. The third trial examined the substitution of MMF by azathioprine with sirolimus.[134] However, as the

dose of sirolimus used in this study (initial dose of 24 mg m^{-2} for first 24 hours, followed by 12 mg m^{-2}) did not conform to the current UK licence dose, this trial was also excluded. Details of the included Rapamune US Study Group trial are provided in Appendix 14.

Addition of sirolimus to dual initial therapy
Two RCTs assessed the impact of the addition of sirolimus to ciclosporin-based dual therapy: by the Rapamune US Study Group[131,132] and the Rapamune Global Study Group.[135,136] The Phase II trial by Kahan and colleagues used sirolimus doses (1 and 3 mg m^{-2})[131,132] that were outside the current licence dose and was therefore excluded. Details of the Rapamune Global Study Group trial are presented in Appendix 14.

Removal of ciclosporin (in the maintenance phase) from sirolimus-based therapy
The reviewers failed to find any RCTs of the required design addressing ciclosporin removal from initial sirolimus-based therapy, that is, randomising patients to either sirolimus plus ciclosporin plus steroid or azathioprine plus ciclosporin plus steroid, with ciclosporin elimination from the sirolimus arm at 3 months.

Instead, two trials were found that randomised individuals to either ciclosporin removal or ciclosporin continuation at 3 months following an initial period of sirolimus-based therapy (i.e. sirolimus plus ciclosporin plus steroid).[103,104] The key problem with this latter design is that it assumes the principle of the efficacy of initial sirolimus based-therapy. These trials were therefore excluded.

Characteristics and quality of evidence

Substitution of azathioprine or MMF with sirolimus in initial and maintenance therapy
The Rapamune US Study Group trial randomised patients in a ratio of 2:2:1 to three arms: sirolimus 2 mg per day (n = 274), sirolimus 5 mg per day (n = 284) and azathioprine 2–3 mg per day (n = 61). No induction therapy was given. The baseline therapy in each arm was ciclosporin (Neoral) and a steroid. Trial participants received either live (65%) or cadaveric kidneys (35%) and 23% of the population were African–American. Outcomes were assessed at 12 months.[132]

The quality of the trial was good and it was given a Jadad score of 4. Although it was described as double blind (both groups were given a placebo for the drug that they did not receive), it was not completely clear who was being blinded. The high number of withdrawals (50%) occurred in all three groups approximately equally; reasons for withdrawal were stated and included unsatisfactory response, adverse events and other medical events.

Addition of sirolimus to dual initial therapy
In this large, multicentre Rapamune Global Study, patients with either cadaveric or living grafts were randomised in a ratio of 2:2:1 to either 2 mg per day (n = 227) or 5 mg per day (n = 219) of sirolimus or placebo (n = 130), in addition to ciclosporin (Neoral)-based dual therapy. Sixty-six patients (11.5%) were black. Patients were followed up for 1 year.

The quality of the trial was good and it was given a Jadad score of 4. It was not completely clear how allocation was concealed. There was a 40% withdrawal rate overall.

Results

Substitution of azathioprine or MMF with sirolimus in initial and maintenance therapy
The 12-month follow-up results are summarised in *Table 13*. There was no significant difference between sirolimus and azathioprine in patient mortality or graft loss. The ARR was significantly reduced (p = 0.03) with sirolimus (21.8% versus 31.1%).

An increase in side-effects was observed in both the sirolimus and azathioprine arms of the trial, although the profile of side-effects appeared to be different for each drug. Moreover, adverse events appeared to be dose dependent and highest for sirolimus 5 mg per day. With 2 mg per day sirolimus there were only significant increases in acne, epistaxis, headache and hypertension. For azathioprine, there was a significant increase in leucopenia. Quality of life was not assessed in this trial.

Addition of sirolimus to dual initial therapy
There was no significant difference between sirolimus and placebo in terms of either patient

TABLE 13 *Results of Rapamune US Study Group trial of sirolimus (2 mg per day) versus azathioprine at 12-month follow-up*

	OR (95% CI)
All-cause mortality	0.58 (0.20 to 1.61)
Graft loss	1.13 (0.48 to 2.68)
BPAR	0.52 (0.34 to 0.81)

TABLE 14 *Results of Rapamune Global Study of sirolimus (2 mg per day) versus placebo at 12-month follow-up*

	OR (95% CI)
All-cause mortality	0.64 (0.23 to 1.81)
Graft loss	0.80 (0.41 to 1.58)
BPAR	0.48 (0.31 to 0.76)

mortality or graft loss at 1 year. The ARR was significantly reduced with 2 mg per day sirolimus (26.9% versus 43.3%) (*Table 14*).

The incidence of adverse events was related to the dose of sirolimus and was highest for the 5 mg per day dose. With a dose of 2 mg per day there was significant increase compared to placebo in thrombocytopenia, hypercholesterolaemia, hyperkalaemia and epistaxis.

Subgroup analysis

Substitution of azathioprine or MMF with sirolimus in initial and maintenance therapy

Data stratification by race showed that African–American patients who received 2 mg per day sirolimus had a significantly ($p = 0.005$) lower incidence of treatment failure (i.e. BPAR, graft loss or patient death) compared with the azathioprine arm. African–American patients had a significantly higher incidence of acute rejection than those of other races (30.2% versus 13.1%) with sirolimus 2 mg per day. The differences in ARR were not significant for the 5 mg per day sirolimus group.

Addition of sirolimus to dual initial therapy

No subgroup analyses of this trial were identified.

Children

Substitution of azathioprine or MMF with sirolimus in initial and maintenance therapy

A separately published subgroup analysis of the children (aged 13–18 years) in the above trial was undertaken[137] (see Appendix 20). There were only 12 children in this trial and they were unequally distributed among the three groups. The patient characteristics, where available, appear similar to those in the main trial. Given that there were so few patients in this subgroup ($n = 12$), no treatment conclusions on the relative impact of sirolimus can be drawn.

Addition of sirolimus to dual initial therapy

The Rapamune Global Study recruited individuals aged 15 years or older. However, the total trial proportions for those under the age of 18 years were not reported, nor were the results in this subpopulation reported.[135]

Summary

- Several RCTs of the use of sirolimus in renal transplantation were identified by the searches.[129–137]
- This systematic review was restricted to RCTs that met the current UK licence for sirolimus, that is, in combination with a ciclosporin emulsion-based regimen and a sirolimus dose of 2 mg per day. Only two RCTs met these inclusion criteria. These trials assessed the impact of either adding sirolimus to a ciclosporin-based dual regimen or substituting azathioprine with sirolimus in a ciclosporin-based regimen. The first of these trials performed a subgroup analysis in children.
- Both trials were placebo controlled and of good methodological quality.
- The addition of sirolimus (2 mg per day) to a ciclosporin (Neoral)-based dual regimen significantly reduced the 12-month ARR (26.9% versus 43.3%) in comparison to a ciclosporin (Neoral)-based dual therapy alone. Graft loss and all-cause mortality were not significantly different. There was an increase in the incidence of side-effects with the addition of sirolimus.
- Substituting azathioprine (2 g per day) with sirolimus (2 mg per day) was associated with a significant reduction in the ARR (21.8% versus 31.1%), although there was no change in graft loss or all-cause mortality. There was increase in side-effects with both azathioprine and sirolimus, although the profiles appeared to be different.
- Neither trial collected quality of life data.
- There is insufficient RCT evidence to assess whether the impact of sirolimus observed in adults with renal transplant is consistent with that in children (<18 years). Sirolimus is not currently licensed in the UK for use in children.

Treatment of acute rejection

Previous reviews and systematic reviews

Only four reviews were found that examined the question of the use of the newer immunosuppressant drugs in the treatment of acute rejection. Three of these reviews assessed the use of tacrolimus[62,66,67] and were based on observational cohort studies only. A more recent review identified two RCTs that examined the role of MMF in the treatment of acute rejection.[122]

Quantity of evidence

In this review three RCTs were identified that examined the role of the newer immunosuppressive drugs in the treatment of renal transplant patients with confirmed acute rejection.[138–141] One trial

examined the role of the tacrolimus and the other two trials examined the role of MMF. A further three small trials of MMF were identified. However, these were excluded on the grounds that patients had either chronic rejection or chronic acute nephropathy. No trials were found using daclizumab, basiliximab or sirolimus. The details of the three included trials are presented in Appendix 15.

Characteristics and quality of evidence

The first trial compared tacrolimus (0.2 mg kg^{-1}) to ciclosporin in 119 patients with BPAR who had failed previous high-dose steroids treatment.[138] The Mycophenolate Mofetil Acute Renal Rejection Group (MMRRR) undertook two separate multicentre trials in patients with first BPAR who had failed previous high-dose steroid treatment. The first US RCT[139] included 150 patients and compared MMF (3 g per day) to high-dose steroids. The second RCT[140] was conducted in centres in the USA and Canada, appeared to include 221 patients and compared MMF (3 g per day) to azathioprine. In neither of these MMF trials did patients require to fail initial high-dose steroids. In the MMRRR 1996 trial patients were pretreated with ALG and OKT3. Although the outcomes varied across these trials, each collected some measure of graft loss. All studies assessed short-term outcome (i.e. at 3 or 6 months) and the MMRRR 1998 trial extended its follow-up to 2 years.[139–141]

The details of the trial methods were consistently poorly reported across the three trials. Where details were provided, trials were described as 'open' and therefore unlikely to have undertaken blinding. Although not reported, it appeared that all trials undertook ITT analysis.

Results

Short-term outcomes

Tacrolimus versus ciclosporin

There was no significant difference in patient mortality or graft loss between the two drugs. However, there was a lower rate of both acute rejection requiring further treatment (6.5% versus 25.8%, $p = 0.0117$) and recurrent rejection at 3 months in the group treated with tacrolimus (8.2% versus 25.9%, $p = 0.011$). Reported adverse events (CMV infections, new diabetes mellitus and hypercholesterolaemia) appeared to be similar for the two groups. Patient-related quality of life was not reported.

MMF versus high-dose steroids or azathioprine

The only common outcome collected across the two MMF studies was cumulative graft loss or death at 6 months. There was a significant reduction in this pooled outcome at 12 months (OR: 0.51, 95% CI 0.28 to 0.92) in the MMF-treated patients. MMF also appeared to be associated with a reduction in both the incidence of subsequent acute rejection and the use of antilymphocyte agents for persistent rejection. Adverse events were comparable in frequency, although different in nature. Patient-related quality of life was not reported.

Long-term outcomes

MMF versus high-dose steroids

In a 3-year follow-up of the MMRRR 1996 trial, patients treated with MMF were less likely than those treated with high-dose steroids to experience a subsequent episode of rejection (42.2% versus 68.8%, $p = 0.0002$) or death or transplant removal (19.6% versus 24.1%, $p = 0.04$).[141]

Subgroup analysis

No subgroup analysis was reported in any of these trials.

Children

All three trials excluded patients under the age of 18 years.

Summary

- Three RCTs were identified that addressed the adjuvant impact of the newer immunosuppressive drugs in patients with BPAR who had failed previous steroid therapy. One trial compared the use of switching from ciclosporin to tacrolimus to ciclosporin, and the other two trials compared switching from azathioprine to MMF or a high-dose steroid.[138–141]
- The level of reporting of these trials was poor and therefore it was difficult to assess their methodological quality.
- Both tacrolimus and MMF appear to be effective adjuvant treatments in the management of acute rejection. Both reduce the subsequent ARR and the need for additional drug therapy.
- These trials did not assess patient-related quality of life.
- No RCT evidence of the role of the newer immunosuppressive drugs in children with BPAR was identified.

Chapter 5

Results: cost-effectiveness review

The aim of this chapter is to assess the relative cost-effectiveness of the newer immunosuppressant drugs for renal transplantation under consideration within this review: daclizumab, basiliximab, tacrolimus, MMF, MPS and sirolimus. This chapter begins with a review of the published cost-effectiveness literature on each of these drugs.

The second section provides a description and critique of the cost-effectiveness models submitted as part of the industry submissions to NICE for this technology appraisal.

Finally, and to reach a more definitive conclusion on the relative cost-effectiveness, the cost per quality-adjusted life-year (QALY) results from a single (meta)model based on differences in BPARs for each drug (derived from the various individual drug systematic reviews reported in Chapter 4) are presented.

Review of economic literature

The identification and selection of previous economic evaluations are summarised in *Figure 2*.

Induction immunosuppressive therapy

Daclizumab

Amount of evidence

One published economic study for daclizumab was identified.[142] This study compared the costs and cost-effectiveness of adding daclizumab to ciclosporin-based triple therapy (see Appendix 16).

Cost analyses

Schniztler and colleagues used 1-year and 10-year economic modelling to compare the costs and cost-effectiveness of a variety of different immunosuppressant drug regimens.[142] One of these drug regimens was the addition of daclizumab to ciclosporin-based triple therapy. Graft survival at 1 year, patient survival and ARRs were derived from published clinical outcomes of the Vincenti trial.[44] Average wholesale prices were used for immunosuppressant drugs. The additional 1- and 10-year costs of daclizumab were estimated to be US$4765 and US$3581, respectively.

Cost-effectiveness

Schniztler combined costs and graft survival to estimate cost-effectiveness. The annual death rate was assumed to 1.5% between 1 and 10 years following transplantation for all treatment regimens. The annual graft failure rate was assumed to be 8% in patients experiencing an acute rejection in the first year after transplantation and 3% in patients who were rejection free. The additional cost of a patient experiencing acute rejection or return to dialysis was assumed to be US$10,000. The annual additional cost of maintenance dialysis was assumed to be US$30,000, more than the cost of a patient in a stable medical condition. A measure of cost-effectiveness – graft survival cost-effectiveness at 1 year and 10 years ($GSCE_1$ and $GSCE_{10}$) – was calculated to reflect the number of surviving grafts expected to be functioning at 1 and 10 years based on a predicted US budget spent on immunosuppression (US$1 million and US$10 million at 1 and 10 years, respectively). Based on this modelled analysis, at 1 year the cost-effectiveness of daclizumab was inferior to triple therapy without daclizumab ($GSCE_1$ 51 versus 65). However, at 10 years the addition of daclizumab was found to have superior cost-effectiveness ($GSCE_{10}$ 56 versus 50).[142]

Summary

- Only one economic analysis for daclizumab was identified.[142]
- This analysis found the additional 1- and 10-year cost of daclizumab to ciclosporin-based therapy to be US$4765 and US$3581, respectively.
- Combining costs and graft survival, at 1 year the cost-effectiveness of daclizumab was inferior to that of daclizumab-free triple therapy. However, at 10 years, the cost-effectiveness of daclizumab was superior to that of daclizumab-free triple therapy.

Basiliximab

Amount of evidence

Six economic studies were identified that compared the costs and outcomes of basiliximab.

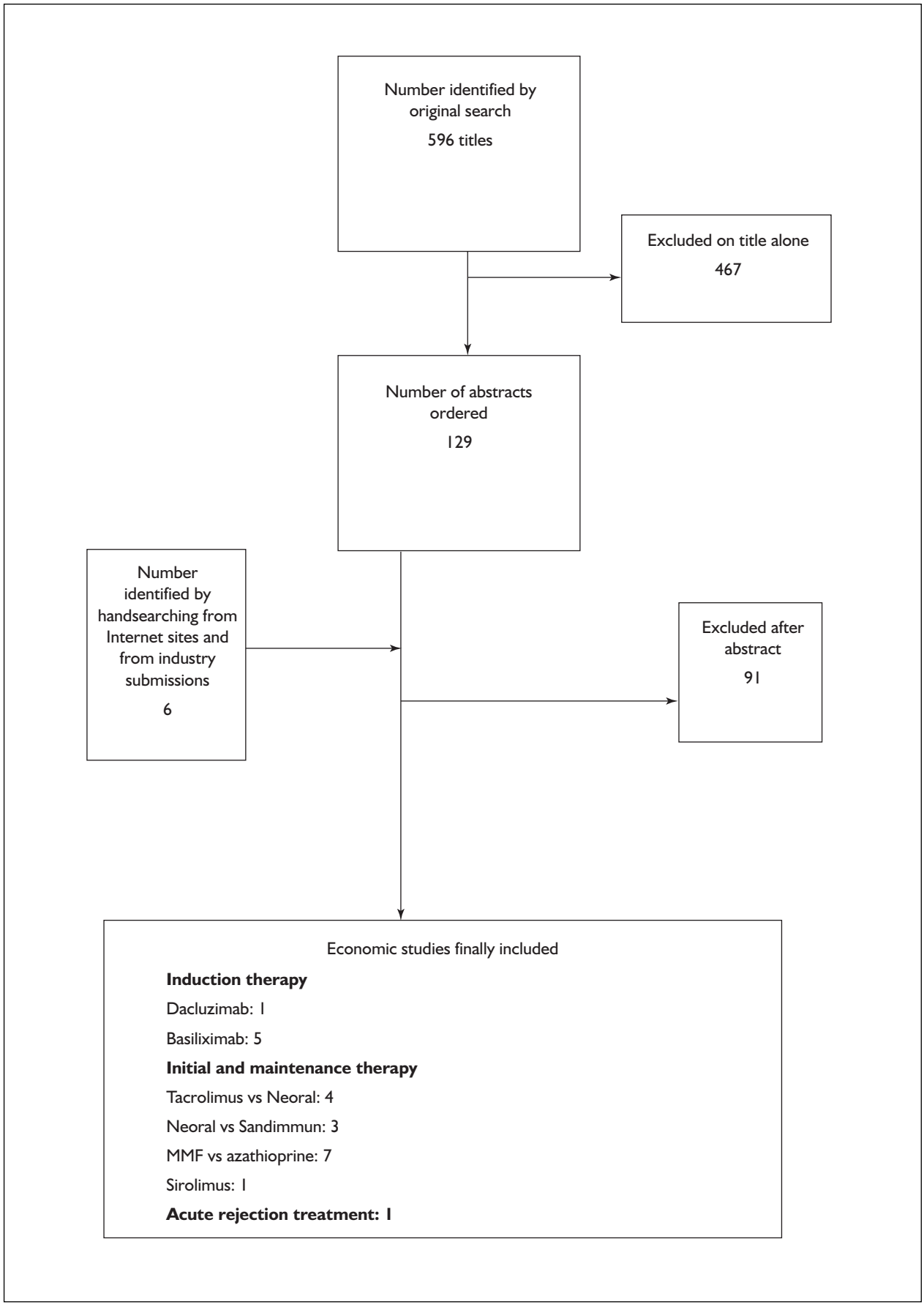

FIGURE 2 *Cost-effectiveness quantity of evidence*

Two studies compared basiliximab to an alternative induction agent[143,144] and the other four studies assessed the addition of basiliximab alone to a ciclosporin-based immunosuppressant regimen.[142,145–147] Four studies were cost–consequence analyses,[144–147] one was a cost-effectiveness analysis[142] and one a cost–utility analysis.[143] One cost–consequence study was conducted from the perspective of the NHS[147] (see Appendix 16).

Cost analyses

The studies were conducted in four countries: the USA, Canada, France and the UK. All included medical costs, drug acquisition costs, and the costs associated with acute rejection and graft failure treatment. Patient and carer costs were not considered. The studies based their costing on resource estimates from RCTs. In addition to assessing costs at 1 year, two studies extrapolated costs to 10 and 15 years.

Given the range of countries in which the studies were conducted, it is not possible to compare their costs directly. However, within each study the total medical costs of basiliximab were compared to total medical costs of control (either placebo or ALG). Three studies reported the 1-year costs per patient of basiliximab to be less than for placebo (no induction therapy). The 5- and 10-year costs were also lower. Only the recent UK-based analysis (reporting in US dollars) found the 1-year medical costs associated with basiliximab to be greater (US$37,113 versus US$37,070). However, all of these 1-year medical cost differences were small and unlikely to reach statistical significance.[147] The 1-year medical costs of basiliximab were substantially lower than for ATG and ALG.

Cost-effectiveness

Using the same modelling methodology described above (Dadizumad section), Schniztler and colleagues[142] combined the costs and graft survival estimates from an RCT[51] that assessed the addition of basiliximab to a ciclosporin regimen. Based on this modelled analysis, at 1 year and 10 years the cost-effectiveness of basiliximab was superior to therapy without basiliximab ($GSCE_1$ 65 versus 51 and $GSCE_{10}$ 52 versus 43).

Polsky and colleagues[143] conducted a cost–utility analysis of the US RCT by Sollinger and co-workers,[57] comparing basiliximab to ATG. This study was performed from the perspective of the US health provider. Resource use was based on clinical trial data and included levels of drug usage and hospitalisation. Costs were based on those in 1997 Medicare and local hospital data. The authors used health state preferences measured by the EuroQol visual analogue scale to calculate the incremental cost–utility of therapy. The mean EuroQol scores were 0.815 at 12 months in patients receiving basiliximab, compared with 0.811 in patients receiving ATG. The mean first year costs were US$45,857 for basiliximab and US$54,729 for ATG, a cost difference of $US6292 (95% CI US$5165 to 7419). One-year quality-adjusted survival was 81.5 for basiliximab and 81.1 for ATG, a difference of 0.45 (95% CI –5.9 to 6.8).

Summary

- Six published economic studies were identified: four studies compared the costs of basiliximab to placebo (i.e. a basiliximab-free regimen) and two studies compared basiliximab to other induction therapies (either ALG or ATG).[142–147] Three of the four studies found that the 1-year total medical costs of basiliximab were lower than placebo. The 1-year medical costs of basiliximab were lower than those of both ATG and ALG.
- Two cost-effectiveness analyses were identified. A US study reported basiliximab to have superior 1- and 10-year graft survival cost-effectiveness to placebo. A Canadian analysis found basiliximab to have a similar QALY gain to ATG at 1 year, but lower costs.
- No studies directly comparing the cost-effectiveness of basiliximab to daclizumab were identified.
- All studies were based on ARRs at 1 year.

Initial and maintenance immunosuppressive therapy

Tacrolimus

Amount of evidence

Six economic studies were identified that compared the costs and outcomes of tacrolimus relative to ciclosporin.[148–155] Four of these six studies considered the Sandimmun formulation of ciclosporin. Four of the studies were conducted in the UK or took the perspective of the NHS (see Appendix 17).

Cost analyses

All six studies assessed the costs of tacrolimus and ciclosporin. Only direct medical costs were included and patient or carer costs were not taken into account. Within medical costs, each study included both the acquisition costs of tacrolimus and ciclosporin, and the treatment costs. Although

the precise treatment costs considered by each study varied, most included the costs associated with each drug in terms of the treatment of acute rejection episodes and graft failure over a 6- or 12-month period post-transplant. Most studies ignored transplant costs.

This group of studies differed in the overall relative costs of the two drugs. Three studies concluded that the overall medical costs associated with ciclosporin were greater than for tacrolimus. Two concluded that there was no difference. Finally, one study concluded that the costs of ciclosporin were less than those of tacrolimus. Given the general lack of detail reported on the methods of costing across the studies, it is not possible to explain this discrepancy. However, two possible explanations are that the precise treatment costs differed across studies, and the magnitude of treatment effect assumed by each study may have also varied. For example, all other things being equal, given the higher cost of tacrolimus a greater reduction in acute rejection episodes is needed in comparison to ciclosporin for costs to be equivalent.

Cost-effectiveness

Three of the studies undertook a formal cost-effectiveness analysis. The first was the Wessex Institute for Health Research and Development report on tacrolimus published in September 1997.[62] The authors calculated the total cost of tacrolimus and ciclosporin (Sandimmun) for the first 12 months following transplantation. This included the cost of primary drugs (tacrolimus or ciclosporin), rejection episodes, haemodialysis and adverse events. Rates of rejection and adverse events were taken from the pooled estimates of RCTs. Overall, treatment with tacrolimus cost £8510 per patient, compared with £6712 for patients treated with ciclosporin, a difference of about £1800 per patient over the year. To derive a cost per QALY, the patient-rated utility values for tacrolimus and ciclosporin were taken from the European trial. This trial reported a gain of between 0.82 and 1.5 QALYs per 100 patients with tacrolimus compared to ciclosporin. Thus, a cost per QALY of between £120,000 and £220,000 in the first year post-transplant was calculated. Based on a number of assumptions, the Booth-Clibborn estimate at 10 years for tacrolimus may be associated with a saving of around £75,000 per patient.[62]

Using a similar methodology, Chilcott and colleagues[63] estimated the first year medical costs of tacrolimus and ciclosporin to be relatively similar (£6086 and £6026 per patient, respectively). However, in subsequent years, the incremental cost of tacrolimus over ciclosporin was higher (£3990 per patient per year on tacrolimus and £2790 per patient per year on ciclosporin). Using ARRs reported in the same two trials used above, it was estimated that this would result in a 4% improvement in graft survival at 5 years for patients treated with tacrolimus. The authors use these data and the costs above to calculate an additional cost for tacrolimus of £30,000 per additional graft saved or patient death avoided. The authors of this report noted that the change in ciclosporin formulation to Neoral could affect its incremental effectiveness, and thus cost-effectiveness.

Craig and colleagues[150] published the most recent economic cost-effectiveness analysis of tacrolimus compared to Neoral following renal transplant. The authors conducted a retrospective cost-effectiveness analysis using 6-month clinical data from the European FK506 multicentre trial.[97] Resource utilisation data (including study drug, concomitant medications, hospitalisation, dialysis and rejection episodes) were collected from study centres and cost data supplied from Italy, Germany and Spain. The differing cost structures for each country resulted in variable cost savings per patient, but all in favour of tacrolimus. Italy had the highest difference (€1776), followed by Germany (€1075) and Spain (€524). The authors commented that the cost advantages were a result of lower overall hospitalisation costs, lower incidence of dialysis and lower costs of graft rejection. Given its lower costs and its improved clinical outcome, tacrolimus was dominant, with a negative cost-effectiveness of –€530 to –1874 per surviving patient, –€781 to –2305 per surviving graft and –€1487 to –9199 per rejection-free graft.

Summary

- Six economic studies were identified that compared the total medical costs of tacrolimus and ciclosporin (Neoral or Sandimmun), three of which included a formal cost-effectiveness analyses.[148–155] In each study the lower treatment costs associated with tacrolimus offset its higher acquisition costs compared to ciclosporin.
- Three cost-effectiveness studies of tacrolimus were identified. Two modelling studies undertaken from a UK perspective demonstrated that the 1-year cost-effectiveness of tacrolimus relative to ciclosporin was relatively unattractive: £120,000–220,000 per QALY or £30,000 per additional graft saved or

patient death avoided. However, a recent European-based retrospective cost-effectiveness analysis using 6-month RCT data concluded that the cost-effectiveness of tacrolimus was 'dominant' at 6 months, that is, compared to ciclosporin, tacrolimus improved clinical outcomes for a lower cost: –€530 to –1874 per surviving patient, –€781 to –2305 per surviving graft and –€1487 to –9199 per rejection-free graft
- This discrepancy in cost-effectiveness estimates is almost certainly a reflection of differences across studies in how the treatment costs associated with tacrolimus and ciclosporin were taken into account.

Mycophenolate (mofetil and sodium)

Amount of evidence

Seven economic studies assessing the costs of MMF were identified.[156–162] Four studies were cost–consequences studies and three were cost-effectiveness analyses. All studies compared MMF to azathioprine (see Appendix 18).

Cost analyses

All seven studies focused on medical costs and included drug acquisition costs as well as the costs associated with acute rejection and graft failure treatment. Patient and carer costs were not considered. The studies based their costing on a variety of different methods including retrospective observational data, RCT data and modelling. With one exception these cost studies were limited to a 6- or 12-month post-transplant time horizon.

Given that the studies were conducted across a number of countries (USA, Canada and Switzerland) and expressed their results in a variety of currencies, it is not readily possible to compare their costs. However, focusing on the total medical cost of MMF compared to azathioprine, five studies estimated that the short-term (6- or 12-month post-transplant) costs of MMF would exceed those of azathioprine[142,157,158,160,162] and two studies estimated that the short-term costs of azathioprine would exceed those of MMF.[156,161] The one study that modelled costs in the longer term found that as at 12 months, the 10-year costs of MMF exceeded those of azathioprine.[142]

Cost-effectiveness

Three published cost-effectiveness studies were identified that compared MMF to AZA.[142,158,161]

Schniztler and colleagues used a 10-year economic modelling of cost-effectiveness to compare a variety of different immunosuppressant drug regimens.[142] Four of these regimens included MMF, one of which compared an induction quadruple-regimen with MMF (2 or 3 g per day) to azathioprine. Graft survival at 1 year, patient survival and ARRs were derived from published clinical outcomes of the US MMF multicentre trial. A cost-effectiveness analysis demonstrated that at 1 year and 10 years the cost-effectiveness of MMF was superior to that of azathioprine ($GSCE_1$ 38 versus 38 and $GSCE_{10}$ 47 versus 50).

Sullivan and colleagues[161] undertook another cost-effectiveness analysis based on the US MMF multicentre trial, although only the 2 g per day MMF dose group was included. The analysis focused on the first transplant year and included healthcare utilisation data collected prospectively within the clinical trial. Costs were obtained from Medicare and annual hospital data, adjusted to 1995 values. The azathioprine and MMF groups were compared in terms of costs of acute rejection episodes, infection episodes, graft survival, the use of dialysis and maintenance drug therapy. The higher acquisition cost of MMF (MMF US$5170 versus AZA US$885 per year) was offset by lower costs in terms of the treatment costs associated with acute rejection and graft failure. As a result, the total first year costs for patients treated with MMF were estimated to be slightly lower than for those treated with azathioprine (US$27,807 versus $29,158). Given that fewer patients in the MMF arm than in the azathioprine arm of the trial experienced an episode of acute rejection (27.9% versus 47.8%), the authors concluded that MMF was dominant in terms of its cost-effectiveness. Sensitivity analysis was conducted by varying assumptions about the incidence of acute rejection, graft failure rates, the incidence of CMV infection, the cost per day of hospitalisation and the acquisition cost of MMF, and varying the amount of rejection treatment administered in outpatient settings. The cost difference between treatment with MMF and azathioprine remained small (within 7%) in all scenarios.

Finally, Keown and colleagues[158] conducted a cost–utility analysis of the Tricontinental MMF trial. This study was performed from the perspective of the Canadian health payer. Clinical outcomes and resource use were based on clinical trial data, in which patients received either an MMF-based (2 or 3 g per day) or an azathioprine-based triple therapy. The analysis focused on the first transplant year and included healthcare utilisation data collected prospectively within the clinical trial, including immunosuppressant drugs,

treatment of acute rejection and infection, and dialysis. Costs were based on 1994 Canadian hospital data. The authors used health state preferences from the Tricontinental trial measured by time trade-off (TTO). The mean TTO scores were 0.83 and 0.85 at 3 and 6 months, respectively, in patients receiving 2 mg per day, compared with 0.82 and 0.86 in patients receiving azathioprine. The mean cost of first year care was US$27,870 for patients receiving MMF and US$27,381 for azathioprine, with an incremental cost-effectiveness ratio (ICER) of Can$14,268 per graft-year gained and Can$50,717 per QALY gained.

Summary

- All six studies that examined the costs of MMF compared to azathioprine consistently showed that the higher acquisition costs of MMF are offset by its lower treatment costs. Whether these studies reported the overall medical cost of MMF to be less or greater than azathioprine was a reflection of differences in how the studies assessed and valued these treatment costs.
- Three cost-effectiveness analyses of MMF were identified,[142,156–162] each of which concluded that MMF may be more cost-effective than azathioprine; compared to azathioprine, MMF was associated with better clinical outcomes for either a greater or similar overall cost.
- One of these three studies reported an ICER of Can$14,268 per graft-year gained and Can$50,717 per QALY gained for MMF relative to azathioprine.

Sirolimus

Amount of evidence

Only one economic evaluation of sirolimus was identified. This study compared the costs of sirolimus to azathioprine (see Appendix 19).

Cost analyses

Manninen and colleagues[163] undertook a US-based cost study comparing sirolimus to azathioprine. Costs included the consequences of treatment, but did not include the actual cost of the study drugs. The patients were a subset of participants in the RCT by Kahan who had complete Medicare claim forms (178 in the sirolimus 2 mg group versus 106 in the azathioprine group).[132] The 1-year treatment costs of the sirolimus group were lower than for the azathioprine group (US$122,033 versus US$126,627). As the variance in costs was large, there was no statistically significant difference in the mean costs between the two groups.

Cost-effectiveness

No studies examining the cost-effectiveness of sirolimus were identified.

Summary

- Only one published cost analysis of sirolimus was identified.[163]
- This cost study indicated that sirolimus has equal 1-year treatment costs to azathioprine.

Treatment of acute rejection

Amount of evidence

Only one RCT[164] was identified that addressed the costs of the newer immunosuppressants (i.e. basiliximab, daclizumab, tacrolimus, MMF or sirolimus) in the context of the treatment of acute rejection. This study undertook a cost-effectiveness analysis of MMF compared to muromonab CD3 in patients with intractable acute rejection.

Cost analyses and cost-effectiveness

Sakamaki and colleagues[164] used a decision-analytic model to compare the medical costs of MMF and muromonab CD3 in patients with intractable acute rejection. Cost data were based on 1996 Japanese hospital reimbursement costs. The estimated cost per graft surviving at 3 months US$13,730 for MMF and US$29,060 for muromonab CD3, an estimated ICER of US$12,400 per graft saved, in favour of MMF. This reduction in cost per graft saved with MMF was robust to a number of sensitivity analyses.

Summary

- Only one study was identified that assessed the cost-effectiveness of the newer immunosuppressant agents in the treatment of acute rejection.[164]
- This study reports a reduction in costs per graft saved of US$12,400 with MMF compared to muromonab CD3 therapy at 3 months.

Chapter 6
Economic analysis

Industry economic models

Five manufacturers' dossiers were submitted to NICE, each of which contained information on clinical and cost-effectiveness evidence as well as an economic model. Three of the submissions focused solely on the company-specific drugs: Fujisawa, tacrolimus; Roche, MMF and daclizumab; and Wyeth, sirolimus. The Novartis submission modelled nine drug combinations; in addition to focusing on basiliximab and MMF/MPS, it considered the cost-effectiveness of daclizumab, tacrolimus, MMF and sirolimus, as well as C_2 Neoral monitoring, as opposed to conventional Neoral monitoring.

Fujisawa economic model

Fujisawa presented two economic evaluations, both based on a comparison of Neoral to tacrolimus. These were a 1-year cost-effectiveness analysis conducted as part of a single-centre RCT and a 10-year cost-effectiveness model.

One-year cost-effectiveness analysis

Model description

The details of this cost-effectiveness analysis are presented in the appendix of the Fujisawa submission in the form of a scientific article.[165] At the time of submission it was stated this manuscript has been submitted for publication. No electronic spreadsheet for this analysis was submitted. This description and critique are therefore based entirely on the text provided within the submission.

The cost-effectiveness was conducted as part of a UK single-centre (University of Wales NHS Trust) RCT comparing ciclosporin (Neoral) to tacrolimus. Details of this RCT are presented elsewhere in this report. The analysis was performed from the NHS perspective, and cost and outcome data were collected for a minimum of 1 year post-transplant follow-up, with mean follow-up times for 2.5 and 2.7 years in the Neoral and tacrolimus groups, respectively.

The treatment outcomes in the analysis were patient survival, survival with a functioning graft, survival with a rejection-free graft and occurrence of acute rejection. A Kaplan–Meier analysis of patient and graft survival was conducted. Patient survival was defined as the period between transplantation and death (whether with a functioning graft, or after return to dialysis). For those patients who were alive at the end of the study, the censored survival time was the period between the date of transplantation and the date of the last assessment. Similarly, graft survival was defined as the period between the date of transplantation and the date of graft failure, or death with a functioning graft.

Resource utilisation data collected alongside the clinical trial and throughout the follow-up period included hospitalisation (during both the initial admission and any subsequent readmissions), dialysis, tests, investigations, study medication and concomitant medication. If graft failure occurred, the number of haemodialysis sessions and days on continuous ambulatory peritoneal dialysis (CAPD) and the use of erythropoietin were also collected. Drugs commonly used by both study groups were not included. Treatment costs for side-effects (e.g. hypertension, lipid abnormalities or diabetes) and costs of the transplant procedure were not included; the costs of these were identical between groups. Unit cost information (1999 prices) was supplied by the trust and applied to the resource utilisation data. Discounting was not performed, although price variations were investigated in sensitivity analyses.

Model results

The trial clinical outcomes are reported in *Table 15*. No *p*-values or confidence interval for the differences between Neoral and tacrolimus were reported. The differences are not statistically significant.

The mean costs associated with the two treatment arms are shown in *Table 16*.

The overall cost of Neoral was £148 lower per patient than for tacrolimus over the follow-up period. The higher acquisition cost of tacrolimus (£9300 versus £6200) was offset by the reduction in downstream costs, mainly rehospitalisations and dialysis.

Based on these differences and clinical outcomes and costs at follow-up, the cost-effectiveness

TABLE 15 *Clinical outcomes*

Outcome	Neoral (*n* = 89)	Tacrolimus (*n* = 90)
Surviving patients (%)	88.8	94.4
Surviving patients with functioning graft (%)	79.8	87.8
Surviving patients with rejection-free graft (%)	52.8	64.6
Acute rejection (%)	47.2	35.6
Simple[a] (%)	23.6	22.2
Complex[b] (%)	23.6	13.3

[a] Responded to a short course of steroids.
[b] Resulted in a change in the maintenance immunosuppression regimen.

TABLE 16 *Costs associated with kidney transplantation over a mean follow-up period of 2.5 years for Neoral and 2.7 years for tacrolimus*

	Neoral (*n* = 89)		Tacrolimus (*n* = 90)	
	Cost per patient (£)	% of total cost	Cost per patient (£)	% of total cost
Hospitalisation	7,679	42.4	6,031	33.1
Dialysis	2,659	14.7	1,238	6.8
Tests/investigations	627	3.5	497	2.7
Study drug	6,170	34.1	9,346	51.2
Concomitant medication	958	5.3	1,130	6.2
Total	18,093	100	18,241	100

TABLE 17 *Cost-effectiveness of Neoral and tacrolimus over a mean follow-up period of 2.5 years for Neoral and 2.7 years for tacrolimus*

	Neoral (£)	Tacrolimus (£)	Difference (£)
Cost per surviving patient	20,384	19,314	1,070
Cost per surviving patient with functioning graft	22,680	20,780	1,900
Cost per patient with rejection-free graft	34,262	28,304	5,958

estimates shown in *Table 17* were reported in the Fujisawa submission, putting the cost per patient per rejection-free graft at £6000.

Model critique

Several issues with this analysis suggest that its conclusions, specifically gains in patient and graft survival with tacrolimus for a relatively low incremental cost, are naive.

- The differences in patient survival or graft survival in this trial at follow-up failed to achieve statistical significance. This observation was consistent with the pooled 1-year analysis of tacrolimus versus Neoral trials. Therefore, although there was an incremental gain with tacrolimus in the number of both patients and grafts surviving, the confidence intervals around these differences include the possibility of a gain in favour of Neoral (*Table 18*).
- Similarly, mean costs are given but without confidence intervals around these estimates.
- Based on these improvements in outcomes, it cannot be ruled out that tacrolimus is both more costly and less effective, that is, Neoral is dominant. In other words, it cannot be concluded tacrolimus is cost-effective.
- A full probabilistic cost-effectiveness analysis of this trial is required. This would combine individual patient clinical outcomes (i.e. patient survival and graft hazard) with individual cost differences. Such an analysis would be able to produce a mean cost-effectiveness estimate with a 95% confidence interval.

Ten-year cost-effectiveness analysis

Model description

This study was designed to assess the long-term clinical and economic outcomes associated with the use of tacrolimus and Neoral following renal

TABLE 18 *Mean (95% CI) absolute risk reduction for the Fujisawa trial*

	Absolute risk reduction Mean (95% CI)
Patient survival	0.057 (–0.02 to 0.14)
Surviving patients with functioning grafts	0.08 (–0.03 to 0.19)
Surviving patients with rejection-free grafts	0.116 (–0.26 to 0.027)

transplantation. It was based on the same clinical trial as the 1-year economic analysis. The model projected costs and outcomes over a 10-year follow-up period.[165] A copy of the accepted manuscript was submitted as part of the Fujisawa submission. A Microsoft Excel 97 version of the model was also made available.

The analysis was conducted from the perspective of a UK transplant unit. Short-term data were taken from the clinical trial and extrapolated based on audit data of survival and graft-survival rates. Short-term resource use and cost data were taken from the clinical trial (as described above), and extrapolated based on the expected changes in patient and graft survival at 3, 5 and 10 years post-transplant, taken from the 1995 UK Transplant Support Service Authority (UKTSSA) Transplant Audit. 1999 prices were used to cost the resource use data, and future costs and outcomes were discounted at 6% and 1.5%, respectively.

The model has three key central assumptions.

- Data at 5 years are estimated from data in Table 10.7 of the UKTSSA Transplant Audit (percentage patient survival: at 3 years = 86%, 5 years = 80%, 10 years = 63%). The rate of change in the percentage of patients surviving is the same for the two cohorts for years 5–10. Therefore, the annual rate of change in percentage patient survival between years 3 and 5 was taken to be (80% – 86%)/2 = –3%, and the annual rate of change between years 5 and 10 (63% – 80%)/5 = –3.4%.
- The rate of change in rejection rates and graft loss is the same as the UK Renal Audit graft survival rates for years 5–10, whichever immunosuppression regimen is used. Data at 5 years were estimated from Table 10.5 of the UKTSSA Transplant Audit (graft survival: at 3 years = 77%, 5 years = 70%, 10 years = 58%). Therefore, the annual rate of change in percentage graft survival between years 3 and 5 was taken to be (70% – 77%)/2 = –3.5%, and the annual rate of change between years 5 and 10 (58% – 70%)/5 = –2.4%. Again, the assumption here was that after 4 years the rate of change in graft survival is the same regardless of the immunosuppressive regimen used. It was assumed that the rate of change in rejection rates is the same as the UK Renal Audit graft survival rates for years 5–10 and this rate of change is independent of the immunosuppression regimen used.
- Costs beyond 4 years were extrapolated, taking account of the different cost for patients with and without a functioning graft. As the percentage of patients with a functioning graft decreases over time, the costs increase owing to the increased need for dialysis. To extrapolate the costs, the average cost for patients with and without a functioning graft in year 3 was projected proportionally; 4-year costs are weighted as follows: [% Graft survival × Average cost for patient with functioning graft + (% Patients surviving – % Graft survival) × Average cost for patient without functioning graft]/% Patient survival.

The assumption here is that costs increase over time as more patients return to dialysis. The economic analysis was conducted using unit cost information collected by the University of Wales Healthcare NHS Trust.

The model results were presented for a single patient and for a cohort of 52 patients, the estimated annual number of renal transplants undertaken in one atypical transplant unit in the UK.

One-way sensitivity analysis was carried out on two parameters reported to be the two key cost drivers: hospital stay and cost of immunosuppressive regimen. Probabilistic sensitivity analysis was also performed to assess the effect of uncertainty in the model.

Model results

The cost-effectiveness results from the model reported in the Fujisawa submission are summarised in *Table 19*.

TABLE 19 *Incremental results for tacrolimus versus Neoral*

	1st year	10th year
Incremental (cumulative) cost for cohort of 52 patients	£6,111	£31,131
Incremental cost per additional survivor	£10,164	£7,809
Incremental cost per additional patient with functioning graft	£3,462	£6,836
Incremental cost per additional patient rejection free	£1,025	£6,371
Costs shown are at 1999 prices: £1 GBP = US$1.42 = €1.50.		

From probabilistic simulation (10,000 Monte Carlo simulations), the average incremental cost per additional survivor was reported to be £8078 (95% uncertainty interval £5394 to £10,763).

Model critique

The 10-year model suffers from the same problem as the 1-year model, in that it assumes a difference in patient and graft survival based on trial data that show non-significant differences. No significant improvement in pooled 3-year graft survival was observed in the meta-analysis.

The additional cost of the tacrolimus regimen cannot be assumed to be linked with a reduction in deaths or improvement in graft survival. In other words, the increase in costs with tacrolimus could be associated with an increase in deaths and decrease in graft survival.

Model rerunning with alternative parameters

Given that both Fujisawa models are predicated on a statistically significant reduction in mortality and improvement in graft survival, which have not been demonstrated in trials, it was not possible to rerun these models with alternative parameter values.Therefore, another approach to assessing the cost-effectiveness of tacrolimus was taken.

- The systematic review demonstrated short-term (1 year) and long-term (3 years) benefits in clinical outcome of tacrolimus in comparison to Neoral: a statistically significant decrease at 1 year in ARR and a decrease, although not statistically significant, in patient and graft survival.
- The question is whether these gains in clinical outcomes are good value given the additional incremental acquisition cost. From the various economic evaluations to date, this is about an additional £1500 per patient per year.
- Accounting for the possible downstream costs differences between tacrolimus (treatment of acute rejections, treatment of graft failure and dialysis as result of graft failure), it appears that this cost difference will decrease between the two drugs. A range of estimates for this cost difference has been proposed, the two extremes being an additional £148 per year (Fujisawa estimate) and £1800 per year (Booth-Clibborn estimate[62]).
- Use of these different costs gives very different ICERs.

Conclusions

The Fujisawa 1- and 10-year economic analyses are based on a single-centre RCT of tacrolimus compared to ciclosporin (Neoral). Taking into account the extrapolation of benefits and net costs, the ICERs for tacrolimus presented by Fujisawa are likely to be overoptimistic.

Novartis economic model

This section reviews the Novartis model, relying mainly on the detail provided in Appendix 7 of the company submission. To ensure a full description, the text has been compared with the spreadsheet model and the formulae in the model were all checked. The results are summarised and critiqued.

Model description

The model is extremely complicated, not least because it comprises at least four main elements. (Seven elements are shown in Figure 1, on page 5 of the main Novartis report. Appendix 7 has the four main elements discussed here.) These are:

1. a Bayesian synthesis of ARRs
2. a long-term model of the impact of acute rejection on graft loss, and
3. a diabetes mellitus post-transplant model, each feeding into
4. a long-term predictive model of graft and patient survival.

In addition, a cost model and a quality of life review feed into the long-term predictive model.

The Bayesian synthesis of ARRs (1, above) provides estimates for each of the nine drug regimens modelled, and feeds into (2), which

predicts long-term graft survival on the basis of short-term ARRs. The diabetes post-transplant model provides estimates of patient survival based on different levels of diabetes by regimens. Elements (2) and (3) are combined in (4), along with costs, life-years and QALYs. Thus, diabetes mellitus and ARR are the two key short-term outcomes that drive long-term graft and patient survival. [The impact of diabetes mellitus is stated several times to be greater than that of ARR on both patient and graft survival. "Experience of one or more episodes of acute rejection is associated with 0.9 year reduction in discounted life expectancy and 1.6 years reduction in graft survival. Experiencing diabetes mellitus post-transplant is associated with a 1.3 year reduction in discounted life expectancy and a reduction of 2.5 years in graft survival" (Appendix 7, p. 36). Although this claim is repeated several times the basis of the comparison is not clear (it seems to apply to those groups who develop acute rejection or diabetes mellitus, which are likely to be of different size). It does, however, underline the importance of diabetes in the model.]

The complications of the model are largely due to the incorporation of a previously developed model of the impact of diabetes on renal transplant patients, comparing those who develop diabetes post-transplant to those who do not.[166] This earlier model was amended to allow the proportions of patients developing diabetes to vary by regimen, and provides estimates of their life expectancy. The proportion of patients who develop diabetes is based on a summary of the literature (see Appendix 7, pp. 20–3) that distinguishes only between tacrolimus and Neoral. Although not stated in the text, the incidence of diabetes in the model for tacrolimus is put at double that for Neoral (14% versus 7% for Neoral and all other strategies).

Bayesian synthesis (WinBugs) model

The rationale for a Bayesian approach, as set out in the introduction of addendum 11 of the Novartis submission, is commendable. Such an approach aims to include all evidence, while allowing for different degrees of uncertainty (due to potential biases, or generalisability) associated with different studies.

However, implicit in such an approach is a requirement to consider individually the relevance and/or the quality of each study for the specific question under consideration, and hence to attach a degree of uncertainty to the evidence from each study. The model used does not do this.

Further, when synthesising non-randomised data, it is preferable to avoid 'naive' methods of analysis that ignore or underutilise intra-RCT comparisons, thereby relying too heavily on simplistic comparisons between arms of different trials. There is a forthcoming HTA methodology monograph on this, by Glenny and co-workers. See Song and colleagues,[167] written by same team, and available online.

The BUGS model in the Novartis synthesis falls into the trap of overdependence on absolute arm results. The model fitted (which uses the log-odds scale) has a term for each trial, m_i, as well as a term for each treatment. The trial term is assumed to come from a random normal distribution, but information on the estimated mean and SD of this distribution (from the model) is not given. The assumption that average trial risks are from an informative random distribution is clearly inappropriate since, for instance, particular treatments may tend to be given to particularly at-risk patients. Although including this trial term is better than having no term, its impact is likely to be similar in direction, and weaker only to the degree that the random distribution is not informative (has larger variance). This is because the value of m_i in a low-risk trial will shrink back towards the overall mean, leaving the treatment effects to deal with the low observed risks. As a result, the treatments trialled mainly on high-risk patients will look bad, while those trialled mainly on low-risk patients will look good. Inspection of Table 5 in the Novartis submission indicates that the rejection rates for an average population given a treatment are very close to the average of the observed rates over the trials, which suggests that all the m_i values are similar in size, and that the treatment effects are having to model all variation (owing to both treatment and intertrial variation in risk).

Long-term impact of acute rejection on graft loss

This is based on a literature review of risk factors for graft loss that claims that acute rejection was the strongest predictor of chronic rejection of graft loss of all the variables. A table from the Novartis submission on the literature on risk factors noted in studies is reproduced as *Table 20*.

Restriction of this literature to that which could be used for quantification of the impact of acute rejection on long-term graft loss reduced the relevant papers to one by Giral and colleagues[168] (a book chapter, not peer reviewed). They explored factors associated with graft loss in 486 consecutive first cadaveric allograft patients all

TABLE 20 *Risk factors associated with graft loss (Novartis literature review)*

Risk factor	No. of papers identifying statistical significance
Acute rejection	50
Recipient age	13
Donor age	11
Race	10
HLA mismatch	9
Serum creatinine	8
Delayed graft function	6
Recipient gender	5
Previous transplant	5
Immunosuppressive treatment	5
Cold ischaemia time	5
Diabetes	4
Panel-reactive antibodies (PRA)	4
Donor source	3
Chronic transplant nephropathy	2
Proteinuria	2
Serum trig	2
Preformed antibody	2
Pretransplant transfusion	2
Donor gender	2
Size of donor kidney	2
Time in dialysis	2
Centre grade	2

treated with a uniform immunosuppressive strategy.[168]

Multivariate analysis of factors associated with graft loss based on Giral[168] was carried out to identify four clinical baseline variables as independent prognostic factors in graft survival: the number of acute rejection episodes, timing of the first rejection episode, graft function at 1 year based on creatinine clearance and the magnitude of PRA. The magnitudes of each of these were referred to as Table 2 (not provided). The Giral paper[168] included a multivariate analysis that showed that acute rejection, along with donor and recipient age, were the statistically significant factors explaining graft loss.

Data limitations prevented use of this multivariate analysis to model graft loss. Instead, Novartis modelled graft loss based on acute rejection only (with numbers of patients experiencing zero, one, two, three or more episodes of acute rejection based on the Giral data). This was compared to assumed baseline survival (based on Kaplan–Meier) and a hazard ratio (based on a Weibull distribution).

Post-transplant diabetes mellitus (PTDM) model
Based on a previously published model[166] that compared the effects of diabetes versus no diabetes in post-transplant patients, this was incorporated with adjustment to allow for the varying percentage of patients developing diabetes, and altering the incidence of PTDM by drug regimen.

The key issue is the proportion with diabetes by drug regimen. The only regimen with a raised incidence is stated to be tacrolimus, based on the systematic review. The text states that "the rates used in the model for tacrolimus and all other treatments are therefore based on a conservative estimate of the entire evidence base" (p. 20), owing to most studies using out-of-date definitions of diabetes. Although not stated in the text, the model uses 7% incidence as a baseline for all regimens other than tacrolimus, for which 14% is used. This figure is not linked to the systematic review (see Table 3), which provides estimates from 13 studies, not all of which are comparable. Thus, tacrolimus is associated with a risk factor for diabetes compared to all other treatments.
The next stage of the model combines acute rejection and diabetes in predicting graft loss, as explained in the submission:

> "The model assumes that the occurrence of acute rejection and diabetes mellitus post transplant are independent and randomly assigns individuals to each group. Similarly the action of diabetes mellitus post transplant and acute rejection on graft loss is assumed to be independent and transition rates for graft loss are estimated for the four patient groups defined, i.e. with/without acute rejection and with/without diabetes mellitus.
>
> The link between acute rejection on graft loss is taken from the review of the determinants of long-term graft survival presented in Section 2 of this report. This review only identifies one study that reports sufficient information with which to populate the long-term model …. The acute rejection rates for individual immunosuppressive strategies are taken from the Bayesian synthesis of the entire acute rejection evidence base reported in Addendum 9. Long-term predictions of graft and patient survival have been generated based upon this study and the outcomes validated against long term follow-up data from trials and from registry database analyses" (p. 23, Appendix 7, Novartis submission).

Detailed examination of the diabetes model showed one mistake and one possible mistake. The mistake related to a double-counting of the risk factors associated with diabetes, which when discussed with the model's developers, the School of Health and Related Research at Sheffield

TABLE 21 *Novartis model: principal treatment strategies (adapted from Novartis submission)*

Strategy	ARR	PTDM	Treatment strategy
1	35%	7%	Neoral + azathioprine
2	24%	14%	Tacrolimus + azathioprine
3	21%	7%	Neoral + MMF or MPS
4	13%	14%	Tacrolimus + MMF or MPS
5	24%	7%	Sirolimus (N + S <3 months)[a]
6	20%	7%	Basiliximab + Neoral + azathioprine
7	12%	7%	Basiliximab + Neoral + MMF or MPS
8	22%	7%	Daclizumab + Neoral + azathioprine
9	10%	7%	Neoral C_2 monitoring + MMF or MPS

[a] Ciclosporin (Neoral)-free regimen after 3 months.
N, Neoral; S, Sirolimus.

(ScHARR), was agreed to be an error. This was rectified and the model was rerun. The second mistake concerned the lack of a half-cycle correction, which is common in such models, but which was missing in the Novartis model. Discussion with ScHARR indicated that while it may have been desirable to include such a correction, it was unlikely to make much difference to marginal estimates, although it would alter absolute values. In rerunning the model, the Birmingham team made a half-cycle correction.

Long-term predictive model of graft and patient survival

The overall results come from the long-term predictive model (RenalTx spreadsheet), which comprised 16 worksheets. These combine the results of data from the above models of diabetes and patient and graft survival with data on costs and utility values.

Patient and graft survival are based on five states over 10 years: acute rejection (AR+), no acute rejection (AR–), hospital dialysis, peritoneal dialysis and dead. Those who are AR– are healthy transplants with graft survival. Those who are AR+ are treated, with some recovering to AR– and others having graft failure which involves reverting to dialysis, which can be hospital or peritoneal.

Death can be from five co-morbidities associated with diabetes or from other causes: diabetic nephropathy, retinopathy, diabetic neuropathy, coronary heart disease and cerebrovascular disease. Diabetic retinopathy and neuropathy rates were based on Eastman and colleagues.[169] Deaths from cerebrovascular and coronary heart disease rates were based on the Framingham equations. Each of these co-morbidities is a submodel, with a total of 19 health states.

Costs are associated with each of these states, using QALYs linked to two states other than dead: successful transplant and dialysis.
The nine strategies modelled and their rates of acute rejection and PTDM are shown in *Table 21*.

The inputs to the model are shown in *Table 22* (from Novartis submission).

Model results

The nine strategies are modelled, each taking several hours to run. The results of the run summarised in the submission are reproduced in *Table 23,* which shows patient and graft survival, QALYs, costs, cost per QALY and net benefit. Several points are worth noting.

- The differences in outcomes by regimen are small, with the QALY range from 6.43 to 6.70, a difference of 0.27 or 4% of the mean. Similar small differences applied to total life-years and graft years.
- Although confidence intervals cannot be readily fitted to ICERs, were such data available they would show wide uncertainty around most if not all of the estimates.
- The total cost per patient varies by drug regimen, with a range of £31,000 over 10 years, a difference of 55% of the mean.
- The results of small differences in QALYs and relatively large differences in costs are high and unstable ICERs. Compared with a baseline strategy of Neoral plus azathioprine, one strategy has an ICER of –£4 million, based on a negligible QALY difference (not apparent at two decimal places) and a cost difference of £18,000 per patient.
- The remainder of the ICERs are much less, with a range from –£13,000 to +£65,000. However,

TABLE 22 *Parameters used in the economic model (adapted from Novartis submission)*

Parameter group	Model parameter	Parameter value
Quality of life	Utility of living with graft	0.84
	Utility of living on dialysis	0.65
Cost of dialysis	% CAPD	37.4%
	Annual cost of CAPD	£19,736
	Annual cost of haemodialysis	£25,756
	Annual cost of dialysis	£23,504
Costs of acute rejection	Cost of steroid-responsive acute rejection (1996)	£7,683
	Cost of steroid-resistant acute rejection (1996)	£16,356
	Annual inflation (as at 2002)	0.022
	Cost of steroid-responsive acute rejection (2002)	£8,754
	Cost of steroid-resistant acute rejection (2002)	£18,636

the same point applies to all of them; that is, small differences in outcomes and large differences in cost.

Basiliximab and MPS
The submission focused on the cost-effectiveness of each of these Novartis drugs compared to their main alternatives.

The results show that basiliximab added to Neoral plus azathioprine, compared to not being added, was dominant, with a QALY gain of 0.13 and cost saving of £1600 per patient over 10 years. Compared to its non-inclusion in triple therapy made up of Neoral, MMF/MPS and steroid, it had a relatively low ICER of £1800. Sensitivity analysis (one-way only) showed basiliximab as relatively attractive in that even in the least favourable scenario it had an ICER value of £16,000.

For MPS (the clinical effectiveness of which was assumed to be equal to MMF), its marginal impact in substituting for azathioprine in a Neoral plus azathioprine regimen gave it an ICER of £65,000. The ICER for MPS fell to £29,000 when Neoral C_2 plus MPS was compared to Neoral plus azathioprine. It should be noted that the inclusion of Neoral C_2 here makes it a new intervention, which may not be legitimate according to the terms of reference (Neoral is the comparator).

Sensitivity analysis (one-way) for MPS shows that for the estimate of £65,000 in substituting for azathioprine the range could be from £35,000 to £283,000.

Model critique

Graft survival model
The presentation (Appendix 7 in the Novartis submission) was poor, with several missing tables, making it difficult to understand.

The modelling of graft survival based on acute rejection required additional assumptions to do with Kaplan–Meier plots, which were compared to assumed baseline curves for both survival and hazard. This was both complex and uncertain, in that it extrapolated from relatively short-term data to 10 years.

Diabetes model
The text was far from clear, with some of the major developments receiving little explanation, particularly in relation to how acute rejection and diabetes mellitus interact. The model was very large (8 gigabytes) and not well explained in the text.

Four groups were stated to have been defined, but neither definitions nor the relevant risk factors were provided in the text. The text did not state that a risk factor of 2 for diabetes on graft loss has been assumed. *Table 24* summarises the reviewers' best understanding of the risk factors for the four groups in the model.

Validating the model

The report's authors claim to have validated the model against four orders of validation:

- expert concurrence
- internal validity
- agreement of predictions with non-source data
- predict–experiment comparison.

The diabetes model is claimed to have received strong clinical input and to have been peer reviewed. The use of acute rejection as a determinant of graft loss is claimed to have been validated "as has been demonstrated by the systematic review".

TABLE 23 *Absolute estimates of cost and clinical outcomes based upon the long-term model of patient and graft survival (adapted from Novartis submission)*

Strategy	Neoral + AZA	Tacrolimus + AZA	Neoral + MMF/MPS	Tacrolimus + MMF/MPS	Sirolimus (N + S <3 months	Simulect + Neoral + AZA	Simulect + Neoral + MMF/MPS	Declizumab + Neoral + AZA	Neoral C_2 monitoring + MMF/MPS
Total life-years (benefit discounted)	7.89	7.89	8.05	8.00	8.01	8.02	8.11	8.03	8.16
Total life-years (cost discounted)	6.36	6.36	6.48	6.44	6.45	6.46	6.53	6.47	6.56
Graft years (benefit discounted)	6.88	6.85	7.13	7.09	7.05	7.10	7.22	7.10	7.33
Graft years (cost discounted)	5.58	5.56	5.77	5.74	5.71	5.74	5.84	5.75	5.92
Time on dialysis (benefit discounted)	1.02	1.04	0.93	0.91	0.96	0.92	0.89	0.94	0.83
Time on dialysis (cost discounted)	0.79	0.80	0.71	0.71	0.75	0.72	0.69	0.72	0.64
Total QALYs	6.44	6.43	6.59	6.55	6.55	6.56	6.64	6.57	6.70
Cost of management	£43,942	£63,038	£55,687	£74,670	£59,002	£44,705	£57,200	£46,812	£55,005
Cost of acute rejection	£4,794	£3,239	£2,904	£1,474	£2,694	£2,443	£1,488	£2,743	£1,411
Total cost	£48,736	£66,277	£58,590	£76,144	£61,696	£47,147	£58,687	£49,555	£56,415
Gross net benefit	£144,397	£126,724	£139,093	£120,252	£134,730	£149,780	£140,660	£147,572	£144,494

AZA, azathioprine.

TABLE 24 *Relative risk factors in the Novartis model*

	No diabetes	Diabetes
No acute rejection	1	2
Acute rejection	2.58	Unclear

Internal validation is claimed by the authors on the basis that the model worked correctly and reasonably predicted the data used to estimate parameters in the model. This is claimed to have been met in the graft survival model by predicting the data in the Giral paper.[168] No such comment is made in relation to the diabetes model.

Fourth order validation is discussed in relation to two approaches: absolute predictive ability and marginal predictive ability (the differences between treatments). Some results are shown for the former, but the lack of long-term data is acknowledged as a serious problem. The marginal predictive value of the model is compared with trial data for several of the favoured Novartis drug regimens and generally favourable results reported.

C_2 monitoring of Neoral in renal transplantation

The Novartis submission undertook a systematic review of the evidence base for C_2 monitoring for Neoral. The submission reported a number of observational predictive studies. Only one RCT in renal transplant was identified that had assessed the benefit of C_2 monitoring: the MO2ART trial.[170] With regard to this RCT, the Novartis submission states, "The current available evidence for Neoral C_2 monitoring indicates that this protocol has the potential for excellent clinical results in terms of avoidance of acute rejection with rates in the region of 10%."

There are several issues regarding the MO2ART trial.

- The trial design involved all patients being allocated to a C_2 regimen for 4 months when they were then randomised to two Neoral doses (1.0–1.2 or 0.8–1.0 $\mu g\ ml^{-1}$). This trial does not compare trough with C_2 monitoring.
- The 10% acute rejection figure for Neoral C_2 monitoring used in the analysis of the Novartis submission comes from both arms of the trial. This figure is based on all acute rejection episodes at 3 months. The ARR at 12 months would certainly be higher. However, this issue is not dealt with in the Novartis submission.
- This MO2ART trial reported results on 117 patients, yet 270/290 were scheduled to be recruited. No explanation for this large fall in patient number is given.

The present authors undertook an updated systematic review, which confirmed that no RCT has compared Neoral trough to Neoral C_2 monitoring. They are aware of one RCT of this type in liver transplant.[171]

In conclusion, there is evidence to demonstrate that for single-point Neoral monitoring, C_2 is a better predictor than trough of acute rejection in renal transplants patients. However, the actual benefit of C_2 Neoral monitoring over Neoral trough monitoring has yet to be confirmed by an RCT. Therefore, the magnitude of reduction in acute rejection episodes associated with C_2 monitoring over conventional trough monitoring in renal transplant patients remains uncertain. All RCTs to date comparing Neoral to tacrolimus have been based on trough monitoring. The additional practical demands of undertaking C_2 Neoral monitoring in routine clinical practice have been highlighted (see professional group submission).

Conclusions

The Novartis model is extremely complex, mainly combining a previous model of PTDM with an acute rejection model. As a result, it is difficult to separate the impact of different assumptions.

One mistake, to do with double-counting of diabetes risk factors, was detected, as was another omission (half-cycle correction). Both of these were rectified and the model was rerun. As discussed below, owing to this being a simulation model, each run provided slightly different results, which made it difficult to establish how important the mistake was.

The diabetes model is extremely complicated. The submission did not justify its choice of five co-morbidities of diabetes, and was unclear on the extent to which the inclusion of diabetes affects the overall results. The diabetes model attributes a risk factor of 2 to tacrolimus compared to all other strategies, an assumption not explained in the text and only apparent from scrutiny of the model.

The differences in outcomes from the Novartis model by strategy are small relative to the costs, giving unstable ICERs. The range of QALY differences is limited to 4% of the mean value, while the range of costs was around 55%.

Sensitivity analysis was only carried out on those drug regimens in which Novartis has a commercial interest. The sensitivity analyses were restricted to one-way comparisons and relied heavily on the ARRs derived from the Bayesian analysis, which provided high and low estimates for both ICERs and net benefit.

Because of the complexity of the model, each run of 10,000 (the number recommended by the originators and the basis of the submission) gives results which differ by several percentage points in the key results. The difference between runs was of the same order of magnitude as that between strategies.

Roche economic model

Model description

Roche provided an economic model to examine the cost-effectiveness of the use of MMF relative to azathioprine. This spreadsheet model was deterministic and provided results as cost per QALY. The model consists of two parts, each of which calculated the incremental cost per QALY.

The year 1 model included drug acquisition costs, the cost of treating acute rejections, and the costs associated with dialysis and graft failure. One-year acute rejection estimates were derived from two large RCTs (Tricontinental and US MMF trials). One-year patient survival was derived from a single RCT (Tricontinental MMF trial), while graft survival was estimated from this trial and US observational audit data. Utilities were derived from three states: transplanted (and well), on dialysis and experiencing graft failure.

The second model provided cost and utility data for years 2–10. Graft and patient survival were extrapolated over the 10-year time horizon from 1-, 3- and 5-year UK observational audit data. A relative risk reduction with MMF in both graft and patient survival was derived from US registry data. The costs associated with dialysis and graft failure were estimated as in the year 1 model, although from years 2 to 10, no cost saving from acute rejections was assumed. Costs of azathioprine and MMF were taken from trial data. It was assumed that with MMF there was a ciclosporin saving effect (i.e. reduction in ciclosporin dose).

The parameter values and assumptions and sources of the Roche model are summarised in Table 1 of their submission. One-way sensitivity analyses were undertaken based on dialysis cost, level of ciclosporin saving, utility values, azathioprine and MMF dose, and relative risk reduction in patient and graft survival.

Model results

The model predicted that over 1 year MMF compared to azathioprine had an incremental increased cost of £51 and incremental gain of 0.011 QALYs, giving a cost per QALY of about £4600. Over 10 years, the model predicted a discounted cost-effectiveness of MMF compared to azathioprine of £23,000 per QALY (incremental cost £5536 and incremental gain in QALY 0.24). The range of 10-year cost per QALY reported by the sensitivity analysis undertaken was –£2297 per QALY to £33,890 per QALY.

Model critique

- Although the year 1 estimates of efficacy of MMF (compared to azathioprine) were derived from RCT evidence, the model uses the results from either one or two trials. A meta-analysis of all relevant trial data should have been undertaken (seven RCTs are available comparing MMF to azathioprine).
- Extrapolation of patient and graft survival to 10 years was based on baseline 1-, 3- and 5-year values from UK observational data. It is unclear why a Gompertz curve was fitted to patient survival and an exponential curve to graft survival.
- The estimate of relative difference in graft and patient survival was derived from US observational data sources. Given differences in renal transplant practices between the USA and UK, this estimate may not be directly transferable.
- It was assumed that all patients on MMF experienced a reduction in ciclosporin dose (ciclosporin saving) of 30%. However, this is based on trial evidence where only a subgroup of patients is switched (with renal malfunction or CAN) and at a period after initial transplantation. In none of these trials was the point of ciclosporin sparing before 6 months. Further, four of these trials only apply this ciclosporin sparing strategy to a subgroup of MMF-treated patients, with either renal function impairment or CAN.
- The model used utility values that did not come directly from RCTs. The RCT by Keown[158] has shown a utility difference between azathioprine and MMF over 3 and 6 months' follow-up of only 0.01.
- The costs of MMF and azathioprine were taken from one trial, rather than the current UK licensed dose.
- All model cost and effectiveness estimates are presented without measures of uncertainty (as point estimates only).
- One-way sensitivity analysis was undertaken, and only for a range of some of the key assumptions and parameter values. It is likely that adjustments to a number of the baseline estimates and assumptions to the model would be cumulative, and this is not truly reflected in the sensitivity analyses.

Model rerunning with alternative parameters

Each of the 1- and 2/10-year Roche model sources and assumptions were scrutinised for their validity. Where possible, the efficacy parameter values used in the model were compared to the values obtained from the Birmingham systematic review and meta-analyses. These comparisons are shown in *Table 34*. In general, the parameter values used in the Roche model fell within the 95% confidence intervals of the Birmingham-derived estimates of these parameters. Where this was the case, these model parameters were left unchanged. However, in four key areas where the Roche model was judged to be unreasonable the model parameters were changed.

1. **Ciclosporin sparing:** the Roche model assumed a reduction in ciclosporin dose of 30% in all patients from the point of transplantation and across the 10-year model horizon. The effect of this was to offset the acquisition of MMF by some £835 per year. Roche presents some trial evidence to support this assumption. However, as discussed above, this trial evidence indicates that the assumption of an immediate reduction in dose across all patients is unreasonable. Instead, this trial evidence indicates that it is much more plausible that after some time, a reduction in ciclosporin dose may occur in a subgroup of patients. To reflect this, the model parameters were altered to reflect no reduction in ciclosporin dose at 1 year and a 10% reduction per year thereafter.
2. **MMF and azathioprine doses:** the azathioprine and MMF doses were adjusted to reflect UK licensed dosages (as per BNF), of MMF 1 g twice per day and azathioprine 2 mg kg^{-1} per day. The model daily costs of MMF and azathioprine were therefore adjusted to £9.08 and £0.90, respectively.
3. **Relative risk for patient survival:** no significant difference was observed in the pooled 3-year patient survival analysis (*Table 11*). Therefore, the relative risk reduction was set to zero.
4. **Extrapolation of graft and patient survival**: the Roche model interpolates across the 10-year horizon an annual graft survival hazard that ranges from 4.9 to 5.5%, and an annual patient survival hazard of 1.6–4.1%. The present meta-analysis of trial data gave a 1- and 3-year graft survival of 87% and 80%, and 1-year and 3-year patient survival of 93% and 91%, respectively. The authors therefore believe that more reflective annual hazards for patient survival and graft survival are 1.0% and 1.5%, respectively.

Rerunning the Roche model based on these preferred parameter values, an incremental cost per QALY of £44,000 (with changes 1–3) and £84,000 (with changes 1–4) was obtained.

Conclusions

Based on this critique of the Roche model and rerunning using preferred model parameter and assumptions, the cost–utility estimates presented in the Roche submission may be viewed as overoptimistic, and the 10-year incremental cost per QALY of MMF compared to azathioprine is likely to be more than £40,000 and possibly as high as £84,000.

Wyeth economic model

Model description

The Wyeth economic model focused mainly on the cost–utility of sirolimus versus ciclosporin, with clinical effectiveness data based on the Rapamune Maintenance Regimen (RMR) trial.[172] Extensive use was made of a University of Wales database, for derivation of both hazard functions and costs. Given that sirolimus was only licensed by the European Medicines Evaluation Agency (EMEA) in 2001 (and the Food and Drug Administration in 1999) for adults at low to moderate risk, relatively few data are available, particularly on its longer term effects.

The model relied on serum creatinine concentration (SCr), a measure of renal function, as a proxy for long-term renal outcome. This was in contrast to the other three company models, all of which used ARR as the main predictor of long-term graft survival. The (ongoing) RMR trial data at 12 and 24 months showed better (lower) creatinine levels in patients on sirolimus than in those on ciclosporin plus sirolimus. The case for creatinine as a predictor of longer term outcomes rests on a single large observational study[173] on US transplant patients (for details see below).

Long-term graft survival model

A discrete event simulation model linked the states of renal transplantation, graft rejection, regrafting, dialysis (haemodialysis and CAPD) and survival for 10 and 20 years post-transplant. Cox proportional hazard submodels estimated patient and graft survival, time to dialysis and acute rejection episodes. The number of haemodialysis events was based on a regression submodel.

The differences in creatinine concentration between sirolimus and ciclosporin from the RMR trial[172] at 2 years formed the basis of the projections for graft and patient survival. Trial

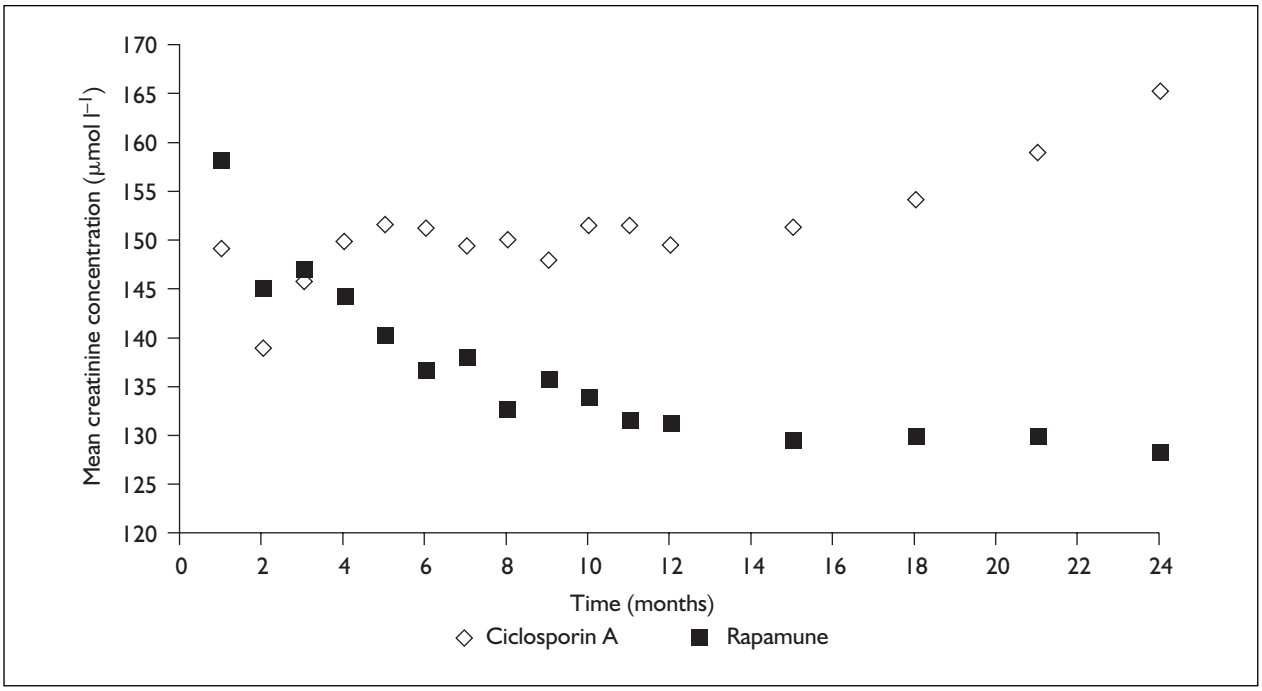

FIGURE 3 *Mean creatinine concentrations with sirolimus plus corticosteroid or ciclosporin plus corticosteroid from clinical trial 310 (reproduced from Wyeth submission)*

data were available up to 24 months (at 3, 12 and 24 months) for creatinine concentration for patients on ciclosporin. Creatinine data for ciclosporin and sirolimus at 36 months were extrapolated (details below). This was justified by the fact that the difference in creatinine concentration was widening after 24 months, according to trial data. *Figure 3* is reproduced from the Wyeth submission.

The trial data on creatinine concentration at different points in time were linked to creatinine levels in the Cardiff database, partly to provide UK data, partly to extrapolate to 36 months, and also to provide estimates of cost. Proportional hazard models were developed based on creatinine at 12, 24 and 36 months, which were used to provide estimates of patient and graft survival at 10 and 20 years. The case is made for preferring 20 to 10 years on the basis of bigger differences between the regimens compared (10 years was deemed to be too short given ARRs under 30% at 1 year).

Cost data were based on the Cardiff database, which had patient-level cost data for each of the states modelled. These included the costs of immunosuppressive regimens, prophylaxis for cardiovascular disease and complications (CMV, bone disease and anaemia).

Utility was linked to two states: transplantation and dialysis, and the time spent in each. Utility values were based on a survey of patients in the Cardiff database, which had a 21% response rate. This study put the difference in utility between transplantation and dialysis at 0.23 (or 0.26 in Table 7.8 in the Wyeth submission, but stated to be 0.27 on p. 5 of the submission). Since no estimates of the cost per QALY other than the final result in terms of incremental cost per QALY were provided, it is not clear which utility value was used.

The results were presented in terms of life-years gained, incremental life-years and incremental cost per QALY. No data were provided on absolute QALYs (but these are estimated below). The results showed sirolimus as dominant over ciclosporin or tacrolimus at both 10- and 20-year follow-up.

Cost model

A simulation model attributed costs according to an individual patient's disease state. The costs of renal transplant therapy were estimated from data at University Hospital Wales (UHW), with reference to appropriate national sources where they were known to be more applicable. These costs included acute rejection events, graft failure, retransplant (up to four), haemodialysis and peritoneal dialysis, and mortality (Wyeth

TABLE 25 *Unit costs used in the model, 2002 prices (adapted from Wyeth submission)*

	Cost per patient (£)
Sirolimus plus azathioprine + steroid	
0–3 months (with ciclosporin)	1,684
4–12 months	5,442
>12 months (maintenance)	4,879
Ciclosporin plus azathioprine plus steroid	
First 6 months	3,156
Maintenance (p.a.)	2,949
Tacrolimus plus azathioprine plus steroid	
First 6 months	2,180
Maintenance (p.a.)	4,251
Transplant (elective)	10,249
Rejection: complications	886
Haemodialysis (p.a.)	21,060
Utility difference transplant: dialysis	0.27

p.a., per annum.

submission, pp. 75–6). The unit costs in the model are summarised in *Table 25*.

Higher creatinine values were associated with increased cost according to the Cardiff database. These included 19 different drugs, six of which were directly related to renal disease (azathioprine, ciclosporin, erythropoetin, MMF, prednisolone and tacrolimus) and the rest to co-morbidities (alfacalcidol, aspirin, atenolol, doxazosin, ganciclovir, iron sulfate, lisinopril, losartan, nifedipine, omeprazole, septrin, simvastatin and titralac). These drugs were related to prophylaxis of CMV and cerebrovascular disease, and treatment of bone disease and anaemia, thus including the drug-related costs of adverse events.

As patients moved from one disease state to another according to their simulated graft and patient survival, changes in creatinine concentration translated into changes in costs. The costs were largely those for care in Cardiff, supplemented by national data.

Key inputs to the model are listed in Appendix 3 and key assumptions in the model in Appendix 4 of the industry submission.

Utility

Utility values associated with the states of haemodialysis, CAPD or a functioning graft were based on a special new study based on Cardiff patients. Utility scores were applied in the model by multiplying the value for cost per discounted year of functioning graft by the difference in health utility between people on dialysis or with a graft (0.27 utilities in the text, 0.23 in Table 7.7 of the company submission). This value is consistent with other estimates. These data were used to estimate differences in utility between patients treated with sirolimus maintenance therapy and those on ciclosporin triple therapy within the trial period, and then to model the difference in utility up to the point of graft failure.

Key steps and assumptions

Use of creatinine to predict graft survival A key step is the use of creatinine to predict long-term graft and patient survival. As noted above, this is based on a single study,[173] which analysed all 105,742 adult renal transplants performed in the USA between 1988 and 1998. A Cox proportional hazards model was used to examine renal function as measured by creatinine in the first year as an independent variable in determining long-term renal graft survival. Age, gender, race and body weight were included in the analysis, along with acute rejections.

Two studies concluded that serum creatinine and the change in creatinine between 6 and 12 months post-transplantation were the most important factors predicting long-term graft survival. Recipients with creatinine >1.5 mg dl^{-1} (132 μmol l^{-1}) and a change in creatinine of 0.3 mg dl^{-1} (26.5 μmol l^{-1}) or more have a substantially lower projected graft half-life than all

other groups, regardless of acute rejection. The analysis also confirmed the importance of donor source (living versus cadaver), donor age, race and presence of diabetes, but suggested that the main factor in improving graft survival over the 11 years of the analysis had been better preservation of renal function within the first year. The authors concluded that events occurring within the first year were of critical importance for long-term graft survival, and that the quality of renal function, as measured by creatinine, at 1 year and its change over time would provide more relevant end-points in comparative trials.

Extrapolation of 36-month creatinine The trial data showed that the creatinine level on ciclosporin was above that for sirolimus and was rising after 12 months, while that for sirolimus was flat, suggesting that the difference would continue to widen at 36 months (see *Figure 3*). The Wyeth model used an estimated creatinine for ciclosporin at 36 months, based on extrapolation based on trial data for 12–24 months. *Figure 3* shows data based on trial 310. To make the Cardiff data compatible with the data, creatinine levels had to be reduced by 72 points or around one-third. These values were then projected to 36 months on the basis of the 12–24-month data. The result was a projected value for creatinine and ciclosporin at 36 months that was well above that for 24 months. A different approach was taken to the prediction of creatinine in sirolimus patients at 36 months. As "there exist no long term real life observations" (p. 82), best fit curves from the RMR trial[172] were used to project to 36 months. The best fitting curve, it was claimed, gave the most conservative (least favourable) values for sirolimus, that is, the same value at 36 months as at 24 months. On this basis, the creatinine difference between ciclosporin and sirolimus was derived for three points in time (12, 24 and 36 months). These results are presented in *Table 26* but are not compared with trial data. As can be seen, the extrapolation to 3 years widens the difference from 37 points at 24 months to 48 points at 3 years.

Methods for extrapolating to 10 years Kaplan–Meier survivorship functions and Cox regression models were used to extrapolate graft and patient survival beyond 3 years.

Renal function There is an assumption that 50% of patients on sirolimus have a decline in renal function. This assumption is stated only in the introduction and is not mentioned in Section 7 of the Wyeth report, on cost-effectiveness modelling:

> "1.3 Results, Cost Utility Analysis
> The results of the base case cost utility analysis are shown in table 1.2.
> It is assumed that use of a non-nephrotoxic immunosuppressant will not damage the kidney or lead to long-term deterioration of graft function. To simulate a clinical situation, the model assumes that fifty percent of patients had a deterioration of kidney function. This conservative approach was taken as the base case analysis."

The rationale for these two stated assumptions, which appear to contradict each other, is not clear. The second assumption would seem more appropriate as part of a sensitivity analysis.

Model results

The results of the base-case cost–utility analysis are shown in *Table 27*.

The incremental cost per QALY analysis produces a set of negative figures for sirolimus versus calcineurin inhibitor-based regimens. Sirolimus dominated both ciclosporin and tacrolimus-based regimens in maintenance immunosuppression.

Model critique

The main criticisms of the model are as follows.

Clarity over structure and process of model
The description of the model is generally poor. An assumption is made without any discussion or justification that a percentage of sirolimus patients have graft function decline (see Key steps and assumptions, above). From the spreadsheet model it becomes clear that 50% of sirolimus patients are

TABLE 26 *Minimum difference (Δ) in mean creatinine concentration (μmol l^{-1}) between sirolimus and alternative immunosuppressive therapy over 3 years of treatment*

	3 months	1 year	2 years	3 years (estimated)
Ciclosporin and tacrolimus (C)	146	150	165	176
Sirolimus (S)	147	132	128	128
Difference (C – S)	–1	18	37	48

TABLE 27 *Results of the cost–utility analysis over 10 years*

	Ciclosporin-based triple therapy	Tacrolimus-based therapy	Rapamune-based therapy
Life-year gained	8.84	8.84	8.86
Life-years gained (discounted)	8.47	8.47	8.48
Cost per life-year gained	£72,646	£82,713	£68,441
Cost per life-year gained (discounted)	£55,493	£63,685	£53,674
Incremental life-years gained	–0.005	–0.007	NA
Incremental cost per life-years gained	–£1,819.72	–£10,011.07	NA
Incremental cost per QALY	–£1,399,784	–£5,500,587	NA

TABLE 28 *Estimation of QALYs by strategy based on company model*

	10-year horizon		
Source parameter	**Sirolimus**	**Tacrolimus**	**Ciclosporin**
Mean years with a functioning graft	7.84	7.11	7.12
Mean discounted years with a functioning graft	7.56	6.72	6.72
Mean years alive	8.86	8.84	8.84
Mean discounted years alive	8.48	8.47	8.47
QALYs: graft			
Graft	5.67	5.04	5.04
Dialysis	0.46	0.88	0.88
Total	6.13	5.92	5.92
Difference	0.22		
%	3.51%		

assumed to have the same decline in renal function as those on ciclosporin and that 27% of patients starting on sirolimus switch within 1 year to ciclosporin, with a further 5% switching in subsequent years. No rationale is provided for these assumptions.

Reliance on creatinine as a proxy for long-term outcomes

As discussed above, this is based on a single, albeit large and peer-reviewed study. The debate between creatinine and acute rejection as predictors of graft survival is controversial and continuing.

Extrapolation of creatinine at 36 months

Considerable effort is put into extrapolating creatinine levels at 36 months, using both the trial data for 12 and 24 months and the UHW data. The reason for this only becomes clear when these data provide the basis of the longer term projections of patient and graft survival.

Extrapolation to 10 and 20 years

The derivation of 10- and 20-year graft and patient survival rates based on models linking creatinine to graft and patient survival at 1, 2 and 3 years is not fully described in the submission. The model extrapolates the 3-year survival curves to 10 years, but the assumptions involved are not explained. Both death.xls and graft GF.xls (where GF is graft failure) rely on curves for 1, 2 and 3 years, with each using extrapolations of the 3-year curve to obtain values for up to 10 years. A single curve is provided for acute rejection over time. It is only from reading the Wyeth submission technical appendix "12.8.2 Renal submission – Manual" that it becomes clear that graft failure for the period beyond 3 years is based on the creatinine levels curve for year 3. How this is done is not explained. An indication of the method is provided in an apparently unpublished paper by McEwan and co-workers, analysing the UHW database, which includes several figures provided in the Wyeth submission (Figures 7.1 and 7.3 are from the McEwan paper without acknowledgment). The latter paper states that these are conventional Kaplan–Meier curves. The same paper appears to be the source of the time from first transplant, but this is not mentioned in the submission.

Costs

The reliance for cost data on the Cardiff database, while welcome in some ways, poses problems in that these costs relate to older regimens, and

include a wide range of costs of treating co-morbidities. Unfortunately, these cannot readily be linked to specific adverse outcomes and thus are not comparable with most of the other models.

Small differences in outcomes leading to unstable ICERs

The differences in life-years and QALYs were small between the different strategies, in the order of 1–3%, which when combined with fairly large cost differences led to high and unstable ICERs. *Table 28* provides estimates of the differences in discounted QALYs between sirolimus and ciclosporin at 10 years. The difference, based on the company model, is 3.3% at 10 years, and a similar analysis for 20 years put the difference at 3.4%.

Comparing company model results

QALY results by model

The section compares the range of QALY gains by model with each other and against the theoretical maximum. The maximum discounted value of 10 years of QALYs at full health (utility 1.0 each year) would be 9.2. However, since patients would at best be in the state of successful transplant, which has a utility value of around 0.8 (depending on the model), the maximum discounted value of 10 years with a transplant is 7.38 (with utility 0.8).

As shown in *Table 29*, for the Novartis model the QALYs amounted to between 83 and 86% of their maximum QALY value. For the Wyeth model the equivalent figures were 88 and 91%. The differences between the models depend largely on the utility values used for transplant and dialysis (0.5 and 0.75 for Wyeth and 0.64 and 0.84 for Novartis).

The striking point is how small the range of QALYs is, at 4% of the mean value in the Novartis model and 3.6% in the Wyeth model. Although the other models did not report the range of their QALYs (owing partly to their emphasis on trials which showed no significant differences in outcomes, and to their interest in exploring cost offsets), their QALY range would be at least as restricted.

Part of the problem is the use of a 10-year time-frame in each of the models, which means that differences in QALYs between drug regimens are unlikely to be large. This is because most patients and grafts survive to 10 years, despite differences in acute rejection between regimens. The problem is that acute rejections are only weakly predictive of longer graft and patient survival.

Utility values

All the company submissions relied heavily on the differences in utility between the states of transplantation and dialysis, rather than on

TABLE 29 *QALY values and range of differences in the models*

			% max.	% max.
	Novartis	**Wyeth**	**Novartis**	**Wyeth**
QALY range				
High	6.7	6.13	86%	91%
Low	6.44	5.915	83%	88%
Difference/mean	4.04%	3.63%		

Values for QALYs for Wyeth were derived. The % max. values refer to the maximum based on the transplant utility values used in each model (Novartis, 0.84; Wyeth, 0.735; Roche, QALYs not provided; Fujisawa, QALYs not provided).

TABLE 30 *Utility values and sources by company*

Health state utility	**Novartis**	**Fujisawa**	**Roche**	**Wyeth**
Transplant	0.84	Not available	0.74	0.73
Haemodialysis	0.65		0.41	0.46
Difference	0.19		0.30	0.27
Source	Hornberger	Booth-Clibborn	Russell *et al.*	Own study (unpublished)
No. of patients	Not known		27	258
Method	Not known		TTO	EQ-5D

differences by immunosuppressive regimen. The reasons for this related to the relatively large and well-established differences due to the former and the lack of supporting evidence for the latter (despite suggestions that the different patterns of sequelae and side-effects of each drug influence patient and clinician preferences).

Each company used a different source for the utility difference between the states of transplantation and dialysis. The sources of these utility values, summarised in *Table 30*, indicate a different source for each company, with the result that the utility gain between transplant and dialysis varied from 0.19 to 0.30, or by over 50%. None of the submissions justified its choice of source (the Novartis submission included a systematic review that focused on utility differences between drug regimens). Fujisawa made relatively little use of quality of life utilities, but referred to estimates compiled by Booth-Clibborn. Roche used a small study by Russell and colleagues, of 27 patients. Wyeth carried out their own study using EuroQol 5 Dimensions (EQ-5D), which despite a 21% response rate had data from 258 patients.

Comparing unit costs by model

This section compares the cost estimates for each model, at the level of unit costs of particular drugs and interventions, cost per drug regimen and total cost per patient.

The unit costs vary between the different models (*Table 31*), with some wide variations, particularly for the most commonly used drugs, ciclosporin, tacrolimus and azathioprine. Ciclosporin had a range (highest to lowest) divided by the mean cost of 27%. For tacrolimus, the Novartis model used a cost that was almost double that of Fujisawa, the parent company. Very different estimates apply to the cost of azathioprine, from £143 per annum by Roche to £1289 per annum by Novartis (both of whom sponsor MMF and MPS as a substitute for azathioprine). One reason for these differences is that Novartis used recommended dosages, whereas the other companies used drug costs as observed in trials (Fujisawa, Roche) or patient databases (Wyeth).

The cost of dialysis showed less variation, all at around £20,000 per annum, but with some differences regarding the percentage of patients on each type of dialysis.

The models differed in the way that they dealt with the cost of graft failure. Two models (Novartis and Roche) included a one-off cost of £11,000–13,000. The Roche model also included a much lower one-off hospital episode associated with acute rejection. Both Wyeth and Fujisawa subsumed the costs of acute rejection under other costs incurred by patients over time followed up.

The Novartis model provides annual drug costs per patient for nine regimens (*Table 32*). The cost of maintenance therapy varied from £4560 to £10,118, and the cost of induction therapy from £1685 to £3608. Since maintenance cost is the main portion of total costs, the fact that the lowest annual cost (almost £5000) was around half of the highest (just over £10,000) is notable.

Total cost per patient over 10 years

The range in the total discounted cost per patient in each drug regimen in each model also varied (*Table 33*). The mean discounted costs per patient were roughly similar in the Novartis and Wyeth models, with a range from £38,000 to £76,000, with a lower cumulative cost per survivor in the Fujisawa model of £23,000 and no comparable data from Roche. The range over the mean was 43% in the Novartis model, 19% in the Wyeth model and 3% in that from Fujisawa (which argued that the higher costs of tacrolimus were offset by reduced health service use). No comparable figures were provided by Roche.

Implications for cost-effectiveness analysis

The wide differences in unit cost for the same drugs between models, along with wide variations in the ratios between the unit costs of drugs in the same regimen, and differences in the range of other costs included, mean that cost-effectiveness comparisons between the models must be handled with caution. This is particularly true where the unit costs for some key comparison drugs are very different, such as for tacrolimus versus ciclosporin and MMF/MPS versus azathioprine.

The wide differences in total cost, combined with small differences in QALYs, mean that incremental cost per QALY estimates are likely to be unstable. Perhaps for this reason, several of the models focused almost entirely on costs, arguing that particular drug regimens were cost saving.

The small differences in outcome result from the literature being based largely on acute rejection at 1 year, or with sirolimus, on graft function at 1 year. Neither of these measures has been shown conclusively to be a reliable predictor of long-term outcomes such as patient or graft survival. As a result, the models have had to rely on single

TABLE 31 *Unit costs (£) used in each model*

Costs	Novartis	Fujisawa	Roche	Wyeth	Range/mean
Drug costs					
Ciclosporin (p.a.)	3,271	2,468	3,063	2,949	0.27
Tacrolimus (p.a.)	6,651	3,461		4,251	0.67
MMF (p.a.)	3,468		3,063		
MPS (p.a.)	3,294				
Basiliximab (once)	1,685				
Daclizumab (once)	3,608				
Sirolimus (maintenance p.a.)	5,450			4,879	
Azathioprine (p.a.)	1,289		143		
Dialysis (average) (p.a.)	23,504			21,060	
Hospital (p.a.)	25,756		22,000		
CAPD (p.a.)	19,736				
Transplant (once)				10,249	
Graft failure (once)	11,225–13,696	13,877–13,522	886		
Cost of functioning graft (p.a.)		4,184			

For Novartis, drug costs are derived from the spreadsheet. The cost of graft failure depends on the ARR. For Roche the costs of azathioprine and MMF were based on a trial, and the cost of ciclosporin on recommended dose. Annual costs per patient for 4 years were based on a trial and followed up via the Cardiff database. For Fujisawa, the drug costs were based on a trial which had 2.5–2.7 years of follow-up, from which annual average drug costs for tacrolimus and ciclosprorin were derived. This trial also provided data on all other drug costs. The data on total cost relate to the cumulative cost per survivor and do not appear to have been discounted. For Wyeth, the drug costs were based on a trial, and other costs from the Cardiff database. The cost of graft failure refers only to hospital treatment. Several other costs associated with maintenance and with graft failure are calculated but do not correspond to the cost headings in the other models.

TABLE 32 *Drug costs by regimen (adapted from Novartis model)*

Immunosuppressive strategy	Cost of maintenance	Cost of induction therapy
Neoral + azathioprine	£4,560	
Tacrolimus + azathioprine	£7,939	
Neoral + MMF or MPS	£6,739	
Tacrolimus + MMF or MPS	£10,118	
Sirolimus (N + S <3 months)[a]	£0	£323
Basiliximab + Neoral + azathioprine	£4,560	£1,685
Basiliximab + Neoral+ MMF or MPS	£6,739	£1,685
Daclizumab + Neoral + azathioprine	£4,560	£3,608
Neoral C_2 monitoring + MMF or MPS	£6,739	

[a] Sirolimus ciclosporin-sparing regimen at 3 months.

TABLE 33 *Total cost per patient over 10 years post-transplant (discounted at 6%)*

	Novartis	Fujisawa	Roche	Wyeth
Total mean cost per patient (discounted) (£)	48,736–76,144	23,803–23,204	NA	51,005–38,527
Range as % mean	43%	3%	NA	19%

studies (Novartis on the Giral study,[168] Wyeth on the Hariharan study[173]) or extrapolation (Roche, Fujisawa). Although the 10-year time-frame contributes to this problem, extension to 20 years, as was included with several models, does not solve the problem in that the differences in QALYs between drug regimens remain small. Only much improved data on the impact of each drug regimen on long-term graft and patient survival will enable the cost-effectiveness of the various strategies to be reliably estimated.

Single model reanalysis or meta-model

Need for a new approach

A new approach was deemed necessary owing to the problems discussed above with each of the company models. These included lack of transparency, lack of schema, not being supplied in 'ready-to-run' format and relatively minor mistakes. The aim was to build on the strengths and insights of each, to run different scenarios and perform sensitivity analyses. The options were either to develop a new model or to adapt one of those submitted. Given the time-frame, the complexity of the topic and the quality of the models submitted, it was decided to adapt one of the submitted models for the present purposes.

Since three out of the four models relied on acute rejection, and the fourth included data on acute rejection, acute rejection was agreed as the key parameter. Acute rejection has been a primary outcome in most trials and has been used widely as a marker for longer term outcomes. Although the authors were aware of the case for using measures of graft function such as serum creatinine as an alternative predictor, the lack of data on serum creatinine for most of the relevant comparisons limited the scope for their use. The decision to focus on acute rejection reduced the options to three. The aim then was to provide a meta-model that explored the relationship between acute rejection and cost per QALY, as well as the factors influencing each of these.

Two criteria were used to select among the three available models. The first was how integrated acute rejection was in each model with other factors such as treatment of rejection, co-morbidities, linkage to duration of graft and patient survival, as well as to costs. Any model in which rejection was linked to some or all of these in a way that was transparent and reasonable was a candidate. Second, to enable the group to build on one of the existing models, that model needed to allow scope for comparing the range of strategies of interest. These two criteria led to the decision to build on the model supplied by Novartis.

The Novartis model had ARR driving graft and patient survival, as well as costs and QALYs. It included five co-morbidities via PTDM in a model previously published in a peer-reviewed paper. It also provided a range of nine therapy options. This provided the basis of what is referred to below as the meta-model.

By contrast, neither the Fujisawa nor the Roche model was driven by acute rejection, as each required additional linkages to be made to run these for different parameter values. The Wyeth model relied on serum creatinine values which were not available for most of the comparisons of interest. It also involved assumptions, some of which were not clear to the present authors.

However, the Novartis model could not be used in precisely the form submitted for the following reasons:

- model errors (double-counting of risk in diabetes patients, lack of half-cycle adjustment)
- results of each simulation run with identical parameter values being slightly different
- reliance on the acute rejection estimates for drugs derived from a Bayesian analysis (see critique above), when the current group's preference was for pairwise comparisons
- lack of clarity regarding the impact that the inclusion of diabetes (the PTDM model) had on results.

After discussion with the model developers, the model errors were corrected. The additional steps that were taken to adapt the Novartis model are outlined in the next section.

Meta-model

A meta-model was desirable for two further reasons, besides rerunning with errors corrected, one to do with simulation models, the other to do with sensitivity analysis. A problem encountered with running any simulation model is that the results vary slightly by run, depending on the complexity of the processes being modelled and the number of 'virtual' patients included in each run. The Novartis model was very complicated and had a recommended run size of 10,000, which meant that each time it was run with its nine strategies, it not only took several hours per strategy, but, worse, each rerun provided results that varied by small but potentially important amounts. For instance, these differences in the first few runs performed were sufficient to reverse the order of some of its comparisons. Each result was 'correct' in that it fell within the confidence interval imposed by the number of virtual patients in each run, but this made it difficult to establish baseline values for comparison. What was required was the population mean underlying each of the sample values from each run. This could only be achieved by running each simulation a considerable number of times.

Without baseline values, sensitivity analysis becomes impossible. Yet any systematic assessment of the relative cost-effectiveness of the various alternative regimens required sensitivity analysis.

One way to surmount these problems, agreed with its designer (Mr Jim Chilcott, ScHARR), was to run the Novartis model repeatedly to provide a sample from which the mean values could be derived. Once the decision had been made to run the model a number of times, the advantages became clear of running it at least once over the full range of acute rejection values. Since the range of acute rejection values suggested in the company submissions spanned 35 points, running the model once for each value would give sufficient results to provide an estimate of a regression line representing the mean value for any particular acute rejection value. Rather than improving the estimate for any single acute rejection rate, the underlying relationship between acute rejection and the outcome of interest could be mapped.

Since acute rejection is driving an integrated, albeit complex set of interactions, it was reasoned that it should have a linear relationship with outputs such as QALYs and costs. The occurrence, or not, of an acute rejection triggers a chain of events, each with an aggregate cost and a QALY value. Increasing the acute rejection by one percentage point has the effect of adding 1% to the relevant output, since each additional patient is identical in the simulation. Thus, a graph of the results of a set of runs that ran systematically through the relevant range of acute rejections would generate a fuzzy line reflecting the random variation by run, with a central estimate and a confidence interval. A straight line could be fitted to this set of points to generate a 'true' meta-line showing the relationship between acute rejection and QALYs. Statistical analysis subsequently confirmed that a straight line was the best fit. Once this line had been derived, a more reliable estimate of its QALY correlate (compared to obtaining the value from one run) could be derived directly from the graph.

The model was run for each acute rejection value from 5 to 39%, and generated the graph shown in *Figure 4*, which also includes the line of best fit. As expected, the line slopes down (negative slope), implying that as acute rejection increases, QALYs decline. The simulation confidence intervals are wide, around ±0.02 QALYs (or around 3%) for each estimate, leading to overlap for adjacent acute rejection estimates.

A similar approach was taken to costs. However, whereas a single line could express the relationship between acute rejection and QALYs, a separate straight line was necessary for each strategy, each with its cost, showing the link between acute rejection and total cost.

The effects of different levels of PTDM were including by running the model for all strategies with a single incidence of 7%. The entire analysis

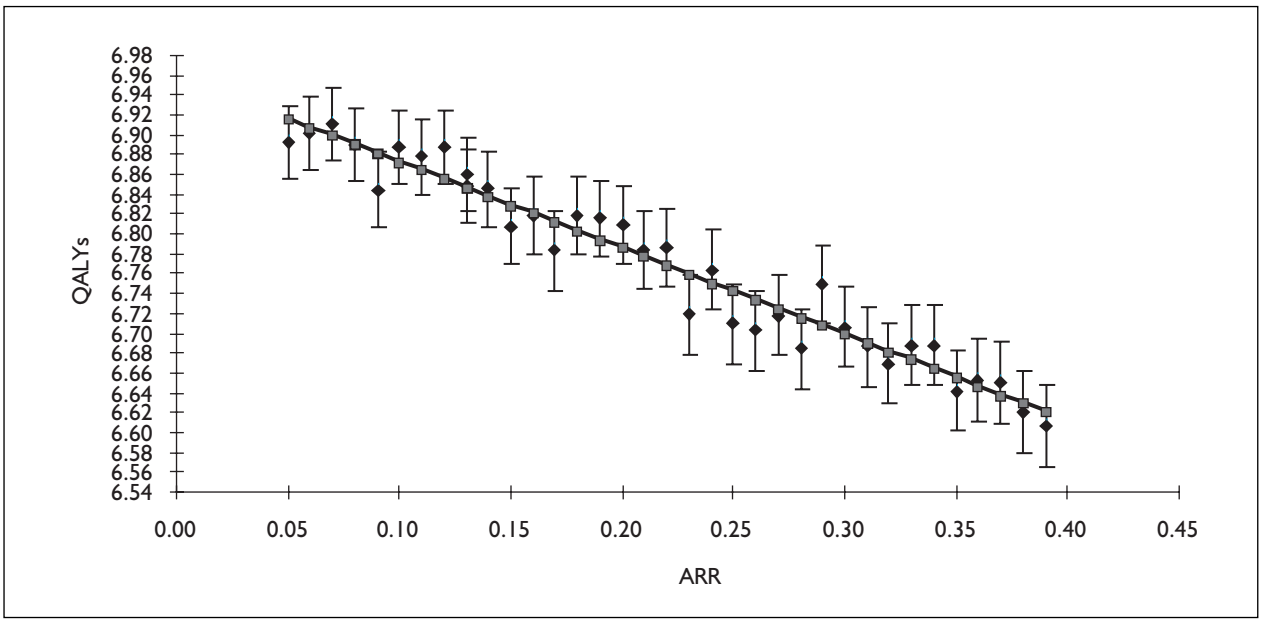

FIGURE 4 *QALYs versus acute rejection rate for PTDM rate at 7%*

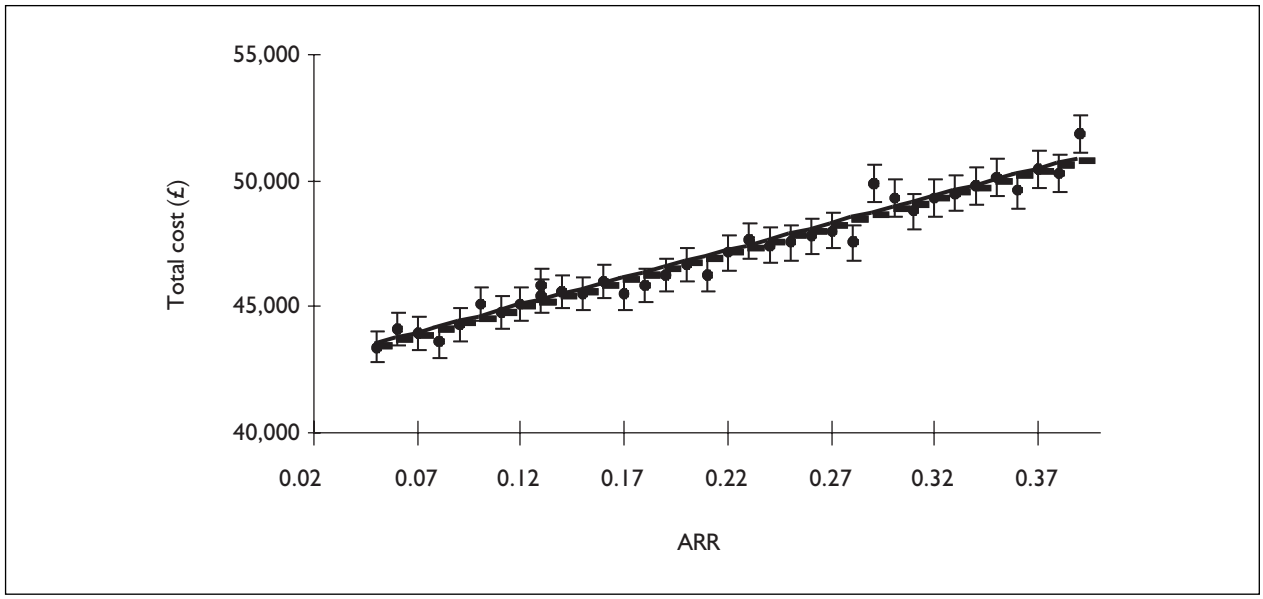

FIGURE 5 *Mean total cost per patient in baseline triple therapy (ciclosporin, azathioprine and steroid) against acute rejection rate*

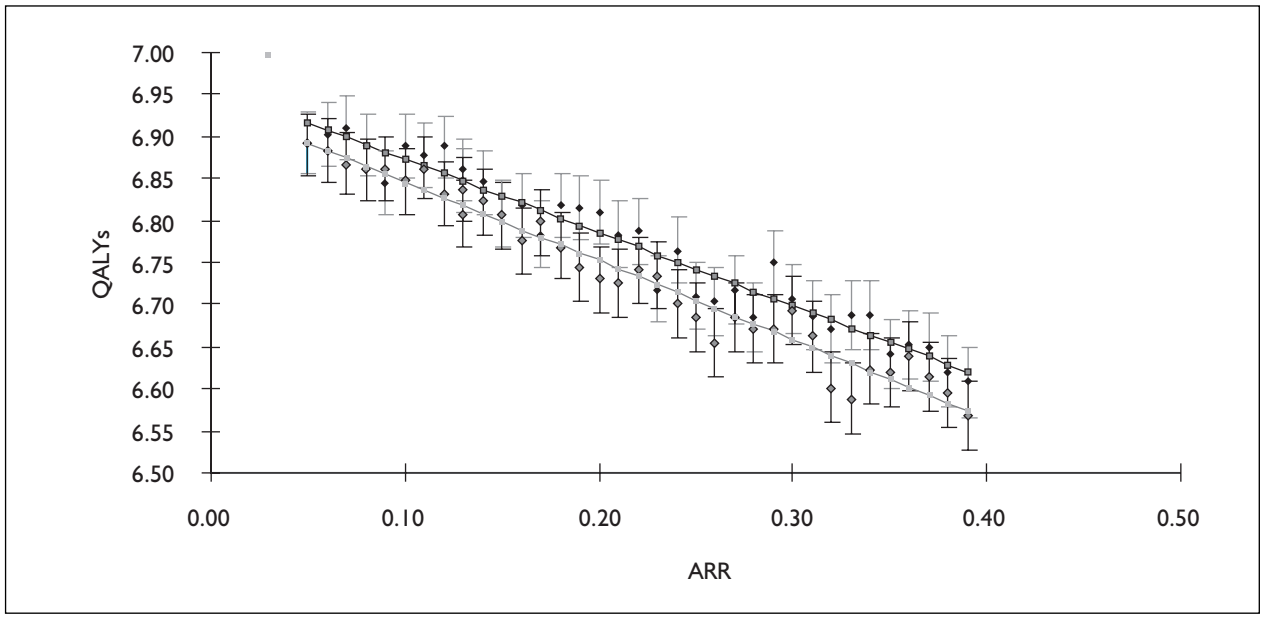

FIGURE 6 *QALY versus acute rejection rate at PTDM incidence of 7% (upper line) and 14% (lower line)*

for cost and QALYs by acute rejection was repeated with the higher (double) value for the incidence of PTDM, as this was the assumption made in the options including tacrolimus.

Similarly, graphs can be shown for total cost, as shown in *Figure 5*. As each of the nine strategies in each run had the same acute rejection value, the QALY value was the same for each. However, as each had different costs, due in part to the different acquisition costs of each drug, a larger number of cost curves was derived. As expected, these show cost increasing with acute rejection.

An integral part of the Novartis model was the inclusion of PDTM, which accounted for much of the complexity of the model. Although PTDM had links to five co-morbidities, in the Novartis model it was allowed to vary between two values, 7% in

general and 14% for maintenance options including tacrolimus. The present strategy was first to explore the impact of diabetes on the meta-relationship between ARR and QALYs (*Figure 6*). The results are as expected, in that the line showing the relationship is worsened for the higher figure of PTDM; in other words, for a given ARR, the QALY gain is worse for the cohort with more diabetes. What is striking is how relatively little difference the inclusion of diabetes makes, which is due to the relatively low incidence in each scenario (7% and 14%).

Similar curves were drawn relating the cost of each drug strategy to acute rejection, but these showed little difference between the costs of each strategy owing to offsetting trends.

In any comparison between two drug regimens, for each change in QALY there is also a change in cost. For any acute rejection level one can read off both cost and QALYs and put these in incremental terms, as shown in *Table 35*.

Parameter values for the meta-model

As discussed above, the Novartis model ran nine strategies, each with a different acute rejection value based on the Bayesian synthesis. Two different values for the incidence of PTDM were also included (double the rate for strategies including tacrolimus). Given the caveats regarding the Bayesian results, due to combining the results of all possible arms of different trials, the current approach was to focus on pairwise comparisons, combining the values from closely related trials. Besides providing more robust estimates, this also allowed confidence intervals based on those trials to be included.

The meta-model described above could be used to fit high and low estimates around the mean QALY differences, but less readily to the cost differences of pairwise comparisons. This was because the acute rejection/QALY line was the same for all strategies having the same incidence of PTDM, but the acute rejection/cost line varied by strategy. When two lines were involved, mapping mean absolute acute rejections on to two cost lines requires additional assumptions, which reduce the precision of the estimates.

Table 34 shows the best pairwise estimates from the systematic reviews of the ARRs, along with difference and 95% confidence intervals. The comparisons differ from those put forward by Novartis and other companies in several ways. First, both variants of ciclosporin, Sandimmun and Neoral, are compared with tacrolimus (both with azathioprine and with MMF). Second, the confidence intervals are based directly on analysis of the relevant trials rather than on the Bayesian synthesis. Third, where no trials have compared the therapies, no values are produced (Bayesian synthesis provides values by indirect comparison). Thus, sirolimus and ciclosporin with C_2 monitoring have no trials, and hence no evidence.

QALYs and costs from acute rejection rate

Table 35 takes the acute rejection values from *Table 34* and expresses them in terms of both QALYs and costs, using *Figures 4–6*. The cost and QALY estimates are combined into ICERs and marginal net benefits for each comparison. Net benefits take a threshold value of cost per QALY and express the net benefit as (QALY ×Threshold £/QALY) – cost. Thus, if 10 QALYs are generated at a cost of £200,000, net benefit = (10 ×£30,000) – £200,000 = 100,000. The advantage of net benefit is that it avoids the very high positive values of ICERs that can result from dividing costs by QALY gains that are close to zero. Confidence intervals can be interpreted in move conventional ways.

A number of points need to be made about the confidence intervals and range estimates in *Table 33*. First, the confidence intervals around the acute rejections cannot be mapped directly to the QALYs, but can be used to generate high and low estimates when the same levels of diabetes are being compared. This applies to options 4–7 in *Table 35*. Different levels of diabetes are assumed, however, when tacrolimus is being compared with ciclosporin-based regimens. Consequently, the high and low estimates are being generated from different curves (see *Figure 6*), which reduces their precision in options 1–3 in *Table 35*. Second, the same problem applies more generally to costs as each drug regimen has a different cost and hence a different line linking cost and acute rejection. As a result, high and low estimates are provided for QALYs, but not for costs.

The ICER results, shown at the bottom of *Table 35*, indicate that basiliximab retains a negative ICER only if compared to ciclosporin plus azathioprine, and not if compared to placebo with ciclosporin plus MMF (when its ICER ranges from positive to negative). This is in direct contrast to the Novartis results. The value of the ICERs varies between £78,000 and £241,000.

TABLE 34 *Summary of results of Birmingham systematic reviews*

Strategy[a]	**n**[b]	**Tacrolimus % ARR**[g]	**Ciclosporin % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
Tacrolimus vs Neoral (with AZA)	3	20.0%	38.9%	–19% (–13 to –25%)	0.39 (0.29 to 0.54)
Tacrolimus vs Neoral (with MMF)	3	12.0%	16.5%	–5% (–12 to +3%)	0.69 (0.36 to 1.32)
Tacrolimus vs Neoral (all trials)	7	18.4%	32.0%	–14% (–9 to –19%)	0.44 (0.33 to 0.58)
Tacrolimus vs Sandimmun (with AZA)	5	22.7%	41.0%	–17% (–22 to –11%)	0.46 (0.36 to 0.61)
		Daclizumab % ARR[g]	**Placebo % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
Daclizumab vs placebo[c]	2	25.2%	40.8%	–16% (–24 to –8%)	0.47 (0.32 to 0.67)
		Basiliximab % ARR[g]	**Placebo % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
Basiliximab vs placebo (AZA + Neoral)	2	20.2%	32.8%	–13% (–21 to –4%)	0.50 (0.31 to 0.80)
Basiliximab vs placebo (MMF + Neoral)	1	15.3%	25.0%	–10% (–24 to +4%)	0.91 (0.38 to 2.14)
Basiliximab vs placebo (Neoral only)	2	34.7%	50.8%	–16% (–23 to –9%)	0.51 (0.38 to 0.68)
Basiliximab vs placebo (all trials)[d]	5	28.4%	41.9%	–14% (–20 to –9%)	0.51 (0.40 to 0.65)
		MMF % ARR[g]	**AZA % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
MMF vs AZA (with ciclosporin)[e]	5	19.4%	34.0%	–14% (–21 to –10%)	0.45 (0.34 to 0.59)
MMF vs AZA (with tacrolimus)	2	11.8%	25.3%	–16% (–32 to +1%)[f]	0.43 (0.10 to 1.84)[f]
MMF vs AZA (all trials)	7	17.8%	32.2%	–15% (–19 to –11%)	0.42 (0.32 to 0.55)
		Sirolimus % ARR[g]	**Ciclosporin % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
Sirolimus vs ciclosporin Sirolimus vs tacrolimus Sirolimus vs MMF	0	No trials identified			
		Neoral + C_2 % ARR[g]	**Neoral + trough % ARR**[g]	**Difference Mean (95% CI)**	**OR Mean (95% CI)**
Neoral C_2 vs Neoral trough	0	No trials identified			

[a] All strategies include steroid.
[b] Number of trials.
[c] Includes one additional trial where patients could receive AZA or MMF.
[d] Does not include 'no therapy' trials.
[e] Ciclosporin, either Sandimmun or Neoral.
[f] Random effects pooling (significant heterogeneity).
[g] Acute rejection rate; corresponds to BPAR rate.

TABLE 35 *Acute rejection rate comparisons, QALYs, costs, ICERs and net benefit*

Intervention comparator with option	Tacrolimus Sandimmun Azathio-prine 1	Tacrolimus Neoral Azathio-prine 2	Tacrolimus Neoral MMF 3	MMF Azathio-prine Neoral 4	MMF Azathio-prine Tacrolimus 5	Basiliximab Placebo Neoral + AZA 6	Basiliximab Placebo Neoral+ MMF 7
ARR							
Intervention	23	20	12	19	12	20	19
Comparator	41	39	17	34	25	33	20
Difference	17	19	5	14	16	13	1
Upper 95% CI	22	25	12	21	32	21	14
Lower 95% CI	11	13	–3	10	–1	4	–12
QALYs							
Intervention	6.734	6.730	6.833	6.816	6.833	6.810	6.816
Comparator	6.583	6.608	6.783	6.688	6.685	6.688	6.810
Difference	0.151	0.123	0.049	0.128	0.147	0.122	0.006
Upper estimate	0.180	0.228	0.051	0.192	0.295	0.196	0.083
Lower estimate	0.048	0.082	–0.072	0.091	–0.009	0.037	–0.071
Costs							
Intervention	67,227	67,227	78,889	58,767	78,889	47,053	60,176
Comparator	53,670	53,670	58,040	48,746	67,308	48,362	59,126
Difference	13,557	13,557	20,849	10,021	11,581	–1,309	1,051
ICER (£/QALY)							
Difference	89,611	110,626	421,382	78,249	78,593	–10,773	178,233
Upper estimate	75,429	59,548	405,453	52,166	39,297	–6,669	12,731
Lower estimate	284,449	166,112	–288,622	109,549	–1,257,496	–35,012	–14,853
Net benefit at £30,000							
Intervention	134,794	134,681	126,089	145,706	126,089	157,243	144,296
Comparator	143,812	144,562	145,454	151,884	133,249	152,287	145,170
Marginal net benefit	–9,018	–9,881	–19,365	–6,179	–7,160	4,955	–874
Upper estimate	–8,165	–6,727	–19,307	–4,258	–2,740	7,199	1,425
Lower estimate	–12,127	–11,109	–23,017	–7,277	–11,857	2,431	–3,173

Net benefit

The results in net benefit terms confirm this result, with only basiliximab versus placebo in a Neoral plus azathioprine regimen showing a marginal net benefit of just over £5000 at a threshold cost per QALY of £30,000, with high and low estimates that remain positive. For all the other comparisons, the marginal net benefit is negative and the high–low range, although generally wide, tends not to cross zero, except for option 7 (basiliximab versus placebo in the Neoral plus MMF regimen).

Conclusions on meta-modelling

The following conclusions may be drawn from the results based on the meta-model.

- The present cost-effectiveness estimates differ considerably from those presented by the companies.
- The cost-effectiveness of basiliximab may be attractive, but is dependent on the adjuvant therapy used. In comparison to a Neoral and azathioprine triple-therapy regimen, basiliximab is dominant (cost saving and greater QALYs). Compared to Neoral and MMF triple therapy, the basiliximab ICER is much less attractive.
- For all other drug comparisons the ICERs are high, ranging from £78,000 to almost £250,000.
- The Sandimmun formulation of ciclosporin has a similar cost-effectiveness to the Neoral formulation, as far as one can judge from the indirect comparisons made for each against tacrolimus.
- The assumptions regarding side-effects due to diabetes have relatively little impact on QALY gains and even less on costs.
- There is no direct RCT evidence on the effectiveness of replacing ciclosporin with sirolimus or on ciclosporin with C_2 monitoring compared to ciclosporine with trough

monitoring. It is therefore not possible to estimate the cost-effectiveness of these interventions.
- The cost-effectiveness estimates are highly sensitive to the ARR used for each drug. Reliance on the direct RCT comparisons rather than the indirect Bayesian synthesis reduces the advantages shown from many of the comparisons made in the Novartis model. Use of the meta-model to translate the trial estimates into cost per QALY produced different and generally higher values than in the Novartis model.
- Very high and unstable results can be generated when small QALY increments between drug comparisons are combined with costs, leading to high values that can switch from negative to positive cost-effectiveness. This is an inherent problem with ratios.
- Use of net benefit solves some of the problems with ICERs and confirms the above results.

Owing to restrictions with the meta-model approach, high and low estimates could be fitted only to QALYs, not to costs. The results of this in terms of ICERs and net benefits showed generally wide uncertainty around the point estimates.

More generally, although the use of the meta-model has advantages in enabling different drug regimens to be compared in some detail, it cannot solve the underlying problem that small QALY gains are projected in all models for all drug regimens. Although each company made the case for the drug that it was sponsoring, the meta-model does not support these claims, with the single exception of basiliximab as an addition to a ciclosporin and azathioprine-based triple therapy. The reasons for the favourable results in the company models are discussed above in the relevant sections. The key point here is that those claims, with the sole exception of basiliximab in Neoral/ciclosporin triple therapy, are not supported by the meta-model.

Chapter 7

Implications for other parties

This review indicated that a number of the newer immunosuppressive drugs have important benefits in terms of a reduction of acute rejection episodes in renal transplant recipients. The long-term impact of these drugs on both long-term graft and patient survival is less clear. As each drug is associated with a variety of different side-effects, the potential benefits of these newer drugs in terms of the quantity and quality of life of patient life are also uncertain.

Chapter 8

Factors relevant to the NHS

Kidney transplantation is the treatment of choice for patients with ESRF: if it is successful, the quality and duration of life are better than achieved with long-term dialysis. Given the finite supply of donors, there is therefore a need to identify drug therapies that both minimise short-term immunosuppression and maximise the life of the graft.

There is no current national clinical guideline for the selection of renal immunosuppressant drugs for renal transplantation. A recent audit of the transplant units across the UK illustrates the wide range of immunosuppressive drug strategies currently used for adult and paediatric renal transplant recipients.

Several of the combinations of drugs or individual drugs assessed in RCTs are not currently licensed in the UK for use in these indications (e.g. the use of sirolimus or MMF with tacrolimus adjuvant therapy).

Chapter 9
Conclusions

Statement of principal findings

The main findings of the systematic review of RCT evidence and cost-effectiveness modelling of the newer immunosuppressive drugs for renal transplantation are as follows.

Induction therapy

Basiliximab reduced the incidence of BPAR at 6 and 12 months compared to placebo, but not compared to other induction agents (either ATG or OKT3). There was no significant gain in either patient survival or graft loss. There was no evidence of an increase in major side-effects with basiliximab. Two published cost-effectiveness analyses indicated that basiliximab was cost-effective compared to placebo. Neither of these economic analyses was conducted from the perspective of the NHS. The present modelling analysis showing the incremental cost implications indicates that the addition of basiliximab is a potentially cost-effective option, although this depends on the background triple therapy regimen; it is more clinically effective, and therefore more cost-effective, when combined with a ciclosporin and azathioprine regimen than a ciclosporin and MMF regimen. Given that this drug is a one-off therapy, its availability is likely to have only a small budget impact on the NHS (up to an additional £2.4 million per annum, in England and Wales).

In comparison to placebo, daclizumab improved both 6- and 12-month BPAR rate and patient survival. There was no improvement in single graft loss or the incidence of major side-effects at 1 year with daclizumab. Compared to OKT3 there was no difference in outcomes. No direct head-to-head RCT comparisons between basiliximab and daclizumab were found. The evidence for the cost-effectiveness of daclizumab was limited to one non-UK study. The drug cost of daclizumab was considerably greater than that of basiliximab.

Initial and maintenance therapy

Tacrolimus reduced the incidence of biopsy-confirmed acute rejection episodes compared to ciclosporin. There was no significant improvement in either 1-year or long-term (up to 5 years) patient survival or graft loss. The magnitude of the acute rejection benefit of tacrolimus was equivalent for the two formulations of ciclosporin (Sandimmun and Neoral). There were important differences in the side-effect profile of tacrolimus and ciclosporin. For example, tacrolimus increases the incidence of PTDM, whereas ciclosporin causes hirsutism. There was a wide discrepancy in both the published and company estimates comparing the cost-effectiveness of tacrolimus and ciclosporin. The modelling analysis indicated that the cost-effectiveness of tacrolimus is relatively unattractive in comparison to ciclosporin (either Sandimmun or Neoral), regardless of the adjuvant therapy (i.e. azathioprine or MMF).

MMF reduced the 6- and 12-month BPAR rate compared to azathioprine. There was no improvement in 1-year patient survival and graft loss with MMF. Although there was some evidence of an improvement in patient survival and graft loss with MMF at 3 years, this improvement was not statistically significant. Published cost-effectiveness analyses have shown that at 1-year post-transplant, MMF is a cost-effective substitute for azathioprine in initial and maintenance immunosuppressant renal transplant therapy. The modelling analysis indicated that the cost-effectiveness of tacrolimus plus MMF was less attractive and depended on how treatment costs are offset.

Compared to azathioprine, MPS appeared to be similar in clinical effect to MMF. This is based on a single RCT. On the basis of an assumption of clinical equivalence to MMF, a relatively attractive cost-effectiveness estimate for MPS was presented by the sponsor. Taking the same assumption, the present modelling indicated that the cost-effectiveness of MPS was likely to be similar to MMF and therefore unattractive.

The positioning of sirolimus in current immunosuppressive therapy for renal transplantation is relatively unclear. Several RCTs were undertaken to evaluate the use of sirolimus in a variety of regimens. Although the company proposed that sirolimus can be used as a ciclosporin-sparing agent, no RCT was identified that has directly addressed this. The cost-effectiveness of sirolimus in initial/maintenance therapy therefore also remains highly uncertain.

The independent use of basiliximab, daclizumab, tacrolimus and MMF each appeared to be associated with a similar absolute reduction in 1-year acute rejection rate (i.e. approximately 15%). However, the effects of these drugs did not appear to be additive (e.g. benefit of tacrolimus with adjuvant MMF is 5% reduction in acute rejection rate compared with 15% reduction with adjuvant azathioprine). Thus, the addition of the one of these drugs to a baseline immunosuppressant regimen is likely to affect adversely the incremental cost-effectiveness of the addition of another.

Treatment of acute rejection episodes

Both tacrolimus and MMF offered clinical benefit as therapies for the treatment of acute rejection. Both reduced the incidence of subsequent acute rejection episodes and the need for additional drug therapy in patients experiencing acute rejection. However, the cost-effectiveness of the use of either drug in the treatment of acute rejection has not been examined in prior publications or in any of the industry models. There is currently no RCT evidence for the use of any of the other newer immunosuppressant drugs in the treatment of acute rejection.

Strengths and limitations of the review

This review has two major strengths.

- It was a comprehensive and systematic review that brought together the evidence for clinical and cost-effectiveness of the each of the newer immunosuppressant drugs for renal transplantation, based on direct drug comparisons and applying consistent methods of critical appraisal and presentation.
- The development and adaptation of a cost-effectiveness model enabled the explicit linkage of the clinical results of the systematic review and cost–utility for each drug.

In contrast, certain limitations were placed on the review.

- The review was restricted to a systematic review of RCT evidence. Although it was recognised that observational studies (such as registries) could provide useful additional information, it was felt that the included designs provided the most appropriate, unbiased evidence for assessing clinical effectiveness. Given the substantial number of RCTs identified and the limited timescale of the review, the authors believe that this restriction was justifiable.
- To estimate long-term effectiveness (and cost-effectiveness), extrapolation from trial 1-year ARR to graft survival was undertaken.
- It is plausible that the clinical effectiveness and therefore the cost-effectiveness of immunosuppressant drugs may vary across particular groups, in particular high-risk groups (e.g. poorly HLA-matched graft recipients, non-heart-beating donor graft recipients, recipients with high panel reactivity, African–American origin recipients and recipients from graft donors aged over 65 years) and children. Few of the included studies undertook a subgroup analysis and only a small number were conducted solely in children or included children. None of the industry cost-effectiveness models examined the relative cost-effectiveness of the newer immunosuppressant drug regimens in patient subgroups.
- The lack of both quality of life data and long-term follow-up in the trials made modelling necessary to assess the long-term cost–utility of individual drugs and drug regimens. A key assumption in the cost-effectiveness modelling framework of this review is the linkage between ARR, graft and patient survival, quality of life and costs. The selection of acute rejection is supported by a systematic review of potential prognostic predictors for graft survival (Novartis submission, Addendum 7). The authors recognise that the prediction of graft survival from ARRs is widely debated. An alternative outcome that has been proposed is graft function (e.g. serum creatinine). The principal advantage of acute rejection is that it was consistently reported across the trials.
- The small gains in incremental quality of life utility observed from modelling are likely to lead to a high degree of uncertainty around the estimates of cost per QALY as presented in this report.

Other issues

The scope of this review was to examine the role of the newer immunosuppressant drugs within induction therapy, initial and maintenance therapy, and treatment of acute rejection. It is recognised that within current clinical practice there is a move towards regimens that may incorporate drug switching or drug tapering within the maintenance phase. This is a developing area of clinical practice and is therefore not directly addressed in this review.

Implications for future research

In undertaking this review of the newer immunosuppressant drugs for renal transplantation, two particular areas for future research were identified.

Clinical trials

The majority of trials to date have been designed solely with drug licensing in mind and are powered to examine short-term changes in clinical outcome such as ARR. Only a very small proportion of the RCTs identified in this review assessed patient-focused outcomes such as quality of life. Since immunosuppressive drugs have both clinical benefits and specific side-effects, the balance of these harms and benefits could best be quantified through future trials using quality of life measures. The design of future trials should be considered with a view to the impact of drugs on particular renal transplant groups, particularly higher risk individuals and children. Finally, there is a need for improved reporting of methodological details of future trials, such as the method of randomisation and allocation concealment.

Registry data

A number of the issues in this field make RCTs difficult to design and undertake. Two particular problems are the use of multiple drug regimens, making head-to-head or incremental drug comparisons very difficult, and the need to assess the long-term outcomes. An alternative option is the use of observational registry data. If possible, such a register should include prospective data on all consecutive UK renal transplant patients. Data capture for each patient should include immunosuppressant regimens (including changes to these regimens), clinical and patient-related (e.g. quality of life) outcomes and patient demographics (e.g. risk status and age group).

Acknowledgements

We gratefully acknowledge the assistance of the following individuals for their clinical advice, methodological advice and comments on drafts of the report: Dr Philip Dyer (Consultant Clinical Scientist, Honorary Reader in Transplantation Science, Transplantation Laboratory, Manchester Institute of Nephrology & Transplantation, Manchester Royal Infirmary, UK), Dr David Milford (Consultant Paediatric Nephrologist, Birmingham Children's Hospital), Dr David Braunholtz (Senior Research Fellow, Department of Public Health and Epidemiology, University of Birmingham, UK), Mr Pelham Barton (Health Economics Facility, Health Services Management Centre, University of Birmingham, UK) and the late Mr AK Duggan (Managing Director, Abacus International, UK).

External peer reviewers

Dr Kesh Baboolal (Consultant Nephrologist, University Hospital, Cardiff), Mr Christopher Watson (Consultant Surgeon, Addenbrooke's Hospital, Cambridge) and Dr Nicholas Webb (Consultant Paediatric Nephrologist, Royal Manchester Children's Hospital, Manchester).

Acknowledgement of assistance does not necessarily imply agreement with the contents and conclusions of the report.

This report was commissioned by the NHS R&D HTA programme.

Contributions of authors

Rebecca Woodroffe (Systematic Reviewer) undertook project coordination and the systematic review of clinical and cost-effectiveness. Catherine Mead (Research Officer) undertook the systematic review of clinical effectiveness and drafting of the background section, and Lily Yao (Research Fellow in Health Economics) carried out assessment of industry models, model checking, quality assurance and the development and running of the 'meta-model'. Andrew Ready (Consultant Surgeon) gave direction and advice on clinical aspects of the report, and Susan Bayliss (Information Specialist) formulated and ran literature searches. James Raftery (Professor of Health Economics) undertook cost-effectiveness modelling, the cost-effectiveness review and drafting of sections of the report, and Rod Taylor (Senior Lecturer in Public Health and Epimemiology) carried out overall project management, systematic review of clinical and cost-effectiveness, statistical analysis and general report drafting.

Publication information: about home unit

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3–6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost–utility analysis) of the intervention.

References

1. Henderson L. Future developments in the treatment of ESRD. A North American perspective. *Am J Kidney Dis* 2000;**35**(4 Suppl 1):S106–16.
2. Wicks MN, Milstead EJ, Hathaway DK, Cetingok M. Family caregivers' burden, quality of life, and health following patients' renal transplantation. *Journal of Transplant Coordination* 1998;**8**:170–6.
3. Opelz G, for the Collaborative Transplant Study. Evaluation of immunosuppressive induction regimes in renal transplantation. *Transplant Proc* 1998;**30**:4029–30.
4. Mallick NP. The costs of renal services in Britain. *Nephrol Dial Transplant* 1997;**12**(Suppl 1):25–8.
5. National Institute for Clinical Excellence. *The clinical and cost effectiveness of home compared with hospital haemodialysis for patients with end-stage renal failure*. London: NICE. URL: http://www.nice.org.uk. Accessed December 2002.
6. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. *N Engl J Med* 2002;**346**:580–90.
7. Vella J, Sayegh M. Risk factors for graft failure in kidney transplantation. UpToDate at URL: http://www.uptodate.com/totm/JASN/Oct-02/topics/11450R0.htm. Accessed October 2002.
8. Pirsch J. Bench to bedside, ischemia and reperfusion injury in clinical transplantation. Conference Report, ASTS Second Annual Winter Symposium 2002. 25–27 January 2002, Miami Beach, FL, USA.
9. Pagtalunan ME, Olson JL, Tilney NL, Meyer TW. Late consequences of acute ischemic injury to a solitary kidney. *J Am Soc Nephrol* 1999;**10**:366–73.
10. UK Renal Registry Year Report 2001. URL: http://www.renalreg.com/RR.htm. Accessed October 2002.
11. United Kingdom Guidelines for Living Donor Kidney Transplantation. URL: http://www.bts.org.uk/standards.htm. Accessed September 2002.
12. Perico N, Remuzzi G. Prevention of transplant rejection: current treatment guidelines and future developments. *Drugs* 1997;**54**:533–70.
13. Mauiyyedi S, Crespo M, Collins AB, Schneeberger EE, Pascual MA, Saidman SL, *et al*. Acute humoral rejection in kidney transplantation: II. Morphology, immunopathology, and pathologic classification. *J Am Soc Nephrol* 2002;**13**:779–87.
14. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int* 1996;**49**:518–24.
15. Aalamain Z. Reducing adverse effects of immunosuppressive agents in kidney transplant recipients. *Progress in Transplantation* 2001; **11**:271–82.
16. Towards standards for organ and tissue transplantation in the United Kingdom. URL: http://www.bts.org.uk/standards.htm. Accessed October 2002.
17. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. *J Am Soc Nephrol* 2000;**11**:1910–17.
18. URL: http://uktransplant.org/. Accessed October 2002.
19. National Kidney Federation. URL: http://www.kidney.org.uk/. Accessed September 2002.
20. Renal Association. *Treatment of patients with renal failure – Recommended standards and audit measures*. 3rd ed. British Association for Paediatric Nephrology. URL: http://bapn.uwcm.ac.uk/.
21. Meier-Kriesche H, Arndorfer J, Kaplan B. Association of antibody induction with short- and long-term cause-specific mortality in renal transplant patients. *J Am Soc Nephrol* 2002;**13**:769–72.
22. Vincenti F. Grand rounds in transplantation: polyclonal vs monoclonal antibody induction therapy in solid organ transplantation. CME at URL: http://www.medscape.com/viewprogram/2075
23. Raimondo M, Burroughs A. Single-agent immunosuppression after liver transplantation: what is possible? *Drugs (New Zealand)* 2002; **62**:1587–97.
24. Chisholm MA. Impact of clinical pharmacy services on renal transplant patients compliance with immunosuppressive medications. *Clin Transpl* 2001;**15**:330–6.
25. Smith J, McDonald R. Progress in renal transplantation for children. *Adv Ren Replace Ther* 2000;**7**:158–71.

26. Bock H. Steroid-resistant kidney transplant rejection: diagnosis and treatment. *J Am Soc Nephrol*, 2001;**12** Suppl 17:S48–52.

27. Samsonov D, Briscoe D. Long-term care of pediatric renal transplant patients: from bench to bedside. *Curr Opin Pediatr* 2002;**14**:205–10.

28. Andoh T, Burdmann E, Bennet W. Nephrotoxicity of immunosuppressive drugs: experimental and clinical observations. *Semin Nephrol* 1997;**17**:34–45.

29. Moudgil A, Jordan S. Renal transplantation in infants and children. *Indian J Pediatr* 1999; **66**:263–75.

30. Ninik A, McTaggart SJ, Gulati S, Powell HR, Jones CL, Walker RG. Factors influencing growth and final height after renal transplantation. *Pediatr Transplant* 2002;**6**:219–23.

31. Hoyer P, Vester U. Refining immunosuppressive protocols in pediatric renal transplant recipients. *Transplant Porc* 2001;**33**:3587–9.

32. Gorantla VS, Barner JH, Jones JWJ, Prabhune K, Maidonado C, Granger DK, *et al*. Immunosuppressive agents in transplantation: mechanisms of action and current anti-rejection strategies. *Microsurgery* 2000;**20**:420–9.

33. Smith S. Immunosuppressive therapies in organ transplantation from organ transplantation: concepts, issues, practice, and outcomes. URL: http://www.medscape.com/viewarticle/437182. Accessed September 2002.

34. British National Formulary. BNF 44. URL: http://www.bnf.org/. Accessed November 2002.

35. British Transplant Society Submission to NICE. The clinical effectiveness and cost effectiveness of immunosuppressive therapy for renal transplantation. London: NICE; October 2002.

36. National Institute for Clinical Excellence. Immunosuppressive therapy for renal transplantation. London: NICE; September 2002.

37. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.

38. British Medical Journal. Guidelines for authors and peer reviewers of economic submissions. URL: http://bmj.com/advice/checklists.shtml#eco. Accessed October 2002.

39. National Institute for Clinical Excellence. Early thrombolysis for the treatment of acute myocardial infarct. HTA Report. URL: http://www.nice.org.uk. Accessed October 2002.

40. Wiseman LR, Faulds D. Daclizumab: a review of its use in the prevention of acute rejection in renal transplant recipients. *Drugs* 2000;**59**:476.

41. Ekberg H, Backman L, Tufveson G, Tyden G. Zenapax (daclizumab) reduces the incidence of acute rejection episodes and improves patient survival following renal transplantation. No 14874 and No 14393 Zenapax Study Groups. *Transplant Proc* 1999;**31**:267–8.

42. Ekberg H, Backman L, Tufveson G, Tyden G, Nashan B, Vincenti F. Daclizumab prevents acute rejection and improves patient survival post transplantation: 1 year pooled analysis. *Transpl Int* 2000;**13**:151–9.

43. Bumgardner GL, Hardie I, Johnson RW, Lin A, Nashan B, Pescovitz MD, *et al*., Phase III Daclizumab Study Group. Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001;**72**:839–45.

44. Vincenti F, Nashan B. Daclizumab: outcome of Phase III trials and mechanism of action. *Transplant Proc* 1998;**30**:2155–8.

45. Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P, *et al*. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998;**338**:161–5.

46. Nashan B, Light S, Hardie IR, Lin A, Johnson JR. Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 1999;**67**:110–15.

47. Charpentier B. Induction versus noninduction protocols in anticalcineurin based immunosuppression. *Transplant Proc* 2001; **33**:3334–6.

48. Lacha J, Simova M, Noskova L, Teplan V, Vitilo S *et al*. Zenapax versus OKT3 prophylaxis in immunologically high risk kidney transplant recipients. *Transplantation* 2000;**69**(S158): Abstract 174.

49. Lacha J, Simova M, Noskova L, Teplan V, Vitko S. Zenapax versus OKT-3 prophylaxis in immunologically high-risk kidney transplant recipients. *Transplant Proc* 2001;**33**:2273–4.

50. Thistlethwaite JR Jr, Nashan B, Hall M, Chodoff L, Lin T-H. Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. *Transplantation* 2000;**70**:784–90.

51. Mulloy LL, Wright F, Hall ML, Moore M. Simulect (basiliximab) reduces acute cellular rejection in renal allografts from cadaveric and living donors. *Transplant Proc* 1999;**31**:1210–13.

52. Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillou JP. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group [published erratum appears in *Lancet* 1997;**350**:1484]. *Lancet* 1997;**350**:1193–8.

53. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation* 1999;**67**:276–84.

54. Onrust SV, Wiseman LR. Basiliximab. *Drugs* 1999;**57**:207–13.

55. Ponticelli C, Yussim A, Cambi V, Legendre C, Rizzo G, Salvadori M, *et al*., Simulect Phase IV Study Group. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001;**72**:1261–7.

56. Folkmane I, Bicans J, Chapenko S, Murovska M, Rosentals R. Results of renal transplantation with different immunosuppressive regimens. *Transplant Proc* 2002;**34**:558–9.

57. Sollinger H, Kaplan B, Pescovitz MD, Philosophe B, Roza A, Brayman K, *et al*. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. *Transplantation* 2001; **72**:1915–19.

58. Lebranchu Y, *et al*. A multicentre randomized trial of simulect versus thymoglobulin in renal transplantation. *Transplantation* 2000;**69**(S258): Abstract 567.

59. Lawen J, *et al*. Basiliximab (Simulect) is safe and effective in combination with triple therapy of Neoral, steroids and Cellcept in renal transplant recipients. *Transplantation* 2000;**69**(S260): Abstract 572.

60. Shidban H, *et al*. Controlled trial of IL2R antibody basiliximab (Simulect) vs low dose OKT3 in cadaver kidney transplant recipients. *Transplantation* 2000;**69**(S156): Abstract 164.

61. Knoll GA, Bell RC. Tacrolimus versus ciclosporin for immunosuppression in renal transplantation: meta-analysis of randomised trials. *BMJ* 1999; **318**:1104–7.

62. Booth-Clibborn N, *et al*. *Tacrolimus after kidney transplantation*. Development and Evaluation Committee Report No. 74. Wessex Institute for Health Research and Development; 1997.

63. Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Guidance Note for Purchasers 99/07. Sheffield: Trent Institute for Health Services Research; 1999.

64. Morris-Stiff G, Richards T, Singh J, Baboolal K, Balaji V, Ostrowski K, *et al*. Pharmaco-economic study of FK 506 (Prograf) and cyclosporin A Neoral in cadaveric renal transplantation. *Transplant Proc* 1998;**30**:1285–6.

65. Neylan JF, Sullivan EM, Steinwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus cyclosporin. *Am J Kidney Dis* 1998;**32**:770–7.

66. Plosker G, Foster R. Tacrolimus. Adis drug evaluation. *Drugs* 2000;**59**:323–89.

67. Peters D. Tacrolimus. *Drugs* 1993;**46**:746–9.

68. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and ciclosporin for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997; **63**:977–83.

68. Miller J, Pirsch JD, Deierhoi M, Vincenti F, Filo RS. FK506 in kidney transplantation: results of the USA randomised comparative phase III study. The FK506 Kidney Transplant Study Group. *Transplant Proc* 1997;**29**:304–5.

70. Filo RS. *Tacrolimus in kidney transplantation: two-year results of the US randomised, comparative, phase III study*. Maryland: DAH American Society of Transplant Physicians and Surgeons; 1997.

71. Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus ciclosporin. *Transplantation* 1998;**65**:515–23.

72. Neylan JF. Effect of race and immunosuppression in renal transplantation after immunosuppression with tacrolimus versus ciclosporin. *Transplant Proc* 1998;**30**:1355–8.

73. Solez K, Vincenti F, Filo RS. Histopathologic findings from 2-year protocol biopsies from a US multicentre kidney transplant trial comparing tacrolimus versus ciclosporin. *Transplantation* 1998;**66**:1736–40.

74. Jensik SC. Tacrolimus (FK506) in kidney transplantation: three-year survival results of the US multicentre, randomised, comparative trial. *Transplant Proc* 1998;**30**:1216–18.

75. Pirsch JD. Cytomegalovirus infection and posttransplant lymphoproliferative disease in renal transplant recipients: results of the US multicentre FK506 Kidney Transplant Study Group. *Transplantation* 1999;**68**:103–5.

76. Vincenti F. Tacrolimus (FK506) in kidney transplantation: three-year survival results of the US multicentre, randomised, comparative trial. *Transplant Proc* 2001;**33**:1019–20.

77. Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporin in kidney transplantation: evidence for improved allograft survival at five years [published erratum appears in *Transplantation* 2002;**73**:1370]. *Transplantation* 2002;**73**:775–82.

78. Shield CF III, McGrath MM, Goss TF. Assessment of health-related quality of life in kidney transplant patients receiving tacrolimus (FK506)-based versus ciclosporin-based immunosuppression. *Transplantation* 1997; **64**:1738–43.

79. Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ. One-year follow-up of open-label trial of FK506 for primary kidney transplantation. *Transplantation* 1996;**64**:436–43.

80. Laskow DA, Vincenti F, Neylan JF, Mendez R, Metas AJ. An open-label concentration-ranging trial of FK506 in primary kidney transplantation. *Transplantation* 1997;**64**:900–5.

81. Schleibner S, Krauss M, Wagner K, Erhard J, Christiaans M, van Hooff J, *et al*. FK 506 versus cyclosporin in the prevention of renal allograft rejection – European pilot study: six-week results. *Transpl Int* 1995;**8**:86–90.

82. Dmitrewski J, Krentz AJ, Mayer AD, Buckles JA, Barnes AD, Smith J, *et al*. Metabolic and hormonal effects of tacrolimus (FK506) or ciclosporin immunosuppression following renal transplantation. *Diabetes Obes Metab* 2001;**2**:287–92.

83. Shapiro R, Jordan M, Scantlebury V, Fung J, Jensen C, Tzakis A, *et al*. FK506 in clinical kidney transplantation. *Transplant Proc* 1991;**23**:3065–7.

84. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, *et al*. Multicentre randomized trial comparing tacrolimus (FK506) and ciclosporin in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. *Transplantation* 1997;**64**:436–43.

85. Hauser IA, Neumayer H-N. Tacrolimus and ciclosporin efficacy in high-risk kidney transplantation: on behalf of the European Multicentre Tacrolimus (FK506) Renal Study Group. *Transpl Int* 1998;**11**(Suppl 1):S73–7.

86. Mayer AD. Four-year follow up of the European Tacrolimus Multicentre Renal Study. *Transplant Proc* 1999;**31**(Suppl 7A):27–8S.

87. Mayer D. Tacrolimus vs ciclosporin in renal transplantation: five year follow-up of the European Multicentre Study. *Am J Transplant* 2002;**2**(S3):238.

88. Ichimaru N, Takahara S, Kokado Y, Wang JD, Hatori M, Kameoka H, *et al*. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Atherosclerosis* 2001;**158**:417–23.

89. Radermacher J, Meiners M, Bramlage C, Kliem V, Behrend M, Schlitt HJ, *et al*. Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506. *Transpl Int* 1998;**11**:3–10.

90. White SA, Jain S, Williams ST, Doughman T, Hayes P, Murphy G, *et al*. Randomized trial comparing Neoral and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. *Transplant Proc* 2000;**32**:600.

91. Williams ST, White SA, Doughman T, *et al*. A randomised trial comparing Neoral (ciclosporin) and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. *Br J Surg* 1999;**86**(Suppl 1):008.

92. Murphy G, White SA, Williams ST, *et al*. Analysis of side effects after renal transplantation using either tacrolimus or Neoral immunosuppression – a prospective randomised study. *Br J Surg* 2000; **87**(Suppl 1):Poster 057.

93. Morris-Stiff G, Ostrowski K, Balaji V, Moore R, Darby C, Lord R, *et al*. Prospective randomised study comparing tacrolimus (Prograf) and cyclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim report of the first 80 cases. *Transpl Int* 1998;**11** (Suppl 1):S334–6.

94. Morris-Stiff G, Singh J, Ostrowski K, Balaji V, Moore R, Darby C, *et al*. Prospective randomized study comparing FK 506 (Prograf) and cyclosporine A (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim report of the first 80 cases. *Transplant Proc* 1998;**30**:1295–6.

95. Jurewicz WA. Immunological and nonimmunological risk factors with tacrolimus and Neoral in renal transplant recipients: an interim report. *Transplant Proc* 1999;**31**(Suppl 7A):64–6S.

96. Morris-Stiff G, Quiroga H, Stockdill G, *et al*. Neoral in cadaveric renal transplantation: 189 patients with a minimum 1-year follow up. *Br J Surg* 2000;**87**(Suppl 1):S001.

97. Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre trial. *Lancet* 2002;**359**:741–6.

98. Del Castillo D. Analysis of primary and recurrent rejection following renal transplantation in a larger, comparative, multicentre trial. *Transplant Proc* 2001;**33**:1259–61.

99. Sperschnieder H. A large, multicentre trial to compare the efficacy and safety of tacrolimus with ciclosporin microemulsion following renal transplantation. *Transplant Proc* 2001;**33**:1279–81.

100. Williams ST, Knight AL, White SA, Doughman TM, Nicholson ML. Preliminary analysis of a randomized trial comparing microemulsion cyclosporine and tacrolimus for recipients of renal transplants from non-heart-beating donors. *Transplant Proc* 2000;**32**:196.

101. Ulsh PJ, Yang HC, Holman MJ, Ahsan N. New strategies using 'low dose' mycophenolate mofetil to reduce acute rejection in patients following kidney transplantation. *Journal of Transplant Coordination* 1999;**9**:144–8.

102. Yang HC, Holman MJ, Langhoff E, Ulsh PJ, Dellock CA, Gupta M, *et al*. Tacrolimus/'low-dose' mycophenolate mofetil versus microemulsion ciclosporin/'low dose' mycophenolate mofetil after kidney transplantation – 1-year follow-up of a prospective, randomised clinical trial. *Transplant Proc* 1999;**31**:1121–4.

103. Johnson C, Ahsan N, Gonwa T, Halloran P, Stegall M, Hardy M, *et al*. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus ciclosporin (Neoral) with mychophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 2000;**69**:834–41.

104. Gonwa TA, Johnson C, Ashan N, *et al*. Two year followup of randomised multicenter kidney transplant study comparing tacrolimus (PG) + azathioprine (AZA) vs ciclosporin (Neoral) + mycophenolate mofetil (MMF) vs tacrolimus + MMF. *Transplantation* 2000;**69**:S113.

105. Raofi V, Holman DM, Coady N, Vasquez E, Dunn TB, Bartholomew AM, *et al*. A prospective randomised controlled trial comparing the efficacy of tacrolimus versus ciclosporin in black recipients of primary cadaveric renal transplants. *Am J Surg* 1999;**177**:299–302.

106. Busque S, Shoker A, Landsberg D, McAlister V, Halloran P, Sharpiro J, *et al*. Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus Neoral/mycophenolate mofetil/steroids in renal transplantation. *Transplant Proc* 2001;**33**:1266–7.

107. Trompeter R, Filler G, Webb NJA, Watson AR, Milford DV, Tyden G, *et al*. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. *Pediatr Nephrol* 2002;**17**:141–9.

108. Filler G, Trompeter R, Webb NJ, Watson AR, Milford DV, Tyden G, *et al*. One-year glomerular filtration rate predicts graft survival in pediatric renal recipients: a randomised controlled trial of tacrolimus vs cyclosporine. *Transplant Proc* 2002;**34**:1935–8.

109. Shah M, Martin J, Schroeder T, Roy M. The evaluation of safety and tolerability of two formulations of cyclosporin; Neoral and Sandimmun. *Transplantation* 1999;**67**:1411–17.

110. Coukell AJ, Posker GL. Cyclosporin microemulsion (Neoral). A pharmacoeconomic review of its use compared with standard cyclosporin in renal and hepatic transplantation [review]. *Pharmacoeconomics* 1998;**14**:691–708.

111. Keown PA. Use of cyclosporin microemulsion in *de novo* and stable renal transplantation; clinical impact, pharmacokinetic consequences and economic benefits. *Transplant Proc* 1996;**28**:2147–50.

112. Korn A, Farber L, Maibucher A, Buchholz B, Offermann G. Long term experience with Sandimmun Neoral: results in *de novo* and stable renal transplant patients after 24 months treatment. *Transplant Proc* 1997;**29**:2945–7.

113. Niese D. A double blind, randomised study of Sandimmun Neoral versus Sandimmun in new renal transplant recipients: results after 12 months. *Transplant Proc* 1995;**27**:1849.

114. Hricik D, for the OLN355 Study Group. Superior renal allografts survival with cyclosporin based immunosuppression: results of a double blind, randomised, prospective comparison of Neoral and Sandimmun in cadaveric renal transplant recipients. *Transplantation* 1999;**67**(S150).

115. Pescovitz MD, Baroni G, Choc MG Jr, Hricik DE, Huang DS, Jin JM, *et al*. Safety and tolerability of cyclosporin microemulsion versus cyclosporin: two year data in primary renal allograft recipients. *Transplantation* 1997;**63**:778–80.

116. European Mycophenolate Mofetil Cooperative Study Group. Placebo controlled study of MMF combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345**:1321–5.

117. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal transplant recipients. *Transplantation* 1995; **60**:1029–37.

118. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; **61**:1029–37.

119. Carl. S, Wiesel M, Staehler G. Mycophenolate mofetil (MMF) for prevention of kidney transplant rejection. A new immunosuppressive agent. International Mycophenolate Mofetil Study Group. *Urologe A* 1998;**37**:282–6.

120. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups [published erratum appears in *Transplantation* 1997;**63**:618]. *Transplantation* 1997; **63**:39–47.

121. Behrend M. Mycophenolate mofetil: suggested guidelines for use in kidney transplantation. *Biodrugs* 2001;**15**:37–53.

122. Young Y, Plosker G. Mycophenolate mofetil. A pharmacoeconomic review of its use in solid organ transplantation. *Pharmacoeconomics* 2002; **20**:675–713.

123. Miladpour AH, Ghods AJ, Nejadgashti H. Effect of mycophenolate mofetil on the prevention of acute renal allograft rejection. *Transplant Proc* 2002;**34**:2089–90.

124. 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**:511–17.

125. Tuncer M, Gurkan A, Erdogan O, Demirbas A, Suleymanlar G, Ersoy FF, *et al*. Mycophenolate mofetil in renal transplantation: five years experience. *Transplant Proc* 2002;**34**:2087–8.

126. Miller J. Tacrolimus and mycophenolate mofetil in renal transplant recipients: one year results of a multicenter, randomized dose ranging trial. *Transplant Proc* 1999;**31**:276–7.

127. Benfield MR, Symons JM, Bynon S, Eckhoff D, Herrin J, Harmon W, Kohaut E. Mycophenolate mofetil in pediatric renal transplantation. *Pediatr Transplant* 1999;**3**:33–37.

128. Salvadori M. Therapeutic equivalence of mycophenolate sodium versus mycophenolate mofetil in *de novo* renal transplant recipients. *Transplant Proc* 2001;**33**:3245–47.

129. Ingle G, Sievers T, Holt C. Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000;**34**:1044–55.

130. UK Drug Information Pharmacists' Group in Conjunction with the National Prescribing Centre. *New drugs in clinical development. Sirolimus*. Monograph No. 3/99/11. November 1999.

131. Kahan BD, Kaplan B, Lorber MI, Winkler M, Cambon N, Boger RS. RAD in *de novo* renal transplantation: comparison of three doses on the incidence and severity of acute rejection. *Transplantation* 2001;**71**:1400–6.

132. Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. *Lancet* 2000; **356**:194–202.

133. Machado PG, Garcia C, Felipe CR, Garcia R, Franco M, Delcelo R, *et al*. A single centre open label randomised trial of the safety and efficacy of the use of sirolimus versus azathioprine in one-haplotype living related kidney transplant recipients – preliminary results. *Transplant Proc* 2001;**33**:1074–5.

134. Kreis H, Cisterne JM, Land W, Wramer L, Squifflet JP, Abramowicz D, *et al.,* for the Sirolimus European Renal Transplant Study Group. Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. *Transplantation* 2000;**69**:1252–60.

135. MacDonald AS, Rapamune Global Study Group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/ciclosporin regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001;**71**:271–80.

136. Ponticelli C, MacDonald AS, Rajagopalan P, Sindhi R, Mathew T. Phase III trial of Rapamune versus placebo in primary renal allograft recipients. *Transplant Proc* 2001;**33**:2271–2.

137. Ettenger RB, Grimm EM. Safety and efficacy of TOR inhibitors in pediatric renal transplant recipients. *Am J Kidney Dis* 2001;**38**(4 Suppl 2): S22–8.

138. Dudley CR, European Tacrolimus Renal Rejection Study Group. Conversion at first rejection: a prospective trial comparing ciclosporin microemulsion with tacrolimus in renal transplant recipients. *Transplant Proc* 2001;**33**:1034–5.

139. MMF Acute Renal Rejection Study Group. MMF for the treatment of refractory, acute, cellular renal transplant rejection. *Transplantation* 1996;**61**:722–9.

140. MMF Acute Renal Rejection Study Group. MMF for the treatment of a first acute renal allograft rejection. *Transplantation* 1998;**65**:235–41.

141. MMF Acute Renal Rejection Study Group. MMF for the treatment of a first acute renal allograft rejection – three year follow up. *Transplantation* 2001;**71**:1091–7.

142. Schnitzler MA, Woodward RS, Lowell JA, Singer GG, Brennan DC. Ten-year cost effectiveness of alternative immunosuppression regimens in cadaveric renal transplantation. *Transplant Proc* 1999;**31**(3B Suppl):19–21S.

143. Polsky D, Weinfurt KP, Kaplan B, Kim J, Fastenau J, Schulman KA. An economic and quality-of-life assessment of basiliximab vs antithymocyte globulin immunoprophylaxis in renal transplantation. *Nephrol Dial Transplant* 2001;**16**:1028–33.

144. Lilliu H, Brun C, Le Pen C, Buchler M, Al Najjar A, Reigneau O, *et al*. Cost-minimization study comparing Simulect versus thymoglobulin in renal transplant induction. *Transplant Proc* 2001;**33**:3197–8.

145. Lorber MI, Fastenau J, Wilson D, DiCesare J, Hall ML. A prospective economic evaluation of basiliximab (Simulect) therapy following renal transplantation. *Clin Transpl* 2000;**14**:479–85.

146. Keown PA, Balshaw R, Krueger H, Baladi JF. Economic analysis of basiliximab in renal transplantation. *Transplantation* 2001;**71**:1573–9.

147. Walters SJ, Whitfield M, Akehurst RL, Chilcott JB. Pharmacoeconomic evaluation of Simulect prophylaxis in renal transplant recipients. *Transplant Proc* 2001;**33**:3187–91.

148. Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL. Cyclosporin: an updated review of the pharmacokinetic properties, clinical efficacy and tolerability of a microemulsion-based formulation (Neoral) in organ transplantation. *Drugs* 2001;**61**:1957–2016.

149. Frampton J, Faulds D. Ciclosporin. A pharmacoeconomic evaluation of its use in renal transplantation. *Pharmacoeconomics* 1993;**4**:366–95.

150. Craig AM, McKechnie T, McKenna M, Klein W, Schindler TM. A cost-effectiveness analysis of tacrolimus versus cyclosporine microemulsion following kidney transplantation. *Transplant Proc* 2002;**34**:1646–8.

151. Olivera D. Economic analysis of Prograf tacrolimus and ciclosporin in the prevention of kidney allograft rejection. 1997.

152. Hutton J. The economics of immunosuppression in renal transplantation. A review of recent literature. *Transplant Proc* 1999;**31**:1328–32.

153. Hardens M, *et al*. Abstract presented at the European Symposium of Pharmacoeconomics, 18–20 May 1994, Ghent, Belgium.

154. Keown P, Lawen JG, Landsberg D, Beauregard-Zollinger L, Riviere M, Leclerc C, *et al*. Economic analysis of Sandimmun Neoral in Canada in stable renal transplant patients. *Transplant Proc* 1995; **27**:1845–8.

155. Kingma I, Ludwin D, Dandavino R, Wolff JL, Loertscher R, Beauregard-Zollinger L, *et al*. Economic analysis of Neoral in *de novo* renal transplant patients in Canada. *Clin Transpl* 1997; **11**:42–8.

156. Baker GM, Martin JE, Jang R, Schroeder TJ, Armitstead JA, Myre S, *et al*. Pharmacoeconomic analysis of mycophenolate mofetil versus azathioprine in primary cadaveric renal transplantation. *Transplant Proc* 1998;**30**:4082–4.

157. Deierhoi MH, *et al*. Cost considerations and the use of mycophenolate mofetil in renal transplantation. 24th Annual Meeting 1998. *Transplantation* 1998;**66**(Suppl 5): Abstract 19.

158. Keown P. Analysis of cost effectiveness and cost utility for immunosuppressive protocols in renal transplantation. *Transplant Proc* 1999;**31**:1140–1.

159. Khosla UM, Martin JE, Baker GM, Schroeder TJ, First MR. One-year, single-center cost analysis of mycophenolate mofetil versus azathioprine following cadaveric renal transplantation. *Transplant Proc* 1999;**31**:274–5.

160. Suleymanlar G, Tuncer M, Sarikaya M, Ersoy F, Aktan S, Yakupoglu G, *et al*. The cost effectiveness of mycophenolate mofetil in the first year after living related renal transplantation. *Transplant Proc* 2001;**33**:2780–1.

161. Sullivan SD, Garrison LP Jr, Best JH. The cost effectiveness of mycophenolate mofetil in the first year after primary cadaveric transplant. US Renal Transplant Mycophenolate Mofetil Study Group. *J Am Soc Nephrol* 1997;**8**:1592–8.

162. Wuthrich RP, Weinreich T, Ambuhl PM, Schwarzkopf AK, Candinas D, Binswanger U. Reduced kidney transplant rejection rate and pharmacoeconomic advantage of mycophenolate mofetil. *Nephrol Dial Transplant* 1999;**14**:394–9.

163. Manninen D, Dong F, Wang F, for the Rapamune US Study Group. Economic evaluation of sirolimus therapy in the first year following renal transplantation. *Transplantation* 2000;**69**(S337): Abstract 871.

164. Sakamaki, *et al*. Abstract PKU6. *Value in Health* 1999;**2**:204–5.

165. Orme ME, Jurewicz WA, Kumar N, McKechnie TC. The cost effectiveness of tacrolimus versus microemulsified cyclosporin: a 10-year model of renal transplantation outcomes. *Pharmacoeconomics* 2003;**21**:1263–76.

166. Chilcott JB, Whiteby SM, Moore R. Clinical impact and health economic consequences of post transplant type 2 diabetes mellitus. *Transplant Proc* 2002;**33** Suppl 5A:33–9S.

167. Song F, Glenny A-M, Altman DG. Indirect comparison in evaluating relative efficacy illustrated by antimicrobial prophylaxis in colorectal surgery. *Control Clin Trials* 2000; **21**:488–97.

168. Giral M, Taddei C, Nguyen JM, *et al*. Single centre analysis of 468 first cadaveric kidney allografts with a uniform ATG-CsA sequential therapy. In Cecka JM, Terasaki PI, editors. *Clinical transplants*. Los Angeles, CA: UCLA Tissue Typing Laboratory; 1996. pp. 257–64.

169. Eastman RC, Javitt JC, Herman WH, Dasbach EJ. Model of complications of NIDDM. (I) Model construction and assumptions and (II) Analysis of the health benefits and cost effectiveness of treating NIDDM with the goal of normoglycaemia. *Diabetes Care* 1997;**20**:725–44.

170. Toselli L, *et al*., MO2ART Study Group. Poster presented at the International Congress of the Transplantation Society, Miami, FL, USA, 2002.

171. Levy, G. Neoral C2 in liver transplant recipients. *Transplant Proc* 2001;**33**:3089–91.

172. Oberbauer R, *et al*. Long term improvement in renal function is shown in patients treated with sirolimus and cyclosporin withdrawal: two year results of the Rapamune Maintenance Regimen trial. International Congress of the Transplantation Society, Miami, FL, USA, 2002; Abstract No. 254.

173. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnhan BA, Johnson CP. Post transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002;**62**:311–18.

174. Boots JMM, van Duijnhoven EM, Christiaans MHL, Nieman FHM, van Suylen RJ, van Hoof JP. Single-centre experience with tacrolimus versus ciclosporin – Neoral in renal transplant recipients. *Transpl Int* 2001;**14**:370–83.

175. Mayer AD, Dmitrewski J, Squifflet JP, Besse T, Grabensee B, Klein B, *et al*. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multicenter Renal Study Group. *Transplantation* 1997;**64**: 436–43.

176. Wong XH, Tang TD, Xu D. Tacrolimus CyA Neoral in combination with MMF and steroids after cadavaric renal transplantation. *Transplant Proc* 2000;**32**:1702–3.

177. Ahsan N, Johnson C, Gonwa T, Halloran P, Stegall M, Hardy M, *et al*. Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus cyclosporine oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: results at 2 years. *Transplantation* 2001;**72**:245–50.

178. Jirasiritham S, Sumethkul V, Mavichak V, Chalermsanyakorn P. The treatment of chronic rejection with mycophenolate mofotil versus azathioprine in kidney transplantation. *Transplant Proc* 2000;**32**:2040–2.

179. McGrath JS, Shehata M. The effect of differing immunosuppressive regimes on the functional and morphologic changes in a rat renal allograft model of chronic rejection. *Transplant Proc* 2001;**33**:2191–2.

180. Jain S, Metcalfe M, White SA, Furness PN, Nicholson ML. Chronic allograft nephropathy: a prospective randomised trial of cyclosporin reduction with or without mycophenolate mofetil. *Transplant Proc* 2001;**33**:2165–6.

Appendix 1

Review search strategies

Cochrane Library (Cochrane Controlled Trials Register)

2002 Issue 3
Date: 13 August 2002

Search strategy

daclizumab
basiliximab
(mycophenolate next mofetil)
mycophenolate
sirolimus
tacrolimus
tacrolimus*:ME
((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)
zenapax
simulect
cellcept
myfortic
rapamune
prograf
rapamycin
MMF
FK506
(((((((#9 or #10) or #11) or #12) or #13) or #14) or #15) or #16) or #17)
(#8 or #18)
(kidney* near transplant*)
(renal next transplant*)
kidney-transplantation*:ME
((#20 or #21) or #22)
(#19 and #23)

MEDLINE (Ovid)

1966 to July 2002
Date: 13 August 2002

Search strategy

1 randomized controlled trial.pt. (162599)
2 controlled clinical trial.pt. (61474)
3 randomized controlled trials.sh. (23780)
4 random allocation.sh. (45143)
5 double blind method.sh. (68918)
6 single-blind method.sh. (6512)
7 or/1-6 (274348)
8 (animal not human).sh. (2569531)
9 7 not 8 (261691)
10 clinical trial.pt. (332273)
11 exp clinical trials/ (132460)
12 (clin$ adj25 trial$).ti,ab. (81078)
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (68056)
14 placebos.sh. (21432)
15 placebo$.ti,ab. (72439)
16 random$.ti,ab. (237083)
17 research design.sh. (31072)
18 or/10-17 (567541)
19 18 not 8 (527412)
20 19 not 9 (276352)
21 comparative study.sh. (988781)
22 exp evaluation studies/ (419935)
23 follow up studies.sh. (252326)
24 prospective studies.sh. (145797)
25 (control$ or prospective$ or volunteer$).ti,ab. (1237511)
26 or/21-25 (2513640)
27 26 not 8 (1909829)
28 27 not (9 or 20) (1541050)
29 9 or 20 or 28 (2079093)
30 daclizumab.mp. (124)
31 basiliximab.mp. (101)
32 (mycophenolate adj mofetil).mp. (1501)
33 (mycophenolate adj sodium).mp. (4)
34 mycophenolate.mp. (1556)
35 exp SIROLIMUS/ or sirolimus.mp. (1828)
36 exp TACROLIMUS/ or tacrolimus.mp. (5870)
37 or/30-36 (8213)
38 zenapax.mp. (10)
39 simulect.mp. (22)
40 cellcept.mp. (48)
41 myfortic.mp. (0)
42 rapamune.mp. (20)
43 prograf.mp. (54)
44 rapamycin.mp. (1813)
45 mmf.mp. (637)
46 fk506.mp. (2467)
47 or/38-46 (4553)
48 37 or 47 (9175)
49 (kidney$ adj transplant$).mp. (26259)
50 (renal adj transplant$).mp. (20046)
51 exp Kidney Transplantation/ or kidney transplantation.mp. (47611)
52 or/49-51 (52136)
53 48 and 52 (1847)
54 53 and 29 (1004)
55 9 or 20 (538043)
56 55 and 53 (627)
57 9 and 53 (329)
58 from 56 keep 1-627 (627)

EMBASE (Ovid)
1980 to July 2002
Date: 13 August 2002

Search strategy
1 randomized controlled trial/ (66077)
2 exp clinical trial/ (243389)
3 exp controlled study/ (1402143)
4 double blind procedure/ (44307)
5 randomization/ (4465)
6 placebo/ (58568)
7 single blind procedure/ (3717)
8 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (84183)
9 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (64015)
10 (placebo$ or matched communities or matched schools or matched populations).mp. (97117)
11 (comparison group$ or control group$).mp. (93011)
12 (clinical trial$ or random$).mp. (412993)
13 (quasiexperimental or quasi experimental or pseudo experimental).mp. (794)
14 matched pairs.mp. (1325)
15 or/1-14 (1709639)
16 exp Interleukin 2 Receptor Antibody/ or daclizumab.mp. (1107)
17 basiliximab.mp. (141)
18 (mycophenolate adj mofetil).mp. (1237)
19 (mycophenolate adj sodium).mp. (4)
20 mycophenolate.mp. (1329)
21 sirolimus.mp. (433)
22 exp Tsukubaenolide/ or tacrolimus.mp. (10100)
23 or/16-22 (11750)
24 zenapax.mp. (200)
25 simulect.mp. (205)
26 cellcept.mp. (449)
27 myfortic.mp. (4)
28 rapamune.mp. (130)
29 prograf.mp. (517)
30 exp RAPAMYCIN/ or rapamycin.mp. (3384)
31 mmf.mp. (612)
32 fk506.mp. (2590)
33 or/24-32 (6797)
34 23 or 33 (13782)
35 (kidney$ adj transplant$).mp. (8409)
36 (renal adj transplant$).mp. (16653)
37 exp Kidney Transplantation/ or kidney transplantation.mp. (34411)
38 or/35-37 (36851)
39 34 and 38 (2605)
40 15 and 39 (1257)

National Research Register
Issue 2 2002
Date: 13 August 2002

Search strategy
Drug names as per MEDLINE; citations were examined to identify whether the patient population was relevant.

Health economics searches

MEDLINE (Ovid)
1966 to August 2002
Date: 4 September 2002

Search strategy
1 economics/ (8979)
2 exp "costs and cost analysis"/ (97428)
3 cost of illness/ (4495)
4 exp health care costs/ (18111)
5 economic value of life/ (4062)
6 exp economics medical/ (9332)
7 exp economics hospital/ (11761)
8 economics pharmaceutical/ (1065)
9 exp "fees and charges"/ (19059)
10 econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (161308)
11 quality of life/ (32329)
12 life style/ (16533)
13 health status/ (19404)
14 health status indicators/ (6593)
15 or/1-14 (296631)
16 kidney transplantation/ (47272)
17 (kidney adj transplant$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (14467)
18 (renal adj transplant$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (20136)
19 or/16-18 (51562)
20 15 and 19 (1478)
21 limit 20 to yr=1992-2002 (950)
22 limit 21 to yr=1997-2002 (586)
23 limit 22 to yr=2000-2002 (263)

EMBASE (Ovid)
1980 to August 2002
Date: 4 September 2002

Search strategy
1 cost benefit analysis/ (14186)
2 cost effectiveness analysis/ (26345)
3 cost minimization analysis/ (444)
4 cost utility analysis/ (674)
5 economic evaluation/ (1180)
6 (cost or costs or costed or costly or costing).tw. (95370)
7 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (44293)

8 (technology adj assessment$).tw. (890)
9 or/1-8 (140882)
10 kidney transplantation/ (30758)
11 (kidney adj transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] (7976)
12 (renal adj transplant$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name, device trade name] (16750)
13 or/10-12 (34772)
14 daclizumab.mp. (160)
15 basiliximab.mp. (147)
16 mycophenolate near mofetil.mp. (0)
17 mycophenolate.mp. (1352)
18 exp SIROLIMUS/ or sirolimus.mp. (3189)
19 TACROLIMUS/ or tacrolimus.mp. (10249)
20 zenapax.mp. (202)
21 simulect.mp. (210)
22 cellcept.mp. (457)
23 rapamune.mp. (137)
24 prograf.mp. (525)
25 rapamycin.mp. (3447)
26 mmf.mp. (622)
27 Tacrolimus/ or fk506.mp. (10468)
28 or/14-27 (13585)
29 13 and 28 (2455)
30 9 and 29 (77)

Health Economic Evaluations Database (OHE)

September 2002
Date: 26 September 2002

Search strategy

Searches on drug names as per MEDLINE; also separate searches on renal transplantation combined with terms relating to decision-analytic modelling, outcome measures/graft survival and equity/resource allocation.

Appendix 2

Inclusion/exclusion proforma

NICE IMMUNOSUPPRESSIVE REGIMENS IN RENAL TRANSPLANTATION
STUDY INCLUSION/EXCLUSION FORM (v 1.0)

Study ID

Citation
Year
Reviewer **RT** **CM**

1.	RCT?	Yes	No	Can't tell
2.	Drug of interest + RCT or trial or study in title?	Yes	No	Can't tell
3.	Drug + outcome of interest in title?	Yes	No	Can't tell
4.	Population – any age humans?	Yes	No	Can't tell
5.	*Adults or children (18 or under)?	Adults	Children	Both
6.	Multiple organ transplant?	Yes	No	Can't tell
7.	Acute therapy trials – >50% had failed high-dose steroid?	Yes	No	Can't tell
8.	Interventions – Initial – any combination with a mAb?	Yes	No	Can't tell
9.	Initial – dual therapy alone?	Yes	No	Can't tell
10.	Initial – triple therapy alone?	Yes	No	Can't tell
11.	Initial therapy – dual + ALG/ATG/OKT3?	Yes	No	Can't tell
12.	Initial therapy – triple + ALG/ATG/OKT3?	Yes	No	Can't tell
13.	Maintenance – any of mAb/MMF/MPS/sirolimus/tacrolimus?	Yes	No	Can't tell
14.	Maintenance – dual therapy?	Yes	No	Can't tell
15.	Maintenance – triple therapy?	Yes	No	Can't tell
16.	Acute – yes to 7 + any of mAb/MMF/MPS/sirolimus/tacrolimus?	Yes	No	Can't tell
17.	Acute – yes to 7 + ALG/ATG/OKT3?	Yes	No	Can't tell
18.	Outcomes – patient survival	Yes	No	Can't tell
19.	Outcomes – graft survival/half-life?	Yes	No	Can't tell
20.	Graft function – serum creatinine/glomerular filtration?	Yes	No	Can't tell
21.	Time to acute rejection?			
22.	Incidence of acute rejection?	Yes	No	Can't tell
23.	Adverse events – CVD, malignancy/diabetes/infection/nephrotoxicity?	Yes	No	Can't tell
24.	Quality of life?	Yes	No	Can't tell
25.	**Growth for children?	Yes	No	Can't tell
26.	Included other (circle one) – incidence/prevalence, economic study/modelling, clinical guidelines, service provision	Yes	No	Can't tell

* Only complete if included on other criteria
** Where applicable from 5

Include if YES to 1–4 and YES to one of 8–17 and YES to one of 18–25
Exclude if YES to 6 or NO to 7
If CAN'T TELL to any question – order full paper

Type of drug
Monoclonal antibodies = basiliximab, dacluzimab, OKT3 (muronomab CD3)
Steroid = methylprednisolone or prednisolone or hydrocortisone
Antiproliferative immunosuppressive = azathioprine (AZA) or mycophenolate mofetil (MMF) or sodium (MPS)
Calcineurin-inhibiting immunosuppressant = Neoral ciclosporin or ciclosporin A, tacrolimus
Antilymphocyte immunoglobulin = ALG, ALT
Non-calcineurin-inhibiting immunosuppressant = sirolimus

Names and mechanism of action
Basiliximab = Simulect = IL-2 inhibitor
Daclizumab = Zenapax = IL-2 inhibitor
ATG, ALG, OKT3 = anti-T-cell, antilymphocyte agents
Azathioprine = purine biosynthesis inhibitor
Mycophenolate mofetil = Cellcept = purine biosynthesis inhibitor
Prednisolone, hydrocortisone = cytokine gene expression blockers
Sirolimus = Rapamune = target of rapamycin (TOR) inhibitor
Tacrolimus = Prograf = FK506 = calcineurin inhibition of IL-2 synthesis
Ciclosporin = Neoral or Sandimmun

Appendix 3

RCT quality assessment criteria

Modified Jadad scale

Initially, quality assessment of RCTs was performed using the Jadad scale, a standard checklist to assess the methodological quality of RCTs. However, it is not possible to perform lifestyle intervention studies in a double-blinded way and since blinding features in the Jadad scoring system, certain aspects were given greater consideration, as suggested by guidance from the Cochrane Collaboration:

- minimisation of selection bias: adequate randomisation and concealment
- minimisation of attrition bias: loss to follow-up and dropouts recorded, with ITT analysis performed; and
- minimisation of observer bias: blinding of assessors to the treatment allocation.

Randomisation

1. Was the study described as randomised (including the use of words such as randomly, random and randomisation?)
2. Was the method used to generate the sequence of randomisation appropriate?
3. Was the method used to generate the sequence of randomisation inappropriate?

Concealment

4. Where possible, was the allocation of intervention or control concealed from the data collectors or assessors?
5. Was the method of concealment appropriate?

Losses to follow-up

6. Was there a description of the withdrawals and dropouts?
7. Was an ITT analysis performed and reported?

Scoring

0–2 = Poor quality/high risk of bias
3 or 4 = Fair quality/moderate risk of bias
5 or 6 = High quality/low risk of bias

Notes

Minimisation of selection bias: randomisation

The method used to generate the sequence of randomisation will be considered appropriate only if it allowed the study participants to have an equal chance of receiving each intervention and if the investigators were unable to predict which intervention would be next.

The method used to generate the sequence of randomisation will be considered inappropriate if methods such as date of birth, date of admission, hospital numbers or alternation were used.

Minimisation of attrition bias: losses to follow-up

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described, including the number and the reasons for withdrawal. If there were no withdrawals this must also be stated.

If there is no statement on withdrawals this item must be given no points.

Intention-to-treat analysis

This form of analysis is applied to clinical trials where patients are allocated to two or more different treatments. Regardless of whether the patient allocated to one form of treatment actually takes it, and even if they take the alternative, they are still analysed with the group to which they were originally allocated.

The other form of analysis is on-treatment analysis, where only patients who complied with their allocated treatment are analysed. ITT analysis is generally the primary analysis, although on-treatment analysis can add some information.

Dropout and non-compliance are not random and may be different in the two (or more) arms. Assuming that treatment has been allocated randomly, the distribution of confounders across the groups is equal at the start of the trial, but is unlikely to be so if only the compliant members of the groups are compared. Only ITT analysis guarantees comparability of the groups. This is a scientific reason for ITT analysis.

Non-compliance and dropout will reduce the statistical power of the comparison. This can be

overcome by increasing the numbers in the trial to account for dropout when doing power calculations, or by only enrolling compliant patients. In some trials this is done by a 'wash-in' period to ensure tolerability, but this is not always feasible.

If dropout and non-compliance are substantial, the ITT analysis may show no worthwhile efficacy, but determining whether taking the treatment results in improvement can still be biologically useful. This information will not be provided by ITT analysis alone.

Appendix 4

Included RCTs and associated papers

Induction therapy

Daclizumab

Review

Wiseman LR, Faulds D. Daclizumab: a review of its use in the prevention of acute rejection in renal transplant recipients. *Drugs* 2000;**59**:476.

Pooled analyses

Bumgardner GL, Hardie I, Johnson RW, Lin A, Nashan B, Pescowitz MD, *et al*. Phase III Daclizumab Study Group. Results of 3-year phase III clinical trials with daclizumab prophylaxis for prevention of acute rejection after renal transplantation. *Transplantation* 2001;**72**:839–45.

Ekberg H, Backman L, Tufveson G, Tyden G. Zenapax (daclizumab) reduces the incidence of acute rejection episodes and improves patient survival following renal transplantation. No 14874 and No 14393 Zenapax Study Groups. *Transplant Proc* 1999;**31**:267–8.

Ekberg H, Backman L, Tufveson G, Tyden G, Nashan B, Vincenti F. Daclizumab prevents acute rejection and improves patient survival post transplantation: 1 year pooled analysis. *Transpl Int* 2000;**13**:151–9.

Vincenti F, Nashan B. Daclizumab: outcome of Phase III trials and mechanism of action. *Transplant Proc* 1998;**30**:2155–8.

RCTs

Charpentier B. Induction versus noninduction protocols in anticalcineurin based immunosuppression.*Transpl Proc* 2001;**33**:3334–6.

Lacha J, Simova M, Noskova L, Teplan V, Vitilo S. Zenapax versus OKT3 prophylaxis in immunologically high risk kidney transplant recipients. *Transplantation* 2000;**69**(S158): Abstract 174.

Lacha J, Simova M, Noskova L, Teplan V, Vitko S. Zenapax versus OKT3 prophylaxis in immunologically high risk kidney transplant recipients. *Transplant Proc* 2001;**33**:2273–4.

Nashan B, Light S, Hardie IR, Lin A, Johnson JR. Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 1999;**67**:110–15.

Vincenti F, Kirkman R, Light S, Bumgardner G, Pescowitz M, Halloran P, *et al*. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998;**338**:161–5.

Basiliximab

Review

Thistlethwaite JR Jr, Nashan B, Hall M, Chodoff L, Lin T-H. Reduced acute rejection and superior 1-year renal allograft survival with basiliximab in patients with diabetes mellitus. *Transplantation* 2000;**70**:784–90.

Pooled analyses

Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999;**67**:276–84.

Mulloy LL, Wright F, Hall ML, Moore M. Simulect (basiliximab) reduces acute cellular rejection in renal allografts from cadaveric and living donors. *Transplant Proc* 1999;**31**:1210–13.

Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillon JP. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997;**350**:1193–8.

RCTs

Folkmane I, Bicans J, Chapenko S, Murovska M, Rosentals R. Results of renal transplantation with different immunosuppressive regimens. *Transplant Proc* 2002;**34**:558–9.

Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation* 1999;**67**:276–84.

Lawen J, *et al*. Basiliximab (Simulect) is safe and effective in combination with triple therapy of Neoral, steroids and Cellcept in renal transplant recipients. *Transplantation* 2000;**69**(S260): Abstract 572.

Lebranchu Y, *et al*. A multicentre randomized trial of simulect versus thymoglobulin in renal transplantation. *Transplantation* 2000;**69**(S258): Abstract 567.

Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillon JP. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group [published erratum appears in *Lancet* 1997;**350**:1484]. *Lancet* 1997;**350**:1193–8.

Ponticelli C, Yussim A, Cambi V, Legendre C, Rizzo G, Salvadori M, *et al*. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001;**72**:1261–7.

Shidban H, *et al*. Controlled trial of IL2R antibody basiliximab (Simulect) vs low dose OKT3 in cadaver kidney transplant recipients. *Transplantation* 2000;**69**(S156): Abstract 164.

Sollinger B, Kaplan B, Pescovitz MD, Philosophe B, Roza A, Brayman K, *et al*. Basiliximab versus antithymocyte globulin for prevention of acute renal allograft rejection. *Transplantation* 2001;**72**:1915–19.

Initial and maintenance therapy

Ciclosporin: Sandimmun versus tacrolimus

Reviews

Booth-Clibborn N, *et al*. Tacrolimus after kidney transplantation. Development and Evaluation Committee Report No. 74. Wessex Institute for Health Research and Development; 1997.

Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Knoll GA, Bell RC. Tacrolimus versus ciclosporin for immunosuppression in renal transplantation: meta-analysis of randomised trials. *BMJ* 1999; **318**:1104–7.

Morris-Stiff G, Richards T, Singh J, Baboolal K, Balaji V, Ostrowski K, *et al*. Pharmaco-economic study of FK 506 (Prograf) and cyclosporin A Neoral in cadaveric renal transplantation. *Transplant Proc* 1998;**30**:1285–6.

Neylan JF, Sullivan EM, Steinwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus ciclosporin. *Am J Kidney Dis* 1998;**32**:770–7.

Peters D. Tacrolimus. *Drugs* 1993;**46**:746–9.

Plosker G, Foster R. Tacrolimus. Adis drug evaluation. *Drugs* 2000;**59**:323–89.

RCTs

Dmitrewski J, Krentz AJ, Mayer AD, *et al*. Metabolic and hormonal effects of tacrolimus (FK506) or ciclosporin immunosuppression following renal transplantation. *Diabetes Obes Metab* 2001;**2**:287–92.

Filo RS. *Tacrolimus in kidney transplantation: two-year results of the US randomised, comparative, phase III study*. Maryland: American Society of Transplant Physicians and Surgeons; 1997.

Hauser IA, Neumayer H-N. Tacrolimus and ciclosporin efficacy in high-risk kidney transplantation: on behalf of the European Multicentre Tacrolimus (FK506) Renal Study Group. *Transpl Int* 1998;**11**(Suppl 1):S73–7.

Ichimara N, Takahara S, Kokado Y, Wang JD, Hatori M, Kameoka H, *et al*. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Arterosclerosis* 2001;**158**:417–23.

Jensik SC. Tacrolimus (FK506) in kidney transplantation: three-year survival results of the US multicentre, randomised, comparative trial. *Transplant Proc* 1998;**30**:1216–18.

Laskow DA, Vincenti F, Neylan JF, Mendez R, Metas AJ. An open-label concentration-ranging trial of FK506 in primary kidney transplantation. *Transplantation* 1997;**64**:900–5.

Mayer AD. Four-year follow up of the European Tacrolimus Multicentre Renal Study. *Transplant Proc* 1999;**31**(Suppl 7A):27–8S.

Mayer AD, Dmitrewski J, Squiffet J-P, Besse T, Grabensee B, Klein B, *et al*. Multicentre

randomised controlled trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection. *Transplantation* 1997; **64**:436–43.

Mayer D. Tacrolimus vs ciclosporin in renal transplantation: five year follow-up of the European Multicentre Study. *Am J Transplant* 2002;**2**(S3):238.

Miller J, Pirsch JD, Deierhoi M, Vincenti F, Filo RS. FK506 in kidney transplantation: results of the USA randomised comparative phase III study. The FK506 Kidney Transplant Study Group. *Transplant Proc* 1997;**29**:304–5.

Neylan JF. Effect of race and immunosuppression in renal transplantation after immunosuppression with tacrolimus versus ciclosporin. *Transplant Proc* 1998;**30**:1355–8.

Neylan JF. Racial differences in renal transplantation after immunosuppression with tacrolimus versus ciclosporin. *Transplantation* 1998;**65**:515–23.

Pirsch JD. Cytomegalovirus infection and posttransplant lymphoproliferative disease in renal transplant recipients: results of the US multicentre FK506 Kidney Transplant Study Group. *Transplantation* 1999;**68**:103–5.

Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and ciclosporin for immunosuppression after cadaveric renal transplantation. *Transplantation* 1997;**63**: 977–83.

Radermacher J, Meiners M, Bramlage C, Kliem V, Behrend M, Schlitt HJ, *et al*. Pronounced renal vasoconstriction and systematic hypertension in renal transplant patients treated with cyclosporin A versus FK506. *Transpl Int* 1998;**11**:3–10.

Schleibner S, Krauss M, Wagner K, Erhard J, Christiaans M, van Hooff J, *et al*. FK506 versus ciclosporin in the prevention of renal allograft rejection – European pilot study: six-week results. *Transpl Int* 1995;**8**:86–90.

Shapiro R, Jordan M, Scantlebury V, Fung J, Jensen C, Tzakis A, *et al*. FK506 in clinical kidney transplantation. *Transplant Proc* 1991;**23**:3065–7.

Shield CF, McGrath MM, FK506 Kidney Transplant Group. Assessment of health-related quality of life in kidney transplant patients receiving FK506-based versus ciclosporin-based immunosuppression. 1997 (citation incomplete).

Shield CF, McGrath MM, Goss TF. Assessment of health-related quality of life in kidney transplant patients receiving tacrolimus (FK506)-based versus ciclosporin-based immunosuppression. *Transplantation* 1997;**64**:1738–43.

Solez K, Vincenti F, Filo RS. Histopathologic findings from 2-year protocol biopsies from a US multicentre kidney transplant trial comparing tacrolimus versus ciclosporin. *Transplantation* 1998;**66**:1736–40.

Vincenti F. Tacrolimus (FK506) in kidney transplantation: three-year survival results of the US multicentre, randomised, comparative trial. *Transplant Proc* 2001;**33**:1019–20.

Vincenti F, Laskow DA, Neylan JF, Mendez R, Matas AJ. One-year follow-up of open-label trial of FK506 for primary kidney transplantation. *Transplantation* 1997;**64**:436–43.

Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and ciclosporin in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation* 2002;**73**:775–82.

Ciclosporin: Neoral versus tacrolimus

Reviews

Morris-Stiff G, Richards T, Singh J, Baboolal K, Balaji V, Ostrowski K, *et al*. Pharmaco-economic study of FK 506 (Prograf) and cyclosporin A Neoral in cadaveric renal transplantation. *Transplant Proc* 1998;**30**:1285–6.

Neylan JF, Sulliran EM, Steinwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus ciclosporin. *Am J Kidney Dis* 1998;**32**:770–7.

RCTs

Busque S, Shoker A, Landsberg D, McAlister V, Halloran P, Shapiro J, *et al*. Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus Neoral/mycophenolate mofetil/steroids in renal transplantation. *Transplant Proc* 2001; **33**:1266–7.

Del Castillo D. Analysis of primary and recurrent rejection following renal transplantation in a larger, comparative, multicentre trial. *Transplant Proc* 2001;**33**:1259–61.

Gonwa TA, Johnson C, Ashan N, *et al*. Two year followup of randomised multicenter kidney transplant study comparing tacrolimus (PG) + azathioprine (AZA) vs ciclosporin (Neoral) + mycophenolate mofetil (MMF) vs tacrolimus + MMF. *Transplantation* 2000;**69**:S113.

Johnson C, Ahsan N, Gonwa T, Halloran P, Stegall M, Hardy M, *et al*. Randomized trial of tacrolimus (prograf) in combination with azathioprine or mycophenolate mofetil versus ciclosporin (Neoral) with mychophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 2000;**69**:834–41.

Jurewicz WA. Immunological and nonimmunological risk factors with tacrolimus and Neoral in renal transplant recipients: an interim report. *Transplant Proc* 1999;**31**(Suppl 7A):64–6S.

Margreiter R. Efficacy and safety of tacolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre trial. *Lancet* 2002;**359**:741–6.

Morris-Stiff G, Ostrowski K, Balaji V, Moore R, Darby C, Lord R, *et al*. Prospective randomised study comparing tacrolimus (Prograf) and ciclosporin (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim results of the first 80 cases. *Transpl Int* 1998;**11**(Suppl 1):S334–6.

Morris-Stiff G, Singh J, Ostrowski K, Balaji V, Moore R, Darby C, *et al*. Randomised study comparing FK506 (Prograf) and cyclosporine A (Neoral) as primary immunosuppression in cadaveric renal transplants at a single institution: interim results of the first 80 cases. *Transplant Proc* 1998;**30**:1295–6.

Morris-Stiff G, Quiroga H, Stockdill G, *et al*. Neoral in cadaveric renal transplantation: 189 patients with a minimum 1-year follow up. *Br J Surg* 2000;**87**(Suppl 1):S001.

Murphy G, White SA, Williams ST, *et al*. Analysis of side effects after renal transplantation using either tacrolimus or Neoral immunosuppression – a prospective randomised study. *Br J Surg* 2000; **87**(Suppl 1):Poster 057.

Raofi V, Holman DM, Coady N, *et al*. A prospective randomised controlled trial comparing the efficacy of tacrolimus versus ciclosporin in black recipients of primary cadaveric renal transplants. *Am J Surg* 1999;**177**:299–302.

Sperschnieder H. A large, multicentre trial to compare the efficacy and safety of tacrolimus with ciclosporin microemulsion following renal transplantation. *Transplant Proc* 2001;**33**: 1279–81.

Trompeter R, Filler G, Webb NJA, Watson AR, Milford DV, Tyden G, *et al*. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. *Pediatr Nephrol* 2002;**17**:141–9.

Ulsh PJ, Yang HC, Holman MJ, *et al*. New strategies using 'low dose' mycophenolate mofetil to reduce acute rejection in patients following kidney transplantation. *J Transplant Coord* 1999; **9**:144–8.

White SA, Jain ST, Williams ST, Doughman T, Hayes P, Murphy G, *et al.* Randomized trial comparing Neoral and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. *Transplant Proc* 2000;**32**:600.

Williams ST, White SA, Doughman T, *et al*. A randomised trial comparing Neoral (ciclosporin) and tacrolimus immunosuppression for recipients of renal transplants procured from different donor groups. *Br J Surg* 1999;**86**(Suppl 1):008.

Williams ST, Knight AL, White SA, Doughman TM, Nicholson ML. Preliminary analysis of a randomized trial comparing microemulsion cyclosporine and tacrolimus for recipients of renal transplants from non-heart-beating donors. *Transplant Proc* 2000;**32**:196.

Yang HC, Holman MJ, Langhoff E, Ulsh PJ, Dellock CH, *et al*. Tacrolimus/'low-dose' mycophenolate mofetil versus mircoemulsion ciclosporin/'low dose' mycophenolate mofetil after kidney transplantation – 1-year follow-up of a prospective, randomised clinical trial. *Transplant Proc* 1999;**31**:1121–4.

Mycophenolate mofetil

Reviews and pooled analyses

Behrend M. Mycophenolate mofetil: suggested guidelines for use in kidney transplantation. *Biodrugs* 2001;**15**:37–53.

Carl S, Wiesel M, Staehler G. Mycophenolate mofetil (MMF) for prevention of kidney transplant rejection. A new immunosuppressive agent. International Mycophenolate Mofetil Study Group. *Urologe A* 1998;**37**:282–6.

Chilcott J, Corcoran M, Rigg KM, Burden RP. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups [published erratum appears in *Transplantation* 1997;**63**:618]. *Transplantation* 1997;**63**:39–47.

Young Y, Plosker G. Mycophenolate mofetil. A pharmacoeconomic review of its use in solid organ transplantation. *Pharmacoeconomics* 2002; **20**:675–713.

RCTs

Ahsan N, Johnson C, Gonwa T, Halloran P, Stegall M, Hardy M, *et al*. Randomized trial of tacrolimus plus mycophenolate mofetil or azathioprine versus ciclosporin oral solution (modified) plus mycophenolate mofetil after cadaveric kidney transplantation: results at 2 years. *Transplantation* 2001;**72**:245–50.

Busque S, Shoker A, Landsberg D, McAllister V, Halloran P, *et al*. Canadian multicentre trial of tacrolimus/azathioprine/steroids versus tacrolimus/mycophenolate mofetil/steroids versus Neoral/mycophenolate mofetil/steroids in renal transplantation. *Transplant Proc* 2001;**33**:1266–7.

European Mycophenolate Mofetil Cooperative Study Group. Placebo controlled study of MMF combined with cyclosporin and corticosteroids for prevention of acute rejection. *Lancet* 1995; **345**:1321–5.

Johnson C, Ahson N, Gonwa T, Halloran P, Stegall M, Hardy M, *et al*. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus ciclosporin (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 2000;**69**:834–41.

Miladpour AH, Ghods AJ, Nejadgashti H. Effect of mycophenolate mofetil on the prevention of acute renal allograft rejection. *Transplant Proc* 2002;**34**:2089–90.

Miller J. Tacrolimus and mycophenolate mofetil in renal transplant recipients: one year results of a multicenter, randomized dose ranging trial. *Transplant Proc* 1999;**31**:276–7.

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. *Transplantation* 2002;**74**: 511–17.

Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal transplant recipients. *Transplantation* 1995; **60**:1029–37.

Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. A blinded, randomized clinical trial of mycophenolate mofetil for the prevention of acute rejection in cadaveric renal transplantation. *Transplantation* 1996; **61**:1029–37.

Tuncer M, Gurkan A, Erdogan O, Demirbas A, Suleymanlar G, Ersoy FF, *et al*. Mycophenolate mofetil in renal transplantation: five years experience. *Transplant Proc* 2002;**34**: 2087–8.

Mycophenolate sodium

RCT

Salvadori M. Therapeutic equivalence of mycophenolate sodium versus mycophenolate mofetil in *de novo* renal transplant recipients. *Transplant Proc* 2001;**33**:3245–7.

Sirolimus

Reviews

Ingle G, Sievers T, Holt C. Sirolimus: continuing the evolution of transplant immunosuppression. *Ann Pharmacother* 2000;**34**:1044–55.

UK Drug Information Pharmacists' Group in Conjunction with the National Prescribing Centre. *New drugs in clinical development. Sirolimus*. Monograph No. 3/99/11. November 1999.

Studies

Ettenger RB, Grimm EM. Safety and efficacy of TOR inhibitors in pediatric renal transplant recipients. *Am J Kidney Dis* 2001;**38**(4 Suppl 2): S22–8.

Kahan BD. Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. *Lancet* 2000; **356**:194–202.

Kahan BD, Kaplan B, Lorber MI, Winkler M, Cambon N, Boger RS. RAD in *de novo* renal transplantation: comparison of three doses on the incidence and severity of acute rejection. *Transplantation* 2001;**71**:1400–6.

MacDonald AS, Rapamune Global Study Group. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/ciclosporin regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. *Transplantation* 2001;**71**:271–80.

Ponticelli C, MacDonald AS, Rajogopalan P, Sindhi R, Mathew T. Phase III trial of Rapamune versus placebo in primary renal allograft recipients. *Transplant Proc* 2001;**33**:2271–2.

Acute rejection treatment

Reviews

Booth-Clibborn N, *et al*. Tacrolimus after kidney transplantation. Wessex Institute for Health Research and Development; 1997.

Peters D. Tacrolimus. *Drugs* 1993;**46**:746–9.

Plosker G, Foster R. Tacrolimus. Adis drug evaluation. *Drugs* 2000;**59**:323–89.

Young Y, Plosker G. Mycophenolate mofetil. A pharmacoeconomic review of its use in solid organ transplantation. *Pharmacoeconomics* 2002; **20**:675–713.

RCTs

Dudley CR, European Tacrolimus Renal Rejection Study Group. Conversion at first rejection: a prospective trial comparing ciclosporin microemulsion with tacrolimus in renal transplant recipients. *Transplant Proc* 2001;33:1034–5.

MMF Acute Renal Rejection Study Group. MMF for the treatment of refractory, acute, cellular renal transplant rejection. *Transplantation* 1996;**61**:722–9.

MMF Acute Renal Rejection Study Group. MMF for the treatment of a first acute renal allograft rejection. *Transplantation* 1998;**65**:235–41.

MMF Acute Renal Rejection Study Group. MMF for the treatment of a first acute renal allograft rejection – three year follow up. *Transplantation* 2001;**71**:1091–7.

Appendix 5

Included economic studies

Daclizumab

Schnitzler MA, Woodward RS, Lowell JA, Singer GG, Brennan DC. Ten-year cost effectiveness of alternative immunosuppression regimens in cadaveric renal transplantation. *Transplant Proc* 1999;**31**(3B Suppl):19–21S.

Basiliximab

Keown PA, Balshaw R, Krueger H, Baladi JF. Economic analysis of basiliximab in renal transplantation. *Transplantation* 2001;**71**: 1573–9.

Lilliu H, Brun C, Le Pen C, Buchler M, AI Najjar A, Reigneau O, *et al*. Cost-minimization study comparing Simulect versus thymoglobulin in renal transplant induction. *Transplant Proc* 2001;**33**:3197–8.

Lorber MI, Fastenau J, Wilson D, DiCesare J, Hall ML. A prospective economic evaluation of basiliximab (Simulect) therapy following renal transplantation. *Clin Transpl* 2000;**14**:479–85.

Polsky D, Weinfurt KP, Kaplan B, Kim J, Fastenau J, Schulman KA. An economic and quality-of-life assessment of basiliximab vs antithymocyte globulin immunoprophylaxis in renal transplantation. *Nephrol Dial Transplant* 2001;**16**:1028–33.

Schnitzler MA, Woodward RS, Lowell JA, Singer GG, Brennan DC. Ten-year cost effectiveness of alternative immunosuppression regimens in cadaveric renal transplantation. *Transplant Proc* 1999;**31**(3B Suppl):19–21S.

Walters SJ, Whitfield M, Akehurst RJ, Chilcott JB. Pharmacoeconomic evaluation of Simulect prophylaxis in renal transplant recipients. *Transplant Proc* 2001;**33**:3187–91.

Tacrolimus versus Ciclosporin

Reviews

Booth-Clibborn N, *et al*. Tacrolimus after kidney transplantation. Wessex Institute for Health Research and Development; 1997.

Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Dunn CJ, Wagstaft AJ, Perry CM, Plosker GL, Goa KL. Ciclosporin Neoral. Adis drug evaluation. *Drugs* 2001;**61**:1957–2016.

Frampton J, Faulds D. Ciclosporin. A pharmacoeconomic evaluation of its use in renal transplantation. *Pharmacoeconomics* 1993;**4**:366–95.

Morris-Stiff G, Richards T, Singh J, Baboolal K, Balaji V, Ostrowski K, *et al*. Pharmaco-economic study of FK 506 (Prograf) and cyclosporin A Neoral in cadaveric renal transplantation. *Transplant Proc* 1998;**30**:1285–6.

Neylan JF, Sullivan EM, Sternwald B, Goss TF. Assessment of the frequency and costs of posttransplantation hospitalizations in patients receiving tacrolimus versus cyclosporin. *Am J Kidney Dis* 1998;**32**:770–7.

Peters D. Tacrolimus. *Drugs* 1993;**46**:746–9.

Plosker G, Foster R. Tacrolimus. Adis drug evaluation. *Drugs* 2000;**59**:323–89.

Studies

Booth-Clibborn N, *et al*. Tacrolimus after kidney transplantation. Wessex Institute for Health Research and Development; 1997.

Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Craig AM, McKechnie T, McKenna M, Klein W, Schindler TM, *et al*. A cost-effectiveness of tacrolimus versus cyclosporine microemulsion following kidney transplantation. *Transplant Proc* 2002;**34**:1646–8.

Morris-Stiff G, Richards T, Singh J, Baboolal K, Balaji V, Ostrowski K, *et al*. Pharmacoeconomic study of FK 506 and ciclosporin Neoral in cadaveric renal transplantation. *Transplant Proc* 1998;**30**:1285–6.

Neylan JF, Sullivan EM, Steinwald B, Goss TF. Assessment of frequency and costs of post

transplantation hospitalisation in patients receiving tacrolimus versus ciclosporin. *Am J Kidney Dis* 1998;**32**:770–7.

Olivera D. Economic analysis of Prograf tacrolimus and ciclosporin in the prevention of kidney allograft rejection. 1997.

Ciclosporin: Sandimmun versus Neoral

Reviews

Dunn CJ, Wagstaff AJ, Perry CM, Plosker GL, Goa KL. Ciclosporin Neoral. Adis drug evaluation. *Drugs* 2001;**61**:1957–2016.

Frampton J, Faulds D. Ciclosporin. A pharmacoeconomic evaluation of its use in renal transplantation. *Pharmacoeconomics* 1993;**4**:366–95.

Hutton J. The economics of immunosuppression in renal transplantation. A review of recent literature. *Transplant Proc* 1999;**31**:1328–32.

Peters D. Tacrolimus. *Drugs* 1993;**46**:746–9.

Plosker G, Foster R. Tacrolimus. Adis drug evaluation. *Drugs* 2000;**59**:323–89.

Studies

Hardens M, *et al*. Abstract presented at the European Symposium of Pharmacoeconomics, 18–20 May 1994, Ghent, Belgium.

Keown P, Lawen JG, Landsberg D, Beauregard-Zollinger L, Riviere M, Leclerc C, *et al*. Economic analysis of Sandimmun Neoral in Canada in stable renal transplant recipients. *Transplant Proc* 1995; **27**:1845–8.

Kingma I, Ludwin D, Dandarino R, Wolff JF, Loertscher R, Beauregard-Zollinger L, *et al*. Economic analysis of Neoral in *de novo* renal transplant recipients. *Clin Transpl* 1997;**11**:42–8.

Mycophenolate mofetil

Reviews

Behrend M. Mycophenolate mofetil. Suggested guidelines for use in kidney transplantation. *BioDrugs* 2001;**15**:37–53.

Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Young Y, Plosker G. Mycophenolate mofetil. A pharmacoeconomic review of its use in solid organ transplantation. *Pharmacoeconomics* 2002; **20**:675–713.

Studies

Baker GM, Martin JE, Jang R, Schroeder TJ, Armitstead JA, Myre S, *et al*. Pharmacoeconomic analysis of mycophenolate mofetil versus azathioprine in primary cadaveric renal transplantation. *Transplant Proc* 1998;**30**: 4082–4.

Deierhoi MH, *et al*. Cost considerations and the use of mycophenolate mofetil in renal transplantation. 24th Annual Meeting 1998. *Transplantation* 1998;**66** (Suppl 5): Abstract 19.

Keown P. Analysis of cost-effectiveness and cost utility for immunosuppressive protocols in renal transplantation. *Transplant Proc* 1999;**31**: 1140–1.

Khosla UM, Martin JE, Baker GM, Schroeder TJ, First MR. One-year, single-center cost analysis of mycophenolate mofetil versus azathioprine following cadaveric renal transplantation. *Transplant Proc* 1999;**31**:274–5.

Schnitzler MA.Ten-year cost effectiveness of alternative immunosuppression regimens in cadaveric renal transplantation. *Transplant Proc* 1999;**31** (3B Suppl):19–21S.

Suleymanlar G, Tuncer M, Sarikaya M, Ersoy F, Atkan S, Yakupoglu G, *et al*. The cost effectiveness of mycophenolate mofetil in the first year after living related renal transplantation. *Transplant Proc* 2001;**33**:2780–1.

Sullivan SD, Garrison LP Jr, Best JH. The cost effectiveness of mycophenolate mofetil in the first year after primary cadaveric transplant. US Renal Transplant Mycophenolate Mofetil Study Group. *J Am Soc Nephrol* 1997;**8**:1592–8.

Wuthrich RP, Weinreich T, Ambuhl PM, Schwarzkopf AK, Candinas D, Binswanger U. Reduced kidney transplant rejection rate and pharmacoeconomic advantage of mycophenolate mofetil. *Nephrol Dial Transplant* 1999;**14**:394–9.

Sirolimus

Manninen D, Dong F, Wang F, for the Rapamune US Study Group. Economic evaluation of sirolimus therapy in the first year following renal transplantation. *Transplantation* 2000;**69**(S337): Abstract 871.

Acute rejection therapy

Sakamaki *et al*. Abstract PKU6. *Value in Health* 1999;**2**:204–5.

Appendix 6

Included quality of life studies

Basiliximab

Polsky D, Weinfurt KP, Kaplan B, Kim J, Fastenau J, Schulman KA. An economic and quality-of-life assessment of basiliximab vs antithymocyte globulin immunoprophylaxis in renal transplantation. *Nephrol Dial Transplant* 2001;**16**:1028–33.

Ciclosporin: Neoral

Booth-Clibborn N, *et al*. Tacrolimus after kidney transplantation. Wessex Institute for Health Research and Development; 1997.

Chilcott J, Corcoran M, Rigg KM. Tacrolimus and mycophenolate mofetil as maintenance immunosuppressants following renal transplantation. Sheffield: Trent Institute for Health Services Research; 1999.

Lee KL, Pang YL, Chou TL, Kee KT, Chung HM. Economic evaluation of therapeutic drug monitoring services in renal transplant recipients treated with cyclosporin. *Transplant Proc* 2000;**32**:1801–6.

Reimer J, Franke GH, Philip T, Heemann U, *et al*. Quality of life in kidney recipients: comparison of tacrolimus and ciclosporin microemulsion. *Clin Transpl* 2002;**16**:48–54.

Shield CF, Jacobs RJ, Wyant S, Das A, *et al.* A cost-effectiveness analysis of OKT3 induction therapy in cadaveric kidney transplantation. *Am J Kidney Dis* 1996;**27**:855–64.

Mycophenolate mofetil

Keown P. Analysis of cost effectiveness and cost utility for immunosuppressive protocols in renal transplantation. *Transplant Proc* 1999;**31**:1140–1.

Appendix 7

Included RCTs of induction with daclizumab

TABLE 36 *Trial characteristics: daclizumab*

Characteristic	Vincenti *et al.*, 1998[45]	Nashan *et al.*, 1999[46] Charpentier, 2001[47]	Lacha *et al.*, 2000, 2001[48,49]
Design	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Prospective, randomised, open-label, single-centre
Country	USA, Canada, Sweden, Australia	USA, Canada, Sweden, Australia	Czech Republic
Years of patient recruitment	NR	NR	NR
Inclusion criteria	First transplant, allograft	NR	NR
Exclusion criteria	Multiple transplants, positive cross-match for T-cell lymphocytes	NR	NR
Follow-up period	12 months initially, extended to 36 months	12 months initially, extended to 36 months	6 months

NR, not reported.

TABLE 37 *Immunosuppressive regimens of studies: daclizumab*

Regimen	Vincenti *et al.*, 1998[45]	Nashan *et al.*, 1999[46], Charpentier 2001[47]	Lacha *et al.*, 2000, 2001[48,49]
Drugs of interest	Daclizumab five doses i.v.: 1 mg kg^{-1} to 100 mg at 24 hours pretransplant, then at 2, 4, 6 and 8 weeks; or placebo	Daclizumab five doses i.v.: 1 mg kg^{-1} to 100 mg at 24 hours pretransplant, then at 2, 4, 6 and 8 weeks; or placebo	Daclizumab 2 mg kg^{-1} perioperative, 1 mg kg^{-1} at 7, 14 and 28 days; or OKT3 5 mg on day 1, 2.5 mg on days 2–7
Other drugs	Sandimmun, AZA, prednisolone	Sandimmun, prednisolone	Ciclosporin, MMF, steroid
Comments			

TABLE 38 *Patient characteristics: daclizumab*

Characteristic	Vincenti et *al.*, 1998[45] (Daclizumab; placebo)	Nashan et *al.*, 1999[46], Charpentier, 2001[47] (Daclizumab; placebo)	Lacha et *al.*, 2000, 2001[48,49] (Daclizumab; OKT3)
Numbers	126; 134 (Total *n* = 260)	140; 133 (Total *n* = 273)	14; 14 (Total *n* = 28)
Mean age (years)	Comparable	46; 44	Comparable
Proportion male (%)	Comparable	67; 74	Comparable
Donor	No significant differences	All cadaveric	NR
Delayed graft function	NR	NR	8; 6
First transplant	All	All	None, all were retransplants
Race or ethnic group (%)	Comparable	94; 96	NR
Cause of ESRD (%) Hypertension Diabetes Glomerulonephritis Heredity Other/uncertain	Comparable	 4; 7 8; 3 41; 43 14; 15 22; 19	NR
Sensitisation (PRA) 0–10% 11–49% 50–100%	Comparable	 85; 87 9; 13 6; 0	Comparable
HLA matches (%) 0 1 2	No significant difference	 6; 6 14; 8 42; 46	Comparable
Graft cold ischaemic time (hours)	No significant difference	23; 22	NR

ESRD, end-stage renal disease.

TABLE 39 *Assessment of trial quality: daclizumab*

Quality criteria	Vincenti et *al.*, 1998[45]	Nashan et *al.*, 1999[46], Charpentier, 2001[47]	Lacha et *al.*, 2000, 2001[48,49]
Method of randomisation stated	NR	NR	NR
Method of allocation concealment stated	NR	NR	NR
Blinding undertaken	Yes	Yes	NR
Withdrawals (%)	NR	Initially 3 dropouts, due to no drugs given or no transplant received	NR
Analysis by ITT	Yes	Yes	NR
Jadad score	2	3	0

TABLE 40 *Outcome results at 12 months: daclizumab*

Outcome	**Vincenti *et al.*, 1998[45] (Daclizumab; placebo)**	**Nashan *et al.*, 1999[46], Charpentier, 2001[47] (Daclizumab; placebo)**	**Lacha *et al.*, 2000, 2001[48,49] (Daclizumab; OKT3)**
Graft survival	95%; 90%	88%; 83%	12/14; 12/14
Patient survival	98%; 96%	99%; 94%	Similar in both groups
Acute rejection	BPAR: 22%; 35%	At 6 months: 28%; 47%	Patients with episode: 7/14; 6/14
Adverse events	No significant differences between placebo and daclizumab Malignancies: 2; 4 patients	Systemic infection: 74%; 72% Local infection: 56%; 54% PTLD: 0; 1 patient	Daclizumab: none OKT3: nine patients with first dose syndrome
Serum creatinine	NR	150; 168 μmol l^{-1}	NR
Treatment withdrawals, discontinuations or cross-overs	85%; 80%	82%; 83%	NR
Non-compliance	95%; 90%	88%; 83%	12/14; 12/14

TABLE 41 *Outcome results at 36 months: daclizumab*

	Vincenti *et al.*, 1998[45] (Daclizumab; placebo)	**Nashan *et al.*, 1999,[46] Charpentier, 2001[47] (Daclizumab; placebo)**
Outcome: timing	36 months, reported in Bumgardner *et al*.[43]	36 months, reported in Bumgardner *et al*.[43]
Serum creatinine	1.8; 1.7	1.7; 1.8
Graft survival	84%; 83%	82%; 78%
Patient survival	92%; 94%	96%; 88%
Side-effects	Malignancies: 7.9%; 6.7%	4.9%; 8.9%
Subgroups	None	None

Appendix 8

Included RCTs of induction with basiliximab

TABLE 42 *Trial characteristics: basiliximab*

Characteristic	Nashan et *al.*, 1997[52]	Kahan et *al.*, 1999[53] (US Simulect study)	Ponticelli et *al.*, 2001[55] (Simulect Phase IV study)	Folkmane et *al.*, 2002[56]	Sollinger et *al.*, 2001[57]	Lebranchu et *al.*, 2000[58] (abstract)	Lawen et *al.*, 2000[59] (abstract)	Shidban et *al.*, 2000[60] (abstract)
Design	Randomised, double-blind, placebo-controlled	Randomised, double-blind, placebo-controlled	Randomised, double-blind placebo-controlled	Randomised, controlled	Randomised, open-label	Randomised	Randomised, double-blind, controlled	Randomised
Country	Europe, Canada, 21 centres	USA, 21 centres	Europe, Mexico, South Africa, Israel, 31 centres	Latvia	USA, six centres	France	Canadian centre; part of Simulect international study group	USA
Years of patient recruitment	1995–1996	NR	NR	1997–1999	NR	NR	NR	January to July 1999
Inclusion criteria	First transplant, cadaveric donor, age 18–75 years, at least one HLA class I or II mismatch, negative pregnancy test, adequate contraception	First transplant, cadaveric or at least one haplotype living donor, age 8–65 years, negative pregnancy test, adequate contraception	Male and female, age 18–70 years, first or second transplant, negative pregnancy test, adequate contraception	First or second transplant, cadaveric donor, age 15–70 years	Age 18–75 years, cadaveric or living related recipients	NR	NR	NR
Exclusion criteria	Multiple transplants, positive cross-match for T-cell lymphocytes, severe active infection	NR	HIV positive, hepatitis, ABO incompatible, prior use of study drugs, PRA >80%. positive T-cell cross-match, asystolic donor, HLA identical, multiple organ transplant, previous induction therapy	NR	HLA-identical recipients, previous transplants, other organ transplants, third or more renal transplant, arrhythmia, prior use of study drugs, pregnancy, history of malignancy, MI, HIV positive	NR	NR	NR
Follow-up period	6-month trial and 6-month follow-up	12 months, extended to 5 years	12 months	12 months	12 months	6 months	6 months	6 months

MI, myocardial infarction.

TABLE 43 *Immunosuppressive regimens of studies included in analysis: basiliximab*

Regimen	Nashan et *al.*, 1997[52]	Kahan et *al.*, 1999[53] (US Simulect study)	Ponticelli et *al.*, 2001[55] (Simulect Phase IV study)	Folkmane et *al.*, 2002[56]	Sollinger et *al.*, 2001[57]	Lebranchu et *al.*, 2000[58] (abstract)	Lawen et *al.*, 2000[59] (abstract)	Shidban et *al.*, 2000[60] (abstract)
Drugs of interest	Basiliximab 20 mg i.v.: two doses on day 0 and day 4; or placebo	Basiliximab 20 mg i.v.: two doses on day 0 and day 4; or placebo	Basiliximab 20 mg i.v.: two doses on day 0 and day 4; or placebo	Basiliximab 2 × 20 mg	Basiliximab 20 mg on days 0 and 4; or ATG 15 mg per day up to day 14	Basiliximab or ATG	Basiliximab or placebo	Basiliximab 20 mg on days 1, 4 and 20; or OKT3 on days 7–10
Other drugs	Neoral, prednisolone	Neoral, steroids	Neoral, steroids, AZA	CsA, prednisolone, AZA or MMF (1) CsA + prednisolone + AZA (2) CsA + prednisolone + MMF (3) Basiliximab + CsA + AZA + prednisolone	Neoral, MMF, steroids	Neoral + MMF + steroids	Neoral + MMF + steroids	All received Neoral, MMF and prednisolone

CsA, ciclosporin A.

TABLE 44 *Patient characteristics: basiliximab*

Characteristic	Nashan et *al.*, 1997[52] (Basiliximab; placebo)	Kahan et *al.*, 1999[53] (US Simulect study) (Basiliximab; placebo)	Ponticelli et *al.*, 2001[55] (Simulect Phase IV study) (Basiliximab; placebo)	Folkmane et *al.*, 2001[56] (Arm 1; arm 2; arm 3)	Sollinger et *al.*, 2001[57] (Basiliximab; ATG)	Lebranchu et *al.*, 2000[58] (abstract) (Basiliximab; ATG)	Lawen et *al.*, 2000[59] (abstract) (Basiliximab; placebo)	Shidban et *al.*, 2000[60] (abstract) (Basiliximab; OKT3; no therapy)
Numbers	193; 87 (Total *n* = 380)	173; 173 (Total *n* = 348)	168; 172 (Total *n* = 340)	= 25; 23; 23 (Total *n* = 71)	70; 65 (Total *n* = 135)	Split not reported (Total *n* = 103)	59; 64 (Total *n* = 123)	22; 20; 41 (Total *n* = 83)
Mean age (years)	49; 48	44.9; 46.2	44.2; 44.2	45.1; 40.6; 39.8	44.5; 49.8	Reported as similar across groups	Average across two arms: 45.7	Reported as no significant differences in demographics in each group
Proportion male (%)	66.3; 63.4	64; 62	65.5; 68.8	NR	53; 65%	Similar across groups	NR	No significant differences
Donor	All cadaveric	Cadaveric: 69%; 71%	Cadaveric: 83.9%; 81.4%	All cadaveric	Cadaveric: 60; 65%	NR	NR	No significant differences
Delayed graft function (%)	35.6; 31.5	17; 20	25.5; 36.9	NR	NR	NR	NR	No significant differences
First transplant	All	All	156; 161	NR	91%; 91% All *De novo*	NR	109 patients were primary graft recipients	No significant differences
Race or ethnic group, proportion white (%)	94.2; 96.2	68; 61	86.9; 87.2	No difference across groups	79; 85	Reported as similar across groups	NR	No significant differences
Cause of ESRD (%)			Data not shown	Data not shown	NR	Reported as similar across groups	NR	No significant differences
Hypertension	7							
Diabetes	4.8	28.9; 22.5%						
Glomerulo-nephritis	40.3							
Heredity	16.7	Other data not shown: no difference across groups						
Other/ uncertain	28.9; 21.6							

continued

TABLE 44 *Patient characteristics: basiliximab (cont'd)*

Characteristic	Nashan *et al.*, 1997[52] (Basiliximab; placebo)	Kahan *et al.*, 1999[53] (US Simulect study) (Basiliximab; placebo)	Ponticelli *et al.*, 2001[55] (Simulect Phase IV study) (Basiliximab; placebo)	Folkmane *et al.*, 2001[56] (Arm 1; arm 2; arm 3)	Sollinger *et al.*, 2001[57] (Basiliximab; ATG)	Lebranchu *et al.*, 2000[58] (abstract) (Basiliximab; ATG)	Lawen *et al.*, 2000[59] (abstract) (Basiliximab; placebo)	Shidban *et al.*, 2000[60] (abstract) (Basiliximab; OKT3; no therapy)
Sensitisation (PRA) (%)	Mean: 7.4; 9.4	6.2; 8.5 Highest pretransplant	1.6; 1.6	Data not shown: no difference	NR	Reported as similar across groups	NR	NR
HLA matches (%)	3.2; 3.0	4.0; 3.9	2.9; 2.9	NR				
0					9; 9	Reported as similar across groups	NR	NR
1					11; 5			
2					20; 18			
Graft cold ischaemic time (hours)	21.4; 20.7	22.1; 21.5	16.3; 15.6		21.2; 21.9	Reported as similar across groups	NR	Reported as slightly higher in basiliximab group
Comments						Abstract only	Abstract only	Abstract only

TABLE 45 *Assessment of trial quality: basiliximab*

Quality criteria	Nashan et *al.*, 1997[52] (Basiliximab; placebo)	Kahan et *al.*, 1999[53] (US Simulect study) (Basiliximab; placebo)	Ponticelli et *al.*, 2001[55] (Simulect Phase IV study) (Basiliximab; placebo)	Folkmane et *al.*, 2002[56] (Arm 1; arm 2; arm 3)	Sollinger et *al.*, 2001[57]	Lebranchu et *al.*, 2000[58] (abstract)	Lawen et *al.*, 2000[59] (abstract)	Shidban et *al.*, 2000[60] (abstract)
Method of randomisation stated	Random number generation	NR, 1:1	Central list	Method not stated	Stratified	NR	1:1	NR
Method of allocation concealment stated	Yes	NR	Yes	NR	NR	NR	NR	NR
Blinding undertaken	Yes	Yes, but method not stated	Yes	No	Open-label	NR	Yes	NR
Withdrawals	Completed: 168/186; 165/190	Completed: 166/174; 166/174	Completed: 151/168; 151/172	NR	3	Yes	NR	NR
Analysis by ITT	Yes	Yes	Yes	No	Yes	Not clear	Not clear	NR
Jadad score	5	2	5	0	3	1	1	0

TABLE 46 *Outcome results at 6 or 12 months: basiliximab*

Outcome	Nashan et *al.*, 1997[52] (Basiliximab; placebo)	Kahan et *al.*, 1999[53] (US Simulect study) (Basiliximab; placebo)	Ponticelli et *al.*, 2001[55] (Simulect Phase IV study) (Basiliximab; placebo)	Folkmane et *al.*, 2002[56] (Arm 1; arm 2; arm 3)	Sollinger et *al.*, 2001[57] (Basiliximab; ATG)	Lebranchu et *al.*, 2000[58] (abstract) (Basiliximab; ATG)	Lawen et *al.*, 2000[59] (abstract) (Basiliximab; ATG)	Shidban et *al.*, 2000[60] (abstract) (Basiliximab; OKT3; no therapy)
Time-point					12 months	6 months	6 months	3 months and 6 months
Graft survival	87.9%; 86.6% 170/190; 162/186	94.6%; 93% 164/173; 161/173	90.5%; 88.4% 152/168; 152/172	Loss: 3/25; 2/23; 2/23	97%; 98% 68/70; 64/65	94%; 100% 49/52; 51/51	94.9%; 92.2% 56/59; 59/64	At 6 months: 91%; 90%; 97%
Patient survival	95.3%; 97.3% 184/190; 182/186	97.1%; 96.0% 168/173; 166/173	97.6%; 97.1% 164/168; 167/172	NR	94%; 97% 66/70; 63/65	97%; 100% 50/52; 51/51	NR	At 6 months: 96%; 100%; 97%
Acute rejection	34.2%; 52.2 51/190; 73/186	35.3%; 49.1% BPAR 61/173; 85/173	18.5%; 29.1% BPAR at 6 months 31/168; 50/172	32%; 21.7%; 17.3% 8/25; 5/23; 14/23	19%; 20% 13/70; 13/65	BPAR (cellular): 8.3%; 5.4% 4/52; 3/51	BPAR: 15.3%; 25.6% 9/59; 17/64	3-month acute rejection: 5%; 20%; 17%
Adverse events	No cytokine release syndrome Infection: 84.7%; 86.6% Malignancies: 3; 2 patients PTLD: 1; 1 patients	Any: 100%; 100% Infection: 75%; 73% Neoplasm: 6; 2 patients	Any: 88.7%; 87.8% Infection: 65.5%; 65.7% Malignancies 3; 6 patients	NR	Serious events: 61%; 66% Infections: 76%; 77% Neoplasms: 1%; 5%	No neoplasia in either group; other side-effects reported as similar in both groups	No malignancies or lymphomas in either group infections: 62.7%; 70.3%	NR
Serum creatinine	Creatinine clearance: 52.2; 54.1	2.0; 2.2	59.49; 58.87	NR	At 4 weeks to 12 months: 1.62; 1.71 mg dl^{-1}	NR	NR	NR
Treatment withdrawals, discontinuations or cross-overs	NR	NR	NR	NR	NR	NR	NR	NR
Non-compliance	NR	NR	NR	NR	NR	NR	NR	NR
Outcome at time-point 2					NA	NA	NA	NA

TABLE 47 *Outcome results at >12 months: basiliximab*

Outcome	**Nashan et *al.*, 1997[52] (Basiliximab; placebo)**	**Kahan et *al.*, 1999[53] (US Simulect study) (Basiliximab; placebo)**	**Ponticelli et *al.*, 2001[55] (Simulect Phase IV study) (Basiliximab; placebo)**
Outcome	None	None	Second transplant acute rejection: 16.7%; 36.4%
Serum creatinine	Good quality, creatinine clearance not serum	NR	NR
Subgroup analysis	NA	Male: 38; 58 Female: 37; 49 <50 years: 38; 60 >50 years: 37; 48 Black: 47; 59 Other: 34; 53 Cadaveric: 42; 58 Living: 28; 47 ARR	NA
Comments		Unusual reporting of side-effects	

Appendix 9

Included RCTs of tacrolimus versus Sandimmun treatment

TABLE 48 *Trial characteristics: tacrolimus versus ciclosporin treatment*

Regimen	Vincenti *et al.*, 1996[79]	Shapiro *et al.*, 1991[83]	Radermacher *et al.*, 1998[89]	US FK506 Kidney Transplant Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots *et al.*, 2001[174]
Design	RCT,[a] multicentre	RCT,[b] single-centre	RCT, single-centre	RCT, open-label, multicentre, Phase III	RCT, open-label, multicentre	RCT, single-centre
Country	USA, five centres	USA	Germany	USA, 19 centres	Europe, 15 centres including UK	The Netherlands
Years of patient recruitment	NR	1989–1991	1993–1994	1993–1994	1993–1994	NR
Inclusion criteria	First transplant	Age >18 years, first transplant	Age ≥ 18 years, first transplant	Age ≥ 6 years, first or second transplant	Age ≥ 18 years	Age ≥ 18 years
Exclusion criteria	Vasculitis, arteritis, liver dysfunction, pregnancy, intolerance to ciclosporin, ALG, ABO donor incompatability, positive serum cross-matches	Previous or concomitant liver transplant	Collagen vascular disease, diabetic nephropathy, significant liver disease, HIV+, other transplants, pregnancy, allo-T-cell antibodies > 20%, ABO donor incompatability, positive T-cell cross-match, leucocytopenia	HIV+, ABO-incompatible grafts, multiple organ transplants, pregnancy, significant liver disease	Allergy or intolerance to ciclosporin or FK506, ABO-incompatible grafts, use of ciclosporin or FK506 in past 28 days, positive T-cell cross-match, HIV+, pregnancy	Recipients of previous solid-organ transplant, ABO-incompatible grafts and still on immunosuppressive drugs, pregnancy, HIV+
Follow-up period	12 months	12 months	6 weeks	12 months	12-months	12 months and 18 months, 2 and 3 years

[a] Tacrolimus dose-ranging study.
[b] Randomised within non-randomised study.

TABLE 49 *Immunosuppressive regimens of studies included in analysis: tacrolimus versus ciclosporin treatment*

Regimen	Vincenti *et al.*, 1996[79]	Shapiro *et al.*, 1991[83]	Radermacher *et al.*, 1998[89]	US FK506 Kidney Transplant Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots *et al.*, 2001[174]
Induction	ALG	None	None	ATGAM or OKT3 for 14 days	None	None
Tacrolimus (mg kg^{-1} per day)	0.4–0.8 oral*	0.1 i.v. to 0.3 oral	0.2–0.3 oral†	Started 1–15 days post-transplant, 0.2 oral	0.1 i.v. to 0.3 oral	0.3§
Azathioprine (mg kg^{-1} per day)	1.4 i.v. then 1–1.5 oral	NR	2 i.v. then 1–2 oral	2–4 i.v. then 1–1.5 oral	2 i.v. then 1–2 oral	2
Prednisolone	2 mg kg^{-1} tapered to 30 mg per day	Range used: 2.5–5.0 mg per day to 17.5–12.0 mg per day	500 mg i.v. preoperatively; 20 mg oral then tapered to 5 mg every 2 weeks	500 mg i.v. preoperatively then 5–0.5 mg kg^{-1} per day, tapered to 7.5–10 mg per day 3 months post-transplant	500 mg i.v., tapered to 20–5 mg per day	
Ciclosporin (mg kg^{-1} per day)	6–14 oral	NR	5–8 oral‡	10 oral	8 oral	8 oral¶
Trough concentration (mg dl^{-1}) at 1 week: Tacrolimus Ciclosporin	*5–14 ng ml^{-1} 15–15 ng ml^{-1} 26–40 ng ml^{-1}	NR	†Maintain trough concentration 5–20 ng ml^{-1} ‡Maintain trough concentration at 100–150 ng ml^{-1}	Median 11.3, median 269 at 1 week	Mean 13.9, mean 254 at 1 week	§After month 3: 7–10 ng ml^{-1} ¶After month 3: 100–150 ng ml^{-1}

TABLE 50 *Patient characteristics (figures are given for tacrolimus; ciclosporin)*

Characteristic	Vincenti et *al.*, 1996[79]	Shapiro et *al.*, 1991[83]	Radermacher et *al.*, 1998[89]	US FK506 Kidney Transplant Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots et *al.*, 2001[174]
Patient numbers	92; 28	28; 29	28; 13	205; 207	303; 145	11; 12
Mean age (years)	44.1; 46.6	36.5; 39.4	41.3; 47.1	43.4; 43.6	46.6; 45.8	45; 47
Proportion male (%)	65; 78	NR	63; 50	60; 62	65; 63	73; 75
Donor	Cadaveric	Cadaveric; living	Cadaveric	Cadaveric	Cadaveric	Cadeveric
Duration of dialysis (years)	NR	NR	4.3; 5.2	NR	NR	NR
First transplant (%)	100; 100	100; 100	89; 85	87; 87	90; 90	82; 75
Race or ethnic group, proportion white (%)	51; 54	NR	NR	56; 59	NR	NR
Diagnosis (%)						
Hypertension	19; 25	NR	59; 50	21; 19	8; 8	NR
Diabetes	26; 25	NR	NR	19; 19	5; 4	0; 0
Glomerulonephritis	16; 25	NR	NR	18; 14	40; 43	NR
Heredity	15; 14	NR	NR	11; 8	15; 14	NR
Other	24; 11	NR	NR	31; 40	32; 31	NR
Sensitisation (PRA)	NR	NR	4.2; 3.1	NR	NR	NR
HLA matches (%):						
0	NR	NR	NR	21; 13	65; 68	NR
1				40; 52	24; 28	
2				40; 36	11; 5	
Graft cold ischaemic time (hours)	NR	33.8; 33.2	22;24	NR	NR	NR

TABLE 51 *Assessment of trial quality: tacrolimus versus ciclosporin treatment*

Quality criteria	Vincenti *et al.*, 1996[79]	Shapiro *et al.*, 1991[83]	Radermacher *et al.*, 1998[89]	US FK506 Kidney Transplant Study Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots *et al.*, 2001[174]
Method of randomisation stated	NR	NR	NR	NR	NR	NR
Method of allocation concealment stated	Yes (central location)	NR	NR	NR	NR	Sealed envelopes
Blinding undertaken (by whom)	No (open study)	NR	NR	Yes (independent clinician)	NR	NR
Withdrawals (%)	29%	NR	17% (12 months)	0 (12 months)	0 (12 months)	21% (reasons given)
Analysis by ITT	Yes (but not for withdrawals)	NR	No	Yes	Yes	NR
Jadad score	2	1	2	1	2	1
Comment				BPAR		

TABLE 52 *Outcome results at 1 year (figures are given for tacrolimus; ciclosporin)*

Quality criteria	Vincenti et *al.*, 1996[79]	Shapiro et *al.*, 1991[83]	Radermacher et *al.*, 1998[89]	US FK506 Kidney Transplant Study Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots et *al.*, 2001[174]
Patient survival	90/92 (98%)*†; 26/28 (92%)*† (ns)	27/28 (96.4%); 26/29 (89.6%) ($p = 0.611$)‡§	NR	196/205 (95.1%); 200/207 (96.6%) ($p = 0.576$)	282/303 (93.0%)¶¶; 140/145 (96.5%) ($p = 0.140$)	NR
Graft survival	85/92 (93%)*†; 25/28 (89%)*† (ns)	25/28 (82.1%); 23/29 (79.1%) ($p = 0.470$)‡§	NR	187/205 (91.2%); 182/207 (87.9%) ($p = 0.289$)	250/303 (82.5%)¶¶; 125/145 (86.3%) ($p = 0.380$)	NR
Graft survival excluding deaths	NR	26/28 (92.8%); 26/29 (89.6%) ($p = 1.000$)	NR	195/205 (95.1%); 188/207 (90.8%) ($p = 0.098$)	265/303 (87.4%); 127/145 (87.6%) ($p = 0.967$)	NR
Acute rejection[a]	12/92 (13.0%)*†; 6/28 (21.4%)*† ($p = 0.46$)	NR	11/33 (33%); 8/15 (53%)	63/205 (30.7%); 96/207 (46.3%) ($p = 0.001$)	73/303 (24.1%); 63/145 (43.4.%) ($p < 0.001$)	NR
Antilymphocyte antibody rejection treatment	Figures not reported (ns)	NR	NR	22/205 (10.7%); 52/207 (25.1%) ($p < 0.001$)	31/303 (10.2%); 30/145 (20.7%) ($p = 0.004$)	NR
Adverse events (events that achieve $p \leq 0.05$)	T = C: nephroxicity, creatinine, GFR, PTDM, infections T > C: nausea/vomiting	T > C: cholesterol concentration T = C: creatinine, uric acid	No differences achieved statistical significance** T > C: plasma glucose††	T > C: tremor, PTDM, purities, allopecia C > T: hypercholesterolaemia, hirsutism, gingivitis, gum hyperplasia C = T: renal function, gastrointestinal disorders, cardiovascular disorders, infection, malignancies	T > C: creatinine concentration, hypergylcaemia, PTDM, tremor, diarrhoea, angina, arrhythmia, fungal infections, angina pectoris C > T: acne, gingivitis, hirsutism, arrhythmia C = T: need for dialysis, MI, hypertension, malignancies	C = T: PTDM***

continued

TABLE 52 *Outcome results at 1 year (figures are given for tacrolimus; ciclosporin) (cont'd)*

Quality criteria	Vincenti *et al.*, 1996[79]	Shapiro *et al.*, 1991[83]	Radermacher *et al.*, 1998[89]	US FK506 Kidney Transplant Study Group, 1999[75]	European Tacrolimus Multicentre Renal Study, 1998[84]	Boots *et al.*, 2001[174]
Quality of life	NR	NR	NR	SF-36:T = C (with exception of general health perceptions T > C) Bergner Physical Appearance scale: T >C[‡‡] Fleming Self-Esteem: T = C	NR	NR
Treatment withdrawals, discontinuations or cross-overs	32/92[‡]; 6/28	NR; 9/29[¶]	NR	14/205 (6.8%)[§§]; 32/207 (15.4%) (p = 0.007)	91/303 (30.0%); 23/145 (15.9%) (p = 0.002)	NR
Comments	*Kaplan–Meier estimates [†]Pooled across tacrolimus doses [‡]Treatment withdrawals	[‡]p-Values not reported [§]Actuarial survival figures [¶]Treatment cross-overs	**At 6 weeks [††]7–9 months following	[‡‡]Higher quality of life [§§]Cross-overs	[¶¶]Actuarial survival rates	***Also no difference at 3 years

[a] One or more episode and biopsy confirmed.
T, tacrolimus; C, ciclosporin; ns, not significant.

TABLE 53 *Outcome results at 18 months (figures are given for tacrolimus; ciclosporin)*

Outcome	US FK506 Kidney Transplant Study Group, 1999[75]
Patient survival	195/205 (95.1%); 198/207 (95.5%)
Graft survival	NR
Graft survival excluding deaths	183/195 (93.7%); 177/198 (89.4%)
Acute rejection[a]	NR
Antilymphocyte antibody rejection treatment	NR
Adverse events	T = C: nephrotoxicity, gastrointestinal and cardiovascular events, malignancies T > C: IDDM, tremor
Quality of life	NR
Withdrawals due to adverse events	NR
Treatment failures	NR

[a] One or more episode and biopsy confirmed.

TABLE 54 *Outcome results at 2 years (figures are given for tacrolimus; ciclosporin)*

Outcome	US FK506 Kidney Transplant Study Group, 1998[73]
Patient survival	Not reported
Graft survival	187/205 (91.2%); 183/207 (88.4%)
Acute rejection[a]	7/79 (8.9%); 6/65 (9.2%) ($p = 0.92$)
Antilymocyte antibody rejection treatment	NR
Adverse events	NR
Withdrawals due to adverse events	NR
Quality of life	NR

[a] One or more episode and biopsy confirmed.

TABLE 55 *Outcome results at 3 or more years (figures are given for tacrolimus; ciclosporin)*

Outcome	US FK506 Kidney Transplant Study Group, 2001[76]	US FK506 Kidney Transplant Group, 2002[77]	European Tacrolimus Multicentre Renal Study, 1999[86]	European Tacrolimus Multicentre Renal Study, 2002[87]
Follow-up	3 years	5 years	4 years	5 years
Patient survival	188/205 (91.7%); 191/207 (92.3%) ($p = 0.773$)	162/205 (79.1%)*; 168/207 (81.4%) ($p = 0.472$)	258/303 (85.2%); 128/145 (88.0%) ($p = 0.127$)‡	252/303 (83.2%); 124/145 (85.3%) ($p = 0.583$)§
Graft survival	168/205 (81.9%); 161/207 (77.8%) ($p = 0.405$)	132/205 (64.3%)*; 127/207 (61.6%) ($p = 0.558$)	218/303 (72.0%); 103/145 (71.3%) ($p = 0.523$)‡	212/303 (70.0%); 94/145 (65.2%) ($p = 0.280$)§
Graft survival excluding deaths	184/205 (89.8%); 164/207 (83.6%) ($p = 0.044$)	NR	NR	NR
Acute rejection[a]			NR	NR¶
Antilymphocyte antibody rejection treatment			NR	NR
Adverse events	T > C: PTDM C > T: cholesterol, triglycerides, LDL, use of lipid-lowering drugs C = T: CMV infection, gastrointestinal disease, renal function, malignancies	T > C: PTDM, fungal dermatitis, pneumonia C > T: creatinine, hypercholesterolaemia, use of antihypertensives, oral moniliasis† C = T: all malignancy	T > C: PTDM C > T: hypercholesterolaemia C = T: CMV infection, creatinine	T = C: malignancies
Treatment withdrawals, cross-over and discontinuations		(43.8%) (higher, figure not reported) ($p = 0.008$)		
Treatment cross-overs	17/205 (8.3%); 50/207 (24.2%) ($p < 0.05$)	19/205 (9.3%); 57/207 (27.5%) ($p < 0.001$)		
Treatment failures				
Quality of life	Not reported	Not reported		

continued

TABLE 55 *Outcome results at 3 or more years (figures are given for tacrolimus; ciclosporin) (cont'd)*

Outcome	US FK506 Kidney Transplant Study Group, 2001[76]	US FK506 Kidney Transplant Group, 2002[77]	European Tacrolimus Multicentre Renal Study, 1999[86]	European Tacrolimus Multicentre Renal Study, 2002[87]
Comments	Trough blood levels at 3 years: Tacrolimus: mean 9.2 ng ml^{-1} Ciclosporin: mean 189.0 ng ml^{-1} Mean dose of steroids: T < C	*Kaplan–Meier estimates Dose: tacrolimus: mean 0.12 Ciclosporin: mean 4.2 Trough blood levels: Tacrolimus: 8.5 ng ml^{-1} Ciclosporin: 174 ng ml^{-1} †More use of lipid-reducing drugs	‡*p*-Values for survival analysis	§*p*-Values not reported ¶Reported only late acute rejections (>12 months)

[a] One or more episode and biopsy confirmed.

TABLE 56 *Subgroup analyses: tacrolimus versus ciclosporin treatment*

Study	Race or ethnic group	High versus low risk
US FK506 Kidney Transplant Study Group	Caucasian vs African–American; Neylan[71,72] at 1 year and 3 years 1 year: acute rejection T < C and PTDM T > C in African–Americans than Caucasians; higher doses of tacrolimus required in African–Americans 3 years: no significant difference in tacrolimus and ciclosporin treatment effects in Caucasians vs African–Americans; higher doses of tacrolimus required in African–Americans	
European Tacrolimus Multicentre Renal Study		High-risk vs low-risk at 1 year T vs C: no significant differences in outcomes in either high- or low-risk patients High-risk vs low-risk: no significant difference in tacrolimus treatment effect or trough level
Comments		High-risk: PRA grade >80% and/or previous transplant functional for >1 year Numbers of patients small and therefore study likely to be underpowered

Appendix 10

Included RCTs of tacrolimus versus Neoral maintenance

TABLE 57 *Trial characteristics: tacrolimus versus ciclosporin maintenance*

Characteristic	White *et al.*, 2000[90]	Morris-Stiff *et al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang *et al.*, 1999[102]	Raofi *et al.*, 1999[105]	Wang *et al.*, 2000[176]	Johnson *et al.*, 2000[103]
Design	RCT, single-centre	RCT, open-label, single-centre	RCT, open-label, multicentre	RCT, open-label, single-centre	RCT, single-centre	RCT, single-centre	RCT, open-label, multicentre
Country	UK	UK	Europe, 50 centres, no UK centres	USA	USA	China	USA
Years of patient recruitment	NR	1996–1998	NR	1996 (entry to trial)	1994–1997	1998–1999	NR
Inclusion criteria	NR	Age ≥ 16 years	Age 18–60 years	First transplant, age ≥ 18 years	First transplant, Black recipients	Age 18–59 years	First transplant, age ≥ 12 years, ≥ 40 kg
Exclusion criteria	NR	NR	Incompatible ABO donor, previous organ transplant (except renal), high risk of allograft rejection (PRA >50%), need for immunosuppressive therapy for other disorders, HIV+, significant liver/gastrointestinal disorder, evidence or history of malignancy	NR	NR	Previous solid-organ transplant, still receiving immunosuppressive drugs, or have received ABO-incompatible transplant, diabetes mellitus, acute tubular necrosis, HBV-DNA/HCV-DNA-RNA positive, pregnant or nursing	Recipient of paediatric *en bloc* kidneys, asystolic graft, multiorgan transplant, living donor or ABO incompatible, HIV+, pregnancy, drug hypersensitivity, receiving prophylactic immunosuppression
Follow-up period	12 months	3 years	6 months	≥ 12 months	12 months	7–17 months (mean 12.1 months)	12 months

TABLE 58 *Immunosuppressive regimens of studies included in analysis: tacrolimus versus ciclosporin maintenance*

Characteristic	White *et al.*, 2000[90]	Morris-Stiff *et al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang *et al.*, 1999[102]	Raofi *et al.*, 1999[105]	Wang *et al.*, 2000[176]	Johnson *et al.*, 2000[103]
Induction	None	None	None	OKT3[§§]	OKT3	None	OKT3 or antithymocyte globulin[¶¶¶]
Tacrolimus (mg kg^{-1} per day)	0.1–0.2*	0.2[‡]	0.30[¶]	0.16[††]	5 mg per day[††]	0.15–0.30***	0.15–0.26[‡‡‡]
Azathioprine (mg kg^{-1} per day)	None	1.5	2 i.v. or oral on day 1, 1–2 oral on days 1–91	MMF[‡‡] 1000 mg per day	2	MMF 2 g per day	MMF 2 g per day
Prednisolone (mg per day)	Dose not reported	20, tapered during 3 months	500 i.v.: oral 20 mg per day with 5 mg per day each 2 weeks tapering to 5 mg	2 ml kg^{-1} per day, tapered to 0.15	500 i.v.: 1 mg kg^{-1} per day, tapering to 0.2 at 6 months	6 mg kg^{-1} i.v. for 3 days, oral 30 tapered to 15	200, tapered to 10
Ciclosporin (mg kg^{-1} per day)	7–15[†]	8[§]	8–10**	8	NR	6–8[†††]	8–10[§§§]
Trough concentration (mg dl^{-1}) at 1 week: Tacrolimus Ciclosporin	*Trough levels at 3 months: 10–15 [†]Trough levels at 3 months: 200–300	[‡]Trough levels: 5–15 [§]Trough levels: 100–200	[¶]10–20 at 3 months, 5–15 at 3–6 months **100–200 at 3 months, 5–15 at 3–6 months	[††]15–20 at 3 months, 10–15 thereafter [‡‡]300–400 at 3 months, 200–300 thereafter	Mean 12.1 at 3 months Mean 224.4 at 3 months	***10–20 ng ml^{-1} up to 3 months, 5–10 thereafter [†††]250–400 ng ml^{-1} up to 3 months, 150–300 thereafter	[‡‡‡]8–16 ng ml^{-1} up to 3 months, 5–15 thereafter [§§§]200–400 ng ml^{-1} up to 3 months, 100–300 thereafter
Comments				[§§]Cases of delayed graft function or postoperative ATG [‡‡]Low-dose MMF	CMV-positive patients also given acyclovir		[¶¶¶]Induction received by patients who experienced delayed graft function within the first day post-transplant

TABLE 59 *Patient characteristics (figures are given for tacrolimus; ciclosporin)*

Characteristic	White et *al.*, 2000[90]	Morris-Stiff et *al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang et *al.*, 1999[102]	Raofi et *al.*, 1999[105]	Wang et *al.*, 2000[176]	Johnson et *al.*, 2000[103]
Patient numbers	29; 24	90; 89	286; 271	30; 30	14; 21	25; 32	72; 75
Mean age (years)	Median 43	Median 44; 48	42.4; 43.8	46; 48	44; 46	38.1	49.9; 45.9
Proportion male (%)	Overall 64	NR	70; 63	50; 63	57; 76	61	60; 59
Donor	Cadaveric/living/ asystolic	Cadaveric	Cadaveric/living related/living unrelated	Cadaveric/living related	Cadaveric	Cadaveric	Cadaveric
Duration of dialysis (years)	NR	NR	NR	2.3; 2.7	NR	NR	NR
First transplant (%)	NR	80; 85	93; 93	100; 100	100; 100	NR	100; 100
Race or ethnic group, proportion white (%)	NR	NR	99; 99	77; 87	0; 0	NR	63; 68
Diagnosis (%)							
Hypertension	NR	NR	NR	10; 30	NR	NR	18; 16
Diabetes	NR	NR	3.8; 4.4	20; 30	29; 24	NR	29; 32
Glomerulonephritis	NR	NR	38.5; 43.9	30; 23.3	NR	NR	14; 13
Heredity	NR	NR	1.0; 0.7	NR	NR	NR	9; 11
Other	NR	NR	–	–	NR	NR	–
Sensitisation (PRA)	NR	NR	NR	NR	NR	NR	0–9%: 85; 92 10–19%: 3; 0 ≥ 20%: 13; 7
HLA matches (%):		Median 2; 2	Mean 2.51; 2.54		Mean 3.8; 4.5	NR	
0	45; 38			47; 57			7; 9
1	48; 62			37; 30			4; 3
2	27; 0			17; 13			24; 13, rest >2
Graft cold ischaemic time (hours)	13; 14	18.8; 18.2	17.5; 17.6	14; 15	25; 26	NR	18.2; 20.0

TABLE 60 *Assessment of trial quality (figures are given for tacrolimus; ciclosporin)*

Characteristic	White *et al.*, 2000[90]	Morris-Stiff *et al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang *et al.*, 1999[102]	Raofi *et al.*, 1999[105]	Wang *et al.*, 2000[176]	Johnson *et al.*, 2000[103]
Method of randomisation stated	NR	NR	NR	NR	Based on patient number†	NR	NR, randomised by centre
Method of allocation concealment stated	NR	NR	NR	NR	NR	NR	NR
Blinding undertaken	NR	NR	NR	NR	NR	NR	Open-label, NR
Withdrawals reported (%)	NR	NR	Yes (14.7%; 29.5%)	NR	NR	NR	NR‡
Analysis by ITT	NR (but undertaken)	NR (but undertaken)	Yes*	Yes	NR (but undertaken)	NR	Yes
Jadad score	1	1	2	1	1	1	1
Comments			*Does not include three patients (1; 2) excluded post-randomisation for not taking drugs		†Group numbers not balanced 14; 21, no explanation given		‡33 treatment cross-overs

TABLE 61 *Outcome results at 1 year (figures are given for tacrolimus; ciclosporin)*

Characteristic	White et *al.*, 2000[90]	Morris-Stiff et *al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang et *al.*, 1999[102]	Raofi et *al.*, 1999[105]	Wang et *al.*, 2000[176]	Johnson et *al.*, 2000[103]
Patient survival	NR	40/40 (100%); 38/40 (93%) ($p = 0.493$)‡	284/286 (99.3%); 267/271 (98.5%) ($p = 0.371$)¶	27/30 (90%); 30/30 (100%) ($p = 0.20$)**	12/14 (85.7%); 20/21 (95.2%) ($p = 0.71$)	25/25 (100%); 32/32 (100%) ($p = 1.00$)	67/72 (93.1%); 67/75 (89.3%) (p=0.381)¶¶
Graft survival	NR	40/40 (100%); 34/40 (85%) ($p = 0.026$)‡	271/286 (94.8%); 249/271 (91.9%) ($p = 0.170$)¶	27/30 (90%); 29/30 (96.6%) ($p = 0.615$)**	12/14 (85.7%); 20/21 (95.2%) ($p = 0.71$)	25/25 (100%); 29/32 (93.7%)	64/72 (88.9%); 65/75 (86.7%) ($p = 0.437$)¶¶
Graft failure excluding deaths	NR	0/40 (0%)§; 6/40 (15.0%) ($p = 0.026$)‡	13/286 (4.5%); 19/271 (7.0%) ($p = 0.211$)¶	0/30 (0%); 1/30 (3.3%) ($p = 1.000$)**	0/14 (0%); 0/21 (0%) ($p = 1.000$)	NR	NR
Acute rejection[a]	8/29 (27.6%); 6/24 (25.0%)* ($p = 0.832$)†	21/90 (23.2%); 37/89 (42.0%) ($p = 0.046$)‡	56/286 (19.6%); 101/271 (37.3%) ($p < 0.0001$)	4/30 (13.3%); 4/30 (13.3%) ($p = 1.000$)**††	2/14 (14.2%); 8/21 (38.1%) ($p = 0.25$)	1/25 (4.0%); 5/32 (15.6%)	11/72 (15.3%); 15/75 (20.0%) ($p = 0.298$)
Antilymphocyte antibody rejection treatment	1/29 (3.4%); 2/24 (8.3%) ($p = 0.584$)†	2/90 (2.3%); 8/89 (9.3%) ($p = 0.047$)§	27/286 (19.6%); 57/271 (21.0%) ($p < 0.0001$)	1/30 (3.3%); 3/30 (10.0%) ($p = 0.612$)**††	2/14 (14.2%); 3/21 (14.2%) ($p = 1.000$)‡‡	0/25 (0%); 1/32 (3.1%) ($p < 0.01$)	3/72 (4.2%); 8/75 (10.7%) ($p = 0.142$)
Adverse events (events that achieve $p \leq 0.05$)	NR	No significant differences reported§	C > T: hypertension, urinary tract disorder, hypercholesterolaemia, hirsutism, gum hyperplasia, bilirubinaemia, gastrointestinal haemorrhage, cholestatic jaundice T > C: diabetes, tremor, hypomagnesaemia, thrombosis, gastritis	No significant differences reported T = C: infections, tremor, seizure, diabetes, gum hyperplasia, diarrhoea	T = C: diabetes, infection, gingival hyperplasia, T < C: creatinine, cholesterol	T = C: infection, PTDM T < C: creatinine	T > C: none C > T: cholesterol, creatinine C = T: infections, diabetes
Quality of life	NR	NR	NR	NR	NR	NR	NR
Treatment withdrawals, discontinuations or cross-overs	NR	1/40 (2.5%); 5/40 (12.5%)§ ($p = 0.16$)‡	1/298 (0.3%); 27/271 (10.0%) ($p < 0.001$)	1/30 (3.3%); 3/30 (10%) ($p = 0.612$)**	0/14 (0%); 2/21 (9.5%) ($p = 0.506$)	5/25 (20%); 0/32 (0%)§§	7/72 (9.7%); 8/75 (10.7%) ($p = 0.556$)

continued

TABLE 61 *Outcome results at 1 year (figures are given for tacrolimus; ciclosporin) (cont'd)*

Characteristic	White et *al.*, 2000[90]	Morris-Stiff et *al.*, 2000[96]	European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Group, 1997[175]	Yang et *al.*, 1999[102]	Raofi et *al.*, 1999[105]	Wang et *al.*, 2000[176]	Johnson et *al.*, 2000[103]
Comments	*All acute rejections †*p*-Values not reported in paper	‡*p*-values not reported §All at 3-month follow-up	¶*p*-Values not reported	**p*-Values not reported ††at 6 months	‡‡*p*-Values not reported	§§Discontinued therapy	¶¶*p*-Values not reported

[a] One or more episode and biopsy confirmed.

TABLE 62 *Outcome results at > 1 year (figures are given for tacrolimus; ciclosporin)*

Outcome	Johnson et *al*., 2000[103] (2 years)	Morris-Stiff et *al*., 2000[96] (3 years)
Patient survival	68/72 (94.4%); 66/75 (88.0%)* ($p = 0.246$)†	86/90 (95.6%)‡; 82/89 (93.1%)‡ ($p = 0.347$)§
Graft survival	60/72 (82.8%); 59/75 (78.1%)* ($p = 0.411$)†	79/90 (87.8%); 68/89 (76.4%) ($p = 0.05$)¶
Graft survival excluding deaths	NR	4/90 (4.4%)‡; 7/89 (7.9%)‡ ($p = 0.347$)§
Acute rejection[a]	12/72 (16.7%); 17/75 (22.7%) ($p = 0.411$)†	
Antilymphocyte antibody rejection treatment	4/72 (5.6%); 9/75 (12.0%) ($p = 0.240$)*	
Adverse events (events that achieve $p \leq 0.05$)	C > T: creatinine T = C: PTDM	
Quality of life	NR	
Treatment withdrawals, discontinuations or cross-overs	NR	
Comments	*Percentages only reported, not clear if actuarial or Kaplan–Meier, assumed actuarial †*p*-Values not reported	‡Cumulative death §*p*-Values not reported ¶Kaplan–Meier analysis

[a] One or more episode and biopsy confirmed.

TABLE 63 *Subgroup analysis: tacrolimus versus ciclosporin maintenance*

Subgroup examined	Race or ethnic group
Johnson *et al*., 2000[103]	African–American 2 years: same results as all-patient analysis, i.e. biopsy-confirmed and steroid-resistant AR for tacrolimus < Neoral

Appendix 11

Sandimmun versus Neoral treatment double-blind RCTs: *de novo* therapy

TABLE 64 *Trial characteristics and acute rejection rates: Sandimmun versus Neoral treatment*

Characteristic	Keown, 1996[111]	Korn *et al.*, 1997[112]	Niese, 1995[113]	Hricik, 1999[114]	Pescovitz *et al.*, 1997[115]
Design	Randomised, double-blind, multicentre	Randomised, double-blind until 12 months, then non-blind, multicentre	Randomised, double-blind, multicentre	Randomised, double-blind, multicentre	Randomised, double-blind, multicentre
Country	Canada/International	Germany	International	USA	USA
Year of publication	1996	1997	1995	1999	1997
Follow-up (months)	23	24	12	24	24
Patient numbers	167	55	86	255	101
Drug + doses	Tapering doses	Predefined trough levels maintained	Trough level monitored	10 mg kg^{-1} per day + steady trough levels	Variable doses of either Sandimmun or Neoral
Other drugs	Prednisolone and AZA	Steroids and AZA	NR	OKT3, steroids and AZA, use of MMF excluded	NR
ARR Neoral	44.2%	35.7%	42.7%	30.5%	0% year 1–2
ARR Sandimmun	60.5%	55.6%	56.1%	29.4%	4% year 1–2
p-Value	0.44	0.062	–	–	–
Comment				Abstract only	

Appendix 12

Included RCTs of MMF versus azathioprine in a ciclosporin-based regimen

TABLE 65 *Trial characteristics: MMF versus azathioprine with ciclosporin*

Characteristic	Johnson et *al.*, 2000[103], Ahsan et *al.*, 2001[177]	US MMF Trial[117]	Tricontinental MMF Trial[118]	Miladpour et *al.*, 2002[123]	Sadek et *al.*, 2002[124]
Design	Randomised, three-arm, parallel group, open-label, prospective	Multicentre, randomised, double-blind, controlled	Multicentre, randomised, double-blind, controlled	Randomised, controlled	Prospective, multicentre, randomised, open-label, parallel group stratified
Country	North America, 15 centres	America	Europe, North America, Australia	Iran	Belgium, Brazil, Canada, Italy, Norway, Spain, Switzerland, UK, 28 centres
Years of patient recruitment	NR	July 1992 to September 1993	August 1992 to September 1994	1997–2000	NR
Inclusion criteria	First cadaveric transplant, men and women, age ≥ 12 years, negative pregnancy test, effective contraception	First transplant, age >18 years	First or second transplant, age >18 years	NR	First transplant, either gender, age 18–70 years, negative pregnancy test
Exclusion criteria	Paediatric *en bloc* recipients, asystolic donor organ, previous transplant, living donor, ABO incompatible with donor, HIV+, lactating, sensitive to tacrolimus, MMF, AZA or castor oil, other immunosuppressants	Malignancies, unable to take oral medication, pregnancy, inadequate contraception, serum positive for HIV, human T-cell leukaemia virus or HB_sAg, peptic ulcer active, severe diarrhoea, gastrointestinal disorders, white cell blood count $<2.5 \times 10^3\ \mu l^{-1}$, platelet count $<100 \times 10^3\ \mu l^{-1}$, contraindication to ciclosporin, prednisolone, AZA, ALG, positive T-cell cross-match	Malignancies, unable to take oral medication, pregnancy, inadequate contraception, serum positive for HIV or HB_sAg, peptic ulcer active, severe diarrhoea, gastrointestinal disorders	NR	Asystolic donors, previous transplant, induction with ALG/ATG/OKT3, positive T-cell match, ABO incompatible, HIV+, gout, malignancy, other drugs, insufficient contraception
Follow-up period	1 year, extended to 3 years	3 years	3 years	6 months	12 months

HB_sAg, hepatitis B surface antigen.

TABLE 66 *Immunosuppressive regimens of studies included in analysis: MMF versus azathioprine with ciclosporin*

Regimen	Johnson et *al.*, 2000[103]	US MMF Trial[117]	Tricontinental MMF Trial[118]	Miladpour et *al.*, 2002[123]	Sadek et *al.*, 2002[124]
Drugs of interest	MMF 2 g vs AZA 1.5–2 g per day	MMF 3 g (n =166); MMF 2 g (n = 165); AZA (n = 164)	MMF 3 g (n =164); MMF 2 g (n = 171); AZA (n = 164)	MMF 2 g; AZA 100–150 mg per day	MMF 2 g: AZA 1–2 mg kg^{-1} (1) MMF→AZA 9 months (2) MMF for 12 months (3) AZA for 12 months
Other drugs	Prednisone, 10 mg per day tacrolimus 8–10 mg kg^{-1} per day. Trough levels of tacrolimus 5–15 ng ml^{-1}. Neoral trough level target 100–300 ng ml^{-1}. OKT3 or ATG in those with delayed graft function	Ciclosporin with trough monitoring, varied dose across centres, prednisone, ATG	Ciclosporin 8–10 mg kg^{-1} initial to 3.7–4.0 mg kg^{-1} at 6 months	Ciclosporin	Neoral+steroid

TABLE 67 *Patient characteristics: MMF versus azathioprine with ciclosporine*

Characteristic	**Johnson et *al.*, 2000[103] (Tacrolimus + AZA; Neoral + MMF; tacrolimus + MMF)**	**US MMF Trial[117] (MMF 3 g; MMF 2 g; AZA)**	**Tricontinental MMF Trial[118] (MMF 3 g; MMF 2 g; AZA)**	**Miladpour et *al.*, 2002[123] (MMF 2 g; AZA)**	**Sadek et *al.*, 2002[124] (Arm 1; arm 2; arm 3)**
Patient numbers	233	499	503	80	158; 162; 157
Mean age (years)	46.5; 45.9; 49.9	46.1 ± 12.6; 45.1 ± 13.2; 45.9 ± 12.2	46 ± 13; 46 ± 13; 47 ± 13	39 (20–68); 37 (19–63)	44.7; 43.9; 43.9
Proportion male (%)	57.9; 58.7; 59.7	57; 59; 57	59.8; 54.1%; 66.9%	52.5%; 45%	64.6; 71.0; 59.9
Donor	All cadaveric	All cadaveric	NR	NR	86; 86; 87
Delayed graft function (%)	32.9; 28.0; 36.1	NR	30; 36; 22	NR	34.4; 29.9; 30.8
First transplant (%)	100	100; 100	82; 76; 82	Not all	NR
Race or ethnic group, proportion white (%)	71.1; 66.7; 62.5	Caucasian: 71.1; 60.5; 62.0 Black: 19.9; 26.3; 24.1 Asian: 1.8; 1.2; 3.6	NR	NR	100%
Cause of ESRD (%)			Three groups balanced for prognostic variables	Two groups 'similar'	89.9; 91.4; 90.4
Hypertension	15.8; 16.0; 18.1	19; 17; 20			
Diabetes	23.7; 32.0; 29.2	22; 22; 21			
Glomerulonephritis	23.7; 17.3; 19.4	23; 15; 14			
Heredity	14.5; 14.7; 12.5	9; 13; 16			
Other/uncertain	11.8; 5.2; 8.4	33; 57; 71			
Sensitisation (PRA)	> 20%: 6.6%; 6.7%; 12.5%	≥ 20%: 2; 10; 2	≥ 20%: 6; 20; 14 (imbalanced statistically)	Two groups similar	7.0; 7.4; 4.5 28.5; 34.0; 33.1 15.8; 14.8; 9.6
HLA matches (%)					
0	9.3; 6.9; 2.7	6; 3; 10	NR	NR	NR
1	4.2; 15.8; 24.0	7; 2; 10			
2	12.5	8; 4; 7			
Graft cold ischaemic time (hours)	18.2; 20.0; 18.2	21.6 ± 12.4; 21.7 ± 13.3; 22.3 ± 13.9	20 ± 7; 21 ± 9; 20 ± 7	NR	NR

TABLE 68 *Assessment of trial quality: MMF versus azathioprine with ciclosporin*

Quality criteria	**Johnson *et al.*, 2000[103] (Tacrolimus + AZA; Neoral + MMF; tacrolimus + MMF)**	**US MMF Trial[117] (MMF 3 g; MMF 2 g; AZA)**	**Tricontinental MMF Trial[118] (MMF 3 g; MMF 2 g; AZA)**	**Miladpour *et al.*, 2002[123] (MMF 2 g; AZA)**	**Sadek *et al.*, 2002[124] (Arm 1; arm 2; arm 3)**
Method of randomisation stated	Before transplant, method not stated	Yes, but method not specified	Yes, stratified	NR	
Method of allocation concealment stated	NR	Syntax coding from assessors, matched placebos	Double capsule format	NR	Stratified
Blinding undertaken	Open-label	Patient and assessors	Patients	NR	Sequential numbers, Almedica drug labelling
Withdrawals (%)	6.5; 10.7; 9.7	Fully described (25.9%); 3/165 (21.2%); 27/164 (22.6%)	Fully described 27% during 6 months: (26%); 46/171 (27%); 82/164 (50%)	One graft loss in AZA	Open-label
Analysis by ITT	Yes	Yes	Yes	NR	16.8; 15.4; 21.7
Jadad score	2	4	5	0	Yes
Comments				Full paper had very limited information, poor quality	

TABLE 69 *Outcome results at 12 months: MMF versus azathioprine with ciclosporin*

Outcome	Johnson et *al.*, 2000[103] (Tacrolimus + AZA; Neoral + MMF; tacrolimus + MMF)	US MMF Trial[117] (MMF 3 g; MMF 2 g; AZA)	Tricontinental MMF Trial[118] (MMF 3 g; MMF 2 g; AZA)	Miladpour et *al.*, 2002[123] (MMF 2 g; AZA)	Sadek et *al.*, 2002[124] (Arm 1; arm 2; arm 3)
Graft survival	Not properly reported, similar across groups 88–89%	152 (91.5%); 156 (94.5%); 147 (89.4%)	146 (89.0%); 151 (88.3%); 140 (86.4%)	Graft loss in AZA group: 1/30 Serum creatinine: 1.3 mg dl^{-1} (0.8–2.3); 1.3 mg dl^{-1} (0.8–2)	91.9%; 90.1%; 89.8%
Patient survival	73/76 (96.1%); 67/75 (89.3%); 67/72 (93.1%)	157 (94.5%); 159 (96.4%); 159 (97.0%)	157 (95.7%); 165 (96.5%); 155 (95.7%)	NR	96.8%; 95.1%; 95.5%
Acute rejection	17%; 20%; 15%	29/156 (17.5%); 33/165 (19.8%); 63/164 (38.0%)	26 (15.9%); 34 (19.7%); 59 (35.5%)	4/40 (10%); 10/40 (25%)	23.4%; 21.0%; 32.5%
Adverse events	Tacrolimus patients had a lower incidence of hyperlipidaemia at 6 months PTDM: 14%; 7%; 7%	Anaemia and hypertension and laboratory tests generally evenly distributed MMF > AZA diarrhoea, gastrointestinal adverse events, CMV infections, malignancies (NB. ATG used in this study)	MMF>AZA abdominal pain, vomiting, diarrhoea, infections, PTLD. AZA>MMF: nausea, thrombocytopenia, hyperkalaemia, hyperglycaemia, hyperbilirubinaemia, malaise, deep thrombophlebitis. Varied by MMF dose: anaemia, leucopenia	MMF>AZA diarrhoea, gastrointestinal bleeding, CMV disease AZA>MMF: leucopenia, thrombocytopenia, increased liver enzymes, jaundice	Increased blood pressure: 25.9; 21.6; 22.3% Leucopenia: 19.6; 18.5; 18.5% Anaemia: 18.4; 17.3; 15.9% Renal dysfunction: 13.9; 21.6; 13.4% Nausea: 16.5; 14.2; 14.6% Vomiting: 9.5; 17.3; 12.1% Diarrhoea: 12.7; 17.3; 8.3% Infection: 69; 75.3; 65.6%
Quality of life	NR	NR	NR	NR	145.5; 150.5; 130.2
Treatment withdrawals, discontinuations or cross-overs		43/166 (25.9%); 35/165 (21.2%); 37/164 (22.6%)	42/164 (26%); 46/173 (27%); 50/166 (30%)	NR	
Non-compliance		2.4%; 3.0%; 1.2%	3%; 2.3%; 3.6%	NR	NR

TABLE 70 *Outcome results at > 12 months: MMF versus azathioprine with ciclosporin*

Outcome	**Johnson et *al*., 2000[103] (Tacrolimus + AZA; Neoral + MMF; tacrolimus + MMF)**	**US MMF Trial[117] (MMF 3 g; MMF 2 g; AZA)**	**Tricontinental MMF Trial[118] (MMF 3 g; MMF 2 g; AZA)**
Follow-up period	2 and 3 years	3 years *n* = 286 but ITT	3 years *n* = 250 but ITT
Serum creatinine	At 2 years, median: 1.35; 1.57; 1.30 At 3 years: 1.60; 1.40; 1.40	1.63; 1.72; 1.8 (NB. Reviewer's estimates from graph)	1.56 ± 0.10; 1.78 ± 0.10; 1.70 ± 0.10
Graft survival	At 2 years*: 84.2%; 76.7%; 82.8% At 3 years*: 73.0%; 79.6%; 79.7%	77.4%; 134/165 (81.1%); 123/164 (74.7%)	84.8%; 146/171 (81.9%); 137/162 (80.2%)
Patient survival	At 2 years: 96.1%; 88.0%; 94.4% At 3 years: 88.0%; 90.3%; 92.1%	87.8%; 148/165 (89.4%); 144/164 (88.1%)	90.9%; 163/171 (95.3%); 148/162 (91.4%)
Acute rejection	At 2 years, BPAR: 18.4%; 22.7%; 16.7% During year 3: *n* = 2/75; 0/73; 2/76	Biopsy-proven: 40% No biopsy-proven rejection: 9.8%	Biopsy-proven: 26.1% No biopsy-proven rejection: 5.7%
Side-effects	More patients required insulin in the tacrolimus + AZA group; one patient developed PTLD in the tacrolimus + MMF group	MMF > AZA: Virtually all of the reported side-effects were higher in the MMF groups with dose-related magnitudes. Exception where AZA > MMF is thrombocytopenia	MMF > AZA: abdominal pain, vomiting, diarrhoea, infections, PTLD AZA > MMF: thrombocytopenia, hyperkalaemia, hyperglycaemia, hyperbilirubinaemia, malaise, deep thrombophlebitis. Varied by MMF dose: nausea, anaemia, leucopenia
Non-compliance (%)		6.0; 9.1; 6.7	6.7; 4.7; 5.6
Subgroups	African–Americans at 2 years: *n* = 17 on tacrolimus + MMF: BPAR 23.5%, graft survival 76.5%, PTDM = 1 *n* = 17 on Neoral + MMF: BPAR 35.3%, graft survival 76.5%, PTDM = 2 *n* = 10 on tacrolimus + AZA: BPAR 30.0%, graft survival 80.0%, PTDM = 1	No	No
Comments	MMF doses less in tacrolimus + MMF group at 3 years; ARRs higher in African–American patients than overall rates. *Graft survival quoted as reported in original report: note anomaly of graft survival at 3 years higher than at 2 years	Clearer reporting of serum creatinine and patient and graft survival would be useful	Features in published pooled analysis with previous two studies

Appendix 13

Included RCTs of initial and maintenance-phase MMF versus azathioprine with tacrolimus-based triple therapy

TABLE 71 *Trial characteristics: MMF versus azathioprine with tacrolimus*

Characteristic	Busque *et al.*, 2001[106]	Miller, 1999[126] (Tacrolimus dose-ranging study)	Tuncer *et al.*, 2002[125]
Design	Randomised, parallel group, open-label, multicentre	Open-label, randomised	Prospective, randomised, non-blinded
Country	Canada, six centres	USA, 13 centres	Turkey
Years of patient recruitment	NR	August 1996 to March 1998	February 1995 to August 1999
Inclusion criteria	First cadaveric organ recipient, adults	Cadaveric organ, first or retransplant, both genders, age ≥ 12 years, ≥ 40 kg	NR
Exclusion criteria	NR		NR
Follow-up period	6 months	12 months	NR

TABLE 72 *Immunosuppressive regimens of studies included in analysis: MMF versus azathioprine with tacrolimus*

Regimen	Busque *et al.*, 2001[106]	Miller, 1999[126] (Tacrolimus dose-ranging study)	Tuncer *et al.*, 2002[125]
Drugs of interest	MMF 2 g, AZA 1.5–2 mg kg^{-1}	MMF 1 g, MMF 2 g, AZA	MMF, AZA
Other drugs	Tacrolimus + MMF + AZA Tacrolimus + AZA + prednisolone Neoral + MMF + prednisolone	Tacrolimus + prednisolone+ OKT3/ATGAM	Ciclosporin A, prednisolone, ATG

TABLE 73 *Patient characteristics: MMF versus azathioprine with tacrolimus*

Characteristic	Busque et *al.*, 2001[106] (Tacrolimus + MMF; tacrolimus + AZA; Neoral + MMF)	Miller, 1999[126] (Tacrolimus dose-ranging study) (MMF 1 g; MMF 2 g; AZA)	Tuncer et *al.*, 2002[125] (MMF; AZA)
Patient numbers	23; 23; 21 (Total $n = 67$)	59; 58; 59 (Total $n = 76$)	38; 38 (Total $n = 76$)
Mean age (years)	NR, stated to be not significantly different	44.0; 44.4; 45.5	34.8; 41.1
Proportion male (%)	No difference across arms	59.3; 62.1; 57.6	71.1; 73.7
Donor	100% cadaveric	100% cadaveric	Six cadaveric, 32 living; nine cadaveric, 29 living
Delayed graft function	22% similar	NR	NR
First transplant (%)	100	91.5; 93.1; 91.5	NR
Race or ethnic group, proportion white (%)	No difference across arms	55.9; 43.1; 49.2	NR
Cause of ESRD: Hypertension Diabetes Glomerulonephritis Heredity Other	No difference across arms	NR	 NR 10; 28 16; 22 2; 36 1; 37
Sensitisation (PRA)	No difference across arms	NR	
HLA matches (%): 0 1 2	No difference across arms	 8.5; 6.9; 8.5 8.5; 6.9; 1.7 6.8; 1.7; 16.9	2.5 mismatches; 2.7 mismatches
Graft cold ischaemic time (hours)	No difference across arms with mean 15 hours	NR	NR

TABLE 74 *Assessment of trial quality: MMF versus azathioprine with tacrolimus*

Quality criteria	Busque et *al.*, 2001[106]	Miller, 1999[126] (Tacrolimus dose-ranging study)	Tuncer et *al.*, 2002[125]
Method of randomisation stated	NR	Randomised at transplant, method not reported	NR
Method of allocation concealment stated	NR	NR	NR
Blinding undertaken	Open-label	Open-label	Non-blind trial
Withdrawals (%)	NR	NR	NR
Analysis by ITT	NR	Yes	No
Jadad score	Poor	Poor	Poor
Comments	2 pages of poor reporting	Kaplan–Meier estimates for patient survival	

TABLE 75 *Outcome results at 6 or 12 months: MMF versus azathioprine with tacrolimus*

Outcome	**Miller, 1999[126] (Tacrolimus dose-ranging study) (MMF; AZA)**	**Busque *et al.*, 2001[106] (MMF; AZA)**
Time-point	12 months	12 months
Graft survival	58/58; 56/59	13%; 27/38 (28.94%)
Patient survival	55/58; 57/59	100%; 97%
Acute rejection	5/58; (8.7%) 19/59 (34.8%)	18.41%; 34.21%
Side-effects	Tacrolimus-treated patients had a better lipid profile	Chronic allograft nephropathy: 18.42%; 21%
Serum creatinine	Tacrolimus + MMF 'lowest'	NR
Withdrawal from treatment/cross-overs	NR	No information
Non-compliance	NR	NR

TABLE 76 *Outcome results at >1 year: MMF versus azathioprine with tacrolimus*

Outcome	**Tuncer *et al.*, 2002[125] (MMF; AZA)**
Time-points	3 and 5 years (Kaplan–Meier estimates)
Results	3-year graft survival: 72; 93% 5-year graft survival: 69; 86% 3-year patient survival: 89; 93% 5-year patient survival: 89; 93%
Comments	Results not statistically significant, insufficient power

Appendix 14

Included RCTs of sirolimus therapy

Substitution of MMF or azathioprine with sirolimus

TABLE 77 *Trial characteristics: substitution with sirolimus*

Trial name	**Kahan, 2000[132]**
Design	RCT, stratified by black recipients and treatment centre
Country	USA
Sponsor	Wyeth Ayerst
Years of patient recruitment	1996–1997
Patient numbers: Intervention 1 Intervention 2	 S1 (2 mg): 284 S2 (5 mg): 274
Control	AZA: 161
Inclusion criteria	ESRD, age ≥ 13 years, >40 kg, women with negative pregnancy test, white cell count $>4 \times 10^9$ l^{-1}, platelets $> 100 \times 10^9$ l^{-1}, triglycerides <5.65 mmol l^{-1}
Exclusion criteria	Systemic infection angina, MI in previous 6 months, continuing treatment for life-threatening arrhythmia, history of malignancy, previous trial drug in 4 weeks, previous use of immunosuppression, concomitant treatment with cytochrome P450 inducers or inhibitors or terferadine, cisapride, astermizole, pimozide, use of antibiotic induction treatment, continuing gastrointestinal disorders likely to interfere with drug absorption, abnormal chest X-ray, known hypersensitivity to macrolide antibiotics, azathioprine, 6-mercaptopurine
Follow-up period	12 months
Clinical end-point	Composite of graft loss, death, loss to follow-up, first occurrence of BPAR within 6 months (efficacy failure)
Safety end-point	
Comments	Bonferroni 0.025 ITT

TABLE 78 *Immunosuppressive regimens: substitution with sirolimus*

	Kahan, 2000[132]
Induction	None
Sirolimus	Single loading dose of either 6 or 15 mg, then 2 or 5 mg per day
Azathioprine	2–3 mg kg^{-1} per day
Ciclosporin (Neoral)	Dose adjusted according to trough concentrations
Trough	200–350 ng ml^{-1} first month 200–300 ng ml^{-1} second month 150–250 ng ml^{-1} thereafter
Steroids	500-mg loading dose, then tapering to 30 mg per day by 6 days, 10 mg per day by 6 months and 5–10 mg per day thereafter
Acute rejection treatment	Not mentioned

TABLE 79 *Patient characteristics: intervention/comparator: substitution with sirolimus*

	Kahan, 2000[132]		
Characteristic	**S1**	**S2**	**C**
Mean age (SD) (years)	44.9 (13.6)	46.8 (13.0)	45.6 (13.0)
Proportion male (%)	(73%)	(62%)	(57%)
Ethnic group (%)			
White	160 (56%)	154 (56%)	92 (57%)
Black	63 (22%)	62 (23%)	41 (25%)
Other	61 (21%)	58 (21%)	28 (17%)
Recipient type (%): First graft, second graft	NR	NR	NR
Donor type (%):			
Living	104 (36%)	107 (39%)	42 (26%)
Cadaver	180 (63%)	167 (61%)	119 (74%)
Asystolic	–		
Duration of dialysis	NR	NR	NR
Cause of ESRD (%):			
Diabetes	59 (21%)	53 (19%)	32 (20%)
Glomerulonephritis	64 (23%)	50 (18%)	18 (11%)
Hypertension	72 (25%)	77 (28%)	47 (29%)
Other	89 (31%)	94 (35%)	634 (40%)
Sensitisation (PRA):			
0–10%	Not given in these categories		
>10%			
HLA matches (%):	Not given in these categories		
0			
1			
2			
Graft cold ischaemic time (hours)	NR	NR	NR

TABLE 80 *Trial quality: substitution with sirolimus*

	Kahan, 2000[132]
Method of randomisation stated (Y/N/CT)	Y (computer generated)
Allocation concealment (Y/N/CT)	Y
Blinding (state who) (Y/N/CT)	Y
Withdrawals (%)	50%
ITT (Y/N/CT)	Y
Overall Jadad score	4

Y, yes; N, no; CT, can't tell.

TABLE 81 *Results: substitution with sirolimus*

	Kahan, 2000[132]		
Outcome	**S1**	**S2**	**C**
Patient survival	269/284 (94.7%)	255/274 (93.1%)	156/161 (96.9%)
Graft survival	268/284 (94.4%)	254/274 (92.7%)	152/161 (94.4%)
Acute rejection	62/284* (21.8%)	40/274* (14.6%)	50/161 (31.1%)
Acute rejection at 6 months	47/284 (16.5%)	31/274 (11.3%)	47/161 (29.2%)
Quality of life	NR		
Growth in children	NR		
Withdrawals due to adverse events at 6 months	19/284 (6.7%)	29/274 (10.6%)	15/161 (9.3%)
All withdrawals	135/284 (47.5%)	131/274 (47.8%)	82/161 (50.9%)
Treatment failures	NR		
Non-compliance	NR		
Creatinine (serum μmol l^{-1}) Creatinine 12-month clearance, mean (SE)	160.0* (4.9) 61.95* (1.36)	171.1* (6.0) 55.48* (1.62)	133.1 (5.1) 67.51 (1.83)

* Statistically significant ($p < 0.05$), pairwise comparison with azathioprine group.

TABLE 82 *Side-effects: substitution with sirolimus*

	Kahan, 2000[132]
Sirolimus > AZA	Acne, diarrhoea, epistaxis, headache, herpes simplex, hirsutism, hypercholesterolaemia, hypertension, hyperlipidaemia, insomnia, lymphocoele, thrombocytopenia
Sirolimus < AZA Sirolimus = AZA	Hyperkalaemia, leucopenia

Addition of sirolimus to initial dual therapy

TABLE 83 *Trial characteristics: addition of sirolimus*

Trial name	**MacDonald *et al.*, 2001[135]; Ponticelli *et al.*, 2001[136]**
Design	RCT
Country	Multicentre (USA, Canada, Australia, Europe)
Sponsor	Wyeth Ayerst
Years of recruitment	1996–1997
Patient numbers: Intervention 1 Intervention 2 Control 1	 S1 (2 mg): 227 S2 (5 mg): 219 C: 130
Inclusion criteria	Age 15–51 years, primary renal allograft, cadaver or living donor, women with negative pregnancy test
Exclusion criteria	Systemic infection, history of clinically significant cardiac abnormalities, malignancy, treatment within 4 weeks of investigational agent, fasting cholesterol >9.1 mmol l^{-1}, triglycerides >5–6 mmol l^{-1}
Study period	12 months
Clinical end-point Safety end-point	Rate of efficacy failure at 6 months including death, graft loss or BPAR
Comments	A 3-year follow-up should be published some time

TABLE 84 *Immunosuppression regimens: addition of sirolimus*

	MacDonald et *al.*, 2001[135]; Ponticelli et *al.*, 2001[136]
Induction	
Sirolimus	Single loading dose of either 6 or 15 mg, then 2 or 5 mg per day
Placebo	NA
Ciclosporin	Neoral dose adjusted according to trough concentrations
Trough	200–400 ng ml^{-1} first month 200–300 ng ml^{-1} second month 150–250 ng ml^{-1} thereafter
Steroids	250-mg loading dose, then tapering to 30 mg per day by 6 days, 10 mg per day by 6 months and 5–10 mg per day thereafter
Acute rejection treatment	High-dose steroid treatment permitted in RCT, any other treatment caused exclusion

TABLE 85 *Patient characteristics: intervention/comparator: addition of sirolimus*

	MacDonald et *al.*, 2001[135]; Ponticelli et *al.*, 2001[136]		
Characteristic	**S1**	**S2**	**Placebo**
Mean age (SD) (years)	45.6 (12.3)	45.1 (12.2)	46 (13.1)
Age range (years)	15–71	17–68	16.72
Proportion male (%)	(65%)	(68%)	(70%)
Ethnic group (%):			
White	172 (76%)	175 (80%)	103 (79%)
Black	26 (11%)	27 (12%)	13 (10%)
Other	29 (12%)	17 (8%)	14 (10%)
Recipient type (%): first graft, second graft			
Donor type (%):			
Living	54 (24%)	45 (20%)	31 (24%)
Cadaver	173 (76%)	174 (79%)	99 (76%)
Asystolic	–		
Duration of dialysis	NR		
Cause of ESRD (%):			
Diabetes	28 (12%)	34 (16%)	17 (13%)
Glomerulonephritis	65 (29%)	51 (23%)	32 (25%)
Hypertension	35 (15%)	27 (12%)	22 (17%)
Other	99 (44%)	107 (49%)	59 (48%)
Sensitisation (PRA): 0–10% >10%)	Not given in these categories		
HLA matches (%): 0 1 2	Not given in these categories		
Graft cold ischaemic time (hours)			
Comments	None statistically significant		

TABLE 86 *Trial quality: addition of sirolimus*

	MacDonald *et al.*, 2001[135]; Ponticelli *et al.*, 2001[136]
Method of randomisation stated (Y/N/CT)	Y (computerised)
Allocation concealment (Y/N/CT)	Y
Blinding (state who) (Y/N/CT)	Patients, investigators
Withdrawals (%)	40% average
ITT (Y/N/CT)	Y
Overall Jadad score	4

TABLE 87 *Results: addition of sirolimus*

	MacDonald *et al.*, 2001[135]; Ponticelli *et al.*, 2001[136]		
Outcome	**S1**	**S2**	**Placebo**
Patient survival	219/227 (96.5%)	208/219 (95.0%)	123/130 (94.6%)
Graft survival	204/227 (89.9%)	199/219 (90.9%)	114/130 (87.7%)
Acute rejection	61/227* (26.9%)	48/219* (21.9%)	56/130 (43.3%)
Quality of life	Not given		
Growth in children	NA		
Withdrawals due to adverse events at 6 months	79/227 (35%)	88/219 (40%)	58 or 59/130 (45%)
Treatment failures	79/227* (35%)	68/219* (31%)	?64/130 (49.5%)
Delayed graft function	Not given		
Non compliance	Not given		
Creatinine mean (SE) mmol l^{-1}	155.9* (4.0)	172.5* (6.1)	136.8 (5.4)

*Statistically significant ($p < 0.05$), pairwise comparison with placebo group.

TABLE 88 *Side-effects: addition of sirolimus*

	MacDonald *et al.*, 2001[135]; Ponticelli *et al.*, 2001[136]
Sirolimus > placebo	Anaemia, epistaxis, hypercholesterolaemia, hypertriglyceridaemia, hyperlipidaemia, arthralgia, rash, thrombocytopenia, herpes simplex, lymphoma
Sirolimus = placebo	Most opportunistic infections, diarrhoea
Sirolimus < placebo	–

Appendix 15

Included RCTs of treatment of acute rejection

Tacrolimus RCTs

TABLE 89 *Immunosuppression regimens: tacrolimus in acute rejection treatment*

Characteristic	Dudley *et al.*, 2001[138]
Country	Europe
Duration and follow-up	3 months
Definition of rejection	BPAR, no further details provided
Previous treatment	(1) CsA, (2) three doses of methylprednisolone
Other inclusion criteria	Adult, first episode of rejection within 6 months of renal transplant
Exclusion criteria	NR
Dose of tacrolimus	0.2 mg kg^{-1}, adjusted to 10–20 ng ml^{-1}
Co-interventions	CsA, IVS, ALG, AZA as needed
Comparator	CsA
Dose	Adjusted to 150–300 ng ml^{-1}
Co-interventions	IVS, ALT, AZA as needed

IVS, intravenous steroids.

TABLE 90 *Patient characteristics: intervention/comparator: tacrolimus in acute rejection treatment*

	Dudeney *et al.*, 2001[138]: S
Mean age	NR
Age range	NR
Gender	NR
Ethnic group	NR
Recipient type (% first graft, second graft)	NR
Donor type	NR
Duration of dialysis	NR
Cause of ESRD	NR
Sensitisation (PRA)	NR
HLA matches	NR
Graft cold ischaemic time	NR

TABLE 91 *Trial quality: tacrolimus in acute rejection treatment*

Randomisation method	NR
Allocation concealment	NR
Blinding	Open
Withdrawals	10 and 29%
ITT analysis	Possibly
Jadad score	2

TABLE 92 *Results (all expressed as ITT; recalculations indicated by italics): tacrolimus in acute rejection treatment*

Outcome (at 3 months)	**Tacrolimus (*n* = 61)**	**Ciclosporin (*n* = 58)**	**Safety**	**Tacrolimus**	**Ciclosporin**
Patient survival (%)	96.7	100.0	Discontinuations	10	29
Resolution of acute episode requiring extra treatment (no. of patients)	4	15	CMV infection	8	7
Graft loss (%)	*8.2*	*6.9*	New diabetes	1	2
Incidence of recurrence (no. of patients)	*5/61*	*15/58*	Mean total cholesterol at study end	5.64 mmol l^{-1}	6.65 mmol l^{-1}
Freedom from treatment failure (%) (Kaplan–Meier)	72.6	43			

MMF RCTs

TABLE 93 *RCTs of acute rejection: MMF in acute rejection treatment*

Characteristic	MMRRR Study Group, 1996[139]	MMRRR Study Group, 1998[140]	Jirasiritham *et al.*, 2000[178]	Jain *et al.*, 2001[179]	McGrath and Shehata, 2001[180]
Date of study	1991–1993	1991–1994	1997–1999	NR	NR
Design	Randomised, open	Randomised, double-blind for 12 months plus open-label for 2 years	Randomised, open	Randomised	Randomised
Sample size	150	221	40	21	30
Country	USA	USA, Canada	Thailand	UK	UK
Duration and follow-up	6 months and 12 months	2 phases: 6–12 months and 3 years	6 months	6 months	6 months (mean 8.1 months)
Definition of rejection	Acute cellular rejection on biopsy	Acute cellular rejection on biopsy, 7 days to 6 months after transplant	Chronic rejection on biopsy (Banff)	CAN on biopsy	Biopsy-proven CAN
Previous treatment	OKT3, ATG for 7 days	No ALG, no new CsA	Not specified	Not specified	CsA, prednisolone, AZA
Other inclusion criteria	Biopsy diagnosis within 48 hours, randomisation, serum creatinine <442 mmol l^{-1}, age >13 years	Age >18 years, established renal function, no dialysis	Not specified	NR	Declining renal function despite standard triple therapy
Exclusion	Severe systemic infection, cytopenia, HIV infection, HB_sAg, gastrointestinal disorders, malignancies	>1 dose IVS, pregnancy, severe infections, HIV, hepatitis B, severe leucopenia or anaemia, malignancy	Other causes of chronic graft deterioration	NR	NR
Dose	1.5 g oral, b.d. up to 3.5 g per day, 6 months	1.5 g oral b.d.	2 g per day	1–2 g per day	2 g per day

continued

TABLE 93 *RCTs of acute rejection: MMF in acute rejection treatment (cont'd)*

Characteristic	MMRRR Study Group, 1996[139]	MMRRR Study Group, 1998[140]	Jirasiritham et *al.*, 2000[178]	Jain et *al.*, 2001[179]	McGrath and Shehata, 2001[180]
Co-interventions	Steroids, CsA	IVS 5 mg kg^{-1} per day for 5 days, tapered for 5 days to 10 mg per day plus CsA as needed	Regular immunosuppression	CsA, steroids	Steroids + AZA
Comparator	High-dose steroids	AZA	AZA	AZA	Tacrolimus
Dose	5 mg kg^{-1} per day for 5 days, tapered for 5 days	1–2 mg kg^{-1} per day	1 mg kg^{-1} per day	1 mg kg^{-1}	0.15 mg kg^{-1}, adjusted to '8–12' levels
Co-interventions	AZA (dose at discretion)	IVS 5 mg kg^{-1} per day for 5 days, tapered for 5 days to 10 mg per day plus CsA as needed	CsA, steroids	CsA, steroids	Steroids + AZA

TABLE 94 *Patient characteristics: MMF in rejection treatment*

Trial author, date	MMRRR Study Group, 1996[139]	MMRRR Study Group, 1998[140] (MMF; AZA)	Jirasiritham *et al.*, 2000[178] (MMF; AZA)	Jain *et al.*, 2001[179]	McGrath and Shehata, 2001[180] (MMF; AZA)
Patient numbers	IVS + triple: 73 (45M, 28F) MMF + triple: 77 (43M, 34F)	113; 108	20, 20	21: allocation NR	15; 15
Mean age (years)	38.6	43.1, 11.6; 43.7, 11.7	40	NR	50.4, 42.6
Gender (% male)	59	63.7; 59.3	77.5	NR	66
Race/ethnicity, proportion white (%)	NR	67%; 69%	NR	NR	NR
Donor	Cadaveric or living	Cadaveric or living non-related	Cadaveric or living related	NR	NR
First transplant	First or second (n = 24)	First (n = 197) or second (n = 24)	NR	NR	Not all, but not reported in detail
Diagnosis (cause)	NR	Diabetes: 24%; 25% Glomerulonephritis: 25%; 14% Hypertension: 11%; 12% Other	NR	NR	NR
Sensitisation	NR	<20% in approximately 90% of patients	NR	NR	NR
HLA match	NR	0: 3%; 5%	NR	NR	NR
Graft cold ischaemic time (hours)	NR	Not reported in detail	NR	NR	171.7; 18.1
Time since transplant	NR	32.4 days; 33.2 days	28.5 months; 38.2 months	NR	84.1 months; 90.4 months

TABLE 95 *Trial quality: MMF in acute rejection treatment*

	MMRRR Study Group, 1996[139]	**MMRRR Study Group, 1998[140]**	**Jirasiritham et *al.*, 2000[178]**	**Jain et *al.*, 2001[179]**	**McGrath and Shehata, 2001[180]**
Randomisation method	NR	NR	NR	NR	NR
Allocation concealment	NR	NR	NR	NR	NR
Blinding	Open	Not described	Open	Not described	Not described
Withdrawals	Poorly described, cannot add up the figures	Poorly described, possibly 8 and 1	0	Not described	None
ITT analysis	Maybe	Yes	Yes	Not clear	Yes

TABLE 96 *Results: MMF in acute rejection treatment*

Trial author, data	MMRRR Study Group, 1996[139]	MMRRR Study Group, 1998, phase 1[140]
Outcome	Graft survival or death at 6 and 12 months Subsequent rejection episodes or treatment failure (death, graft loss, premature termination, adverse event) Time to rejection[a] Courses of additional treatment (number of patients with 1 or more) Renal function	% patients requiring ALT for refractory or recurrent rejection (defined after biopsy) at 6 months First use of ALS
Result intervention	11/77 (8% at 12 months) 22/77 (6 months) 25% at day 97 19 NR	33/113 19/113
Result comparator	19/73 (31.5) 37/73 (6 months) 25% at day 23 26 NR	56/108 45/108
Safety	Death Malignancies Adverse events Discontinuations due to adverse events Opportunistic infections (total number)	Adverse events Discontinuations due to adverse events
Result intervention	2 3 72/77 patients 8 of 77 27	All patients 10.20
Result comparator	2 1 53/71 patients 1 of 71 25	98% 17.70%

[a] Confirmed by biopsy.

Appendix 16

Included daclizumab and basiliximab economic and quality of life studies

TABLE 97 *Characteristics of daclizumab and basiliximab economic studies*

Characteristic	Schnitzler et *al.*, 1999[142]	Lorber et *al.*, 2000[145]	Polsky et *al.*, 2001[143]	Lilliu et *al.*, 2001[144]
Country	USA	USA	USA	France (French francs, then convert to Euros)
Comparison(s)	MMF, ATG, daclizumab, basiliximab	Basiliximab + Neoral + prednisolone vs Neoral + prednisolone	Basiliximab + early Neoral, ATG + late Neoral quadruple therapy	Basiliximab vs ATG
Design	Cost-impact	Economic evaluation as part of RCT	Cost–utility	Cost-minimisation pharmacoeconomics study
Population	Used USRDS database = UNOS 13 612 patients and information from Sollinger (2001),[57] Vincenti (1998)[45]	Kahan (1999)[53]: US multicentre study	US multicentre, open-label, clinical trial, 1997–1999 (n = 138), Sollinger (2001)[57]	CHI-F-02 trial (n = 100)
Perspective	Healthcare provider	Healthcare provider	Healthcare provider	Hospital
Medical costs considered	Graft loss costs	Direct costs only, diagnostic tests and invasive procedures, laboratory tests, inpatient days	Drug costs, hospitalisation	Direct costs per patient in French francs, medication, hospital stays, dialysis, consultations, cost of infectious episodes per patient
Source and year of costs	Medicare billing and payment records	Case report forms, Medicare resource-based relative value scale, Red Book (1997)	Hospital bills, Medicare (1997)	Diagnosis-related group, hospital costs from Paris Hospital, drugs at ex-factory price
Discount rate	Costs subject to 5% discount rate	No	No	No
Time-frame	1 year and 10 years	1 year	2 years	1 year

TABLE 98 *Results of daclizumab and basiliximab economic studies*

	Schnitzler *et al.*, 1999[142]	**Lorber *et al.*, 2000[145]**	**Polsky *et al.*, 2001[143] (Basiliximab; ATG)**	**Lilliu *et al.*, 2001[144] (Basiliximab; ATG)**
Per-patient costs	Daclizumab, 1 year: $18,012; $13,247 Basiliximab, 1 year: $14,077; $14,227 Daclizumab 10 years: $98,545; 94,964 Basiliximab, 10 years: $95,567; $96,590		Induction drug costs: $2378; $8670 Initial hospitalisation costs: $26,644; $35,545	Treatment costs: €2964; €2298 Initial hospitalisation costs: €10,907; €11,967 Mean cost of infections: €1056; €1790
Benefits			EuroQol visual analogue scale at 1 year: 81.5; 81.1 Difference = 0.45	
Cost-effectiveness			High risk: $46,035; $59,258 Low risk: $46,010; $51,690	
Sensitivity analysis	No	Yes: varied cost of hospitalisation and consultation	No	No
Authors' conclusion	No strong conclusions; antilymphocytes not necessarily cost-effective in the short term owing to added cost of agent; better cost-effectiveness at 10 years owing to better clinical results	Induction with basiliximab + Neoral + steroids is therapeutically beneficial and contained the costs in the first year; basiliximab reduced the ARR without increased cost overall	Basiliximab + early Neoral were cost saving compared with ATG + late Neoral; lower first year post-transplant costs; similar differences in high-risk subjects	Saving of €1158 per patient in the basiliximab arm, which largely compensates for the initial higher drug price; saving due to less expensive infectious episodes and shorter hospital stay; favours use of basiliximab over ATG

TABLE 99 *Characteristics of basiliximab economic studies*

Characteristic	Keown et *al*., 2001[146]	Walters et *al*., 2001[147]
Country	Canada	UK (ScHARR)
Comparison	Basiliximab 20 mg 0, 4 days vs placebo + Neoral + prednisolone	Basiliximab + ciclosporin + AZA + steroid Placebo + ciclosporin + AZA + steroid
Design	Economic benefit	Pharmacoeconomic evaluation prospective alongside RCT, Ponticelli
Population	380 patients, RCT, 21 centres in seven countries, Nashan	340 patients in RCT in 31 centres, 12 countries, Ponticelli
Perspective	Health service	Payer
Medical costs considered	Primary hospital drug use, treatment of rejection, rehospitalisation, dialysis	Drug unit costs annual unit dialysis (Malik, 1997) Hospital costs HRG UK
Source and year of costs	Hospital pharmacy, electrical cost dictionary based on economic evaluation of renal transplantation in Canada (1999)	US dollar exchange rates, purchasing power parity (1996)
Discount rate	1.49%, assumes basiliximab at zero cost	None stated
Time-frame	1 year extended to 5 years	6 months projected to 1 year

TABLE 100 *Results of basiliximab economic studies*

	Keown et *al*., 2001[146] (Basiliximab; placebo)	Walters et *al*., 2001[147] (Basiliximab; placebo)
Per-patient costs	1 year: $50,339; $55,393 5 years: $130,592; $141,690 Initial hospitalisation and dialysis: $13,916; $15,538 Incremental cost of graft loss: $2295; $2548 Treatment of acute rejection: $2886; $3329	6-month total cost: $34,821; $34,172 1-year total: $37,113; $37,070
Benefits		
Cost-effectiveness		ICER: $4669 NNT: 8 over 6 months
Sensitivity analysis	The most influential parameters affecting results were reduced length of initial and repeat hospitalisation	Difference in costs remained statistically non-significant after nephrectomy costs were excluded
Authors' conclusion	Basiliximab is the dominant therapy; saving per patient per year $1554	Over 6 months clinical benefit of basiliximab realised without significant increase in overall cost
Comments	Basiliximab zero cost	

NNT, number needed to treat.

Appendix 17

Included tacrolimus and ciclosporin economic and quality of life studies

TABLE 101 *Characteristics of tacrolimus versus ciclosporin economic studies*

Characteristic	Olivera, 1997[151]	Morris-Stiff et *al.*, 1998[64]	Neylan et *al.*, 1998[65]	Booth-Clibborn et *al.*, 1997[62]	Chilcott et *al.*, 1999[63]	Craig et *al.*, 2002[150]
Country	UK	UK	USA	UK	UK	Europe (not UK)
Comparison(s)	Tacrolimus-based triple therapy vs Sandimmun-based triple therapy	Tacrolimus-based triple therapy* vs Neoral-based triple therapy*	Tacrolimus-based triple therapy vs Sandimmun-based triple therapy	Tacrolimus-based triple therapy vs Sandimmun-based triple therapy	Tacrolimus-based triple therapy vs Sandimmun-based triple therapy	Tacrolimus-based triple therapy vs Neoral-based triple therapy
Design	RCT (European multicentre trial, 2 UK centres)	Non-randomised prospective cost study	RCT (US FK506 multicentre trial)*	Modelling	Modelling	RCT (European multicentre trial)
Population(s)/ indication(s)	482 cadaveric renal transplant recipients	100 consecutive cadaveric renal transplant recipients	412 cadaveric renal transplant recipients	Rates of rejection episodes and haemodialysis obtained from systematic review of RCTs	Based on 1-year US and UK FK506 results	557 renal transplant recipients
Perspective	Direct medical	Direct medical	Direct medical	Direct medical	Direct medical	Direct medical
Medical costs considered (source):						
Drug costs	✓	✓	✓	✓	✓	✓
Transplant operation	×	✓	✓	×	×	×
Hospital/ICU stay	×	✓	✓	×	×	×
Postoperative dialysis	✓	✓	?	✓	×	✓
Rescue therapy	✓	✓	?	✓	✓	✓
Graft nephrectomy	×	✓	?	×	×	×
Readmission	×	✓	✓	×	×	✓
Investigations/biopsies	✓	✓	✓	✓	✓	✓
Source of medical costs	National databases and hospital finance systems	Not stated	Charge data in participating centres and Medicare	BNF, local costs	Local costs from a single hospital centre	Local costs from 50 centres
Patient costs considered	None	None	None	None	None	None
Year of costs	1996	1996/1997	1993/1994	1997	Drugs 1997, hospital 1994/95	NR

continued

TABLE 101 *Characteristics of tacrolimus versus ciclosporin economic studies (cont'd)*

Characteristic	Olivera, 1997[151]	Morris-Stiff *et al.*, 1998[64]	Neylan *et al.*, 1998[65]	Booth-Clibborn *et al.*, 1997[62]	Chilcott *et al.*, 1999[63]	Craig *et al.*, 2002[150]
Discount rate	NA	NA	NA	NR	NR	NA
Time-frame	12 months	6 months	12 months	12 months and 14 years	12 months and 2 and 3 years	6 months
Comments		*AZA and prednisolone; no difference in ARR identified				

TABLE 102 *Results of tacrolimus versus ciclosporin economic studies*

Per patient	Olivera, 1997[151]	Morris-Stiff et *al.*, 1998[64]	Neylan et *al.*, 1998[65]	Booth-Clibborn et *al.*, 1997[62]	Chilcott et *al.*, 1999[63]	Craig et *al.*, 2002[150]
Overall medical costs						
Tacrolimus	£1,110*	£12,982	US$53,435	£8,510	£6,086	
Ciclosporin	£3,620*	£13,200	US$61,191	£6,710	£6,026	
Difference[a]	–£2,150* ($p = 0.0001$)	–£218	–US$7,756 ($p = 0.046$)	+£1,800	+£60[§]	–€524 to –€1776[††]
Benefits	NR	NR	NR			NR
Tacrolimus				0.912 QALY		
Neoral				0.904 QALY		
Difference				+0.008 QALY[†]	+4% graft survival[¶]	
Cost-effectiveness	NR	NR	NR	£225,000 per QALY[†‡]	£30,000/graft or life saved[**]	–€530 to –€1,874 per surviving patient; –€781 to €2,305 per surviving graft; –€4,587 to €9,199 per rejection free graft
Sensitivity analysis	Drug costs; hospitalisation costs; tests and diagnostic test costs	NR	Intensity of therapeutic monitoring; missing data; neither altered conclusion	QALY figures from both US and European RCTs used; did not alter conclusion	Most favourable and most unfavourable ARRs; costs highly sensitive to this assumption with range –£574 to +£454	Cost of hospitalisation, study drug and concomitant medication; did not alter conclusions
Conclusion	Tacrolimus costs < ciclosporin	No significant difference in cost	Tacrolimus costs < ciclosporin		Tacrolimus costs = ciclosporin; recommends tacrolimus only probably cost-effective in high-risk patients	Tacrolimus dominant to Neoral

continued

TABLE 102 *Results of tacrolimus versus ciclosporin economic studies (cont'd)*

Per patient	**Olivera, 1997[151]**	**Morris-Stiff *et al.*, 1998[64]**	**Neylan *et al.*, 1998[65]**	**Booth-Clibborn *et al.*, 1997[62]**	**Chilcott *et al.*, 1999[63]**	**Craig *et al.*, 2002[150]**
Comments	*Costs for treating acute rejection episodes		Authors believe that difference is driven by fewer acute rejection episodes	Cost savings achieved as result of lower incidence of acute rejection episodes †Upper QALY gain 0.015 and cost per QALY £120,000 ‡Over 14 years £89,000 saving and 1.2 gain in QALY: dominant	§+£964 if Neoral, assuming different acute rejection profile compared to Sandimmun ¶5-year figure based on extrapolation from first year ARRs **Based on cost difference of £1,200; not clear where this figure comes from	††Range by country Study undertaken retrospectively

[a] Negative values indicate cost of tacrolimus < ciclosporin.

TABLE 103 *Characteristics of Neoral versus Sandimmun economic studies*

	Hardens et *al*., 1994[153]	**Keown et *al*., 1995[154]**	**Kingma et *al*., 1997[155]**
Country	Germany, Austria, Switzerland, Italy	Canada	Canada
Comparison(s)	*De novo* Sandimmun vs Neoral	*De novo* Sandimmun vs Neoral	*De novo* Sandimmun vs Neoral
Design	Two RCTs	RCT, double-blind	RCT, double-blind
Population(s)/indication(s)	86 stable renal transplant patients	30 stable renal transplant patients	41* stable renal transplant patients
Perspective	Direct medical	Direct medical	Direct medical
Medical costs considered (source):			
Drug costs	✓	✓	✓
Transplant operation	×	×	×
Hospital/ICU stay	✓	×	×
Postoperative dialysis	?	×	×
Rescue therapy	?	✓	✓
Graft nephrecotomy	?	×	×
Readmission	✓	✓	✓
Investigations/biopsies	?	✓	✓
Source of medical costs	NR	Hospital and provincial	Hospital and provincial
Patient costs considered	None	None	None
Year of costs	NR	1992/93	1994
Discount rate	NA	NA	NA
Time-frame	3 months	3 months	3 months
Comments	Retrospective collection of data		*Three patients excluded for reasons of protocol violation Retrospective collection of resource data

TABLE 104 *Results of Neoral versus Sandimmun economic studies*

Per patient	Hardens *et al.*, 1994[153]	Keown *et al.*, 1995[154]	Kingema *et al.*, 1997[155]
Overall healthcare costs, mean (SD)			
Sandimmun		Can$3,000	Can$15,475 (10,315)
Neoral		Can$2,228	Can$13,621 (8,754)
Difference[a]	–Swiss Fr2,969*	–Can$772	–Can$1854 (ns)
Benefits			
Tacrolimus			
Neoral			
Difference			
Cost-effectiveness			
Sensitivity analysis		Highest and lowest prices or tariffs for each resource parameter; did not change the conclusions	Highest and lowest hospital cost estimates; did not change the conclusions
Conclusion	Benefit due to lower use of additional immunosuppressive drugs and fewer hospitalisations	Benefit due to lower dose that could be maintained with Neoral and fewer hospitalisations/tests	Benefit due to fewer hospitalisations
Comments	*Range across countries: –Swiss Fr2,169 to –4,451	Authors raise the limitation that costs were collected retrospectively	Authors raise the limitation that costs were collected retrospectively

[a] Negative values indicate cost of Neoral < Sandimmun.

TABLE 105 *Tacrolimus versus ciclosporin quality of life studies*

Characteristic	Reimer *et al.*, 2002	Shield *et al.*, 1997[78]	Booth-Clibborn *et al.*, 1997[62]
Design	Single-centre assessment at two time-points over 12 months	Multicentre RCT, US FK506 Study	Modelling
Country	Germany	USA	UK
Population	Mean age 44 years, mean duration with graft 51 months	(See clinical effectiveness section)	Based on review of 1-year data from US and European FK596 RCTs
Drug regimens compared	Tacrolimus + AZA + prednisolone	Tacrolimus + AZA + prednisolone	Ciclosporin (Sandimmun) + AZA + prednisolone
	Ciclosporin (Neoral) + AZA + prednisolone	Ciclosporin (Sandimmun) + AZA + prednisolone	Tacrolimus + AZA + prednisolone
Quality of life measures used	SF-36, End-Stage Renal Disease Symptom Checklist (ESRD-SCL)	SF-36, Berger Physical Appearance scale	Rosser scale (quality of life determined from utility weights applied to rejection episodes)
Comments			

Appendix 18

Included MMF versus azathioprine economic and quality of life studies

TABLE 106 *Characteristics of MMF and azathioprine economic studies*

Characteristic	Khosla et *al.*, 1999[159], Baker et *al.*, 1998[156]	Suleymanlar et *al.*, 2001[160]	Wuthrich et *al.*, 1999[162]	Deierhoi et *al.*, 1998[157]
Design	Cost consequence, modelling based on historical observational study	Cost consequence, observation study with matched control	Cost consequence, observational study with historical controls	Cost consequence
Country	USA	Turkey	Switzerland	USA
Population	33 MMF patients, 1995, vs 43 AZA patients, 1990–1996, cadaveric renal transplant recipients	Living related renal transplant recipients, 17 MMF, 17 AZA	40 MMF, 40 AZA	50 MMF and 50 AZA patients, March 1995 and August 1995; similar demographics across groups
Drugs compared	MMF vs AZA	MMF vs AZA	MMF vs AZA	All had OKT3, prednisolone and ciclosporin maintenance immunosuppression
Perspective	Health service	Health service	Health service	NR
Costs	Drug costs, dialysis, hospitalisation, AR treatment	Hospitalisation, dialysis, AR treatment, graft loss, acute rejection treatment	Drugs, acute rejection treatment, biopsy, hospitalisation	NR
Source and year of costs	Health system acquisition cost records, local department figures, HBOC Trenstar system, consumer price index (1996)	NR	NR	NR
Discounting	NA	NA	NA	NA
Time-frame	1 year	1 year	6 months	1 year

TABLE 107 *Results of MMF and azathioprine economic studies*

Per patient	**Khosla *et al.*, 1999[159], Baker *et al.*, 1998[156] (MMF; AZA)**	**Suleymanlar *et al.*, 2001[160] (MMF; AZA)**	**Wuthrich *et al.*, 1999[162] (MMF; AZA)**	**Deierhoi *et al.*, 1998[157] (MMF; AZA)**
Costs	Total cost per patient: US$69,610; US$78,473	Infection rate similar in both groups Total cost per patient: US$16,667; US$14,614. ($p = 0.525$)	Total cost per patient: Swiss Fr13,136; 10,555	1 year cost: US$115,000; US$110,000
Benefits	MMF < AZA: hospitalisations, graft loss, need for IL-2 therapy			
Cost-effectiveness	Not undertaken	Not undertaken	Not undertaken	Not undertaken
Sensitivity analysis	Not undertaken	Not undertaken	Not undertaken	Not undertaken
Conclusion	MMF reduced overall costs in first year compared to AZA despite higher acquisition costs, as lower cost offset from acute rejection treatment in both incidence and severity	MMF more expensive drug than AZA, but does not include cost of maintenance therapy due to reduced number and severity of acute rejection and hospitalisation; also cost-effective in living related patients in this study	MMF is more expensive than AZA	MMF is more expensive than AZA

TABLE 108 *Characteristics of MMF and azathioprine economic studies*

Characteristic	Sullivan et *al*., 1997[161]	Keown, 1999[158]	Schniztler et *al*., 1999[142]
Design	Cost-effectiveness, based on RCT (Sollinger *et al*., 1995, US MMF trial)	Cost–utility, based on RCT (Tricontinental MMF trial) and modelling	Cost-effectiveness, based on RCT (Sollinger *et al*., 1995, US MMF trial) and modelling
Country	USA	Canada	USA
Population	165 MMF, 164 AZA	335 MMF, 164 AZA	165 MMF, 164 AZA
Drugs compared	MMF (2 g per day) vs AZA	MMF vs AZA	MMF (2 g per day) vs AZA
Perspective	Health service	Health service	Health service
Costs	Acute rejections, graft survival, adverse events, drug costs	Dialysis, acute rejection, infection, drug costs	Drug costs, acute rejection, graft failure
Source and year of costs	Medicare and national hospital (data converted to 1995)	Canadian hospitals (1994)	Medicare (year not stated)
Discounting	NA	NA	NR
Time-frame	1 year	6 months	1 and 10 years

TABLE 109 *Results of MMF and azathioprine economic studies*

Per patient	Sullivan et *al*., 1997[161] (MMF; AZA)	Keown, 1999[158] (MMF; AZA)	Schniztler et *al*., 1999[142] (MMF; AZA)
Costs	Total cost per patient per year: US$27,807; US$29,158	Total cost per patient per year: Can$27,870; Can$27,381	Year 1: total cost per patient: US$22,690; US$22,080 Year 10: total cost per patient: US$126,434; US$99,980
Benefits/utility	Graft survival: 89.3%; 84.8%	3 months: 0.83; 0.82 6 months: 0.85; 0.86	Graft survival (%): Year 1: 40%; 38% Year 10: 58%; 47%
Cost-effectiveness	MMF dominant: cost saving and improved clinical outcome	Incremental cost–utility of $53,811 per QALY	1-year GSCE: 40; 38 10-year GSCE: 50; 47
Sensitivity analysis	Results remain stable after plausible variations in ARR, graft survival and infection rates	NA	None undertaken
Conclusion	Compared to AZA, MMF regimen is cost-effective in primary cadaveric recipients in the first year	MMF is cost-effective in the first year	Years 1 and 10: MMF more cost-effective than AZA

Appendix 19

Included sirolimus economic and quality of life studies

TABLE 110 *Characteristics of sirolimus economic studies*

	Manninen *et al.*, 2000[163]
Country	USA
Comparisons	Sirolimus vs AZA
Design	Costs study based on RCT data
Population	Living and cadaveric renal transplant recipients
Perspective	Medical insurance payer (Medicare)
Medical costs considered:	
Drug costs	
Transplant operation	✓
Hospital/ICU stay	✓
Postoperative dialysis	✓
Rescue treatment	?
Graft nephrectomy	?
Readmission	?
Investigations/biopsies	?
Source of medical costs	Medicare claims
Patient costs	No
Year of costs	Not given
Discount rate	NA
Time-frame	1 year
Comment	Very few details available

TABLE 111 *Results of sirolimus economic studies*

Per patient	**Manninen *et al.*, 2000[163]**
Overall medical costs, mean (SD):	
Sirolimus	US$122,033 (81,324)
AZA	US$126,627 (74,553)
Difference	–US$4,549
Benefits	NA
Cost-effectiveness	NA
Sensitivity analysis	No
Conclusion	No clear difference in costs
Comments	

Appendix 20

Included paediatric RCTs

TABLE 112 *Characteristics of paediatric trials*

Characteristic	Trompeter *et al.*, 2002[107]	Ettenger and Grimm, 2001[137]
Design	RCT, open-label multicentre	RCT (paediatric subgroup of Kahan, 2000)
Country	Canada	USA
Years of patient recruitment	1996–1999	1996–1997
Inclusion criteria	age ≤ 18 years, ≥ 10 kg	NR (age 13–18 years)
Exclusion criteria	HIV+, incompatible ABO organ, hypersensitive to CsA or tacrolimus, previous organ transplant other than kidney, PRA ≥ 50% or required induction therapy	ditto
Follow-up period	6 and 12 months (but set up a 5-year follow-up)	12 months

TABLE 113 *Immunosuppressive regimens of paediatric studies included in analysis*

Regimen	Trompeter *et al.*, 2002[107]	Ettenger and Grimm, 2001[137]
Induction	None	None
Regimen	Tacrolimus (mg kg^{-1} per day), oral, not given or i.v. 0.3*	Single loading dose of either 6 mg or 15 mg then 2 mg or 5 mg daily
	AZA 2–4 mg kg^{-1} per day up to day 8, then 2 mg kg^{-1} per day†	2–3 mg kg^{-1} per day
	Prednisone initial 300–600 mg m^{-2} tapered to 10–20 mg m^{-2}	Dose adjusted according to trough concentrations
	Ciclosporin (mg kg per day) 300 mg m^{-2} †	200–350 ng ml^{-1} first month, 200–300 ng ml^{-1} second month, 150–250 ng ml^{-1} thereafter
Trough concentration (mg dl^{-1}) at 1 week: Tacrolimus Ciclosporin	*10–20 ng ml^{-1} up to day 30, then 5–10 ng ml^{-1} †100–200 ng ml^{-1}	500 mg loading dose then tapering to 30 mg per day by days, 10 mg per day by 6 months and 5–10 mg per day thereafter
Comments	Patients switched to MMF were withdrawn	

TABLE 114 *Patient characteristics for paediatric trials*

Characteristic	Trompeter *et al.*, 2002[107] (Tacrolimus; ciclosporin)	Ettenger and Grimm, 2001[137] (Sirolimus; ciclosporin)
Patient numbers	105; 99	
Mean age (years)	10.5; 10.1	17.2; 16.0; 15.0
Proportion male (%)	62; 60	3/6; 1/3; 2/3 1/6; 0/3; 0/3 2/6; 2/3; 1/3
Donor	Cadaveric/living relative	NR
Duration of dialysis (years)	NR 77%; 81%*	3/6; 1/3; 0/3 3/6; 2/3; 3/3 –
First transplant (%)	91; 86	
Race or ethnic group proportion white (%)	87; 88	NR
Diagnosis (%): Hypertension Diabetes Glomerulonephritis Heredity Other	 NR NR 9; 9 42; 45	0%
Sensitisation (PRA)	NR	NR
HLA matches (%): 0 1 2	 NR†	NR
Graft cold ischaemic time (hours)	NR	NR
Comments	*On dialysis previously †Different system reported	

TABLE 115 *Assessment of trial quality: paediatric trials*

Quality criteria	Trompeter *et al.*, 2002[107]	Ettenger and Grimm, 2001[137]
Method of randomisation stated	Conducted centrally, stratified randomisation	Yes (computer generated)
Method of allocation concealment stated	Sealed envelopes	Yes
Blinding undertaken	Open study	Yes
Withdrawals (%)	22/37	50%
Analysis by ITT	Yes	Yes
Jadad score	4	4

TABLE 116 *Outcome results of paediatric trials*

	Trompeter et *al.*, 2002[107] (12 months) (Tacrolimus; ciclosporin)	**Trompeter et *al.*, 2002[107] (24 months) (Tacrolimus; ciclosporin)**	**Ettenger and Grimm, 2001[137] (12 months)**
Patient survival	100/103 (97.1%); 90/93 (96.8%)† ($p = 0.899$)*	100/103 (97.1%); 89/93 (96.6%) ($p = 0.661$)¶	100% across all arms
Graft survival	93/103 (90.2%); 78/93 (83.9%)‡ ($p = 0.175$)*	93/103 (90.2%); 74/93 (79.6%)** ($p = 0.037$)	100% across all arms
Graft survival excluding deaths	93/103 (90.2%); 78/93 (83.9%)‡ ($p = 0.175$)*	NR	NR
Acute rejection[a]	17/94 (18.1%); 37/86 (43.0%) ($p < 0.001$)†§		0% across all arms
Antilymphocyte antibody rejection treatment	6/103 (5.8%); 20/93 (21.5%) ($p = 0.001$)†		
Adverse events (events that achieve $p \leq 0.05$)	T > C: hypomagnesaemia, diarrhoea C > T: hypertrichosis, influenza syndrome, gum hyperplasia C = T: hypercholesterolaemia, PTLD, diabetes, infections, malignancies, hypertension	NR T > C: GFR	
Quality of life	NR	NR	
Treatment withdrawals, discontinuations or cross-overs	22/103 (21.3%); 34/93 (6.6%) ($p = 0.019$)* **p*-Value not reported		2/3 (66.7%)
Comments	†6 months ‡12 months §Subsample biopsied	¶*p*-Value not reported **12 months	

[a] One or more episode and biopsy confirmed.

Appendix 21

Ongoing UK trials

TABLE 117 *Ongoing UK trials, sourced from the National Research Register*

Research centre location	Details of study
University Hospitals of Leicester NHS Trust	Multicentre, randomised, open-label study to compare conversion from ciclosporin to sirolimus versus standard therapy in established renal allograft recipients on maintenance therapy with mild to moderate renal insufficiency (UK-RAP-09, due January 2004)
The Lothian University Hospital NHS Trust	Phase II, open-label, single-centre, randomised study of tacrolimus plus sirolimus compared with tacrolimus plus azathioprine and corticosteroids in *de novo* renal allograft recipients (due August 2003)
Cambridge Consortium	Prospective, randomised controlled trial of MMF as a treatment for progressive renal transplant dysfunction (due October 2002)
Oxford John Radcliffe Hospital NHS Trust	Randomised controlled trial of conversion to sirolimus-based immunosuppression in patients with poor graft function and at risk of chronic allograft nephropathy (due December 2002)
Cambridge Consortium	Randomised, open-label study of continuous therapy with ciclosporin and sirolimus versus induction with ciclosporin and sirolimus followed by continuous therapy with sirolimus in renal allograft recipients (due April 2003)
Great Ormond Street Institute for Child Health	Open, multicentre, randomised, parallel group study to compare the safety and efficacy of a steroid triple regimen with and without the induction of the monoclonal antibody basiliximab in children after kidney transplantation (due September 2002)
University Hospital NHS Trust Birmingham	MMF in the management of chronic allograft nephropathy; a prospective randomised analysis of renal biopsy and clinical outcomes (due February 2003)

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Tom Walley,
Director, NHS HTA Programme,
Department of Pharmacology &
Therapeutics,
University of Liverpool

Professor Bruce Campbell,
Consultant Vascular & General
Surgeon, Royal Devon & Exeter
Hospital

Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing, University of
Bristol

Dr John Reynolds, Clinical
Director, Acute General
Medicine SDU, Radcliffe
Hospital, Oxford

Dr Ron Zimmern, Director,
Public Health Genetics Unit,
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Tom Walley,
Director, NHS HTA Programme,
Department of Pharmacology &
Therapeutics,
University of Liverpool

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology of
Ageing, Department of Social
Medicine, University of Bristol

Deputy Chair,
Professor Jenny Hewison,
Professor of Health Care
Psychology, Academic Unit of
Psychiatry and Behavioural
Sciences, University of Leeds
School of Medicine

Dr Jeffrey Aronson
Reader in Clinical
Pharmacology, Department of
Clinical Pharmacology,
Radcliffe Infirmary, Oxford

Professor Ann Bowling,
Professor of Health Services
Research, Primary Care and
Population Studies,
University College London

Professor Andrew Bradbury,
Professor of Vascular Surgery,
Department of Vascular Surgery,
Birmingham Heartlands
Hospital

Professor John Brazier, Director
of Health Economics,
Sheffield Health Economics
Group, School of Health &
Related Research,
University of Sheffield

Dr Andrew Briggs, Public
Health Career Scientist, Health
Economics Research Centre,
University of Oxford

Professor Nicky Cullum,
Director of Centre for Evidence
Based Nursing, Department of
Health Sciences, University of
York

Dr Andrew Farmer, Senior
Lecturer in General Practice,
Department of Primary Health
Care, University of Oxford

Professor Fiona J Gilbert,
Professor of Radiology,
Department of Radiology,
University of Aberdeen

Professor Adrian Grant,
Director, Health Services
Research Unit, University of
Aberdeen

Professor F D Richard Hobbs,
Professor of Primary Care &
General Practice, Department of
Primary Care & General
Practice, University of
Birmingham

Professor Peter Jones, Head of
Department, University
Department of Psychiatry,
University of Cambridge

Professor Sallie Lamb, Research
Professor in Physiotherapy/Co-
Director, Interdisciplinary
Research Centre in Health,
Coventry University

Professor Julian Little,
Professor of Epidemiology,
Department of Medicine and
Therapeutics, University of
Aberdeen

Professor Stuart Logan,
Director of Health & Social
Care Research, The Peninsula
Medical School, Universities of
Exeter & Plymouth

Professor Tim Peters, Professor
of Primary Care Health Services
Research, Division of Primary
Health Care, University of
Bristol

Professor Ian Roberts, Professor
of Epidemiology & Public
Health, Intervention Research
Unit, London School of
Hygiene and Tropical Medicine

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Professor Mark Sculpher,
Professor of Health Economics,
Centre for Health Economics,
Institute for Research in the
Social Services, University of York

Professor Martin Severs,
Professor in Elderly Health
Care, Portsmouth Institute of
Medicine

Dr Jonathan Shapiro, Senior
Fellow, Health Services
Management Centre,
Birmingham

Ms Kate Thomas,
Deputy Director,
Medical Care Research Unit,
University of Sheffield

Professor Simon G Thompson,
Director, MRC Biostatistics
Unit, Institute of Public Health,
Cambridge

Ms Sue Ziebland,
Senior Research Fellow,
Cancer Research UK,
University of Oxford

Current and past membership details of all HTA 'committees' are available from the HTA website (www.ncchta.org)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann Professor Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Dr Paul Cockcroft, Consultant Medical Microbiologist/Laboratory Director, Public Health Laboratory, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, Addenbrooke's Hospital, Cambridge

Dr David Elliman, Consultant in Community Child Health, London

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales Swansea

Dr John Fielding, Consultant Radiologist, Radiology Department, Royal Shrewsbury Hospital

Dr Karen N Foster, Clinical Lecturer, Dept of General Practice & Primary Care, University of Aberdeen

Professor Antony J Franks, Deputy Medical Director, The Leeds Teaching Hospitals NHS Trust

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), Department of Health, London

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medical Devices Agency, London

Dr William Rosenberg, Senior Lecturer and Consultant in Medicine, University of Southampton

Dr Susan Schonfield, CPHM Specialised Services Commissioning, Croydon Primary Care Trust

Dr Margaret Somerville, Director of Public Health, Teignbridge Primary Care Trust

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Head of Division of Reproductive & Child Health, University of Birmingham

Dr Dennis Wright, Consultant Biochemist & Clinical Director, Pathology & The Kennedy Galton Centre, Northwick Park & St Mark's Hospitals, Harrow

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds, Clinical Director, Acute General Medicine SDU, Oxford Radcliffe Hospital

Professor Tony Avery, Professor of Primary Health Care, University of Nottingham

Professor Stirling Bryan, Professor of Health Economics, Health Services Management Centre, University of Birmingham

Mr Peter Cardy, Chief Executive, Macmillan Cancer Relief, London

Dr Christopher Cates, GP and Cochrane Editor, Bushey Health Centre

Professor Imti Choonara, Professor in Child Health, University of Nottingham, Derbyshire Children's Hospital

Mr Charles Dobson, Special Projects Adviser, Department of Health

Dr Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Dr Karen A Fitzgerald, Pharmaceutical Adviser, Bro Taf Health Authority, Cardiff

Mrs Sharon Hart, Managing Editor, *Drug & Therapeutics Bulletin*, London

Dr Christine Hine, Consultant in Public Health Medicine, Bristol South & West Primary Care Trust

Professor Stan Kaye, Professor of Medical Oncology, Consultant in Medical Oncology/Drug Development, The Royal Marsden Hospital

Ms Barbara Meredith, Project Manager Clinical Guidelines, Patient Involvement Unit, NICE

Dr Frances Rotblat, CPMP Delegate, Medicines Control Agency, London

Professor Jan Scott, Professor of Psychological Treatments, Institute of Psychiatry, University of London

Mrs Katrina Simister, New Products Manager, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry

Dr Helen Williams, Consultant Microbiologist, Norfolk & Norwich University Hospital NHS Trust

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular and General Surgeon, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Head of Clinical Support & Health Protection, Directorate of Health and Social Care (North), Department of Health, Manchester

Dr Aileen Clarke, Reader in Health Services Research, Public Health & Policy Research Unit, Barts & the London School of Medicine & Dentistry, Institute of Community Health Sciences, Queen Mary, University of London

Mr Matthew William Cooke, Senior Clinical Lecturer and Honorary Consultant, Emergency Department, University of Warwick, Coventry & Warwickshire NHS Trust, Division of Health in the Community, Centre for Primary Health Care Studies, Coventry

Dr Carl E Counsell, Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd, Consultant Paediatrician, Derbyshire Children's Hospital

Professor Gene Feder, Professor of Primary Care R&D, Barts & the London, Queen Mary's School of Medicine and Dentistry, University of London

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of Orthopaedic Surgery, South Tees Hospital NHS Trust

Ms Bec Hanley, Freelance Consumer Advocate, Hurstpierpoint

Ms Maryann L. Hardy, Lecturer, Division of Radiography, University of Bradford

Professor Alan Horwich, Director of Clinical R&D, The Institute of Cancer Research, London

Dr Phillip Leech, Principal Medical Officer for Primary Care, Department of Health, London

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Mike McGovern, Senior Medical Officer, Heart Team, Department of Health, London

Professor James Neilson, Professor of Obstetrics and Gynaecology, Dept of Obstetrics and Gynaecology, University of Liverpool, Liverpool Women's Hospital

Dr John C Pounsford, Consultant Physician, North Bristol NHS Trust

Dr Vimal Sharma, Consultant Psychiatrist & Hon Snr Lecturer, Mental Health Resource Centre, Victoria Central Hospital, Wirrall

Dr L David Smith, Consultant Cardiologist, Royal Devon & Exeter Hospital

Professor Norman Waugh, Professor of Public Health, University of Aberdeen

Expert Advisory Network

Members

Professor Douglas Altman,
Director of CSM & Cancer Research UK Med Stat Gp, Centre for Statistics in Medicine, University of Oxford, Institute of Health Sciences, Headington, Oxford

Professor John Bond,
Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Mr Shaun Brogan,
Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE,
Chief Executive, Office of the Chief Executive. Trust Headquarters, Altnagelvin Hospitals Health & Social Services Trust, Altnagelvin Area Hospital, Londonderry

Ms Tracy Bury,
Project Manager, World Confederation for Physical Therapy, London

Mr John A Cairns,
Professor of Health Economics, Health Economics Research Unit, University of Aberdeen

Professor Iain T Cameron,
Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark,
Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Mary Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson,
Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Professor Howard Stephen Cuckle,
Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Professor Nicky Cullum,
Director of Centre for Evidence Based Nursing, University of York

Dr Katherine Darton,
Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux,
Professor of Paediatric Epidemiology, London

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles,
Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby,
Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Mr Leonard R Fenwick,
Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Professor David Field,
Professor of Neonatal Medicine, Child Health, The Leicester Royal Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn,
Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Ms Grace Gibbs,
Deputy Chief Executive, Director for Nursing, Midwifery & Clinical Support Servs, West Middlesex University Hospital, Isleworth

Dr Neville Goodman,
Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Alastair Gray,
Professor of Health Economics, Department of Public Health, University of Oxford

Professor Robert E Hawkins,
CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor F D Richard Hobbs,
Professor of Primary Care & General Practice, Department of Primary Care & General Practice, University of Birmingham

Professor Allen Hutchinson,
Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Dr Duncan Keeley,
General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping,
Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Rajan Madhok,
Medical Director & Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor David Mant,
Professor of General Practice, Department of Primary Care, University of Oxford

Professor Alexander Markham,
Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Castle Mullen

Professor Alistair McGuire,
Professor of Health Economics, London School of Economics

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Consultant in Public Health Medicine, Southampton City Primary Care Trust

Dr Sue Moss,
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Jon Nicholl,
Director of Medical Care Research Unit, School of Health and Related Research, University of Sheffield

Mrs Julietta Patnick,
National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler,
Professor of Liaison Psychiatry, University Mental Health Group, Royal South Hants Hospital, Southampton

Professor Chris Price,
Visiting Chair – Oxford, Clinical Research, Bayer Diagnostics Europe, Cirencester

Ms Marianne Rigge,
Director, College of Health, London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Dr Ken Stein,
Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter

Professor Sarah Stewart-Brown,
Director HSRU/Honorary Consultant in PH Medicine, Department of Public Health, University of Oxford

Professor Ala Szczepura,
Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor,
Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster,
Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278