

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

**Technology Assessment Report commissioned by the NETSCC HTA Programme on behalf of the National Institute for Health and Care Excellence: HTA 09/46/01**

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## 1. Title of the project

The effectiveness and cost-effectiveness of immunosuppressive regimens in renal transplantation in adults, of basiliximab and rabbit anti-human thymocyte immunoglobulin as an induction therapy and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept as maintenance therapy (including a review of TA85): a systematic review and economic evaluation.

## 2. Name of TAR team and project 'lead'

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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 in 2003 on the clinical effectiveness and cost-effectiveness of immunosuppressive therapy technologies for renal transplant (Woodroffe and colleagues, 2005). For induction therapy, the two interventions under consideration are:

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

The following seven interventions are included for initial and long-term maintenance therapy:

- mycophenolate mofetil (non-proprietary [Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, Wockhardt], CellCept® [Roche], Arzip [Zentiva], Myfenax [TEVA UK])
- mycophenolate sodium (Myfortic® [Novartis])
- sirolimus (Rapamune® [Pfizer])
- immediate-release tacrolimus (Adoport® [Sandoz], Prograf® [Astellas], Capexion® [Mylan], Tacni® [TEVA UK], Vivadex® [Dexcel], Modigraf® [Astellas], Perixis® [Accord Healthcare])
- prolonged-release tacrolimus (Advagraf® [Astellas])
- everolimus (Certican® [Novartis])
- belatacept (Nulojix® [Bristol-Myers Squibb])

#### 4. Background

End stage renal failure (ESRF) occurs when the kidneys develop severe and irreversible impairment of function, so that the patient would die unless given dialysis or renal transplantation. The preferred treatment for this condition is transplantation because the quality and duration of life are better than that achieved with long-term dialysis.<sup>1</sup> However, in order to reduce the risk of rejection and prolong survival of the graft, transplantation must be supported by immunosuppressive therapy.

During 2013-2014, 2547 kidney transplants were performed in England, with 1631 from deceased donors and 916 from living donors.<sup>2</sup> As of 31 March 2014, 4914 patients remain on the transplant list.<sup>2</sup>

Immunosuppression treatment for kidney transplantation can be categorised into prevention of graft rejection (induction, initial and long-term maintenance therapy) and the treatment of established acute allograft rejection (which is not included in this appraisal). By the end of

2012, over 27,600 adults in the UK were receiving immunosuppressive therapy following renal transplantation.<sup>3</sup>

#### Induction therapy

This is a short course of intensive immunosuppression administered around the time of surgery, with the aim of 'switching off' the immune system for approximately 2 weeks post-transplant.<sup>1</sup>

Many of the induction immunosuppressive agents currently used in the UK are biological agents, including monoclonal (basiliximab) and polyclonal (rabbit anti-human thymocyte immunoglobulin) antibodies. Daclizumab, which was reviewed in technology appraisal 85 has since had the marketing authorisation withdrawn at the request of the manufacturer.<sup>4</sup>

#### Initial maintenance therapy

This is usually triple therapy using a calcineurin inhibitor (e.g. ciclosporin or tacrolimus) in combination with a steroid (e.g. prednisolone) and an antiproliferative agent (e.g. mycophenolate). Occasionally, dual therapy (calcineurin inhibitor plus a steroid) or, more rarely, monotherapy (calcineurin inhibitor alone) can be used. Duration of initial therapy varies widely, with estimates ranging from 14 days to 6 months post-transplantation.<sup>1</sup>

#### Long-term maintenance therapy

This is generally the same treatment as initial therapy, usually at a reduced dose as the transplanted kidney becomes more immunologically stable.<sup>5</sup> It is typically continued throughout the survival of the graft.

### **5. Current evidence**

The conclusions from the previous review were:<sup>1</sup>

- The newer immunosuppressant drugs (basiliximab, daclizumab, tacrolimus and mycophenolate mofetil) consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy.
- The independent use of basiliximab, daclizumab, tacrolimus and mycophenolate mofetil was associated with a similar absolute reduction in 1-year acute rejection rate. However, the benefits of these drugs did not appear to be additive. Therefore the addition of one of these drugs to a baseline immunosuppressant regime 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, together with the side-effect profile associated with each drug, translated into changes in health-related quality of life (HRQoL).
- Given the relatively short duration of trials, the impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain.
- In the previous appraisal's economic modelling the independent assessment group's analyses did not support the manufacturers' claims about the cost-effectiveness of their drugs. The only regimen which the independent economic analysis supported (i.e. which yielded positive net benefits) was basiliximab versus placebo in a Neoral® with azathioprine regimen. For all other drug comparisons the mean ICERs ranged from £78,000 to £250,000 and there was wide uncertainty around the point estimates of net benefit.

## **6. Decision problem**

### **6.1. Purpose of the decision to be made**

The assessment will address the question: "What is the clinical-effectiveness and cost-effectiveness of immunosuppressive regimens in renal transplantation in adults, of basiliximab and rabbit anti-human thymocyte immunoglobulin as an induction therapy and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenoate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept as a maintenance therapy (including review of TA85)?"

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 initial and maintenance therapy). Otherwise, the economic analyses will have to make base case assumptions about the most likely treatment sequences that either evidence supports and/or are feasible and acceptable in the current NHS. In other words, this will have to be decided on the basis of the range of treatment sequences and study designs (especially which treatments or sequences of treatments were randomised) represented in the effectiveness studies included in our systematic review (i.e., we cannot model treatment sequences for which there is no relevant clinical evidence), combined with consulting clinical experts about whether any treatment sequences for which there is evidence are not feasible within the NHS.

## 6.2. Interventions

A total of nine interventions will be assessed in this review, two for induction therapy and seven for initial and long-term maintenance therapy. 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]) is a monoclonal antibody which acts as an interleukin-2 receptor antagonist. It has a UK marketing authorisation for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adults. It is intended to be used alongside ciclosporin and corticosteroid-based immunosuppression in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin, corticosteroids and either azathioprine or mycophenolate mofetil.<sup>4</sup>

**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.<sup>4</sup>

For initial or maintenance therapy:

**Tacrolimus** is a calcineurin inhibitor which is available in a prolonged-release formulation (Advagraf® [Astellas Pharma]) and immediate-release formulations (Adoport® [Sandoz]; Capexion® [Mylan]; Modigraf® [Astellas Pharma]; Perixis® [Accord Healthcare]; Prograf® [Astellas Pharma]; Tacni® [Teva]; Vivadex® [Dexcel Pharma]). All of these formulations have UK marketing authorisations for the prophylaxis of transplant rejection in adults undergoing kidney transplantation.<sup>4</sup>

**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.<sup>4</sup>

**Mycophenolate mofetil** is a prodrug of mycophenolic acid which acts as an antiproliferative agent (Arzip® [Zentiva], CellCept® [Roche], 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.<sup>4</sup>

**Mycophenolate sodium** is an enteric coated formulation of mycophenolic acid (Myfortic® [Novartis]). As above, this formulation 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.<sup>4</sup>

**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. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2 to 3 months, and may be continued, with corticosteroids, only if ciclosporin can be progressively discontinued.<sup>4</sup>

**Everolimus** (Certican® [Novartis]) is a proliferation signal inhibitor and is an analogue of sirolimus. Everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation.<sup>4</sup>

### 6.3. Place of the interventions in the treatment pathway

Since the publication of NICE technology appraisal guidance 85, new technologies have received marketing authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (mycophenolate sodium, belatacept, and a prolonged-release formulation of tacrolimus). The marketing authorisation for daclizumab has been withdrawn while other treatments included in the NICE technology appraisal 85 are now available generically. Also, a 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.

NICE guidance (Technology Appraisal 85)<sup>6</sup> recommends the following:

- Basiliximab or daclizumab, used as part of a calcineurin-inhibitor-based immunosuppressive regimen, are recommended as options for induction therapy in the prophylaxis of acute organ rejection in adults undergoing renal transplantation. The induction therapy (basiliximab or daclizumab) with the lowest acquisition cost should be used (note, the marketing authorisation for daclizumab has been withdrawn at the request of the manufacturer<sup>4</sup>).<sup>6</sup>

- Tacrolimus is an alternative to ciclosporin when a calcineurin inhibitor is indicated as part of an initial or a maintenance immunosuppressive regimen in renal transplantation for adults. The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for individual people.<sup>6</sup>
- Mycophenolate mofetil is recommended for adults as an option as part of an immunosuppressive regimen only: where there is proven intolerance to calcineurin inhibitors, such as nephrotoxicity leading to risk of chronic allograft dysfunction, or in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor.<sup>6</sup>
- Sirolimus is recommended for adults as an option as part of an immunosuppressive regimen only in cases of proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitating complete withdrawal of these treatments.<sup>6</sup>

These recommendations contain advice that may result in some medicines being prescribed outside the terms of their marketing authorisation. Clinicians prescribing these drugs should ensure that patients are aware of this, and that they consent to their use in such circumstances.<sup>6</sup>

#### **6.4. Relevant comparators**

The main comparators of interest for induction therapy are:<sup>4</sup>

- regimens without monoclonal or polyclonal antibodies
- the other interventions under consideration

The main comparators of interest for initial and long-term maintenance therapy are:<sup>4</sup>

- a calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids
- the other interventions under consideration

#### **6.5. Population**

The population will be adults undergoing kidney transplantation only. The donor may be either living-related, living-unrelated or deceased. Patients receiving multi-organ transplants<sup>4</sup> and those who have received transplants and immunosuppression previously will be excluded.

If evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered, including:<sup>4</sup>

- 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**

Evidence in relation to the following kinds of outcomes will be considered:<sup>4</sup>

- patient survival
- graft survival
- graft function
- time to and incidence of acute rejection
- severity of acute rejection
- adverse effects of treatment
- HRQoL

## **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 (Simulect® [Novartis]), rabbit anti-human thymocyte immunoglobulin (Thymoglobuline® [Sanofi-Aventis]), mycophenolate mofetil (non-proprietary or CellCept® [Roche]), mycophenolate sodium (Myfortic® [Novartis]), sirolimus (Rapamune® [Pfizer]), immediate-release tacrolimus (Adoport® [Sandoz], Prograf® [Astellas], Capexion® [Mylan], Tacni® [TEVA UK], Vivadex® [Dexcel], Modigraf® [Astellas], Perixis® [Accord Healthcare]), prolonged-release tacrolimus (Advagraf® [Astellas]), sirolimus (Rapamune® [Pfizer]), everolimus (Certican® [Novartis]) and belatacept (Nulojix® [Bristol-Myers Squibb]).

The review will update the previous review of clinical effectiveness undertaken in 2002 to inform NICE's TA85 Guidance.<sup>6</sup> As an update it will therefore:



- conduct new searches and apply study selection processes for sources published from 2002 onwards
- include those pre-2002 published studies reviewed in the previous technology assessment for NICE (unless the study does not fall within our inclusion criteria), and any subsequent reports of those studies
- conduct quality assessment on all included studies
- perform data extraction on post-2002 studies. Data extracted for the previous technology assessment will be used for the pre-2002 studies

The review will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.<sup>7</sup>

### **7.1. Search strategy**

The search strategy will comprise the following main elements:

- searching of electronic databases 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 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 randomised controlled trials (RCTs). The following trials registries will be searched: Current Controlled Trials; Clinical Trials.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 (manually).

The databases will be searched from search end-date of the last MTA on this topic (2002).

The searches will be developed using the search strategies detailed in the MTA by Woodroffe and colleagues as the starting point (see Appendix A for more information).<sup>1</sup>

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

## **7.2. Inclusion/exclusion criteria**

The inclusion and exclusion criteria will be applied to both new search results and full-text reports included from the previous technology assessment (TA85).<sup>1</sup>

### **7.2.1. Inclusion criteria**

The inclusion criteria are as reported in Table 1. The review of clinical effectiveness will include any RCT reporting at least one of the outcomes of interest. However, if any outcomes of interest are lacking RCT evidence or if the RCTs do not provide an adequate length of follow-up, we will extend our search and inclusion criteria to controlled clinical trials. Furthermore, these criteria would also be relaxed for consideration of adverse events, where non-randomised and observational studies may be included. However, scoping searches indicate sufficient RCT evidence should be available.

Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of the results to be undertaken. Systematic reviews and clinical guidelines will be included as sources of references for finding further RCTs and to compare with our systematic review.

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.

**Table 1. Inclusion criteria (PICOS) as per the final scope issued by NICE and accompanying notes<sup>4</sup>**

<b>Population</b>	Adults undergoing kidney transplantation only 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
<b>Intervention(s)</b>	<p><b><u>Induction therapy regimens containing:</u></b></p> <p><b>Basiliximab</b> (Simulect® [Novartis])</p> <p><b>Rabbit anti-human thymocyte immunoglobulin</b> (Thymoglobuline® [Sanofi-Aventis])</p> <p><b><u>Initial and long-term maintenance therapy regimens containing:</u></b></p> <p><b>Mycophenolate mofetil</b> (non-proprietary [Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz, Wockhardt], CellCept® [Roche], Arzip [Zentiva], Myfenax [TEVA UK])</p> <p><b>Mycophenolate sodium</b> (Myfortic® [Novartis])</p> <p><b>Sirolimus</b> (Rapamune® [Pfizer])</p> <p><b>Immediate-release tacrolimus</b> (Adoport® [Sandoz], Prograf® [Astellas], Capexion® [Generics], Tacni® [TEVA UK], Vivadex® [Dexcel], Perixis® [Accord])</p>	Under an exceptional directive from the Department of Health, these interventions may be appraised outside their licensed authorisations (to reflect their use in clinical practice) where there is compelling evidence of safety and effectiveness.

	<p>Healthcare], Modigraf® [Astellas])</p> <p><b>Prolonged-release tacrolimus</b> (Advagraf® [Astellas])</p> <p><b>Everolimus</b> (Certican® [Novartis])</p> <p><b>Belatacept</b> (Nulojix® [Bristol-Myers Squibb]).</p>	
<b>Comparator(s)</b>	<p><b><u>Induction therapy</u></b></p> <p>Regimens without monoclonal or polyclonal antibodies</p> <p>One of the other interventions under consideration</p> <p><b><u>Initial and long-term maintenance therapy regimens containing:</u></b></p> <p>A calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids</p> <p>One of the other interventions under consideration</p>	
<b>Outcomes</b>	<p>Patient survival</p> <p>Graft survival</p> <p>Graft function</p> <p>Time to and incidence of acute rejection</p>	<p>Overall survival</p> <p>Graft loss defined as return to chronic dialysis, retransplant, graft removal or death.</p> <p>Serum creatinine, (estimated) glomerular filtration rate, urine protein excretion.<sup>8</sup></p> <p>Increased serum creatinine levels or biopsy</p>

	Severity of acute rejection	Hyperacute rejection (within 72 hours), acute rejection according to Banff classification (Grade I, II, III). <sup>9</sup>
	Adverse effects of treatment	Such as cardiovascular complications, malignancies, diabetes, infections and nephrotoxicity. <sup>1</sup>
	Health-related quality of life	Health-related quality of life – data on validated quality of life measures; e.g. EQ-5D, SF-36, KTQ-25
<b>Study design</b>	RCTs  Systematic reviews of RCTs (to be used to cross-check for any additional RCTs and to compare the findings of our review with)	For the purpose of this review, a systematic review will be defined as one that has: a focused research question; 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 synthesis of the included evidence, whether narrative or quantitative.

### 7.2.2. Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. Studies, such as non-randomised trials, which are considered methodologically weaker in terms of either study design or the method used to assess outcomes will be excluded from the results, unless the evidence from RCTs is insufficient.

The following publication types will be excluded from the analysis:

- non-randomised studies
- animal models
- preclinical and biological studies

- narrative reviews, editorials, opinions
- non-English language papers
- reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality

### **7.3. 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 1. Initially, 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. At each step studies which do not satisfy those criteria will be excluded; abstract-only studies will be included provided sufficient methodological details are reported to allow critical appraisal of study quality.

### **7.4. Data extraction strategy**

Included full papers will be split between two reviewers for the purposes of data extraction using a standardised data specification form, and checked independently by another. Information extracted and tabulated will include details of the study's design and methodology, 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 a third reviewer if necessary. Where multiple publications of the same study are identified, data will be extracted and reported as a single study.

### **7.5. 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<sup>10</sup> or criteria based on those proposed by the NHS Centre for Reviews and Dissemination for RCTs.<sup>7</sup>

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.

## 7.6. 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. If data allows, a network meta-analysis will be performed.

The following subgroups will be considered:

- level of immunological risk (including human leukocyte antigen compatibility and blood group compatibility)
- people at high risk of rejection within the first six 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)

If evidence allows, 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 above inclusion criteria will be examined. As such, studies not within scope, where the intervention is identical in both study arms, but dose reduction or withdrawal of corticosteroids or CNIs occurs in one arm (but not the other), will not be included.

## 7.7. Publication bias

Reporting bias\* in our systematic review and meta-analyses will be assessed according to recommendations in the Cochrane Handbook for Reviewers.<sup>11</sup> This may include researching trials that have only ever appeared as conference abstracts in previous reviews.

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\* Where the term 'reporting bias' covers all types of publication, language, outcome, location etc biases defined in the Cochrane Handbook.

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 reported 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**

#### **Search strategy**

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.

#### **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 (Section 7.2, page 10), 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).
- Full cost-effectiveness analyses, cost–utility analyses and cost–benefit analyses will be included. (Economic evaluations which only report average cost-effectiveness ratios will only be included if the incremental ratios can be easily calculated from the published data.)
- Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS.
- Only economic evaluations from UK, USA, Canada, Australia, and western Europe will be included as these settings may include data generalizable to the UK.

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

### **Quality assessment**

Studies meeting the criteria for inclusion will be assessed by one reviewer using the checklist developed by Evers and colleagues (2005).<sup>12</sup> Where studies are based on decision models they will be further quality assessed using the checklist developed by Philips and colleagues (2004; 2006).<sup>13,14</sup>

### **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 PSS using a decision analytic model. The aims of the economic modelling are:

1.To estimate the lifetime incremental QALYs and incremental costs of the defined 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

2.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

3.To enable better 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/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 the explicit permission will be sought from NICE a non-standard software package (i.e., other than Excel, DATA, R or WinBUGS) is needed.<sup>15</sup>

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 TSD 13 with the support of Paul Tappenden in our expert advisory group.<sup>16</sup> Conceptual models will be initially developed with our local clinical expert (Jason Moore). 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 (TA85) relied on a surrogate relationship between acute rejection and graft/patient survival or 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 2013.<sup>15</sup>

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)<sup>16</sup> and the methodological discussion paper 'Methods for establishing parameter values for decision analytic models' commissioned by the UK Dept. of Health and produced by InterTASC (January 2005). In addition to systematic reviews and RCTs, other relevant UK studies will be considered if appropriate.

ICERs estimated from Consultee manufacturer 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**

Ideally, the measurement of changes in health-related quality of life (HRQL) should be reported directly from patients. The value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D will be the preferred measure of HRQL for the purposes of estimating QALYs. In the absence of reliable EQ-5D utility data from relevant trials or patient groups, the use of alternative sources for utility weights for health states will be informed by the NICE Guide to the methods of technology appraisal (2013).<sup>15</sup>

### **8.2.2. Time horizon, perspective and discounting**

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 National Health Services and Personal Social Services. Both costs and QALYs will be discounted at 3.5%.<sup>15</sup>

## 9. Handling of information from the manufacturers

All data submitted by the manufacturers/sponsors will be considered if received by NICE no later than 5pm on 08/10/2014. Data arriving after this date may not be considered.

The industry submissions will be:

1. Critically appraised for integrity and quality of evidence.
2. Used as a source of data, to identify studies not located by the searches and that meet the review inclusion criteria.
3. 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 guidance on 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 identified in the outcomes provided.

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 or others, 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 (e.g. within the modelling software files).

## 10. Expertise in this TAR team

Name	Institution	Expertise
<b>Rob Anderson</b>	PenTAG, University of Exeter Medical School	Systematic reviewing and economic evaluation. Project director and guarantor
<b>Mary Bond</b>	PenTAG, University of Exeter Medical School	Systematic reviewing and project management

<b>Helen Coelho</b>	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
<b>Chris Cooper</b>	PenTAG, University of Exeter Medical School	Information scientist
<b>Louise Crathorne</b>	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical and cost effectiveness review)
<b>Marcela Haasova</b>	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
<b>Tracey Jones-Hughes</b>	PenTAG, University of Exeter Medical School	Systematic reviewer (clinical effectiveness), project management
<b>Linda Long</b>	PenTAG, University of Exeter Medical School	Systematic reviewing (clinical effectiveness review)
<b>Jason Moore</b>	Royal Devon and Exeter Hospital, Devon	Consultant in renal medicine
<b>Ruben Mujica-Mota</b>	PenTAG, University of Exeter Medical School	Health economist, cost effectiveness review and economic evaluation
<b>Tristan Snowsill</b>	PenTAG, University of Exeter Medical School	Economic modelling and economic evaluation

**Other external experts:** We are also collaborating with Paul Tappenden, Deputy Technical Director for the SchARR Technology Assessment Group, David Game, Consultant Nephrologist, Guy's Hospital and Jacob Akoh, Consultant General and Transplant Surgeon, Plymouth Hospitals NHS Trust.

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

## 11. TAR centre

The Peninsula Technology Assessment Group is part of the University of Exeter Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments 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.

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
- Bosutinib for previously-treated chronic myeloid leukaemia: a single technology appraisal
- 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
- Dasatinib and Nilotinib for the 1st line treatment of chronic phase chronic myeloid Leukaemia (CML): a systematic review and economic model
- Bevacizumab, Cetuximab, and Panitumumab for in colorectal cancer (metastatic) after failure of 1st line chemotherapy: a systematic review and economic model
- The psychological consequences of false positive mammograms: a systematic review
- 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 critique of the submission from Napp
- 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
- Ofatumumab (Arzerra®) for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab: a critique of the submission from GSK
- Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: a critique of the submission from Novartis
- The clinical and cost-effectiveness of sunitinib for the treatment of gastrointestinal stromal tumours: a critique of the submission from Pfizer
- The clinical- and cost effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene
- Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic model
- Machine perfusion systems and cold static storage of kidneys from deceased donors.
- The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults
- The harmful health effects of recreational Ecstasy: A systematic review of observational evidence
- Assessment of surrogate outcomes in model-based cost effectiveness analyses within UK health technology reports: a methodological review
- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in adults and children aged 12 years and over.

- Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years.
- The effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: a systematic review and economic model.
- The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease: a systematic review and economic model
- The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high grade glioma: a systematic review and economic evaluation.
- Surveillance of cirrhosis for the development of hepatocellular carcinoma: systematic review and economic analysis.
- Surveillance of Barrett's oesophagus: exploring the uncertainty.
- The cost effectiveness of testing for hepatitis C in former injecting drug users.
- Do the findings of case series vary systematically by methodological characteristics.
- The effectiveness and cost effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
- The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
- Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
- Systematic review of endoscopic Sinus Surgery for Nasal Polyps.
- Screening for hepatitis C in GUM clinic attenders and injecting drug users.
- The effectiveness and cost effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.

## 12. Competing interests of authors

None

## 13. Timetable/milestones

Action	Expected due date
Draft protocol due	17 June 2014

Final protocol due	8 July 2014
Consultee information meeting	5 September 2014 (TBC)
Consultee submissions due to NICE	8 October 2014
Progress report due	22 October 2014
Draft assessment report due	23 December 2014
Assessment report due	28 January 2014
1 <sup>st</sup> Appraisal Committee meeting	1 April 2015



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## 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 25<sup>th</sup> 2014

Searcher: Chris

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

### 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 14<sup>th</sup> 2014

Searcher: Chris

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

**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 25<sup>th</sup> 2014

Searcher: Chris

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