NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the company(ies), the consultees and their nominated clinical experts and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- What is the Committee's view on the **clinical effectiveness evidence** identified in the systematic reviews?
  - Do the outcomes adequately capture the benefits of treatment? What is the likely impact of immunosuppressive therapies on quality of life?
  - Consultees outlined groups of people for whom each drug may be considered in clinical practice; is there evidence to suggest additional benefits of any drugs in specific subgroups?
- What is the Committee's view on the clinical effectiveness of **induction therapies**, compared with each other or with no induction?
- What is the Committee's view on the clinical effectiveness of **maintenance therapies**?

  - Is there evidence to suggest statistically and clinically significant differences between maintenance drugs or between particular regimens?
  - The Assessment Group noted substantial heterogeneity in the network meta-analysis. Is the evidence from this analysis suitable for decision making?
- What is the Committee's view on the **adverse events** associated with immunosuppressive therapies? Are there any important differences between drugs or regimens?

Cost effectiveness

- What is the Committee's view on the **economic models** presented by the Assessment Group and the companies?
  - Are the model structures and the assumptions they contain appropriate?
  - The Assessment Group modelled quality of life using a utility decrement for each health state, whereas Novartis also incorporated declining graft function over time; what is the most appropriate approach for modelling utilities?
  - The Assessment Group's model did not take into account the effect of adherence to medication; is there evidence to suggest particular drugs or regimens improve adherence, and should this be included in the model?
  - Has the model appropriately captured the costs of drug acquisition and other treatments? Is the Assessment Group's approach to using list prices and hospital acquisition costs appropriate?
- What is the Committee's view on the **results** of the cost effectiveness analyses?
  - Which drugs and regimens are cost effective options?
  - Some of the differences in costs and quality-adjusted life years (QALYs) between treatment options are small; how does the Committee interpret the size of the incremental costs and QALYs between drugs?
- Some of the regimens included in the Assessment Group's model are outside the terms of the marketing authorisations of the drugs; is there sufficient evidence to consider making recommendations for these combinations?
- Consultees noted that some drugs may be particularly cost effective in specific subgroups, but the Assessment group identified limited evidence; is there sufficient evidence to consider recommendations for particular subgroups?

1 Background: clinical need and practice

1.1 Kidney transplantation is used to treat people with established renal failure, which is severe and irreversible impairment of kidney function. After a kidney transplant, immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney (or 'graft') and prolong its survival.

1.2 Between April 2013 and March 2014, 2931 kidney transplants were performed in adults in the UK, including 2506 performed in adults in England. At the end of 2013, approximately 29,600 adults in the UK were receiving immunosuppressive therapy after kidney transplantation, including 24,800 people in England.

1.3 Immunosuppressive therapy can be categorised as induction therapy, initial maintenance therapy, and long-term maintenance therapy (Table 1). Treatment aims to prevent acute rejection and optimise function of the transplanted kidney while minimising the risk of short- and long-term consequences of immunosuppression (such as the risk of infection, cancer and cardiovascular disease).

Table 1 Categories of immunosuppressive therapies

Induction	• May be used for up to 2 weeks around the time of transplantation • Intensive immunosuppressive therapy, often involving polyclonal or monoclonal antibodies (for example, anti-human thymocyte immunoglobulin, basiliximab)
Initial maintenance	• Starts immediately after transplantation, continues for 3–6 months • Treatment options used in clinical practice include calcineurin inhibitors (ciclosporin or tacrolimus) and antiproliferative agents (e.g. azathioprine, sirolimus or mycophenolic acid), which are often used in combination regimens with or without corticosteroids
Long-term maintenance	• Carries on from initial maintenance, continues lifelong • Often the same as initial maintenance therapy, but with a reduced dose

1.4 The choice of immunosuppressive therapy is informed by a number of factors including the level of immunological risk, determined by risk factors such as age and antibody reactivity (assessed using measures such as human leukocyte antigen and panel reactive antibody status and the calculated reaction frequency).

1.5 NICE guidance on immunosuppressive therapy for kidney transplantation in adults is provided by technology appraisal 85 (TA85), published in September 2004. It recommended basiliximab, daclizumab, tacrolimus, mycophenolate mofetil and sirolimus, in certain circumstances, as options for immunosuppressive therapy for renal transplant in adults. Since the publication of TA85, new technologies have received marketing authorisations for induction therapy (rabbit anti-human thymocyte immunoglobulin) and maintenance therapy (mycophenolate sodium, belatacept, a prolonged-release formulation of tacrolimus, and everolimus). Some of the treatments included in TA85 are now available generically, and the marketing authorisation for daclizumab has been withdrawn.

Technology Appraisal 85 – summary of considerations

Induction therapies

1.6 The Committee considered that basiliximab and daclizumab (now withdrawn) were clinically and cost effective options for preventing acute rejection in people at low or moderate immunological risk. The Committee heard that these treatments were more commonly used in people at high immunological risk, although this is outside their marketing authorisations. It heard that there was a need for additional options in this patient group, and considered that there was no reason to anticipate that these drugs would be less effective in the high-risk group.

1.7 The Committee considered that there was no convincing evidence that either basiliximab or daclizumab should be preferred. As the costs are

potentially quite different, it recommended that the drug regimen with the lowest acquisition cost should be used unless contraindicated.

Maintenance therapies

1.8 The Committee considered that tacrolimus was at least as effective as ciclosporin and had a different side effect profile. Given that it appeared to be cost effective, tacrolimus was recommended as an option.

1.9 Clinical evidence suggested that mycophenolate mofetil was clinically effective compared with azathioprine; however, the economic modelling suggested that when combined standard-dose ciclosporin, it was unlikely to be cost effective. The Committee understood that when optimistic assumptions were made about ciclosporin dose reductions, mycophenolate mofetil appeared to be cost effective. It was persuaded that when ciclosporin dose reduction or avoidance is required, mycophenolate mofetil was likely to be cost effective.

1.10 The Committee noted that there were no studies directly comparing the licensed dose of sirolimus with standard calcineurin inhibitor-based regimens. Based on the available evidence, the Committee did not consider that sirolimus was more effective than standard ciclosporin-based immunosuppression. However, it understood that there was an important need for treatment options when calcineurin inhibitors are not tolerated, so sirolimus was recommended as an option in this situation.

2 The technologies

Induction therapy

Basiliximab

2.1 Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody which acts as an interleukin-2 receptor antagonist. It has a UK marketing authorisation for the prophylaxis of acute organ rejection in de novo allogeneic renal transplantation in adults. The summary of product

characteristics states it is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in 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.

2.2 Basiliximab is administered intravenously, in two doses of 20 mg each (one 2 hours before transplantation and the second 4 days after).

2.3 The summary of product characteristics states that the following adverse reactions occur in at least 20% of people treated with basiliximab: constipation, pain, nausea, peripheral oedema (swelling of the feet and ankles), hypertension, anaemia, headache, hyperkalaemia (high potassium in the blood), high cholesterol, postoperative wound complications, weight gain, increase in blood creatinine, hypophosphataemia (a deficiency of phosphates in the blood), diarrhoea and urinary tract and upper respiratory tract. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 Basiliximab is available in 10-mg and 20-mg vials, at a net price of £758.69 and £842.38 respectively (excluding VAT; British national formulary online [accessed June 2015]), equating to £1684.76 per course of treatment (2 doses of 20 mg). Costs may vary in different settings because of negotiated procurement discounts.

Rabbit anti-human thymocyte immunoglobulin

2.5 Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline, Sanofi) is a gamma immune globulin, generated by immunising rabbits with human thymocytes. It has a UK marketing authorisation for the prevention of graft rejection in renal transplantation. The summary of product characteristics states it is usually used in combination with other immunosuppressive drugs.

2.6 R-ATG is administered intravenously, at a dose of 1 to 1.5 mg/kg/day for 3 to 9 days after transplantation of a kidney (a cumulative dose of 3 to 13.5 mg/kg).

2.7 The summary of product characteristics states that the following adverse reactions occur in at least 10% of people treated with r-ATG: fever; infection; and a reduced number of lymphocytes, neutrophils or platelets in the blood (that is, lymphopenia, neutropenia or thrombocytopenia). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.8 R-ATG is available in 25-mg vials, at a net price of £158.77 (excluding VAT; British national formulary online [accessed June 2015]), equating to £1428.93 to £7144.65 per course for a 70 kg person. Costs may vary in different settings because of negotiated procurement discounts.

For maintenance therapy

Tacrolimus

2.9 Tacrolimus is a calcineurin inhibitor and is available in a prolonged-release formulation (Advagraf, Astellas Pharma) and immediate-release formulations (Adoport, Sandoz; Capexion, Mylan; Modigraf, Astellas Pharma; Perixis, Accord Healthcare; Prograf, Astellas Pharma; Tacni, Teva; Vivadex, Dexcel Pharma). All of these formulations have UK marketing authorisations for the prophylaxis of transplant rejection in adults undergoing kidney transplantation, and all are administered orally. Prograf can also be administered intravenously. The summary of product characteristics recommends an initial dose of 0.2–0.3 mg/kg/day orally or 0.05–0.1 mg/kg/day intravenously, and states that the dosage is usually reduced in the post-transplant period. The Commission on Human Medicines advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only.

2.10 The summary of product characteristics states that the following adverse reactions occur in at least 10% of people treated with immediate-release tacrolimus: infection, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, insomnia, tremor, headache, hypertension, diarrhoea, nausea and renal impairment. The summary of product characteristics states for prolonged-release tacrolimus also states that abnormal liver function tests occur in at least 10% of people. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.11 The average cost of immediate-release tacrolimus is £0.52 per mg (Commercial Medicines Unit, Drug and pharmaceutical electronic market information, 2014). This equates to £50.96–£76.44 per week for an initial dose of 0.2–0.3 mg/kg/week in a 70 kg person. Prolonged-release tacrolimus is available as 0.5 mg, 1 mg, 3 mg and 5 mg capsules, at a net price of £1.07–£1.43 per mg (excluding VAT; British national formulary online [accessed June 2015]). This equates to £112.11–£210.47 per week for an initial dose of 0.2–0.3 mg/kg/week in a 70 kg person. Costs may vary in different settings because of negotiated procurement discounts.

Belatacept

2.12 Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept has a UK marketing authorisation for prophylaxis of graft rejection in adults receiving a renal transplant, in combination with corticosteroids and a mycophenolic acid. The summary of product characteristics recommends that an interleukin-2 receptor antagonist is added to this belatacept-based regimen.

2.13 Belatacept is administered intravenously, at a dose of 10 mg/kg on the day of transplantation, followed by 10 mg/kg on days 5, 14, 28, 56 and 84 and 5 mg/kg every 4 weeks from then on.

2.14 The summary of product characteristics states that the following adverse reactions occur in at least 20% of people treated with belatacept: diarrhoea, anaemia, urinary tract infection, peripheral oedema (swelling of the feet and ankles), constipation, hypertension, fever, nausea, graft dysfunction, cough, vomiting, leukopenia (a reduced number of white blood cells), hypophosphataemia (a deficiency of phosphates in the blood) and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.15 Belatacept is available in 250-mg vials, at a net price of £354.52 (excluding VAT; British national formulary online [accessed June 2015]). For a 70 kg person, this equates to £6,381.36 for the first 12 weeks and £709.04 every 4 weeks from week 16 onwards. Costs may vary in different settings because of negotiated procurement discounts.

Mycophenolic acid

2.16 Mycophenolic acid is an antiproliferative agent and is available as a prodrug formulation mycophenolate mofetil (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), and as a sodium salt administered in enteric-coated tablets (Myfortic, Novartis Pharmaceuticals). Mycophenolate mofetil and mycophenolate sodium have UK marketing authorisations for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation.

Mycophenolate mofetil

2.17 Mycophenolate mofetil can be administered orally or intravenously, at a recommended dose of 2 g/day.

2.18 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with mycophenolate mofetil: viral, bacterial and fungal infections; leukopenia;

thrombocytopenia; anaemia; vomiting; abdominal pain; diarrhoea and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.19 The average cost of mycophenolate mofetil is £0.38 per g (Commercial Medicines Unit, Drug and pharmaceutical electronic market information, 2014), equating to £5.28 per week. Costs may vary in different settings because of negotiated procurement discounts.

Mycophenolate sodium

2.20 Mycophenolate sodium is administered orally, at a recommended dose of 1.44 g per day.

2.21 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with mycophenolate sodium: leukopenia, diarrhoea, and viral, bacterial and fungal infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.22 Mycophenolate sodium is available in 180-mg and 360-mg tablets, at a net price of £4.48 per g (excluding VAT; British national formulary online [accessed June 2015]), equating to £62.69 per week. Costs may vary in different settings because of negotiated procurement discounts.

Sirolimus

2.23 Sirolimus (Rapamune, Pfizer) is a non-calcineurin inhibiting immunosuppressant and acts as an antiproliferative. It has a UK marketing authorisation for the prophylaxis of organ rejection in 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, and may be continued only if ciclosporin can be progressively discontinued.

2.24 Sirolimus is administered orally at a recommended dose of 6 mg initially, followed by 2 mg per day for 2–3 months then adjusted to obtain blood trough levels of 4–12 ng/ml.

2.25 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with sirolimus: fever; hypertension; decreased levels of platelets, red blood cells, potassium or phosphates in the blood; increased levels of cholesterol, sugar, triglycerides, creatinine or lactate dehydrogenase in the blood; urinary tract infection; pain; lymphocele; peripheral oedema; acne; diarrhoea; constipation and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.26 Sirolimus is available as 0.5-mg, 1-mg and 2-mg tablets and a 1-mg/ml oral solution, at a net price of £2.88–£4.60 per mg (excluding VAT; British national formulary online [accessed June 2015]), equating to £16.24–27.60 initially followed by £37.90–64.40 per week. Costs may vary in different settings because of negotiated procurement discounts.

Everolimus

2.27 Everolimus (Certican, Novartis Pharmaceuticals) is also a non-calcineurin inhibiting immunosuppressant that acts as an antiproliferative, and is an analogue of sirolimus. It has a marketing authorisation for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving an allogeneic renal or cardiac transplant. The summary of product characteristics states that everolimus should be used in combination with ciclosporin for microemulsion and corticosteroids.

2.28 Everolimus is administered orally at an initial dose of 1.5 mg/day.

2.29 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with everolimus: infections; diabetes; insomnia; anxiety; pain; pericardial or pleural effusion (fluid in the space around the heart or lungs); hypertension; venous

thromboembolic events; cough; dyspnoea; gastrointestinal disorders; peripheral oedema; impaired healing; fever; decreased levels of platelets, red blood cells, white blood cells or potassium in the blood; and increased levels of cholesterol or triglycerides in the blood. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.30 Everolimus is available in 0.1-mg, 0.25-mg, 0.5-mg, 0.75-mg and 1-mg tablets, at a net price of £9.90 per mg (Novartis submission). This equates to £103.95 per week. Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation in adults.

3.2 Some of the recommendations in Technology appraisal 85 are outside the marketing authorisations for the respective drugs (concerning the use of the treatments in people with high immunological risk and in unlicensed drug combinations). For the current appraisal, 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.

3.3 During the maintenance phases, people may experience episodes of acute rejection which require short courses of additional immunosuppressive therapy. This technology appraisal only considers the prevention of organ rejection; the treatment of episodes of acute rejection is outside the scope.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol

Population	Adults undergoing kidney transplantation	Includes transplants from living-related, living-unrelated and deceased donors. Immunosuppression for multi-organ transplantation, treatment of acute rejection and people who have previously had a transplant were not included.
Interventions	**Induction therapy** For prevention of organ rejection, regimens containing: • Basiliximab • Rabbit anti-human thymocyte immunoglobulin **Initial and long-term maintenance therapy** For prevention of organ rejection, regimens containing: • Mycophenolate mofetil • Mycophenolate sodium • Sirolimus • Prolonged-release tacrolimus • Immediate-release tacrolimus • Everolimus • Belatacept	Clinical-effectiveness evidence was presented for all interventions and combinations for which data were available. Cost-effectiveness results were presented for 16 immunosuppressive regimens, based on those in current use in the NHS or which could plausibly be used in the NHS (based on clinical expert advice), for which there was sufficient clinical evidence.
Comparators	**Induction therapy** • Regimens without monoclonal or polyclonal antibodies • Interventions should also be compared with each other **Initial and long-term maintenance therapy** • 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.	As per the scope.

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	Graft function is primarily measured using the estimated glomerular filtration rate (eGFR). Severity of acute rejection is primarily based on the Banff classification. The systematic review of adverse events focussed on cardiovascular complications, malignancy, diabetes, infections and nephrotoxicity.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the scope
Other considerations	If evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered, including: • 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). If evidence allows, the appraisal will consider treatment regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors. The use of immunosuppressive drugs in patients receiving multiple organ transplants (for example, combined kidney and pancreas transplantation) is excluded from this appraisal.	The Assessment Group did not identify sufficient evidence to consider the listed subgroups or to consider regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors.

4 Clinical-effectiveness evidence

Systematic review

4.1 The Assessment Group (AG) conducted a systematic review of randomised controlled trials (RCTs) and systematic reviews published between 2002 and November 2014. Studies included in previous technology appraisals of immunosuppressive therapies for kidney transplantation in adults and children (technology appraisals 85 and 99) were also screened for inclusion. The inclusion and exclusion criteria for the systematic review were matched to the decision problem (see section 3).

4.2 Clinical effectiveness results were presented as a narrative review, a series of pooled analyses comparing individual drugs, and network meta-analyses of all induction therapies and all maintenance therapies. The AG focussed on the results for 6 key outcomes: mortality, graft loss, graft function, and incidence, time to and severity of acute rejection. Adverse events are presented separately, below (see section 4.30). Although the AG searched for evidence on health-related quality of life, none was available.

4.3 The systematic review initially identified 89 RCTs, including 14 studies of induction therapies, 73 of maintenance therapies and 2 studies examining both induction and maintenance therapies. In its response to the consultation on Assessment Report, the marketing authorisation holder for rabbit anti-human thymocyte immunoglobulin (r-ATG) highlighted that the AG had incorrectly included 4 studies as studies of r-ATG; it stated that these trials used anti-T-lymphocyte immunoglobulin (ATG-Fresenius) or equine-derived antithymocyte globulin (ATGAM) but that these drugs were not interchangeable with r-ATG. The AG noted that 1 of these 4 studies was a 3-arm trial including basiliximab, and was therefore retained for the basiliximab analyses. The AG provided additional network meta-analyses excluding the non-r-ATG studies.

4.4 The AG highlighted that the identified clinical studies were of varying quality; all appeared to have limitations and most had reporting omissions. The AG presented a full quality assessment for the studies (AR pages 89–92 and appendix 4), but stated that this should be interpreted with caution. The AG considered that only 11 trials adequately matched the current NHS in the UK (although it noted following consultation that no studies were excluded from the systematic review on the basis of the quality assessment or applicability to the NHS). Full details of the study characteristics are presented in the Assessment Report, sections 4.2.3 and 4.2.4.

Clinical effectiveness results: induction therapies

Basiliximab versus placebo or no induction

4.5 The AG identified 8 studies that compared basiliximab with placebo or no induction (referred to as 'no induction' in this document). Six of the 8 studies included a maintenance regimen comprising 3 agents (ciclosporin and corticosteroids with azathioprine, n=4, or mycophenolate mofetil, n=2), and the remaining 2 included maintenance therapy of ciclosporin and corticosteroids alone.

4.6 Pooled results showed that basiliximab was associated with a statistically significant reduction in acute rejection compared with no induction at 1 year (odds ratio [OR] 0.53, 95% confidence interval [CI] 0.40–0.70). The AG stated that the corresponding results at 6 months were inconclusive because of substantial heterogeneity and a lack of statistical significance, although the point estimate favoured basiliximab. Similarly, for the outcomes of mortality at 6 months, graft loss at 6 months and 1 year, and severity of acute rejection at 6 months, the odds ratios suggested a possible benefit with basiliximab compared with no induction, but statistical significance was not reached. No significant differences between basiliximab and no induction were seen in pooled analyses of mortality at 1 year and graft function at 6 months and 1 year.

4.7 Longer-term outcomes are reported in 1 study, Sheashaa et al. (2013). The findings were broadly consistent with the pooled results. Statistically significant reductions in acute rejection associated with basiliximab were observed at 3 and 10 years, and no statistically significant differences between basiliximab and no induction were seen in mortality or graft function at 3, 5, 7 and 10 years.

4.8 The AG's network meta-analysis indicated that basiliximab is significantly more effective than no induction for the outcomes of acute rejection (OR 0.52, 95% credible interval [CrI] 0.41–0.65) and graft function (mean difference 2.11 ml/min/1.73 m^2, 95% CrI -0.45–4.68). The AG stated that there is little evidence to suggest that basiliximab is more effective than no induction for reducing graft loss or mortality.

R-ATG versus no induction

4.9 The AG initially identified 5 studies that compared r-ATG with no induction. Following consultation, 3 of these studies were excluded as they did not use r-ATG (see section 4.3), and the AG presented a revised network meta-analyses. It should be noted that revised pooled analyses were not presented, so the results should be interpreted with caution. Both of the 2 studies comparing r-ATG with no induction included maintenance therapy comprising ciclosporin, azathioprine and corticosteroids.

4.10 The pooled analysis demonstrated a statistically significant reduction in acute rejection associated with r-ATG compared with no induction at 1 year (OR 0.34, 95% CI 0.22–0.52); however, 3 of the 4 pooled studies did not use r-ATG. Two individual studies (Charpentier [2003] and Sheashaa [2008]) also showed significant reductions in acute rejection associated with r-ATG at 6 months and 5 years respectively; similarly, the latter of these did not use r-ATG. The AG noted that the reporting of time to acute rejection varied between studies. No significant differences

between r-ATG and no induction were observed in mortality, graft loss or graft function.

4.11 The AG's revised network meta-analysis indicated that r-ATG is significantly more effective than no induction for preventing acute rejection (OR 0.36, 95% CrI 0.24–0.54). The AG stated that there is little evidence to suggest that r-ATG is more effective than no induction for reducing graft loss or mortality or improving graft function.

Basiliximab versus r-ATG

4.12 The AG identified 5 RCTs that provided head-to-head comparisons between basiliximab and r-ATG. Of these, 1 included equine-derived antithymocyte globulin and a second included anti-T-lymphocyte immunoglobulin (rather than r-ATG), and so were excluded from the revised network meta-analysis after consultation. It should be noted that revised pooled analyses were not presented, so the results should be interpreted with caution. All 5 studies included a maintenance regimen comprising ciclosporin, mycophenolate mofetil and corticosteroids.

4.13 The AG's pooled analyses identified no statistically significant differences between basiliximab and r-ATG in mortality, acute rejection, graft loss, graft function or time to acute rejection, at any of the timepoints assessed. The AG noted that the odds ratio for graft loss at 1 year suggested a benefit associated with r-ATG in this outcome, although the result was not statistically significant (OR 1.44, 95% CI 0.70–2.98). It also highlighted that studies by Lebranchu et al. (2002) and Mourad et al. (2004) reported differences in graft function and time to acute rejection favour of basiliximab, although again the results were not statistically significant.

4.14 The AG's revised network meta-analysis suggested that r-ATG may be more effective than basiliximab for the outcome of acute rejection, although the 95% credible interval for the odds ratio crosses 1 (OR 0.70, 95% CrI 0.47–1.03). There was no evidence to suggest a significant

difference between r-ATG and basiliximab for the outcomes of mortality, graft loss or graft function.

Table 2 Results of the Assessment Group's network meta-analysis (fixed-effects model) for induction therapy

Treatment comparison	Odds ratio (95% CrI)			Mean difference (95% CrI)
	Graft loss	Mortality	Acute rejection	Graft function
Basiliximab vs placebo/no induction	0.82 (0.56 to 1.18)	0.99 (0.53 to 1.85)	**0.52 (0.41 to 0.65)**	**2.11 (-0.45 to 4.68)**
r-ATG vs placebo/no induction	0.77 (0.39 to 1.47)	0.84 (0.33 to 2.07)	**0.36 (0.24 to 0.54)**	-3.95 (-11.80 to 3.94)
r-ATG vs basiliximab	0.94 (0.50 to 1.75)	0.84 (0.36 to 1.96)	0.70 (0.47 to 1.03)	-6.06 (-13.46 to 1.37)

Notes: an odds ratio <1 favours the first treatment in the comparison; a mean difference >0 favours the first treatment in the comparison. Evidence suggesting a difference between treatments is in bold text.

Abbreviations: r-ATG, rabbit anti-human thymocyte immunoglobulin; 95% CrI, 95% credible interval. Source: assessment report errata, tables 1 and 2.

Clinical effectiveness results: maintenance

4.15 The AG presented clinical effectiveness results for the 7 maintenance drugs from a series of head-to-head comparisons using pooled data and from its network meta-analysis. The head-to-head comparisons presented in the Assessment Report are outlined in Table **3**. Statistically significant differences between the drugs are summarised in the paragraphs below; non-significant results are not shown unless particularly pertinent.

Table 3 Summary of head-to-head comparisons presented in the Assessment Report

	Tacrolimus	**Belatacept**	**Mycophenolate**	**Sirolimus**	**Everolimus**	**Ciclosporin**	**Azathioprine**
Tacrolimus	**Y(1)**†	Y(1)	**Y(3)**	**Y(1,2)**	-	**Y(1,3,4)**	-
Belatacept			-	-	-	**Y(1)**	-
Mycophenolate			Y(5)‡	**Y**(5,6,**7**)	Y(1,2,5)	-	**Y(5)**
Sirolimus					-	**Y(1,4)**	-
Everolimus						**Y(2)**	-

Y(x) indicates the comparison was included in the Assessment Report, for combinations including: 1, mycophenolate mofetil; 2, mycophenolate sodium; 3, sirolimus; 4, azathioprine; 5, ciclosporin; 6, belatacept; 7, tacrolimus
†Immediate- vs prolonged-release; ‡mycophenolate mofetil vs mycophenolate sodium
Bold indicates 1 or more statistically significant difference was observed (described below)
The Assessment Group also presented a comparison of tacrolimus with mycophenolate mofetil versus ciclosporin with azathioprine

Tacrolimus

4.16 **Versus ciclosporin:** Pooled comparisons suggested that, when used in combination with azathioprine, tacrolimus was associated with fewer episodes of acute rejection after 1–4 years and less severe acute rejection after 1–2 years. When combined with mycophenolate mofetil, tacrolimus was associated with a reduction in the incidence and time to acute rejection and improvement in graft function at 1–3 years, compared with ciclosporin. Similarly, graft function at 6 months and 1 year was greater with tacrolimus in combination with sirolimus, compared with ciclosporin in the same combination.

4.17 **Versus mycophenolate mofetil:** When combined with sirolimus, mycophenolate mofetil was associated with significantly greater graft function than tacrolimus at 2 years.

4.18 **Versus sirolimus:** Tacrolimus in combination with mycophenolate mofetil was associated with significantly lower acute rejection, compared with sirolimus in combination with mycophenolate mofetil. Similarly, for the

combination with mycophenolate sodium, the odds ratio for acute rejection appeared to favour tacrolimus (compared with sirolimus), although this did not reach statistical significance.

4.19 **Immediate-release versus prolonged-release tacrolimus:** Comparison of immediate-release and prolonged-release tacrolimus (in combination with mycophenolate mofetil) showed no consistent significant differences. In 1 study, immediate-release tacrolimus was associated with significantly greater graft function at 6 months, although no significant difference was seen at 1 year in a pooled analysis. Analysis of 2 studies suggested that immediate-release tacrolimus was associated a reduction in the most severe classification of acute rejection. Conversely, there was a trend towards improvement in the incidence of acute rejection with prolonged-release tacrolimus at 6 months, although this did not reach statistical significance and no significant difference was observed at 1 year.

Belatacept

4.20 **Versus ciclosporin:** Belatacept in combination with mycophenolate mofetil was associated with significantly improved graft loss at 5 years and significantly improved graft function at 1, 3 and 5 years, compared with ciclosporin in the same combination (although the latter outcome was associated with substantial heterogeneity so should be interpreted with caution). In this comparison, there was a trend towards improved mortality with belatacept, but the effect did not reach statistical significance. Conversely, belatacept was associated with significantly greater acute rejection than ciclosporin at 5 years.

Mycophenolate mofetil and mycophenolate sodium

4.21 **Versus azathioprine:** When combined with ciclosporin, mycophenolate mofetil was associated with fewer acute rejections than azathioprine at 6 months.

4.22 **Versus tacrolimus:** When combined with sirolimus, mycophenolate mofetil was associated with significantly greater graft function than tacrolimus at 2 years.

4.23 **Versus sirolimus:** Sampaio et al. (2008) reported a significantly greater mean time to acute rejection with sirolimus compared with mycophenolate mofetil (both in combination with tacrolimus).

4.24 **Mycophenolate mofetil versus mycophenolate sodium:** Comparison between mycophenolate mofetil and mycophenolate sodium was reported in only 1 trial. The AG noted that there appeared to be no discernible difference between arms for any of reported outcomes; although a significant benefit in graft function with mycophenolate sodium was seen at 6 months and 1 year, this effect was lost at later time points.

Sirolimus

4.25 **Versus mycophenolate mofetil:** Sampaio et al. (2008) reported a significantly greater mean time to acute rejection with sirolimus compared with mycophenolate mofetil (both in combination with tacrolimus).

4.26 **Versus ciclosporin:** Sirolimus in combination with mycophenolate mofetil was associated with significantly reduced graft function compared with ciclosporin with mycophenolate mofetil after 2–5 years. However, when combined with azathioprine, sirolimus appeared to significantly improve graft function at 6 months and 1 year (1 study).

4.27 **Versus tacrolimus:** Tacrolimus in combination with mycophenolate mofetil was associated with significantly lower acute rejection, compared with sirolimus in combination with mycophenolate mofetil. Similarly, for the combination with mycophenolate sodium, the odds ratio for acute rejection appeared to favour tacrolimus (compared with sirolimus), although this did not reach statistical significance.

Everolimus

4.28 **Versus ciclosporin:** Mjornstedt et al. (2012) reported a comparison of everolimus with ciclosporin (both in combination with mycophenolate sodium), and saw a significant increase in the odds of acute rejection at 1 year with everolimus.

Network meta-analysis

4.29 The AG noted that there is substantial heterogeneity in all of the network meta-analyses, and considered that the results should be interpreted with caution. It stated that none of the maintenance regimens performed consistently well across all 4 outcomes assessed in the NMA (mortality, graft loss, acute rejection and graft function), although some differences between regimens were observed for some outcomes. It should be noted that in the network meta-analyses, mycophenolate mofetil and mycophenolate sodium were assumed to be the same drug, and similarly, immediate-release and prolonged-release tacrolimus were assumed to be the same drug.

- **Mortality:** The network meta-analysis suggested that belatacept in combination with mycophenolate mofetil may be more effective at reducing mortality than tacrolimus and sirolimus (both in combination with mycophenolate mofetil).
- **Graft loss:** The analysis revealed no evidence to suggest that any of the treatments were better than the others for this outcome.
- **Acute rejection:** The analysis identified a number of statistically significant differences between regimens for this outcome. Of particular note, ciclosporin in combination with azathioprine was significantly worse than tacrolimus in combination with azathioprine, mycophenolate mofetil or sirolimus and than ciclosporin in combination with mycophenolate mofetil or everolimus. In addition, everolimus in combination with mycophenolate mofetil was significantly worse than tacrolimus or ciclosporin in combination with mycophenolate mofetil and than tacrolimus in combination with sirolimus. The AG stated that

because of wide confidence intervals, there was a great deal of uncertainty associated with the results.

- **Graft function:** Similarly, the analysis of graft function identified several statistically significant differences. The results suggest that a number of regimens (specifically tacrolimus with azathioprine or sirolimus, ciclosporin with everolimus, and ciclosporin or tacrolimus with mycophenolate mofetil) were superior to ciclosporin with azathioprine, and that tacrolimus or belatacept with mycophenolate mofetil were superior to ciclosporin with mycophenolate mofetil. Tacrolimus with azathioprine provided improved results compared with tacrolimus with sirolimus and compared with ciclosporin with mycophenolate mofetil or sirolimus. However, as for the analysis of acute rejection, limited conclusions can be drawn because of the wide confidence intervals.

Table 4 Summary of the Assessment Group's network meta-analyses for maintenance therapy. The table shows median treatment effects (and 95% credible intervals) compared with a regimen of ciclosporin and azathioprine

Regimen	**Odds ratios** *Lower is better*			**Graft function (difference in eGFR [a])** *Higher is better*
	Mortality	**Graft loss**	**Acute rejection**	
Tacrolimus and azathioprine	1.38 (0.74 to 2.60)	1.13 (0.67 to 2.15)	**0.58 (0.36 to 0.93)**	**9.31 (4.32 to 14.28)**
Ciclosporin and mycophenolic acid	0.94 (0.45 to 1.95)	0.76 (0.35 to 1.44)	**0.47 (0.25 to 0.88)**	1.61 (−4.16 to 7.41)
Tacrolimus and mycophenolic acid	1.53 (0.63 to 3.71)	0.69 (0.28 to 1.55)	**0.40 (0.19 to 0.79)**	**6.53 (0.38 to 12.68)**
Belatacept and mycophenolic acid	0.47 (0.15 to 1.38)	0.62 (0.20 to 1.78)	0.81 (0.34 to 1.94)	**10.54 (2.47 to 18.66)**
Ciclosporin and everolimus	1.40 (0.52 to 3.65)	0.63 (0.20 to 1.58)	**0.46 (0.21 to 0.99)**	4.85 (−2.84 to 12.58)
Tacrolimus and sirolimus	1.38 (0.49 to 3.88)	1.19 (0.38 to 3.35)	**0.38 (0.16 to 0.93)**	−0.34 (−8.53 to 7.85)
Sirolimus and mycophenolic acid	1.72 (0.68 to 4.31)	1.06 (0.38 to 2.43)	**0.43 (0.22 to 0.92)**	3.84 (−2.72 to 10.43)

eGFR, estimated glomerular filtration rate. Note. a: mean difference in ml/min/1.73 m^2. Evidence suggesting a difference between the regimen and the comparator (ciclosporin and azathioprine) is in bold text. Source: tables 118, 120, 122 and 124 of assessment report; full details of all comparisons included in the network meta-analysis can be found in these tables.

Adverse events

4.30 The AG summarised adverse event data from all the identified clinical trials, and presented meta-analyses of the data in Appendix 7 of the Assessment Report. The report focussed on 5 groups of adverse events: new-onset diabetes, malignancy, post-transplant lymphoproliferative disorders, infections, and cytomegalovirus (CMV) infections. The AG's economic model also included dyslipidaemia as an adverse event; the clinical effectiveness evidence for this outcome is summarised below (see section 4.34).

Induction

4.31 In its review of individual studies, the AG identified evidence to suggest that r-ATG may be associated with significantly more CMV infections than both basiliximab and no induction therapy, although 1 study found a significant difference in favour of r-ATG. No significant differences between induction treatments were observed in the 3-arm comparison study (Kyllonen [2007]), but this study used anti-T-lymphocyte immunoglobulin (rather than r-ATG) so should be interpreted with caution. Similarly, 2 studies identified a statistically significance between r-ATG and basiliximab in the incidence of infections, although 2 other studies found no such difference (1 of which used equine-derived antithymocyte globulin rather than r-ATG). No significant differences between r-ATG, basiliximab and no induction were observed in new-onset diabetes or malignancy.

4.32 In the pooled analysis, the AG noted a statistically significant reduction in malignancy with basiliximab, compared with r-ATG (OR 0.23, 95% CI

0.06–0.95). In addition, the analysis suggested that r-ATG is associated with a significant increase in CMV infections compared with no induction (OR 1.67, 95% CI 1.05–2.66). None of the other results from the pooled analysis reached statistical significance. It should be noted that these results were not updated after the removal of 4 studies of r-ATG following consultation.

Maintenance

4.33 The AG's meta-analysis identified a number of significant differences between maintenance therapies in the incidence of diabetes and CMV infections. In particular, tacrolimus and sirolimus increased the rate of new-onset diabetes compared with ciclosporin (tacrolimus vs ciclosporin: OR 2.22, 95% CI 1.42–3.46; ciclosporin vs sirolimus: OR 0.60, 95% CI 0.37–0.98). Conversely, belatacept was associated with a significant reduction in new-onset diabetes compared with ciclosporin (ciclosporin vs belatacept: OR 2.17, 95% CI 1.15–4.09). Sirolimus and everolimus were both associated with significantly reduced rates of CMV infection, compared with ciclosporin and mycophenolate respectively (ciclosporin vs sirolimus: OR 2.47, 95% CI 1.42–4.31; mycophenolate mofetil vs everolimus: OR 5.81, 95% CI 3.25–10.40). Tacrolimus was associated with a significantly reduced rate of all infections compared with sirolimus (OR 0.68, 95% CI 0.47–0.98). There were no further statistically significant differences between treatments in the incidence of adverse events.

4.34 As part of the economic modelling, the AG identified evidence to suggest that everolimus and sirolimus may be associated with an increased risk of dyslipidaemia. The AG carried out a fixed effect meta-analysis of 10 studies, and confirmed that everolimus and sirolimus were indeed associated with a significant increase in dyslipidaemia, compared with regimens that don't contain these drugs (OR 1.74, 95% CI 1.43–2.12).

Table 5 Results of the Assessment Group's meta-analyses of adverse events. **(A)** Induction therapies

	Odds ratio (95% confidence interval)									
	New-onset diabetes		Post-transplant lymphoproliferative disorders		Malignancy		Infection		CMV infection	
	vs placebo/no induction	Basiliximab vs r-ATG	vs placebo/no induction	Basiliximab vs r-ATG	vs placebo/no induction	Basiliximab vs r-ATG	vs placebo/no induction	Basiliximab vs r-ATG	vs placebo/no induction	Basiliximab vs r-ATG
Basiliximab	3.79 (0.43–33.64)	1.83 (0.43–7.72)	0.98 (0.06–15.77)	0.15 (0.01–2.87)	0.62 (0.22–1.76)	**0.23 (0.06–0.95)**	0.98 (0.80–1.20)	0.86 (0.63–1.17)	0.80 (0.56–1.13)	1.05 (0.55–2.02)
r-ATG	0.88 (0.31–2.52)		-		1.66 (0.15–18.93)		-		1.67 (1.05)–2.66	

r-ATG, rabbit anti-human thymocyte immunoglobulin. Odds ratios less than 1 favours the intervention (that is, the first drug in the comparison).

(B) Maintenance therapies

	Odds ratio (95% confidence interval)											
	New-onset diabetes			Malignancy			Infection			CMV infection		
	vs ciclosporin	vs tacrolimus	vs MPA	vs ciclosporin	vs tacrolimus	vs MPA	vs ciclosporin	vs tacrolimus	vs MPA	vs ciclosporin	vs tacrolimus	vs MPA
Tacrolimus[a]	**2.22 (1.42–3.46)**	0.86 (0.46–1.58)†		1.36 (0.54–3.39)	1.32 (0.45–3.85)†		1.12 (0.84–1.49)			0.80 (0.59–1.09)	0.85 (0.27–2.65)†	
Mycophenolate mofetil[a]		1.59 (0.71–3.59)[b]	1.06 (0.33–3.37)‡			1.01 (0.29–3.56)‡	0.86 (0.54–1.37)		1.15 (0.78–1.68)‡			0.96 (0.60–1.52)‡
Belatacept[b]	**2.17 (1.15–4.09)**	3.41 (0.13–86.87)		1.08 (0.27–4.29)	3.41 (0.13–86.87)		1.07 (0.75–1.53)			0.92 (0.59–1.44)	2.29 (0.20–26.58)	
Everolimus[b]			0.87 (0.26–2.84) 0.45 (0.17–1.19)‡	1.02 (0.14–7.39)		0.19 (0.01–4.12) 3.49 (0.38–62.20)‡	0.79 (0.45–1.38)		1.66 (0.77–3.57) 1.74 (0.72–4.20)‡	1.54 (0.63–3.79)		**5.81 (3.25–10.40)** 0.29 (0.05–1.69)‡
Sirolimus[b]	**0.60 (0.37–0.98)**	1.23 (0.75–2.01)	0.71 (0.36–1.37)	1.30 (0.31–5.44)	0.83 (0.32–2.19)	0.52 (0.05–5.82)	0.89 (0.41–1.96)	**0.68 (0.47–0.98)**		**2.47 (1.42–4.31)**	1.66 (0.97–2.84)	1.00 (0.30–3.34)

MPS, mycophenolic acid. † Immediate vs prolonged release; ‡ vs mycophenolate sodium (all other comparisons with mycophenolic acid are vs mycophenolate mofetil).

[a] Indicates odds ratio less than 1 favours intervention (that is, the first drug in the comparison); [b] Indicates odds ratio less than 1 favours the comparator (that is, the second drug in the comparison). Evidence suggesting a difference between treatments is in bold text.

The AG also presented adverse event data for post-transplant lymphoproliferative disorders, and some comparisons with azathioprine. For brevity, these comparisons are omitted; full details can be found in Appendix 7 of the Assessment Report (page 682–713).

Company submissions – clinical effectiveness evidence

4.35 Astellas presented a systematic review of the efficacy and safety of tacrolimus, identifying a total of 33 relevant RCTs. All of the studies identified by Astellas that were eligible for inclusion in the AG's review were identified in its searches. The company presented the results as a head-to-head meta-analysis comparing immediate-release tacrolimus with ciclosporin, sirolimus, everolimus and prolonged-release tacrolimus and comparing prolonged-release tacrolimus with ciclosporin; it also presented an indirect comparison between tacrolimus and everolimus and belatacept. Based on the head-to-head comparisons, the company concluded that immediate-release tacrolimus was associated with significantly lower acute rejection compared with ciclosporin, sirolimus and everolimus and significantly improved graft survival compared with sirolimus. It stated that prolonged-release tacrolimus was non-inferior to the immediate-release formulation, and highlighted registry data [redacted]. Based on the indirect comparison, the company identified significant differences between tacrolimus and belatacept for acute rejection (in favour of tacrolimus) and renal function (in favour of belatacept vs immediate-release tacrolimus); no significant differences between tacrolimus and everolimus were observed.

4.36 Bristol-Myers Squibb presented clinical efficacy evidence for belatacept, based on 2 RCTs (BENEFIT and BENEFIT-EXT) and 1 phase II study. The AG considered that the company's systematic review was unlikely to have identified all relevant studies of this technology. From the evidence it identified, the company concluded that belatacept was associated with better preservation of kidney function than ciclosporin, despite higher incidence and severity of acute rejection. The rates of mortality and graft survival were similar with belatacept and ciclosporin. The company stated that belatacept was associated with better cardiovascular and metabolic

risk profiles than ciclosporin, and suggested that belatacept may provide a reduction in the development of antibody-mediated rejection. The company proposed that belatacept may provide most benefit for people at risk of an early loss of graft function and those at risk of non-adherence to oral therapies.

4.37 Novartis presented a systematic review of the effectiveness and safety of mycophenolate sodium and everolimus. The AG stated that the company's systematic review was systematic, robust and transparent, although it did not identify any additional studies that were eligible for inclusion in the AG's review. The company identified 13 studies of mycophenolate sodium (including 7 RCTs) and 14 studies of everolimus (including 8 RCTs). The company concluded that mycophenolate sodium showed equivalent efficacy to mycophenolate mofetil, but with fewer gastrointestinal side effects. It stated that everolimus in combination with reduced-dose ciclosporin was non-inferior in clinical efficacy to regimens containing a calcineurin inhibitor and mycophenolic acid (and showed a non-significant improvement in renal function in 1 trial), and was associated with a reduced risk of CMV infection and neoplasms.

4.38 Sandoz presented clinical effectiveness evidence focussing on their branded formulation of tacrolimus (Adoport). The AG noted that the systematic review was transparent and replicable, although it could not exclude the possibility of reporting bias and did not identify any additional eligible studies for inclusion in the systematic review. The company identified 1 RCT (a pharmacokinetic study) and 24 non-randomised studies. It concluded that Adoport had similar pharmacokinetics and dosing requirements, clinical efficacy and safety to Prograf, in people who have had kidney transplants.

Summary

4.39 The AG's review of clinical effectiveness evidence for induction therapies suggested that:

- Basiliximab and r-ATG significantly reduce acute rejection compared with no induction; basiliximab also improves graft function in this comparison. No statistically significant improvements were seen in other outcomes.
- There was little evidence of a significant difference between basiliximab and r-ATG in any outcomes.

4.40 The AG's review of clinical effectiveness evidence for maintenance therapies suggested that:

- Tacrolimus appeared to provide improvements compared with ciclosporin and sirolimus for acute rejection (both comparisons) and graft function (versus ciclosporin). There were no consistent significant differences between immediate- and prolonged-release formulations.
- Belatacept significantly improved graft function and graft loss compared with ciclosporin, but was associated with more acute rejection. It was also associated with improvements in mortality in the network meta-analysis.
- Mycophenolate mofetil was associated with fewer acute rejections compared with azathioprine and greater graft function compared with tacrolimus. There were no discernible differences between mycophenolate mofetil and mycophenolate sodium.
- Sirolimus was associated with significantly longer time to acute rejection than mycophenolate mofetil.
- Everolimus was associated with significantly more acute rejection than ciclosporin.

4.41 The AG's network meta-analysis contained substantial heterogeneity, and none of the regimens performed consistently well across all outcomes.

Ciclosporin with azathioprine and everolimus with mycophenolate sodium appeared to be significantly worse than several other regimens for preventing acute rejection, and ciclosporin with azathioprine or mycophenolate sodium performed poorly in comparisons of graft function. However, the AG stated that because of limitations in the analyses, limited conclusions can be drawn.

4.42 The AG's review of adverse events suggested that:

- Basiliximab was associated with a significant reduction in malignancy compared with r-ATG, whereas r-ATG significantly increased the risk of CMV infection compared with no induction.
- The risk of new-onset diabetes was increased by tacrolimus and sirolimus, but reduced by belatacept, compared with ciclosporin.
- Sirolimus and everolimus were associated with significantly reduced rates of CMV infection, but increased rates of dyslipidaemia, compared to other classes of immunosuppressant.

4.43 Evidence presented in the company submissions suggested:

- Tacrolimus is associated with lower acute rejection compared with ciclosporin, sirolimus, belatacept and everolimus and improved graft survival compared with sirolimus.
- Belatacept was associated with better preservation of kidney function than ciclosporin, despite higher incidence and severity of acute rejection. BMS stated that belatacept was associated with better cardiovascular and metabolic risk profiles than ciclosporin, and may provide a reduction in the development of antibody-mediated rejection.
- Mycophenolate sodium showed equivalent efficacy to mycophenolate mofetil, but with fewer gastrointestinal side effects.
- Everolimus in combination with reduced-dose ciclosporin was non-inferior in clinical efficacy to regimens containing a calcineurin inhibitor and mycophenolic acid.

4.44 The AG conducted a thorough and independent review of the clinical effectiveness evidence. However, it commented that there were some limitations in the evidence. In particular, there was insufficient evidence to perform subgroup analyses, there was substantial heterogeneity in the clinical trials, the reported studies were of varying quality, and very few trials reported longer-term follow-up.

5 Comments from other consultees

5.1 Submissions were received from [redacted], clinical expert nominated by the Cochrane Renal Group, and from the British Transplantation Society, the Efficacy and Safety of Prescribing In Transplantation (ESPRIT) Group, and Kidney Research UK. Responses to consultation on the Assessment Report were received from [redacted], clinical expert nominated by Bristol-Myers Squibb, and from 5 companies (Astellas, Novartis, Sandoz, Sanofi and Teva), the British Transplantation Society, the ESPRIT Group, Health Improvement Scotland, and NHS England.

Consultee submissions

5.2 Consultees described that in current clinical practice, immunosuppressive regimens for kidney transplantation typically include basiliximab, tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids. They highlighted that the availability of additional drugs and combinations may help avoid people being denied access to transplants. Consultees commented on each of the drugs under consideration:

- Rabbit anti-human thymocyte immunoglobulin (r-ATG) is considered when a high risk of rejection is anticipated.
- Tacrolimus is considered to be more effective than ciclosporin. The once-daily (prolonged-release) preparation may have advantages for improving adherence. Tacrolimus is often given at a lower dose than specified in the marketing authorisation, which affects its cost.

- Sirolimus and everolimus are thought to have adverse effects on wound healing, but may improve graft function and may be particularly valuable in people with a history of cancer.
- Mycophenolate mofetil and mycophenolate sodium may be useful for reducing steroid use. Like tacrolimus, mycophenolate is often used at a lower dose than specified in the licences, with implications for its cost.
- Belatacept is expected to be beneficial for improving adherence and for people who cannot take or cannot digest oral therapies. Consultees highlighted evidence to suggest belatacept may reduce the long-term adverse effects of calcineurin inhibitors (such as kidney damage, high blood pressure and dyslipidaemia), although they expressed concerns about possible links to post-transplant lymphoproliferative disorders.

5.3 The professional group highlighted that, although most clinical trials report outcomes after 1 year, patient and graft survival after 10–30 years is crucial. It stated that evidence is available from registry sources such as NHS Blood and Transplant. The clinical expert argued that consideration should be given to “lifestyle” outcomes such as the ability to return to work.

5.4 Consultees highlighted that consideration should be given to the use of generic drugs for immunosuppression. They noted that calcineurin inhibitors have a narrow therapeutic index, and so should meet stringent bioequivalence criteria in people who have had kidney transplants. The ESPRIT group emphasised the recommendations from the Commission on Human Medicines, which advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only; ESPRIT considered that this recommendation should be widened to also include ciclosporin and mycophenolate drugs.

5.5 Consultees considered additional considerations for the appraisal, and noted that adherence to immunosuppressive regimens is a factor in determining long-term outcomes. They suggested that the once-daily regimen for prolonged-release tacrolimus and the once-monthly

administration of belatacept may help to support adherence. The patient group also noted that the risk–benefit balance differs for older people who have kidney transplants, and so this group should be considered in subgroup analyses.

5.6 The professional group stated that competitive tendering processes have resulted in most immunosuppressive drugs being purchased below their list price. It stated that the actual acquisition cost should be used in economic analyses.

5.7 Several consultees noted that alemtuzumab may be considered as an induction therapy. It should be noted that alemtuzumab does not have a marketing authorisation as an immunosuppressive therapy in kidney transplantation; [redacted]. Consequently, alemtuzumab cannot be considered in this appraisal.

Responses to consultation on the Assessment Report

5.8 Consultees noted a number of queries regarding the systematic review of clinical effectiveness. In particular, consultees noted that the review had focussed only on randomised controlled trials, and had not included non-randomised studies, pharmacokinetic evaluations and registries. In addition, the included studies were of variable quality, may not fully represent clinical practice, and did not provide much long-term evidence. They highlighted concerns regarding dosing, noting that doses may be adjusted during treatment and the dosages of drugs used in clinical trials may not closely match clinical practice. Sanofi noted that 4 studies had been inappropriately included for r-ATG; the Assessment Group (AG) accepted this argument, and presented revised analyses (see section 4.3). The AG acknowledged the limitations in the evidence available.

5.9 Consultees highlighted that limited information was presented on subgroups. Consultees considered that while the most common regimen

in clinical practice is basiliximab with tacrolimus and mycophenolate mofetil, other drugs and regimens may be useful in specific populations. In particular:

- R-ATG may be valuable in people with high immunological risk of rejection.
- Mycophenolate sodium may be beneficial for people who have gastrointestinal adverse reactions with mycophenolate mofetil.
- Everolimus was proposed to be an option for people at high risk of cytomegalovirus (CMV) infection (although the AG noted that a reduction in CMV infection with everolimus was included in its model; it stated that in an exploratory analysis with a high baseline CMV risk, everolimus remained non-cost effective).

The AG emphasised that insufficient evidence was available from the identified clinical trials for robust subgroup analyses.

5.10 Consultees raised a number of queries regarding the AG's economic analysis.

- Consultees expressed concerns about the drug acquisition costs used in the model, regarding differences between drugs and the availability of discounts. The AG emphasised that only nationally available discounts should be included in the analysis, and that the prices used closely match the costs to NHS hospitals.
- Novartis suggested an alternative approach for modelling quality of life, whereby utilities would be adjusted based on graft function. The AG noted uncertainties in the long-term evidence to support this approach.
- Sanofi queried the costs of CMV prophylaxis and drug monitoring; the clinical expert noted the CMV prophylaxis varies between centres. The AG noted that this is not a major driver of the model results.
- The clinical expert noted that anaemia was assumed not to vary between regimens, but in practice was likely to be more common with

sirolimus than other drugs. The AG stated that this would reduce the cost effectiveness of sirolimus.

- The British Transplant Society queried the use of a Weibull model to extrapolate survival. The AG considered that the model was unlikely to have substantially overestimated survival, and that this modelling was not expected to affect the overall conclusions.
- Astellas noted that the model did not consider the effect of adherence to once-daily dosing regimens. The AG considered that there was limited evidence, and recommended caution in using this surrogate outcome.
- NHS England considered that some additional regimens should have been modelled. The AG acknowledged this limitation, and stated that it was driven by a lack of clinical trial evidence.
- Consultees queried the limited inclusion of malignancy and cardiovascular outcomes; malignancy was noted to be a key outcome of transplantation and a major cause of death. The AG stated that malignancy would only affect the cost effectiveness conclusions if different agents were associated with different rates of this outcome.
- Novartis identified some programming errors in the AG's economic model. The AG corrected these errors in its revised analyses, presented following consultation.

6 Cost-effectiveness evidence

6.1 The Assessment Group (AG) conducted a systematic review of economic evidence from the UK, USA, Canada, Australia and Western Europe (it clarified following consultation that non-UK studies were included to complement UK studies and inform the methods and key drivers for the AG's model). The AG identified 15 studies, including 3 of induction treatments in adults in the UK and 5 of maintenance treatments in adults in the UK. The AG highlighted that the UK-based studies of induction treatments provided useful information on the resource use and short-term outcomes associated with the drugs, although it highlighted some

limitations of the studies. Similarly, the UK-based studies of maintenance therapies provided some information, but were limited in their validity for the current appraisal. In particular, the AG identified the economic analysis conducted for Technology Appraisal 85, and highlighted that the model had not fully accounted for uncertainty and had not taken into account the recently identified effect of renal function on clinical and economic outcomes.

The Assessment Group's economic model

6.2 The AG presented an economic model based on a discrete-time state transition structure, with a time horizon of 50 years and a cycle length of 3 months. The model took the perspective of the NHS and Personal Social Services, and costs and health effects were discounted at a rate of 3.5% per year.

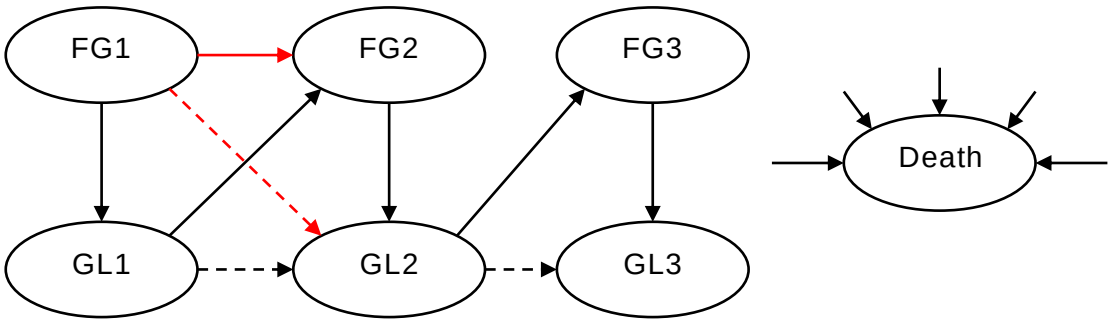
6.3 The model comprised 7 states (Figure 1).

- Throughout the model, patients were assumed to have a functioning kidney transplant ('functioning graft' states), to be dependent on dialysis ('graft loss' states) or to have died ('death' state).
- At the start of the model, following kidney transplantation, most patients entered the first functioning graft state. The remaining patients started the model in the first graft loss state; this reflected the possibility that the transplant would not function at all (termed 'primary non-function').
- From the first functioning graft state, patients could transition to the first graft loss state when the transplanted kidney stopped functioning. Alternatively, they may have a second transplant before the graft stopped working (termed 'pre-emptive retransplantation') and would enter one of the subsequent states.
- From the first graft loss state, patients received a second transplant ('retransplantation') and entered one of the subsequent states.
- When patients received a second transplant (either retransplantation or pre-emptive retransplantation), they could transition to the second

functioning graft state and then, when the second transplant stopped functioning, to the second graft loss state. Alternatively, if the second transplant was not successful (primary non-function), patients transitioned directly to the second graft loss state.

- From the second graft loss state, a third transplant was modelled; this was modelled similarly to the second transplant, although it could not be pre-emptive.
- Mortality was modelled by transition to the 'death' state (referred to as 'death with functioning graft' and 'death following graft loss').

Figure 1 Health states in the Assessment Group's economic model



FG, functioning graft; GL, graft loss; dashed arrows indicated primary non-function; red arrows indicate pre-emptive retransplantation. Source: assessment report, Figure 87.

6.4 Transitions between health states were determined by 3 key factors: mortality, graft loss, and rates of transplantation. An underlying rate for each of these factors was derived from registry data; the underlying rates of mortality and graft loss were then adjusted for each immunosuppressive regimen using clinical effectiveness data. The underlying rates and adjustments were derived as follows:

- **Mortality:** This factor is split into 2 elements – death before graft loss (that is, from the functioning graft states; termed 'death with a functioning graft') and death following graft loss (that is, from the graft loss states).

  - The underlying rate of death with a functioning graft was based on data from the UK Transplant Registry. In the first year, this underlying rate was adjusted for each regimen using survival data from the AG's network meta-analysis directly. In subsequent years, the rate was adjusted based on the rate of new-onset diabetes with each treatment regimen, combined with a surrogate relationship between diabetes and death.
  - The underlying rate of mortality following graft loss was based on the rate of mortality associated with dialysis, obtained from the UK Renal Registry. This was not adjusted according to the immunosuppressive regimen.
- **Graft loss:** The underlying rate of graft loss was based on graft survival data (censored for death), taken from the UK Transplant Registry and extrapolated beyond 1 year using a Weibull model. In the first year, the underlying rate was adjusted for each immunosuppressive regimen to match the rates of graft loss seen in the AG's network meta-analysis. In subsequent years, the rate was adjusted according to a surrogate relationship between graft loss and 3 variables: acute rejection, new-onset diabetes and graft function at 12 months. The surrogate relationship was built using a published figure for the effect of each of the 3 variables on graft loss, combined with the treatment effect of each regimen on that variable (as observed in the network meta-analysis).

6.5 The AG modelled health-related quality of life using an age- and gender-dependent baseline utility score, combined with a utility decrement for the functioning graft and graft loss health states. The baseline score was derived from the Heath Survey for England (2012). A utility decrement of 0.053 was applied to the functioning graft states, based on a published meta-analysis of data using the EuroQol (EQ-5D) questionnaire, for people living with a kidney transplant. The same meta-analysis was used to derive utility decrements associated with haemodialysis (0.277) and peritoneal dialysis (0.264), which were applied to the graft loss states. In

addition, the AG assumed that new-onset diabetes would reduce quality of life, by modelling an additional utility decrement for each treatment regimen; this was based on a decrement of 0.06 for each case combined with the rate of new-onset diabetes for the individual immunosuppressive regimens.

6.6 The model calculated the costs associated with each immunosuppressive regimen, including the following categories: drug acquisition, drug administration and monitoring, patient follow-up, dialysis and re-transplantation, prevention and management of adverse events, and treatment of acute rejection. In the base case, drug acquisition costs were taken from the Commercial Medicines Unit's electronic market information tool (eMit) when possible, and from the published list price or company submission otherwise; for belatacept, the AG assumed that partially used vials were not shared between patients. The costs of adverse events included new-onset diabetes, prevention and treatment of infections (including cytomegalovirus [CMV]), dyslipidaemia and anaemia. The rate of new-onset diabetes was estimated for each maintenance regimen, and the rates of CMV infection and dyslipidaemia were adjusted from a common baseline for any regimens containing sirolimus or everolimus; rates of anaemia were assumed to be constant for all regimens. Costs estimates were based on NHS reference costs where available, and from costing studies presented by Bristol-Myers Squibb (BMS) and data from University Hospital Wales and Royal Devon and Exeter Hospital.

6.7 The AG modelled a total of 16 immunosuppressive regimens, representing those it understood to be in current use in the NHS or which could plausibly be used and for which there was sufficient evidence. Some of these regimens were outside the marketing authorisations for the respective drugs (Table 6). Induction agents and maintenance regimens were combined assuming independence. It assumed that all regimens included corticosteroids. Because the AG's network meta-analysis did not distinguish between mycophenolate mofetil and mycophenolate sodium,

clinical effectiveness estimates and adverse event rates for regimens containing mycophenolate sodium were taken from the mycophenolic acid arm of the network meta-analyses and adjusted them using head-to-head comparisons between mycophenolate mofetil and mycophenolate sodium. Similarly, as immediate- and prolonged-release tacrolimus were not distinguished in the network meta-analysis, for regimens containing prolonged-release tacrolimus the AG adjusted results for immediate-release tacrolimus using head-to-head comparisons. For all regimens, the model assumed that following retransplantation, all patients switched to the same regimen (basiliximab, tacrolimus and mycophenolate mofetil) for the second and subsequent transplant.

Table 6 Summary of the immunosuppressive regimens modelled by the Assessment Group

Regimen			Licensed?
Induction	**Maintenance**		
Basiliximab	Ciclosporin	+ azathioprine	Yes
	Ciclosporin	+ mycophenolate mofetil	Yes
	Ciclosporin	+ mycophenolate sodium	Unclear (1)
	Tacrolimus	+ mycophenolate mofetil	No (2)
	Belatacept	+ mycophenolate mofetil	Unclear (3)
	Sirolimus	+ mycophenolate mofetil	No (2)
r-ATG	Ciclosporin	+ azathioprine	Yes
	Ciclosporin	+ mycophenolate mofetil	Yes
	Tacrolimus	+ mycophenolate mofetil	No (2)
No induction	Ciclosporin	+ azathioprine	Yes
	Ciclosporin	+ mycophenolate mofetil	Yes
	Ciclosporin	+ everolimus	Yes
	Tacrolimus	+ azathioprine	Yes
	Tacrolimus	+ mycophenolate mofetil	No (2)
	Tacrolimus	+ sirolimus	No
	Tacrolimus-PR	+ mycophenolate mofetil	No (2)

r-ATG, rabbit anti-human thymocyte immunoglobulin; tacrolimus-PR, tacrolimus prolonged-release.
All maintenance regimens also included corticosteroids
(1) Basiliximab is indicated in combination with ciclosporin and azathioprine or mycophenolate mofetil.
(2) Mycophenolate mofetil is indicated in combination with ciclosporin and corticosteroids; the summary of product characteristics states that the risk:benefit of mycophenolate mofetil in combination with tacrolimus or sirolimus has not been established.
(3) Basiliximab is indicated with ciclosporin-based therapy. However, belatacept is recommended for use with an IL-2 receptor antagonist (for example, basiliximab).

6.8 As a result of comments on the AG's economic model received during consultation, the AG presented a revised economic analysis as an

erratum to the Assessment Report. The revised analyses corrected errors in the programming of the economic model and used revised clinical effectiveness evidence from the updated network meta-analysis (excluding the studies incorrectly included for rabbit anti-human thymocyte immunoglobulin [r-ATG], see section 4.3). The results presented below are based on the AG's revised analysis.

Cost effectiveness evidence – results of the Assessment Group's model

6.9 The AG presented the results of its model in 2 ways: firstly, as a series of comparisons between individual immunosuppressive drugs (with common concomitant treatments), and secondly, as a simultaneous comparison between all 16 regimens.

6.10 For the induction treatments, the AG presented comparisons between basiliximab, r-ATG and no induction, in the context of 3 different maintenance regimens. In all analyses, basiliximab dominated (that is, was more effective and less costly than) both r-ATG and no induction (Table 7). R-ATG was more costly and more effective than no induction, and was associated with incremental cost effectiveness ratios (ICERs) of £63,150 to £332,971 per quality-adjusted life year (QALY) gained.

6.11 For the maintenance treatments, the AG presented results for all 7 drugs, compared with each other and with ciclosporin and azathioprine where possible. In these analyses, only immediate-release tacrolimus and mycophenolate mofetil appeared cost effective if the maximum acceptable ICER were £30,000 per QALY gained. Immediate-release tacrolimus dominated prolonged-release tacrolimus, sirolimus and ciclosporin (in 1 of 4 comparisons). Compared with belatacept and ciclosporin (3 of 4 comparisons), immediate-release tacrolimus was less costly and less effective than the comparator, with ICERs ranging from £131,035 to £388,740 per QALY lost. Mycophenolate mofetil dominated sirolimus and azathioprine (4 comparisons) and was less costly and less effective than

mycophenolate sodium (£144,449 per QALY lost) and everolimus (£1,532,379 per QALY lost). All the other interventions were either dominated or were more effective and more costly than their respective comparators with ICERs greater than £50,000 per QALY gained (Table 8).

6.12 In the simultaneous comparison of the 16 regimens, all except 4 were dominated or extendedly dominated: basiliximab in combination with tacrolimus and mycophenolate mofetil, ciclosporin and mycophenolate mofetil, ciclosporin and mycophenolate sodium and belatacept and mycophenolate mofetil were therefore compared in an incremental analysis. Of these, basiliximab with tacrolimus and mycophenolate mofetil was the least costly and least effective; the remaining regimens were associated with ICERs significantly greater than £100,000 per QALY gained compared with the next, less costly alternative (Table 9).

6.13 The AG presented a probabilistic sensitivity analysis using 10,000 iterations. The results of the probabilistic analysis were mostly broadly similar to the deterministic analysis; there were no substantial discrepancies between the costs in the 2 analyses, and few discrepancies between the QALYs. The largest discrepancy was for the regimen of basiliximab, ciclosporin and mycophenolate sodium: because of substantial uncertainty in the mortality estimate for this regimen, the probabilistic analysis predicted 0.1133 fewer QALYs than the deterministic analysis. This led to some changes in the ICERs in the pair-wise comparison of maintenance drugs (although the AG's conclusions remained unchanged) and to basiliximab, ciclosporin and mycophenolate sodium becoming dominated in the simultaneous comparison of regimens. Cost-effectiveness acceptability curves are presented in the AG's corrected results, pages 17 to 27; the curves show no changes in which treatments have the highest probabilities of cost effectiveness over the range of cost-effectiveness thresholds from £1000 to £50,000 per QALY gained.

6.14 The AG explored uncertainties in the model structure using 4 scenario analyses.

- In the first scenario, the effect of the surrogate relationship between graft survival and acute rejection, graft function and new-onset diabetes was gradually reduced. Basiliximab remained the only cost effective induction agent in all except the most extreme scenarios. Similarly, mycophenolate mofetil remained cost effective (at a maximum acceptable ICER of £20,000–£30,000 per QALY gained) in all scenarios. Immediate-release tacrolimus became less cost effective when the effect of the surrogate relationship was substantially reduced.
- The AG explored the effect of possible nephrotoxicity associated with calcineurin inhibitors (ciclosporin and tacrolimus), by reducing the rate of graft loss for calcineurin inhibitor-free regimens. As the rate of graft loss with calcineurin inhibitor-free regimens decreased, their cost effectiveness increased. The AG identified a scenario in which sirolimus was equally cost effective compared with tacrolimus (although belatacept remained not cost effective in all scenarios); in this scenario, graft survival with sirolimus at 5- and 10-years post transplant was 89% and 85% respectively, compared with 87% and 76% respectively in the base case (Figure 2).
- The AG presented a scenario in which it used the published list prices for all drugs (rather than the eMIT prices). The costs associated with ciclosporin, tacrolimus, azathioprine and mycophenolate mofetil increased, leading to increases in costs for all regimens. Although the cost effectiveness of induction therapies was largely unaffected, marked differences in the cost effectiveness of maintenance drugs compared with the base case were seen. In particular, the cost effectiveness of ciclosporin improved relative to tacrolimus, and that of azathioprine improved relative to mycophenolate mofetil. In addition, the cost effectiveness of newer maintenance drugs (prolonged-release tacrolimus, sirolimus, everolimus and mycophenolate sodium) improved marginally, but the AG stated that none were predicted to be cost

effective if the maximum acceptable ICER were £30,000 per QALY gained.

- The AG explored the acquisition and administration costs for belatacept. The threshold analysis predicted that, based on its current list price, belatacept would not be cost effective compared with tacrolimus (at a maximum acceptable ICER of £20,000–£30,000 per QALY gained), even if the administration cost were set to zero.
- Following consultation on the Assessment Report, the AG presented an additional scenario [redacted].

Table 7 Summary of pair-wise cost-effectiveness comparisons of induction therapies from the Assessment Group's model (deterministic results)

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	
	Total	Incr	Total	Incr	Incr	vs no induction
With ciclosporin + azathioprine						
No induction	£101,595	—	10.7711	—	Dominated	
r-ATG	£104,570	£2,975	10.8182	0.0471	Dominated	£63,150
Basiliximab	£98,244	-£6,326	10.9029	0.0848	—	Dominant
With ciclosporin +mycophenolate mofetil						
No induction	£97,429	—	10.9145	—	Dominated	
r-ATG	£101,940	£4,511	10.9281	0.0135	Dominated	£332,971
Basiliximab	£95,219	-£6,720	11.0247	0.0966	—	Dominant
With tacrolimus+mycophenolate mofetil						
No induction	£92,226	—	10.8884	—	Dominated	
r-ATG	£97,146	£4,920	10.9047	0.0163	Dominated	£301,516
Basiliximab	£90,405	-£6,741	10.988	0.0832	—	Dominant

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobuline
Source: developed from Assessment Group's revised results, table 207 and economic model (ICER vs no induction).

Table 8 Summary of pair-wise cost-effectiveness comparisons of maintenance therapies from the Assessment Group's model (deterministic results)

	Tacrolimus (IR)	Tacrolimus (PR)	Belatacept	Mycophenolate mofetil	Mycophenolate sodium	Sirolimus	Everolimus
Tacrolimus (IR)		-£14,303 / 0.0964 = dominant (1)	-£119,004 / -0.3061 = £388,740 (2)			-£24,144 / 0.0869 = dominant (2)	
Tacrolimus (PR)	£14,303 / -0.0964 = dominated (1)						
Belatacept	£119,004 / 0.3061 = £388,740 (2)					£94,860 / 0.3931 = £241,333 (2)	
Mycophenolate mofetil					-£16,321/ -0.1130 = £144,449 (3)	-£33,313 / 0.2861 = dominant (4)	-£78,725 / -0.0514 = £1,532,379 (5)
Mycophenolate sodium				£16,321 / 0.1130 = £144,449 (3)			
Sirolimus	£24,144 / -0.0869 = dominated (2)		-£94,860 / -0.3931 = £241,333 (2)	£33,313/ -0.2861 = dominated (4)			
Everolimus				£78,725 / 0.0514 = £1,532,379 (5)			

	Ciclosporin	Azathioprine
Tacrolimus (IR)	-£5,203 / -0.0261 = £199,118 (1) -£4,815 / -0.0367 = £131,035 (2) -£4,794 / -0.0234 = £205,214 (6) -£8,276 / 0.0986 = dominant (7)	
Tacrolimus (PR)	-£9,100 / 0.1225 = dominated (1)	
Belatacept	£114,189 / 0.2694 = £423,890 (2)	
Mycophenolate mofetil		-£3,025 / 0.1218 = dominant (3) -£4,166 / 0.1435 = dominant (4) -£1,093 / 0.0188 = dominant (5) -£2,631 / 0.1099 = dominant (8)
Mycophenolate sodium		£13,296 / 0.2348 = £56,635 (3)
Sirolimus	£19,329 / -0.1237 = dominated (2)	£32,220 / -0.2674 = dominated (5)
Everolimus		£74,559 / 0.1949 = £382,647 (4)

Each box shows: incremental cost / incremental QALYs = ICER. (X) indicates the pair-wise comparison was included in the Assessment Report, for the intervention and comparator in combination with: 1, mycophenolate mofetil; 2, basiliximab + mycophenolate mofetil; 3, basiliximab + ciclosporin; 4, ciclosporin; 5, tacrolimus; 6, r-ATG + mycophenolate mofetil; 7, azathioprine; 8, r-ATG + ciclosporin

ICER, incremental cost-effectiveness ratio; IR, immediate-release; PR, prolonged-release; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin.

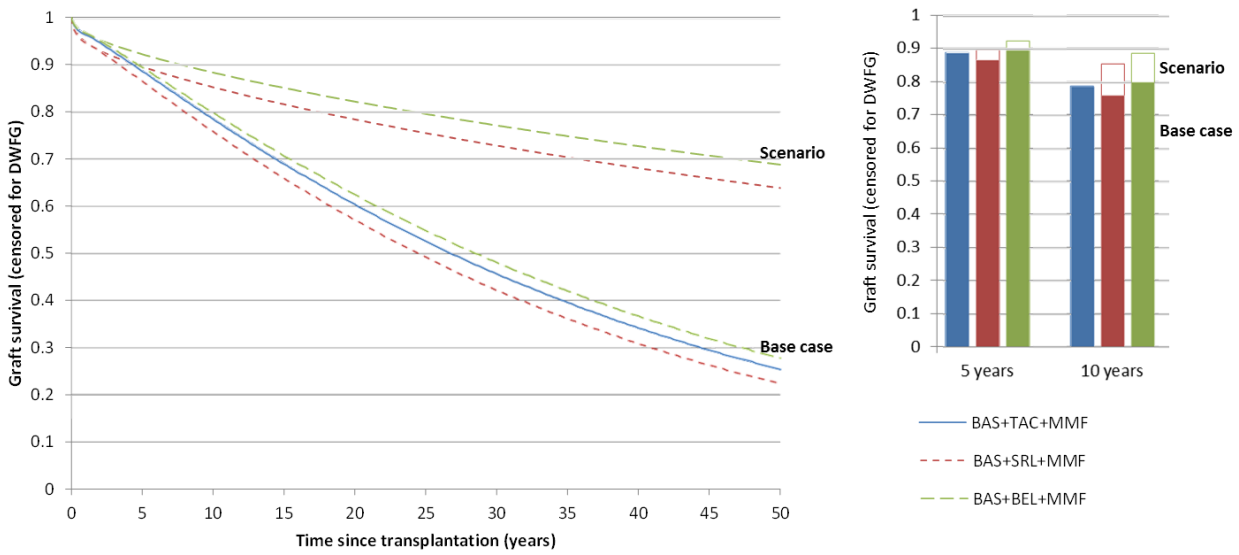
Source: developed from Assessment Group's revised results, table 208 and economic model. Where not available directly, incremental costs and QALYs calculated using the economic model.

Table 9 Summary of simultaneous comparison of all regimens in the Assessment Group's economic model.

Regimen	Discounted costs		Discounted QALYs		ICER
	Total	Incr	Total	Incr	
Regimens on the cost-effectiveness frontier					
Basiliximab +tacrolimus +mycophenolate mofetil	£90,405	—	10.9880	—	—
Basiliximab +ciclosporin +mycophenolate mofetil	£95,219	£4,815	11.0247	0.0367	£131,035
Basiliximab +ciclosporin +mycophenolate sodium	£111,540	£16,321	11.1377	0.1130	£144,449
Basiliximab +belatacept +mycophenolate mofetil	£209,409	£97,869	11.2941	0.1564	£625,761
Dominated regimens					
Tacrolimus +sirolimus	£125,539.25		10.6023		Dominated
Ciclosporin +azathioprine	£101,595.33		10.7711		Dominated
Tacrolimus prolonged-release +mycophenolate mofetil	£106,529.38		10.7920		Dominated
R-ATG +ciclosporin +azathioprine	£104,570.33		10.8182		Dominated
Tacrolimus +azathioprine	£93,318.96		10.8696		Dominated
Tacrolimus +mycophenolate mofetil	£92,226.13		10.8884		Dominated
Basiliximab +sirolimus +mycophenolate mofetil	£114,548.72		10.9010		Dominated
Basiliximab +ciclosporin +azathioprine	£98,243.88		10.9029		Dominated
R-ATG +Tacrolimus +mycophenolate mofetil	£97,146.16		10.9047		Extendedly dominated
Ciclosporin +mycophenolate mofetil	£97,429.02		10.9145		Dominated
R-ATG +ciclosporin +mycophenolate mofetil	£101,939.74		10.9281		Extendedly dominated
Ciclosporin +everolimus	£176,154.33		10.9659		Dominated

ICER, incremental cost-effectiveness ratio; Incr, incremental; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin.
Source: Assessment Group's revised results, table 209 and economic model.

Figure 2 Assessment Group's scenario analysis: 5- and 10-year graft survival in the base case and in the scenario in which the rate of graft loss for calcineurin inhibitor-free regimens was reduced such that sirolimus was equally cost effective compared with tacrolimus



BAS, basiliximab; BEL, belatacept; DWFG, death with functioning graft; MMF, mycophenolate mofetil; SRL, sirolimus; TAC, tacrolimus.

Company's economic models

6.15 Economic models were presented by Astellas, BMS and Novartis.

Astellas

6.16 Astellas presented a 6-state Markov model (Figure 3) with a 1-year cycle length and a 25-year time horizon. The model represented the clinical pathway of patients receiving immunosuppression based on the rates of acute rejection, graft loss, retransplantation and mortality. The rate of acute rejection was derived for each immunosuppressant drug from the company's clinical effectiveness review; in addition, the company assumed that prolonged-release tacrolimus was associated with improved adherence compared with the immediate-release formulation, and that this led to a decrease in the risk of acute rejection. Patients who experienced acute rejection were assumed to have a higher risk of graft loss after the episode. Rates of graft loss and mortality were taken from

data from NHS Blood and Transplant and the UK Renal Registry. Health-related quality of life was calculated by applying utility scores to each of the health states, based on EQ-5D data from a study conducted at the University Hospital of Wales. Costs included acquisition costs for immunosuppressive drugs (including induction therapy with basiliximab in each regimen; based on list prices), treatment of acute rejection episodes, dialysis, retransplantation and adverse effects of treatment. Costs and QALYs were discounted at a rate of 3.5% per year in the base case.

6.17 The company presented the results for each immunosuppressive drug in comparison with immediate-release tacrolimus (Table 10). In the base case, belatacept and everolimus were dominated by immediate-release tacrolimus, whereas prolonged-release tacrolimus was dominant. Sirolimus was less costly and less effective than immediate-release tacrolimus, with ICERs of £1,651,801 and £170,681 per QALY lost (for sirolimus in calcineurin inhibitor-minimisation and -avoidance regimens respectively). The model results were similar in all sensitivity analyses, except for the scenario based on graft survival data from the SYMPHONY study, in which sirolimus was dominated by immediate-release tacrolimus. [redacted].

Figure 3 Model structure – Astellas

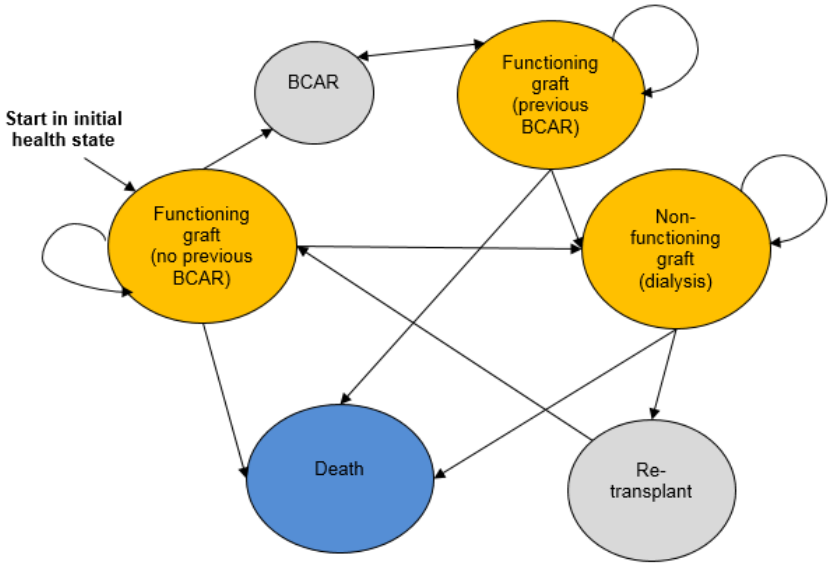


Table 10 Economic model results – Astellas

	Prograf (immediate-release tacrolimus)	**Advagraf** (prolonged-release tacrolimus)	**Belatacept**	**Everolimus**	**Sirolimus I**	**Sirolimus II**
Total costs (£)	130,118	118,907	163,740	142,995	104,905	119,371
Life years	11.81	12.03	11.73	11.79	11.80	11.74
QALYs	8.01	8.21	7.94	7.99	7.99	7.94
Incremental costs		11,212	-33,622	-12,876	25,213	10,747
Incremental QALYs		-0.20	0.07	0.02	0.02	0.07
ICER (Cost (£)/QALY)	-	Prograf dominated by Advagraf	Belatacept dominated by Prograf	Everolimus dominated by Prograf	1,651,801	170,681
ICER: Prograf vs. comparator; Sirolimus I: calcineurin-inhibitor minimisation; Sirolimus II: calcineurin-inhibitor avoidance.						

6.18 The AG highlighted a number of concerns regarding the Astellas model, summarised in detail on pages 358–360 of the Assessment Report. The AG noted that the company had omitted ciclosporin as a comparator, which affects the interpretation of the results. It highlighted that the analysis did not include the effect of graft function on health and cost outcomes and considered that survival estimates for the functioning graft

state may have been underestimated. It noted that the comparison between immediate- and prolonged-release tacrolimus was based on a relationship between non-adherence and clinical outcomes, but that this effect was not accounted for with other regimens. The AG also expressed concerns about the drug dosages used for each treatment and the costs and QALYs associated with dialysis following retransplantation.

Bristol-Myers Squibb

6.19 BMS presented an analysis of the cost effectiveness of belatacept compared with tacrolimus and ciclosporin, based on a 36-month initial phase followed by a longer-term Markov model with a lifetime time horizon (Figure 4). In the initial phase, data from clinical trials and the company's network meta-analysis was used to establish graft function, graft loss, incidences of post-transplant complications (new-onset diabetes, post-transplant lymphoproliferative disorder and acute rejection) and death. Patients then entered the Markov model based on their kidney function, and progressed through it according to extrapolated curves for graft loss and mortality based on data from US studies. Health-related quality of life was estimated by applying utility estimates to the functioning graft state (split by eGFR) and graft loss state and utility decrements associated with the 3 post-transplant complications listed above. Resource use was estimated using an observational database study (PORTRAIT), combined with separate costs for immunosuppressive regimens (based on list prices) and post-transplant complications. All costs and QALYs were discounted at a rate of 3.5% per year.

6.20 The base case analysis indicated that belatacept was more costly and more effective than both ciclosporin and tacrolimus. Belatacept was associated with ICERs of £95,053 and £147,334 per QALY gained, compared with ciclosporin and tacrolimus respectively (Table 11).

6.21 In addition to the base case analysis, the company presented a subgroup analysis of people whose expected graft survival is likely to be short –

specifically, people with a post-transplant estimated glomerular filatration rate (eGFR) of less than 30 ml/min/1.73 m^2. In this analysis, belatacept was predicted to dominate both ciclosporin and tacrolimus (Table 11).

6.22 The AG commented that the BMS model captures the key clinical outcomes and incorporates the effects of renal function and acute rejection on costs, longer-term clinical outcomes and quality of life. It highlighted that using the results of the cost study presented by BMS represented a major strength of the model. However, it considered that the model had methodological limitations. The AG noted that the transition probabilities may not be generalisable to the UK population, the efficacy differences between drugs at 3 years were inappropriately applied from the start of the model (and discounting was not applied in this period), and the model included a non-validated assumption of a linear decline in eGFR after 3 years. The AG also noted limitations in the subgroup analyses, highlighting in particular that the definition of people with a short expected life expectancy was based on eGFR after 1 year (and so, by definition, could not be identified before starting treatment).

Figure 4 Model structure – Bristol-Myers Squibb

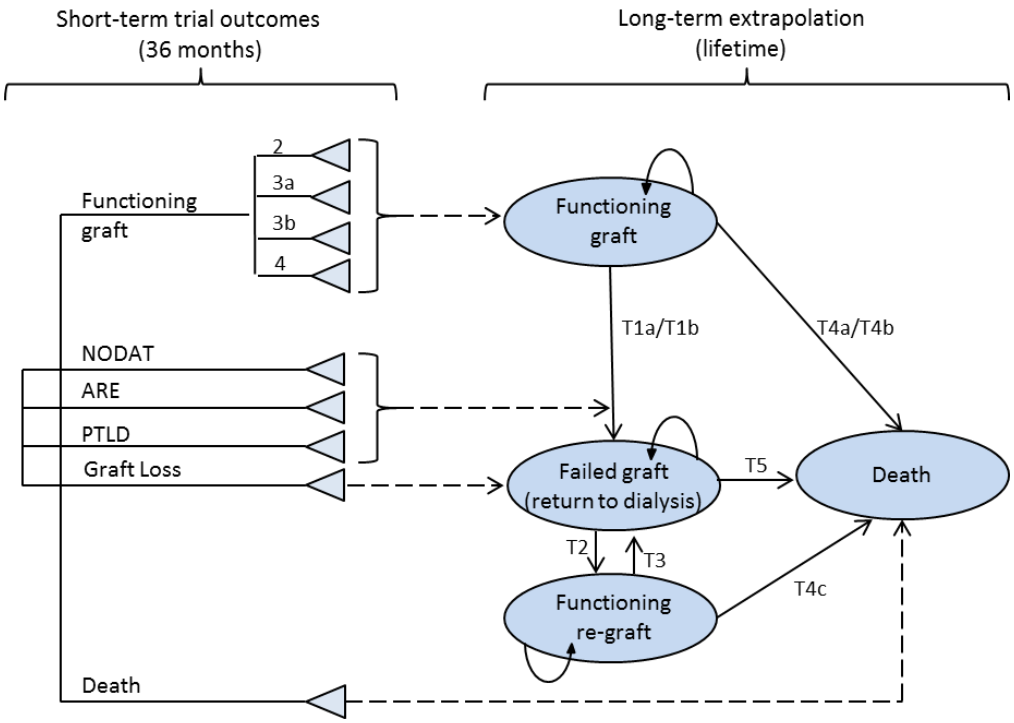


Table 11 Economic model results – Bristol-Myers Squibb

Base case

	Belatacept	Ciclosporin	Difference	Tacrolimus	Difference
Total Discounted Cost	£296,503	£204,287	£92,216	£205,502	£91,001
Total Discounted Life Years	14.76	13.52	1.25	13.81	0.95
Total Discounted QALYs	7.14	6.17	0.97	6.53	0.62
Incremental cost per QALY			**£95,053**		**£147,334**
QALY, quality-adjusted life year					

Subgroup analysis

	Belatacept	Ciclosporin	Difference	Tacrolimus	Difference
Total Discounted Cost	£252,718	£254,196	-£1,478	£256,884	-£4,166
Total Discounted QALYs	4.22	3.76	0.46	3.76	0.46
Incremental cost per QALY			**Dominant (-£3,237)**		**Dominant (-£9,126)**
QALY, quality-adjusted life year * Average cost of Neoral (10mg 60-cap pack, 25mg and 50mg, 30-cap pack) used as the cost ciclosporin in subgroup analysis: year 1, £3,342.28; Year 2, £2,625.42, year 3, £2,433.02.					

Novartis

6.23 Novartis presented a patient-level simulation model, in which individual patients were followed through a pathway based on acute rejection, graft failure, retransplantation and death (Figure 5). The model used 1-month cycles and a lifetime horizon to capture the cost effectiveness of everolimus in combination with reduced-dose ciclosporin and mycophenolate sodium in combination with standard-dose ciclosporin, compared with mycophenolate mofetil in combination with standard-dose ciclosporin or tacrolimus. Movement between health states and incidences of adverse events were based on clinical parameters for each regimen (with the exception of mortality), derived from the company's literature review. Mortality was calculated from the general population, adjusted according to the patient's eGFR. The model captured health-related quality of life by applying published EQ-5D data to each patient according to their eGFR; in addition, adverse events were associated with disutilities drawn from published data. Costs were calculated based on drug acquisition (using list prices and eMIT as appropriate), health state resource use (including patient follow-up, treatment of acute rejection,

dialysis and retransplantation) and adverse event costs. Following consultation, Novartis submitted additional economic analyses, including correction of errors it identified in the programming of the model (see section 6.26).

6.24 In the base-case analysis (uncorrected results), everolimus in combination with ciclosporin dominated tacrolimus in combination with mycophenolate mofetil. Following correction of errors in the model, everolimus in combination with ciclosporin was associated with an ICER of £17,182 per QALY gained compared with mycophenolate mofetil in combination with ciclosporin. Mycophenolate sodium dominated mycophenolate mofetil (both in combination with ciclosporin).

6.25 The company's deterministic sensitivity analysis indicated that the results were consistently most sensitive to the utility score for people with stage 3 chronic kidney disease and the time to retransplantation; the company concluded that the model results were robust, with few parameters affecting the overall conclusions. The company presented scenario analyses exploring the effect of treatment discontinuation, and found that all results were sensitive to this variable.

6.26 Following consultation, Novartis submitted additional economic analyses. It corrected errors identified in the programming of the model, and presented analyses exploring the effect of utility assumptions, and matching costs and efficacy parameters to the AG's model. The company also incorporated the effect of new-onset diabetes and implemented a variable rate of graft survival over time (based on a Weibull model), to match the AG's assumptions. In the company's revised base case, everolimus in combination with ciclosporin was associated with an ICER of £100,459 per QALY gained compared with ciclosporin in combination with mycophenolate mofetil. Mycophenolate sodium was associated with an ICER of £27,327 per QALY gained, compared with mycophenolate mofetil (both in combination with ciclosporin). The company noted that incorporating the AG's costs, efficacy parameters and new-onset diabetes

assumptions had small effects on the ICER, whereas the methods of utility estimation had a large impact on the analysis results.

6.27 The AG stated that the key strength of the Novartis model was that it took into account the effect of clinical events (specifically acute rejection, graft and patient survival, and graft function) on costs and health outcomes. However, it was concerned that clinical outcomes were based on evidence from selected single trials and not from a systematic review or meta-analysis. It also considered that there was a major flaw in the assumption that graft failure occurs independently of graft function and acute rejection. In addition, the AG noted that although some adverse events were included, new-onset diabetes had been omitted. The AG highlighted some limitation in the cost data, which the company addressed in revised analyses, submitted following consultation. In reviewing the company's revised analyses, the AG stated that it was unable to precisely reproduce the reported results and highlighted some modelling errors. It considered that the revised analyses retained the key limitations of the original model, although some of these were addressed in scenario analyses (in particular, the use of clinical effectiveness estimates from the AG's systematic review). The AG acknowledged the company's approach to modelling utility based on graft function, noting that this was a limitation in the AG's model; however, it emphasised that there is too much uncertainty in the medium and long-term changes in renal function to be confident that Novartis's approach is better. The AG stated that it was questionable whether the company's subgroup analysis of mycophenolate sodium as a second-line therapy was sufficiently robust to support the cost effectiveness of this treatment.

Figure 5 Model structure – Novartis

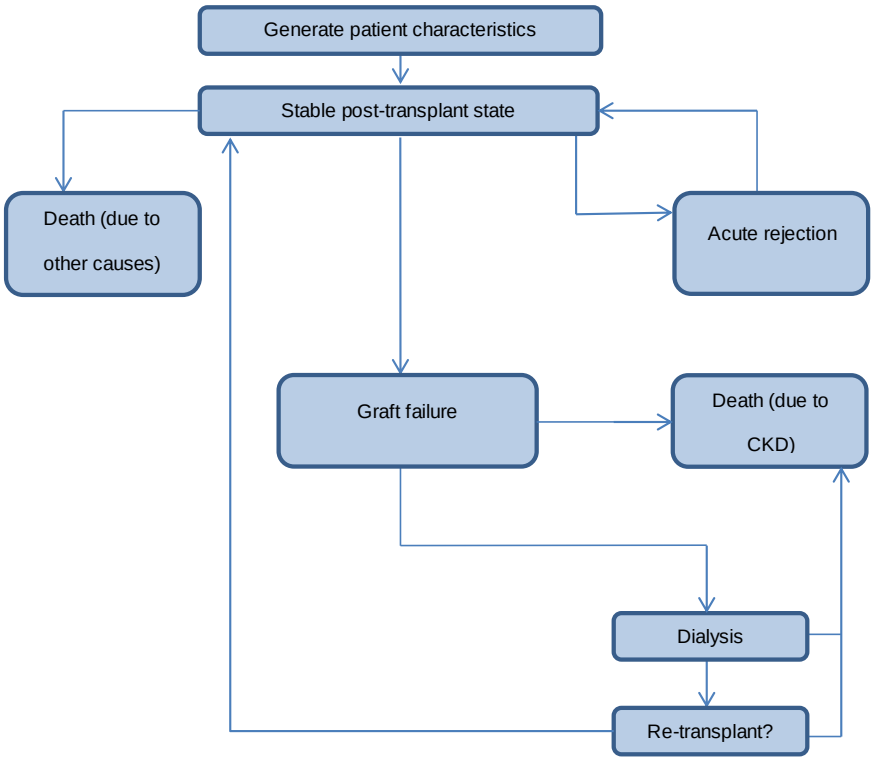


Table 12 Economic model results – Novartis

Technology	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER (£/QALY)
EVE + CsA[1]	£135,358	8.86	-£5,614	1.49	Dominant
TAC + MMF[1]	£140,972	7.37			
EVE + CsA[2]	£162,014	7.60	£20,473	1.19	£17,182
MMF + CsA[2]	£141,540	6.41			
EC-MPS + CsA[2]	£124,388	7.46	-£17,330	1.04	Dominant
MMF + CsA[2]	£141,669	6.42			

Notes: 1, Uncorrected results – the company did not present revised results for the comparison of EVE + CsA vs TAC + MMF following correction of errors in the model; these rows show uncorrected results. 2, Results corrected following consultation on the Assessment Report.

CsA = ciclosporin; EC-MPS = enteric-coated mycophenolate sodium; EVE = everolimus; ICER = incremental cost-effectiveness ratio; Lys = life-years; QALYs = quality-adjusted life-years; MMF = mycophenolate mofetil; TAC = tacrolimus

Summary

6.28 The AG's economic analyses of induction therapies suggested that:

- Basiliximab dominated both r-ATG and no induction.
- R-ATG was more costly and more effective than no induction, with ICERs of £63,100 to £333,000 per QALY gained.

6.29 The AG's economic analyses of maintenance therapies suggested that:

- Immediate-release tacrolimus dominated prolonged-release tacrolimus, sirolimus and ciclosporin (in 1 of 4 comparisons) and was less costly and less effective than belatacept and ciclosporin (3 of 4 comparisons), with ICERs of £131,035 to £388,740 per QALY lost.
- Mycophenolate mofetil dominated sirolimus and azathioprine, and was less costly and less effective than mycophenolate sodium (£144,000 per QALY lost) and everolimus (£1,530,000 per QALY lost).
- All the other interventions were either dominated or were more effective and more costly than their respective comparators with ICERs greater than £50,000 per QALY gained.

6.30 The AG's simultaneous comparison of the 16 modelled regimens found that all except 4 regimens were either dominated or extendedly dominated. Of these, basiliximab with tacrolimus and mycophenolate mofetil was the least costly and least effective, and the remainder were associated with ICERs greater than £100,000 per QALY gained compared with the next, less costly alternative.

6.31 Three companies presented economic analyses:

- Astellas: prolonged-release tacrolimus dominated immediate-release tacrolimus, which in turn dominated belatacept and everolimus. Sirolimus was less costly and less effective than immediate-release tacrolimus, with ICERs of £1,652,000 and £171,000 per QALY lost.
- BMS: belatacept was more costly and more effective than both ciclosporin and tacrolimus, with ICERs of £95,100 and £147,300 per QALY gained respectively. In people whose expected graft survival is likely to be short, belatacept dominated ciclosporin and tacrolimus.

- Novartis: everolimus (with ciclosporin) was dominated by mycophenolate mofetil (with tacrolimus), and was associated with an ICER of £59,700 per QALY gained compared with mycophenolate mofetil (with ciclosporin). Mycophenolate sodium was associated with an ICER of £10,600 per QALY gained, compared with mycophenolate mofetil (both with ciclosporin).

6.32 The AG highlighted a number of limitations in the company models. It also commented on several differences between the models presented, noting in particular the choice of regimens, the use of surrogate outcomes and clinical effectiveness outcomes, costs for drug acquisition, drug administration and dialysis, and utility values. Comparing the models presented by the companies with its own, the AG commented that the less favourable results seen in the AG's model (compared with the company models) could mostly be attributed to the use of specific RCTs rather than a systematic review and meta-analysis, differences in the use of surrogate endpoints and the use of US data for extrapolations. It noted that the lower estimates of graft survival in the AG's model led to smaller cost differences between regimens, and the AG's more complete and realistic costings and smaller differences in utility between functioning graft and graft loss states tended to reduce the effect on QALYs of clinical effectiveness differences between drugs (relative to the company models). Full details of the comparison between the AG and company models can be found in section 7.4.3 of the Assessment Report.

6.33 The AG commented that its economic analysis provides a thorough evaluation of the cost effectiveness of the interventions, aligned with the reference case and UK NHS setting, with clinical evidence taken from a systematic review. It acknowledged a number of limitations and uncertainties in the analysis (described in section 8.2 and 8.3 of the Assessment Report):

- The analysis did not include consideration of changes in graft function over time, the effect of steroid reduction, differences in the severity of

acute rejection, treatment discontinuation or switching (including delayed introduction of sirolimus) or the effect of medication adherence, and did not fully model all adverse events. There was also insufficient evidence to support subgroup analyses.

- The calculation of costs did not consider transport costs for haemodialysis or continuing immunosuppression following graft loss.
- The model included a number of assumptions, including assuming that graft function obeyed proportional hazards, that the effects of induction and maintenance regimens were independent, and that acute rejection, new-onset diabetes and graft function were independent.
- There remain a number of uncertainties, in particular the predicted survival differences between regimens (as there is limited long-term evidence from RCTs), the effects of immunosuppression on health-related quality of life, the costs associated with new-onset diabetes and the availability of discounts from the list price for immunosuppressive drugs.

7 Equality issues

7.1 During scoping, for this appraisal, consultees noted that Jehovah's witnesses are sometimes unwilling to be treated with intravenous human immunoglobulin. Consideration should be given to the treatment options available for people who are unwilling to receive human blood products, to ensure that any recommendations do not directly or indirectly discriminate on the basis of religion.

7.2 Astellas noted that people from ethnic minority groups are often less well matched to the donated kidney. It notes that changes to the matching criteria have allowed more people from these groups to receive transplants. This may imply that the availability of effective immunosuppressants may be particularly beneficial for people from ethnic minority groups.

7.3 No other equality issues were identified in the Assessment Report, company submissions or consultee submissions.

8 Innovation

8.1 Astellas stated that the development of a prolonged-release formulation of tacrolimus provides a more convenient, once-daily regimen that is easy to adhere to. It cites evidence that non-adherence is a major factor in preventable graft loss. Astellas also states that reduced intra-patient variability in the pharmacokinetics of tacrolimus, combined with improved adherence, may reduce the risk of antibody-mediated rejection and improve long-term outcomes.

8.2 Bristol-Myers Squibb stated that belatacept is delivered as an intravenous infusion and therapeutic monitoring is not required; it considered that this represents a step-change in the management of kidney transplants.

8.3 Novartis stated that everolimus is considered innovative as it has a different mode of action to calcineurin inhibitors and may improve patient and graft survival with fewer side effects compared with sirolimus, azathioprine or mycophenolate mofetil.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care. NICE clinical guideline 182 (2014).
- Immunosuppressive therapy for renal transplantation in adults. NICE technology appraisal guidance 85 (2004).
- Immunosuppressive therapy for renal transplantation in children and adolescents. NICE technology appraisal guidance 99 (2006).
- Machine perfusion systems and cold static storage of kidneys from deceased donors. NICE technology appraisal guidance 165 (2009).
- Chronic kidney disease. NICE quality standard 5 (2011).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Immunosuppressive therapy for renal transplantation in children and adolescents (review of existing guidance 99). NICE technology appraisal. Anticipated publication January 2016.

NICE pathways

- There is a NICE pathway on chronic kidney disease, which is available from http://pathways.nice.org.uk/pathways/chronic-kidney-disease.

Appendix B: Clinical efficacy section of the European public assessment report

- Basiliximab: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000207/WC500053538.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000207/WC500131049.pdf
- Rabbit anti-human thymocyte immunoglobulin: the UK Public Assessment Report is available on the archived pages of the Medicines and Healthcare Products Regulatory Agency. To access it, go to http://www.mhra.gov.uk/public-assessment-reports/, search for 'thymoglobuline', click on the link, then select 'view the item you were looking for in the UK Government Web Archive'
- Mycophenolate mofetil (CellCept): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000082/WC500021861.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000082/WC500137564.pdf
- Mycophenolate sodium: Not available online; SPC: https://www.medicines.org.uk/emc/medicine/14917
- Sirolimus: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000273/WC500046434.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion_-_Variation/human/000273/WC500046440.pdf
- Prolonged-release tacrolimus (Advagraf): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000712/WC500022237.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000712/WC500022239.pdf
- Immediate-release tacrolimus (Modigraf): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000954/WC500030473.pdf,

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000954/WC500060693.pdf

- Everolimus: Not available online; SPC: https://www.medicines.org.uk/emc/medicine/30306
- Belatacept: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002098/WC500108357.pdf, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/002098/WC500112770.pdf