Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance TA99)

Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Care Excellence

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1 Title of the project

The effectiveness and cost-effectiveness of immunosuppressive regimens in renal transplantation in children and adolescents, of basiliximab and rabbit anti-human thymocyte immunoglobulin as an induction therapy and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, belatacept, sirolimus, and everolimus as a maintenance therapy (a review of TA99): a systematic review and economic evaluation.

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3 Plain English Summary

This project will review and update the evidence presented to the National Institute of Health and Care Excellence (NICE) on the clinical effectiveness and cost-effectiveness of immunosuppressive regimens for renal transplantation in children and adolescents.[1]

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

4 Background

Since the first successful kidney transplantation in 1950, kidney transplantation became the treatment of choice in people with established renal failure.[2] In the UK, a total of 861 children and young people under 18 years old with established renal failure were treated at paediatric nephrology centres in 2012; 80% had a functioning kidney transplant, 11% were receiving haemodialysis and 9% were receiving peritoneal dialysis.[3] Between April 2012 and March 2013, 121 kidney transplant operations were performed in the UK for children and adolescents under 18 years of age.[4]

Immunosuppressive therapy must be implemented in order to reduce the risk of organ rejection and prolong survival of the graft; however, high levels of immunosuppression may also increase the risk of infections and malignancy.[2] In 2012, approximately 690 children and adolescents in the UK were receiving immunosuppressive therapy after kidney transplantation.[4]

Children and adolescents represent a distinct group, and can differ from adults in several important aspects, including: the cause of established renal failure, the complexity of the surgical procedure, the metabolism and pharmacokinetic properties of immunosuppressants, the developing immune system and immune response following organ transplantation, the measures of success of the transplant

procedure, the number and the degree of comorbid conditions, the susceptibility to post-transplant complications, and the degree of adherence to treatment.[1, 4]

Immunosuppression therapy for kidney transplantation can be categorised into induction therapy, initial maintenance therapy and long-term maintenance therapy.[1]

Induction Therapy

The aim is to prevent acute rejection, optimise the function of the transplanted organ, and minimise the risk of infections and complications. Induction therapy may be used for up to two weeks around the time of transplantation.[4]

Many of the induction immunosuppressive agents currently used in the UK are biological agents, including monoclonal antibodies (such as basiliximab) and polyclonal antibodies (such as rabbit anti-human thymocyte immunoglobulin). There seems to be some degree of variation in the use of induction therapy in the paediatric population in the UK. According to our clinical experts, biological agents do not appear to be routinely used in the paediatric population (e.g., Bristol Royal Hospital for Children and London Great Ormond Street Hospital). Nevertheless, they are routinely used in some hospitals (e.g., Birmingham Children's Hospital).

Initial and Long-Term Maintenance Therapy

The aim of initial and long-term maintenance therapy is to prevent acute rejection, optimise the function of the transplanted organ, and minimise the long-term consequences of immunosuppression such as an increased risk of cancer, infection and cardiovascular disease.[4] Triple therapy, consisting of a calcineurin inhibitor (CNI; usually tacrolimus) in combination with an antiproliferative agent (e.g., mycophenolate mofetil or azathioprine) and a steroid (e.g., prednisolone), is typically used in this population (e.g., in Bristol Royal Hospital for Children, London Great Ormond Street Hospital and Birmingham Children's Hospital). Duration of initial therapy varies widely, with estimates ranging from 14 days to 3 months post-transplantation.[5] Long-term maintenance therapy is often the same as initial

maintenance therapy, but with a reduced dose as the transplanted kidney becomes more stable.[4] It is typically continued throughout the life of the graft.[1]

In addition, a short course of high dose immunosuppression therapy can be used for the treatment of acute graft rejection.[1] However, the appraisal of agents for the treatment of episodes of acute rejection is outside the scope of this appraisal.[4]

The previous appraisal (TA99) found limited evidence in children and adolescents with only three randomised control trials (RCTs).[1] As a result, RCT evidence from adult populations was also incorporated.[1] In addition, systematic reviews of non-randomised comparative studies were used to identify non-randomised evidence if no RCT evidence in children was found.[1] Encouragingly, ten ongoing RCT's in children and adolescents were identified in the previous appraisal.[1]

5 Current evidence

The main findings and conclusions from the previous review (TA99) were[1]:

- Limited RCT evidence of the benefits and harms of the use of immunosuppressive agents (basiliximab, daclizumab, mycophenolate mofetil, mycophenolate sodium, tacrolimus and sirolimus) in children with kidney transplants was found; no evidence was identified for mycophenolate sodium, and only adult RCT evidence was identified for mycophenolate mofetil and daclizumab.

- In general, compared with a regimen of ciclosporin, azathioprine and steroid, the newer immunosuppressive agents consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence of the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life was limited (the model utilised in the TA99 did not include side-effects).

- The addition of induction therapy (daclizumab or basiliximab) was found to be a dominant strategy, resulting in cost savings and increased quality-adjusted life years (QALYs).

- The mean incremental cost-effectiveness ratios (ICERs) of tacrolimus regimens relative to ciclosporin regimens was £145,500/QALY, however, the ICERs were highly sensitive to key model parameter values.

- The ICER of mycophenolate mofetil relative to azathioprine regimens was £195,500/QALY, however the ICER was also sensitive to model parameters.

6 Decision problem

6.1 Purpose of the decision to be made

The assessment will address the following question[4]:

What is the clinical-effectiveness and cost-effectiveness

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

in renal transplantation in children and adolescents (including review of TA99)?

Depending on the availability of evidence, this question may be best addressed as two decision problems (one regarding the choice of induction therapy, one regarding the choice of maintenance therapy). If only one decision problem is considered, the economic analysis will have to make base-case assumptions about the most likely treatment sequences. These assumptions will be informed by the treatment sequences and study designs represented in the studies included in our systematic review, because we cannot model treatment sequences for which there is no relevant clinical evidence. We will pay particular attention to which treatments or sequences of treatments were randomised. We will also consult clinical experts about whether the treatment sequences used in trials are feasible within the NHS.

6.2 Interventions

This technology assessment report will consider nine pharmaceutical interventions. Two are used as an induction therapy in renal transplantation in children and adolescents and seven are used as a part of maintenance therapy in renal transplantation in children and adolescents. The two interventions considered for induction therapy are basiliximab and rabbit anti-human thymocyte immunoglobulin. The seven interventions considered for maintenance therapy are immediate and prolonged-release tacrolimus, mycophenoate mofetil, mycophenolate sodium, belatacept, sirolimus, and everolimus (summarised in Table 1 [page 7]). Where appropriate, the interventions will be appraised as part of combination regimens. Under an exceptional directive from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. Accordingly, the review will include studies that used drugs outside the terms of their marketing authorisations.

For induction therapy:

Basiliximab (Simulect® [Novartis Pharmaceuticals]) is a monoclonal antibody which acts as an interleukin-2 receptor antagonist. It has a UK marketing authorisation for prophylaxis of acute rejection in allogeneic renal transplantation in paediatric patients (1-17 years). The summary of product characteristics states it is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.[4]

Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline® [Sanofi]) is a gamma immune globulin. It has a UK marketing authorisation for the prevention of graft rejection in renal transplantation. The summary of product characteristics states it is usually used in combination with other immunosuppressive drugs. It is administered intravenously. The UK marketing authorisation is not restricted to adults only.[4]

Table 1 List of interventions

Therapy	Intervention	MA in children	Preparations
Induction therapy:	➢ Basiliximab	✓	Simulect® (Novartis pharmaceuticals)
	➢ Rabbit anti-human thymocyte immunoglobulin	✓	Thymoglobuline® (Sanofi)
Maintenance therapy:	➢ Immediate-release tacrolimus	✓	Adoport® (Sandoz)
		✓	Capexion® (Mylan)
		✓	Modigraf® (Astellas)
		✓	Perixis® (Accord Healthcare)
		✓	Prograf® (Astellas)
		✓	Tacni® (TEVA UK)
		✓	Vivadex® (Dexcel)
	➢ Prolonged-release tacrolimus	**X**	Advagraf® (Astellas)
	➢ Belatacept	**X**	Nulojix® (Bristol-Myers Squibb)
	➢ Mycophenolate mofetil	✓	non-proprietary (Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, Wockhardt)
		✓	Arzip® (Zentiva)
		✓	Myfenax® (TEVA UK)
		✓	CellCept® (Roche produtcts)
	➢ Mycophenolate sodium	**X**	Myfortic® (Novartis Pharmaceuticals)
	➢ Sirolimus	**X**	Rapamune® (Pfizer)
	➢ Everolimus	**X**	Certican® (Novartis Pharmaceuticals)

Notes: MA = Marketing authorisation for children and adolescents: refers to whether or not the technology has a UK marketing authorisation for children and adolescents.

For maintenance therapy:

Tacrolimus is a calcineurin inhibitor which is available in an **immediate-release** formulation (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]). All of these formulations of tacrolimus have UK marketing authorisations for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisations include adults and children.[4]

Tacrolimus is also available in a **prolonged-release** formulation (Advagraf® [Astellas Pharma]). It has a UK marketing authorisation for prophylaxis of transplant rejection in kidney allograft recipients. The marketing authorisation is restricted to adults. The Commission on Human Medicines advises that all oral tacrolimus (including both short release and prolonged–release tacrolimus) medicines in the UK should be prescribed and dispensed by brand name only.[4]

Belatacept (Nulojix® [Bristol-Myers Squibb]) is designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept has a UK marketing authorisation for prophylaxis of graft rejection in adults receiving a renal transplant, in combination with corticosteroids and a mycophenolic acid. The summary of product characteristics recommends that an interleukin-2 receptor antagonist for induction therapy is added to this belatacept-based regimen. The summary of product characteristics states that the safety and efficacy of belatacept in children and adolescents 0 to 18 years of age have not yet been established. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[4]

Mycophenolate mofetil is a prodrug of mycophenolic acid which acts as an antiproliferative agent (Arzip® [Zentiva], CellCept® [Roche Products], Myfenax® [Teva]; generic mycophenolate mofetil is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt). It has a UK marketing authorisation for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. The UK marketing authorisation is not restricted to adults (dosage recommendations for children aged 2-18 years are included in the summary of product characteristics).[4]

Mycophenolate sodium is an enteric coated formulation of mycophenolic acid (Myfortic® [Novartis Pharmaceuticals]). This formulation has the same UK marketing authorisation as mycophenolate mofetil, however, this is restricted to adults. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.[4]

Sirolimus (Rapamune® [Pfizer]) is an antiproliferative with a non-calcineurin inhibiting action. It has a UK marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2 to 3 months. It may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued. This formulation does not have a UK marketing authorisation for the prophylaxis of transplant rejection in renal transplantation in children and adolescents. [4]

Everolimus (Certican ® [Novartis Pharmaceuticals]) is a proliferation signal inhibitor and is an analogue of sirolimus.[4] Everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation in adults, adolescents, or children.[4]

In summary, **everolimus**, **prolonged-release tacrolimus, belatacept**, **mycophenolate sodium** and **sirolimus** are not currently licensed for the prophylaxis of transplant rejection in renal transplantation in children and adolescents.

6.3 Current NICE guidance

Current NICE guidance on “Immunosuppressive therapy for renal transplantation in children and adolescents (TA99)” considered the use of basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus in relation to a standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid following renal transplantation in children and adolescents. The TA99 recommends[6]:

Induction therapy:

- Basiliximab or daclizumab, used as part of a ciclosporin-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in children and adolescents undergoing renal transplantation, irrespective of immunological risk. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used, unless it is contraindicated.[6]

Maintenance therapy:

- Tacrolimus is recommended as an alternative option to ciclosporin when a CNI is indicated as part of an initial or a maintenance immunosuppressive regimen for renal transplantation in children and adolescents. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for the individual patient.[6]

- Mycophenolate mofetil is recommended as an option as part of an immunosuppressive regimen for child and adolescent renal transplant recipients only when[6]:
  - there is proven intolerance to CNIs, particularly nephrotoxicity which could lead to risk of chronic allograft dysfunction, or
  - there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a CNI until the period of high risk has passed.

- The use of mycophenolate mofetil in corticosteroid reduction or withdrawal strategies for child and adolescent renal transplant recipients is recommended only within the context of randomised clinical trials.[6]

- Mycophenolate sodium (not licensed for use in children) is currently not recommended for use as part of an immunosuppressive regimen in child or adolescent renal transplant recipients.[6]

- Sirolimus is not recommended for children or adolescents undergoing renal transplantation except when proven intolerance to CNIs (including nephrotoxicity) necessitates the complete withdrawal of these treatments.[6]

- As a consequence of following this guidance, some medicines may be prescribed outside the terms of their UK marketing authorisation. Healthcare professionals prescribing these medicines should ensure that children and adolescents receiving renal transplants and/or their legal guardians are aware of this, and that they consent to the use of these medicines in these circumstances.[6]

Since the publication of NICE technology appraisal guidance 99, the marketing authorisation for daclizumab has been withdrawn. Also, new technologies have received marketing authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (belatacept, a prolonged-release formulation of tacrolimus, and an oral suspension of immediate-release tacrolimus). In addition, another new technology (everolimus) has been studied as an immunosuppressant in renal transplantation, although it does not currently have a UK marketing authorisation in this therapy area.

6.4 Relevant comparators

For induction therapy the comparators are[4]:

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

For maintenance therapy the comparators are[4]:

- A calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids
- Interventions should also be compared with each other

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

6.5 Population and relevant sub-groups

Population:

The population will be children and adolescents under 18 years of age undergoing kidney transplantation. The kidney donor may be living-related, living-unrelated or deceased. Patients receiving multi-organ transplants and those who have received transplants and immunosuppression previously will be excluded.[4]

If data allows, the following subgroups will be considered[4]:

- Different age groups;
- Level of immunological risk (including human leukocyte antigen compatibility and blood group compatibility);
- People at high risk of rejection within the first 6 months;
- People who have had a re-transplant within 2 years;
- Previous acute rejection;
- People at high risk of complications from immunosuppression (including new-onset diabetes).

6.6 Outcomes to be addressed

The outcome measures to be considered are[4]:

- Patient survival;
- Graft survival;
- Graft function;
- Time to and incidence of acute rejection;
- Severity of acute rejection;
- Growth;
- Adverse effects of treatment;
- Health-related quality of life.

6.7 Other considerations

Several of the drugs being appraised (everolimus, sirolimus, belatacept, prolonged-release tacrolimus and mycophenolate sodium) do not have UK marketing authorisation for use in immunosuppressive regimens in renal transplantation in children and adolescents.

Under an exceptional directive from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness.

In addition (if evidence allows), adherence to treatment and the use of treatments in conjunction with either corticosteroid or CNI reduction or withdrawal strategies will be considered. To achieve this, only studies that meet the inclusion criteria (Section 7.2, page 15) will be examined. As such, studies where the intervention is identical in both study arms, but dose reduction or withdrawal of corticosteroids or CNIs occurs in one arm, will not be included.

7 Methods for synthesis of evidence of clinical effectiveness

The assessment report will include a systematic review of the evidence for the clinical effectiveness of basiliximab, rabbit anti-human thymocyte immunoglobulin, mycophenolate mofetil, mycophenolate sodium, sirolimus, immediate-release tacrolimus, prolonged-release tacrolimus, everolimus and belatacept (all interventions are listed in Table 1 [page 7]).

The review will update the previous review of clinical effectiveness undertaken in TA99.[1] As an update it will therefore:

- Conduct new searches and apply study selection processes for sources published from 2002 onwards. The searches will be shared with the parallel HTA 09/46/01 appraisal: Immunosuppressive therapy for kidney transplantation in adults; a review of technology appraisal guidance 85 (therefore the searches will be limited by date: 2002-current).
- Include those studies (unless the study does not fall within our inclusion criteria) published before 2004 that were reviewed in the previous technology assessment TA99 (searches for TA99 were done in 2004).
- Conduct quality assessment on all included studies.
- Perform data extraction on post-2004 studies. Data extracted for the previous technology assessment will be used for the pre-2004 studies.

The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[7]

7.1 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases (including trial registries) using an appropriately sensitive search strategy designed and executed by an information specialist.
- Contact with experts in the field.
- Scrutiny of bibliographies of retrieved papers.

The searches will be shared with the parallel HTA 09/46/01 appraisal: Immunosuppressive therapy for kidney transplantation in adults; a review of technology appraisal guidance 85. The searches will be limited by date (2002-current) and to English language.

The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); CENTRAL (The Cochrane Library, Wiley Interface), Web of Science (including conference proceedings citation index; Thomson Reuters); since scoping searches indicate the RCT evidence base to be sufficient, a study design search filter will be used to limit to RCTs. The following trials registries will be searched: Current Controlled Trials; ClinicalTrials.gov; FDA website; EMA website.

A separate search will be undertaken to locate systematic reviews. The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); CDSR, DARE, HTA (The Cochrane Library, Wiley Interface) and HMIC (OVID). This search will use a pragmatic filter to limit to systematic reviews.

Studies included on full-text will be forwards (using Web of Science) and backwards citation chased (i.e. manually scanning the each study's reference list).

The searches will be developed using the search strategies detailed in the technology assessment report developed for technology appraisal 99 by Yao and

colleagues (2006),[1] and the technology assessment report developed for technology appraisal 85 by Woodroffe and colleagues (2005)[5] as the starting point (see Appendix A for more information). The searches will not include any population (age) filter; the search will be shared with the parallel HTA 09/46/01 appraisal: "Immunosuppressive therapy for kidney transplantation in adults; a review of technology appraisal guidance 85".

In addition, studies that are included in the manufacturers' submissions and that meet our inclusion criteria will also be considered for inclusion in the review.

All references will be exported into Endnote X7 (Thomson Reuters) where automatic and manual de-duplication will be performed.

7.2 Inclusion criteria

The inclusion criteria are summarised in Table 2 (page 17).

The clinical effectiveness review will include:

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

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

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

7.3 Exclusion criteria

Studies published as abstracts or conference presentations will only be included if sufficient details are available to allow an appraisal of the methods and the assessment of the results to be undertaken.

The following publication types will also be excluded from the analysis:

- Individual non-randomised studies;
- Animal models;
- Preclinical and biological studies;
- Narrative reviews, editorials, opinions;
- Non-English language papers.

Table 2. Inclusion criteria (PICOS) as per the final scope issued by NICE and accompanying notes[4]

	PICOS	Notes
Population	**Children and adolescents undergoing kidney transplantation and receiving immunosuppressive therapy**	Multi-organ transplantation, the treatment of episodes of acute rejection, and individuals who have previously received a renal transplant and immunosuppression are outside the scope of this appraisal.
Interventions	**Induction therapy regimens containing:** **Basiliximab** (Simulect® [Novartis Pharmaceuticals]) **Rabbit anti-human thymocyte immunoglobulin** (Thymoglobuline® [Sanofi]) **Initial/Maintenance therapy regimens containing**: **Mycophenolate mofetil** (non-proprietary [Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, Wockhardt], CellCept® [Roche Products], Arzip [Zentiva], Myfenax [Teva]) **Mycophenolate sodium** (Myfortic® [Novartis Pharmaceuticals]) **Sirolimus** (Rapamune® [Pfizer]) **Immediate-release tacrolimus** (Adoport® [Sandoz], Prograf® [Astellas], Capexion® [Generics], Tacni® [Teva], Perixis® [Accord Healthcare], Vivadex® [Dexcel], Modigraf® [Astellas]) **Prolonged-release tacrolimus** (Advagraf® [Astellas]) **Everolimus** (Certican® [Novartis Pharmaceuticals]) **Belatacept** (Nulojix® [Bristol-Myers Squibb]).	Under an exceptional directive from the Department of Health, these interventions may be appraised outside of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness.

Comparators	**Induction therapy** ➢ Regimens without monoclonal or polyclonal antibodies, for example regimens that include methylprednisolone ➢ Interventions should also be compared with each other **Initial/Maintenance therapy regimens containing:** ➢ A calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids ➢ Interventions should also be compared with each other	Where appropriate the interventions will be appraised as part of combination regimens.
Outcomes	➢ Patient survival ➢ Graft survival ➢ Graft function ➢ Time to and incidence of acute rejection ➢ Severity of acute rejection ➢ Adverse effects of treatment ➢ Health-related quality of life	
Study design	RCTs Systematic reviews which include non-randomised studies evaluating the interventions of interest in children and adolescents	

7.4 Study selection

Studies retrieved from the searches will be selected for inclusion through a two-stage process according to the inclusion/exclusion criteria specified in Table 2 (page 17). First, abstracts and titles returned by the search strategy will be screened for inclusion independently by two researchers. Disagreements will be resolved by discussion, with involvement of a third reviewer when necessary. Full texts of identified studies will be obtained and screened in the same way. Abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality.

7.5 Data extraction strategy

Data from included full papers will be extracted using a standard data specification form, and checked independently by another reviewer. In cases where a single study has been reported in multiple publications, the data will be extracted and reported as a single study.

Information extracted and tabulated will include details of the study's design and methods, descriptions of the treatments, treatment combinations and treatment sequences compared, baseline characteristics of participants and results including any adverse events if reported. Where there is incomplete information on key data, we will attempt to contact the study's authors to gain further details. Discrepancies will be resolved by discussion, with involvement of another reviewer if necessary.

7.6 Quality assessment strategy

The methodological quality of each included study will be assessed by one reviewer and checked by a second reviewer, using the CONSORT 2010 checklist,[8] or criteria based on those proposed by the NHS Centre for Reviews and Dissemination for randomised controlled trials.[7]

The potential generalisability of the study will also be assessed, as well as the judged applicability to the current organisation, clinical pathways and practices of the NHS in England.

7.7 Methods of analysis/synthesis

Data will be tabulated and discussed in a narrative review. If appropriate (i.e., if a number of studies which report data relating to a given outcome are comparable in terms of key features such as their design, populations, and interventions), meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses.

Where appropriate, meta-analysis will be carried out using STATA and/or WinBUGS software, with the use of fixed and/or random-effects appropriate to the assembled datasets. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the $\chi 2$ test for homogeneity and the I^2 statistic. In addition, if data allows, a network meta-analysis will be considered.

If evidence allows, the subgroups defined in section 6.5 (page 11) will be considered in the analyses.

We will also compare our results with those from the parallel HTA 09/46/01 appraisal “Immunosuppressive therapy for kidney transplantation in adults”.

Reporting bias (where the term ‘reporting bias’ covers all types of publication, language, outcome, location, and other biases defined in the Cochrane Handbook) in our systematic review and meta-analyses will be assessed. We will follow best practice as recommended in the Cochrane Handbook, who have dedicated a whole chapter to the avoidance, identification and investigation of possible reporting bias (e.g., investigation of the likelihood of publication bias using funnel plots if the number of included studies is sufficient).[9] This may include researching trials that have only ever appeared as conference abstracts in previous reviews or only in trial registers.

In addition, the reported outcomes and methods of analysis in included RCTs will be compared with those described in the registered protocols of those trials, and any discrepancies or uncertainties noted. Where there are potentially includable trials in trial registries for which no reports or papers are found, these will be documented and efforts made to find out whether the trial was conducted, completed, and whether the findings are available. Conversely, where a reported RCT is not recorded in a trial registry, this will be clearly noted.

8 Methods for synthesising evidence of cost-effectiveness

The aims of the review of economic studies are:

- To gain insights into the key trade-offs between resource use, costs and outcomes related to immunosuppression treatment in renal transplant patients (including insights into the key health states or clinical events which drive either costs and/or clinical effectiveness and quality of life outcomes).
- To get an overview of the alternative modelling approaches that have been adopted in this disease and treatment area.
- To provide a summary of the findings of previous relevant cost-utility, cost-effectiveness, and cost-benefit studies generalisable to the UK.

8.1 Review of economic studies relevant to the decision problem

8.1.1 Search strategy

The searches will be shared with the parallel HTA 09/46/01 appraisal: Immunosuppressive therapy for kidney transplantation in adults; a review of technology appraisal guidance 85.

The following electronic databases will be searched: MEDLINE (Ovid); MEDLINE-in-Process (Ovid); EMBASE (Ovid); NHS EEDS (The Cochrane Library, Wiley Interface), HEED (Wiley), and Econlit (EBSCO). A search filter

will be used to limit to cost-effectiveness and health economic studies. The searches will be limited by date (2002-current) and to English language.

Relevant studies identified and included in the manufacturers' submissions will also be included.

8.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review of economic evaluations will be identical to those for the systematic review of clinical effectiveness (see section 7.2 [page 15] and section 7.3 [page 16]), except:

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

Based on the above inclusion/exclusion criteria, study selection will be made by two reviewers.

8.1.3 Quality assessment

Studies meeting the criteria for inclusion will be assessed by one reviewer using the checklist developed by Evers and colleagues (2005).[10] Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips and colleagues (2004; 2006).[11, 12]

8.1.4 Data synthesis

Economic studies will be summarised and synthesised using tabulated data and narrative synthesis.

8.2 Economic Modelling

A new cost-effectiveness analysis will be carried out from the perspective of the UK NHS and personal social services (PSS) using a decision analytic model. The aims of the economic modelling are:

- To estimate the lifetime incremental QALYs and incremental costs of the defined interventions and comparators according to NICE reference case methods (or with only limited deviations from NICE reference case methods due to deficiencies in available data), and assess the likelihood that the different interventions would be considered cost-effective within the NHS.

- To describe and explore the impact of structural and parameter uncertainty on the estimates of incremental costs and QALYs and cost-effectiveness measures and decisions.

- To enable an explanation of the differences in cost-utility estimates between the manufacturers' economic analyses and those by the assessment group.

The evaluation will be constrained by available evidence. The evaluation will produce estimates of incremental cost per QALY gained, unless there is insufficient evidence to estimate utility values or health-related quality of life (HRQoL). It is likely that a single decision model will be developed in Excel, although the complexity of the decision problem may mean that multiple models need to be developed or that another software package needs to be used. NICE will be informed if these situations materialise, and explicit permission will be sought from NICE if a non-standard software package is needed (i.e., other than Excel, DATA, R or WinBUGS).[13]

Model structure will be determined on the basis of available research evidence and clinical expert opinion. We will follow the conceptual modelling approach described in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 13 with the support of Paul Tappenden in our expert advisory group.[14] Conceptual models will be initially developed with our local clinical experts (Dr Jan Dudley and Dr Stephen Marks). These conceptual models will then be validated by other clinical experts (at least one) in our expert advisory group.

The sources of parameter values that determine the effectiveness of the interventions being compared will be obtained from our own systematic review of clinical effectiveness or other relevant research literature. If required parameters are not available from good quality published studies in the relevant patient group, we may use data from manufacturer submissions to NICE or from other unpublished data, or where no clinical data is available, from expert opinion.

Resource use will be specified and valued from the perspective of the NHS and PSS. The resource use associated with different health states or clinical events will be obtained or estimated either from trial data, manufacturer submissions, other published sources, or – where published sources are unavailable – relevant expert contacts or NHS Trusts. Unit cost data will be identified from national NHS and PSS reference cost databases for the most recent year, or, where these are not relevant, will be extracted from published work and/or manufacturer submissions to NICE. If insufficient data are retrieved from published sources, costs may be derived from individual NHS Trusts or groups of Trusts.

Economic analyses in the previous appraisal (TA99) relied on a surrogate relationship between acute rejection and graft/patient survival or between graft function at 24 months (measured using serum creatinine concentrations) and graft/patient survival. It is possible that a new economic model would also rely on one or more surrogate relationships, in which case such surrogate relationships would be evidence-based and the inherent uncertainties of such

relationships should be explored and quantified in line with the Guide to the Methods of Technology Appraisal.[13]

Analysis of uncertainty will focus on cost–utility, assuming cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis (PSA). The outputs of PSA will be presented using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Search strategies for additional information regarding model parameters or topics not covered within the clinical effectiveness and cost-effectiveness reviews will be based on the NICE Decision Support Unit Technical Support Document on 'Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models' (TSD 13)[14] and the methodological discussion paper 'Methods for establishing parameter values for decision analytic models' commissioned by the UK Department of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs, other relevant UK studies will be considered if appropriate.

The time horizon of our analysis will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

The perspective will be that of the NHS and Personal Social Services. Both costs and QALYs will be discounted at 3.5% per annum.[13]

ICERs estimated from manufacturers' models will be compared with the respective ICERs from the Assessment Group's model, and reasons for large discrepancies in estimated ICERs will be explored and, where possible, explained.

8.2.1 Methods for measuring and valuing health effects

In TA99 the utilities from TA85 (i.e., from adults) were directly applied to children and adolescents. We will prefer to obtain utilities directly relevant to the child and adolescent populations rather than apply utilities from adults,

although quantity and quality of evidence may result in utilities from adults being the closest approximation available.

Measuring health effects

The NICE methods guide reference case[13] states that the measurement of changes in HRQoL should be reported directly from patients (Methods Guide Section 5.3.1), or where this is not possible, data should be obtained from the person who acts as their carer (Methods Guide Section 5.3.3). In the case of children too young to self-report we will prefer utilities based on HRQoL measurements reported by parents/guardians. For children old enough to self-report and for adolescents we will prefer HRQoL measurements reported directly from patients.

The EQ-5D has been validated for use in adolescents (aged 12 years and upwards) but not in children (aged under 12 years). For adolescents we will prefer HRQoL measured using EQ-5D (Methods Guide Section 5.3.5), or if such data is not available, we will attempt to identify alternative sources as per the NICE methods guide.[13] For children we will prefer HRQoL measured using a generic preference-based measure validated for use in children which has a UK valuation set, or which can be mapped to EQ-5D.

Valuing health effects

The value of changes in patients' HRQoL (that is, utilities) should be based on a valuation of public preferences from a representative sample of the UK population using a choice-based method (Methods Guide Section 5.3.4). We will, therefore, prefer UK population valuations over non-UK population valuations, and representative population samples over samples not representative of the population. We will have no preference (since none is indicated in the reference case) over whether respondents are asked to value: from the perspective of self (i.e., an adult) experiencing the measured health state (perhaps modified for adult-relevant descriptors); or from the perspective of self, imagined as a child or adolescent, experiencing the measured health state; or from a 3rd person perspective, imagining another as a child or adolescent experiencing the measured health state.

8.2.2 Further considerations

If evidence allows, the cost-effectiveness of the treatments in different relevant subgroups of patients as defined in section 6.5 (page 11) will be explored, where appropriate with the estimation of sub-group specific cost-effectiveness ratios.

9 Handling of information from the manufacturers

All data submitted by the manufacturers/sponsors will be considered if received by NICE no later than 4/11/2014 at 5pm. Data arriving after this date may not be considered.

The industry submissions will be:

- Critically appraised for integrity and quality of evidence.
- Used as a source of data, to identify studies not located by the searches and that meet the review inclusion criteria.
- Used to compare any submitted industry model(s) with the independent economic assessment.

Any economic evaluations included in the company submission will be assessed against NICE's Guide to the Methods of Technology Appraisal and will also be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Where the TAR team have undertaken further analyses, using models submitted by manufacturers/sponsors or via de novo modelling and cost-effectiveness analysis, a comparison will be made of the alternative models used for the analysis.

Tabulated summaries and technical commentaries on the economic models used in the manufacturer submissions will be provided. This will not be a full critique as for a single technology appraisal but will be used to reflect on the results from the PenTAG de novo model and to discuss any differences in outcomes.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report

(followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

10 Expertise in this TAR team

Name	Institution	Expertise
Rob Anderson	PenTAG, University of Exeter Medical School	Systematic reviewing and economic evaluation. Project director and guarantor
Mary Bond	PenTAG, University of Exeter Medical School	Systematic reviewing and project management
Chris Cooper	PenTAG, University of Exeter Medical School	Information specialist
Louise Crathorne	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical and cost effectiveness review)
Jan Dudley	Bristol Royal Hospital for Children	Consultant in renal medicine
Marcela Haasova	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review) and project management
Tracey Jones-Hughes	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
Stephen Marks	Great Ormond Street Hospital London	Consultant in renal medicine
Ruben Mujica-Mota	PenTAG, University of Exeter Medical School	Health economist, cost effectiveness review and economic evaluation
Tristan Snowsill	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation

Other PenTAG resources: Depending on the agreed scope of work we will draw on other PenTAG resources as required.

Other external experts: We are also collaborating with Paul Tappenden (Deputy Technical Director, ScHARR Technology Assessment Group), Fiona Gamston (Renal Nurse, Birmingham Children's Hospital), and Jacob Akoh

(Consultant General and Transplant Surgeon, Plymouth Hospitals NHS Trust).

11 About PenTAG

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

Recent health technology assessment projects include:

- The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model (2014).
- Bosutinib for previously-treated chronic myeloid leukaemia: a single technology appraisal (2013).
- A systematic review and economic evaluation of intraoperative tests (RD-100i OSNA system and Metasin test) for detecting sentinel lymph node metastases in breast cancer (2013).
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model (2012).
- Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate: a single technology appraisal (2011).

- The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model (2011).
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a single technology appraisal (2011).
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model (2010).
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a single technology appraisal (2010).
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a single technology appraisal (2009).
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: a single technology appraisal (2009).
- The Effectiveness and Cost-Effectiveness of Methods of Storing Donated Kidneys from deceased donors: A Systematic Review and Economic Model (2009).
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model (2008).

12 Timetable/milestones

Final protocol	31st July 2014
Consultee information meeting (date TBC)	5th September 2014
Industry submissions to NICE	4th November 2014
Progress report due	25th November 2014
Submit draft report to NICE	19th January 2015
Submit final report to NICE	24th February 2015
1st committee meeting	6th May 2015
2nd committee meeting	7th July 2015

13 Competing interests of authors

None.

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15 Appendices

Appendix A: MEDLINE search strategies

Clinical effectiveness

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Wednesday, June 25th 2014

Searcher: Chris Cooper

Hits: 1733

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	79018
2	(Kidney$ adj3 transplant$).ti,ab,kw.	32881
3	(Renal adj3 transplant$).ti,ab,kw.	40257
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	34902
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	44456
6	1 or 2 or 3 or 4 or 5	110404
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody" or "IL2RA" or "ILR2").ti,ab,kw.	1218
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw.	6211
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw.	16604
10	Tacrolimus/	12637
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw.	200
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw.	26852
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw.	19705
14	Sirolimus/	13097
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw.	2717
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	69655
17	6 and 16	9244
18	Randomized Controlled Trial.pt.	376270

19	(random$ or RCT or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.	799275
20	clinical trial.pt.	488493
21	("controlled trial$" or "clinical trial$").ti,ab.	321777
22	18 or 19 or 20 or 21	1251568
23	17 and 22	2381
24	limit 23 to yr="2002 -Current"	1733

Notes: N/A

File: N/A

15.1 Systematic Reviews

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Monday, April 14th 2014

Searcher: Chris Cooper

Hits: 37

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	78394
2	(Kidney$ adj3 transplant$).ti,ab,kw.	32397
3	(Renal adj3 transplant$).ti,ab,kw.	39989
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	34402
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	44017
6	1 or 2 or 3 or 4 or 5	109283
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody").ti,ab,kw.	1007
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw.	6174
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw.	16395
10	Tacrolimus/	12483
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw.	186
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw.	26391
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw.	19037
14	Sirolimus/	12753
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw.	2585
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	68008
17	6 and 16	9117
18	(systematic adj3 review).ti,ab,kw.	49312
19	17 and 18	37

Notes: N/A

File: N/A

15.2 Cost effectiveness (economics and model)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

Host: OVID

Data Parameters: 1946 to Present

Date Searched: Wednesday, June 25th 2014

Searcher: Chris Cooper

Hits: 343

Search Strategy:

Search Strategy:

#	Searches	Results
1	Kidney Transplantation/	79018
2	(Kidney$ adj3 transplant$).ti,ab,kw.	32881
3	(Renal adj3 transplant$).ti,ab,kw.	40257
4	((kidney or renal) adj3 (recipient$ or dono$ or donation$ or replac$)).ti,ab,kw.	34902
5	((graft$ or allograft$ or homograft$ or allogeneic) and (kidney$ or renal)).ti,ab,kw.	44456
6	1 or 2 or 3 or 4 or 5	110404
7	(Basiliximab or Basiliximabum or Simulect or "interleukin 2 receptor antibody" or "IL2RA" or "ILR2").ti,ab,kw.	1218
8	((rabbit$ adj3 Anti-thymocyte$1) or (rabbit$ adj3 Antithymocyte$1) or (rabbit$ adj3 thymocyte$1) or (rabbit$ adj3 polyclonal) or (rabbit$ and ATG) or RATG or thymoglobulin$2).ti,ab,kw.	6211
9	(Tacrolimus or Fujimycin or Prograf or Advagraf or Adoport or Capexion or Modigraf or Perixis or Tacni or Vivadex or Protopic or Tsukubaenolide or "FK 506" or "FK-506" or "FK506" or "fr-900506").ti,ab,kw.	16604
10	Tacrolimus/	12637
11	(Belatacept or Nulojix or "lea29y" or "lea 29y" or "bms 224818").ti,ab,kw.	200
12	("Mycophenolic acid" or MPA or Mycophenolate or Arzip or CellCep$1 or Myfenax or Myfortic or Mofetil).ti,ab,kw.	26852
13	(Sirolimus or Rapamune or Rapamycin or "ay 22-989").ti,ab,kw.	19705
14	Sirolimus/	13097
15	(Everolimus or Zortress or Certican or Afinitor or Evertor or "SDZ RAD").ti,ab,kw.	2717
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	69655
17	6 and 16	9244
18	Economics/	26984
19	exp Economics, Pharmaceutical/	2538
20	exp Economics, Medical/	13566

21	exp Economics, Hospital/	19519
22	(pharmacoeconomic* or socioeconomics or economic$).ti,ab,kw.	174587
23	ec.fs.	335455
24	exp "Costs and Cost Analysis"/	181300
25	Cost of Illness/	17672
26	(cost* or cba or cea or cua or (value adj2 money) or pric$ or fiscal or funding or financial or finance or budget$ or (expenditure$ not Energy)).ti,ab,kw.	500586
27	(cost* or cba or cea or cua or (value adj2 money) or pric$ or fiscal or funding or financial or finance or budget$ or (expenditure$ not Energy)).ti,ab,kw.	500586
28	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	852233
29	17 and 28	421
30	limit 29 to yr="2002 -Current"	343

Notes: N/A

File: N/A