

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using immunosuppressive therapy for kidney transplant in adults, in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 9) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using immunosuppressive therapy for kidney transplant in adults in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: 26 August 2015

Second Appraisal Committee meeting: 4 November 2015

Details of membership of the Appraisal Committee are given in section 8, and a list of the sources of evidence used in the preparation of this document is given in section 9.

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

1 Appraisal Committee's preliminary recommendations

- 1.1 Basiliximab, when used as part of an immunosuppressive regimen that includes a calcineurin inhibitor, is recommended as an option to prevent organ rejection in adults having a kidney transplant.^{1,2}
- 1.2 Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended within its marketing authorisation as an option to prevent organ rejection in adults having a kidney transplant. Treatment should normally be started with the least expensive product.
- 1.3 Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an option to prevent organ rejection in adults having a kidney transplant. Treatment should normally be started with the least expensive product.^{2,3}
- 1.4 Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in adults having a kidney transplant.
- 1.5 Adults whose treatment with rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus or belatacept was started within the NHS before this guidance was published, should be able to

continue treatment until they and their NHS clinician consider it appropriate to stop.

¹ At the time the ACD was released (July 2015), the use of basiliximab in combination with tacrolimus was outside the terms of the marketing authorisation for basiliximab. If this combination is prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. For further information, see the General Medical Council's guidance on [Good practice in prescribing and managing medicines and devices](#).

² The statutory funding requirement does not apply to drugs that are used outside the terms of their marketing authorisation.

³ At the time the ACD was released (July 2015), mycophenolate mofetil had a marketing authorisation in combination with ciclosporin, so the use of mycophenolate mofetil in combination with tacrolimus was outside the terms of the marketing authorisation. If mycophenolate mofetil in combination with tacrolimus is prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. For further information, see the General Medical Council's guidance on [Good practice in prescribing and managing medicines and devices](#).

2 Clinical need and practice

- 2.1 Kidney transplant is used to treat established kidney 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.
- 2.2 Between April 2013 and March 2014, 2931 kidney transplants were done in adults in the UK, including 2506 in adults in England. At the end of 2013, approximately 29,600 people in the UK were having immunosuppressive therapy after kidney transplant, including 24,800 people in England.
- 2.3 Immunosuppressive therapy aims to prevent acute rejection and optimise the function of the transplanted kidney, while minimising the adverse effects of immunosuppression (such as increased risk of infection, cancer, diabetes and cardiovascular disease). Immunosuppressive therapy can be categorised as induction therapy and maintenance therapy. Induction therapy is an intensive

immunosuppression regimen that is used for up to 2 weeks around the time of transplant and may include polyclonal or monoclonal antibodies. Maintenance therapy starts immediately after transplant and continues for life.

- 2.4 NICE guidance on [immunosuppressive therapy for kidney transplantation in adults](#) was published in 2004. It recommended basiliximab, daclizumab, tacrolimus, mycophenolate mofetil and sirolimus, in certain circumstances, as options for immunosuppressive therapy for kidney transplant in adults. Since that appraisal, the marketing authorisation for daclizumab has been withdrawn, 5 new technologies (rabbit anti-human thymocyte immunoglobulin, mycophenolate sodium, belatacept, a prolonged-release formulation of tacrolimus, and everolimus) have received marketing authorisations, and some of the technologies have become available generically.

3 The technologies

Induction therapy

Basiliximab

- 3.1 Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody that acts as an interleukin-2 receptor antagonist. It has a marketing authorisation in the UK for the prophylaxis of acute organ rejection in adults having a kidney transplant. The summary of product characteristics states basiliximab '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'.

- 3.2 Basiliximab is administered intravenously, in 2 doses of 20 mg each (one 2 hours before the surgery and the second 4 days after).
- 3.3 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.
- 3.4 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 [BNF] online [accessed June 2015]), equating to £1684.76 per course of treatment (2 doses of 20 mg).

Rabbit anti-human thymocyte immunoglobulin

- 3.5 Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline, Sanofi) is made by injecting human thymus cells into rabbits. The drug contains immunoglobulins (antibodies) that attach to and destroy some of the cells of the immune system. It has a marketing authorisation in the UK for the prevention of graft rejection in kidney transplant. The summary of product characteristics states it is usually used in combination with other immunosuppressive drugs.
- 3.6 r-ATG is administered intravenously, at a dose of 1 to 1.5 mg/kg/day for 3 to 9 days after a kidney transplant (a cumulative dose of 3 to 13.5 mg/kg).

- 3.7 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.
- 3.8 r-ATG is available in 25 mg vials, at a net price of £158.77 (excluding VAT; BNF online [accessed June 2015]), equating to £1428.93 to £7144.65 per course for a 70 kg person.

Maintenance therapy

- 3.9 Some drugs in this appraisal contain the same active ingredient but in different formulations. Tacrolimus is a calcineurin inhibitor and is available in an immediate-release formulation and a prolonged-release formulation. Mycophenolic acid is an antiproliferative agent. It is available as a prodrug called mycophenolate mofetil and a sodium salt called mycophenolate sodium.

Immediate-release tacrolimus

- 3.10 Brands of immediate-release tacrolimus include Adoport (Sandoz), Capexion (Mylan), Modigraf (Astellas Pharma), Perixis (Accord Healthcare), Prograf (Astellas Pharma), Tacni (Teva) and Vivadex (Dexcel Pharma). All of these formulations have marketing authorisations in the UK for the prophylaxis of transplant rejection in adults having a kidney transplant, and all are administered orally, twice a day. Prograf can also be administered intravenously.
- 3.11 For all brands of immediate-release tacrolimus, 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 period after the transplant.

- 3.12 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. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.13 The average cost paid by the NHS for immediate-release tacrolimus capsules is £0.52 per mg (excluding VAT; data from the Electronic Market Information Tool [eMIT], Commercial Medicines Unit). This equates to £50.96–£76.44 per week for an initial dose of 0.2–0.3 mg/kg/day in a 70 kg person.

Prolonged-release tacrolimus

- 3.14 Prolonged-release tacrolimus (Advagraf, Astellas Pharma) is administered orally as a capsule, once a day. It has a marketing authorisation in the UK for the prophylaxis of transplant rejection in adults having a kidney transplant. The summary of product characteristics recommends an initial dose for adults of 0.2–0.3 mg/kg/day. The dosage is usually reduced in the period after the transplant.
- 3.15 The summary of product characteristics states that the following adverse reactions occur in at least 10% of people treated with prolonged-release tacrolimus: infection, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, insomnia, tremor, headache, hypertension, diarrhoea, nausea, renal impairment and abnormal liver function. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.16 Prolonged-release tacrolimus (Advagraf) 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; BNF online [accessed June 2015]). This

equates to £112.11–£210.47 per week for an initial dose of 0.2–0.3 mg/kg/day in a 70 kg person. Advagraf is available at a discounted price through a national tender agreement. The level of discount is commercial in confidence, so cannot be reported here. Another brand of prolonged-release tacrolimus, Envarsus (Chiesi), obtained a marketing authorisation after the scope was finalised. The brand name 'Envarsus' was not included in the AG's search for evidence and Chiesi was not asked to submit evidence as part of the appraisal.

Belatacept

- 3.17 Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept, in combination with corticosteroids and a mycophenolic acid, has a marketing authorisation in the UK for prophylaxis of graft rejection in adults having a kidney transplant. The summary of product characteristics recommends that an interleukin-2 receptor antagonist is added to this belatacept-based regimen.
- 3.18 Belatacept is administered intravenously, at a dose of 10 mg/kg on the day of the transplant, followed by 10 mg/kg on days 5, 14, 28, 56 and 84 and then 5 mg/kg every 4 weeks from then on.
- 3.19 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.

- 3.20 Belatacept is available in 250 mg vials at a net price of £354.52 (excluding VAT; BNF online [accessed June 2015]). For a 70 kg person, this equates to £6381.36 for the first 12 weeks and £709.04 every 4 weeks from week 16 onwards.

Mycophenolate mofetil

- 3.21 Mycophenolate mofetil (non-proprietary) has a marketing authorisation in the UK, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute transplant rejection in people having a kidney transplant. It can be administered orally or intravenously, at a recommended dose of 2 g/day.
- 3.22 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.
- 3.23 The average cost paid by the NHS for mycophenolate mofetil capsules is £0.38 per g (excluding VAT; data from eMIT, Commercial Medicines Unit), equating to £5.28 per week.

Mycophenolate sodium

- 3.24 Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals), in combination with ciclosporin and corticosteroids, has a marketing authorisation in the UK for the prophylaxis of acute transplant rejection in adults having a kidney transplant. It is administered orally, at a recommended dose of 1.44 g per day.
- 3.25 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with mycophenolate sodium: leukopenia; diarrhoea; viral, bacterial and fungal infections; hypertension; decreased levels of calcium or

potassium in the blood; increased levels of uric acid in the blood and joint pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 3.26 Mycophenolate sodium is available in 180 mg and 360 mg tablets, at a net price of £4.48 per g (excluding VAT; BNF online [accessed June 2015]), equating to £45.13 per week.

Sirolimus

- 3.27 Sirolimus (Rapamune, Pfizer) is an antiproliferative that blocks a protein called mammalian target of rapamycin (mTOR). It has a marketing authorisation in the UK for the prophylaxis of organ rejection in adults having a kidney transplant, who are at low to moderate immunological risk. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2–3 months, and may be continued only if ciclosporin can be progressively discontinued.
- 3.28 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.
- 3.29 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.
- 3.30 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 £2.71–£4.60 per mg

(excluding VAT; BNF online [accessed June 2015]), equating to £16.24–27.60 initially followed by £37.90–64.40 per week.

Everolimus

- 3.31 Everolimus (Certican, Novartis Pharmaceuticals) is an antiproliferative that blocks mTOR. It has a marketing authorisation for the prophylaxis of organ rejection in adults having a kidney transplant, who are at low to moderate immunological risk. The summary of product characteristics states that everolimus should be used in combination with ciclosporin and corticosteroids. Everolimus is administered orally at an initial dose of 1.5 mg/day.
- 3.32 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with everolimus: infections; diabetes; headache; insomnia; anxiety; pain; pericardial or pleural effusion (fluid in the space around the heart or lungs); hypertension; venous thromboembolic events; cough; dyspnoea; abdominal pain; diarrhoea; nausea; vomiting; 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.
- 3.33 Everolimus is available in 0.25 mg, 0.5 mg and 0.75 mg tablets, at a net price of £9.90 per mg (MIMS, June 2015). This equates to £103.95 per week.
- 3.34 Costs for all of the technologies may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (section 8) considered evidence from a number of sources (section 9). Under an exceptional directive from

the Department of Health, the Appraisal Committee could consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there was compelling evidence of their safety and effectiveness.

Clinical effectiveness

4.1 The Assessment Group (AG)'s systematic review found 86 randomised controlled trials, including 11 studies of induction therapies, 73 studies of maintenance therapies and 2 studies examining both induction and maintenance therapies. Of the 86 studies, 23 were included in the appraisal of [immunosuppressive therapy for kidney transplantation in adults](#), and 63 were identified in the updated systematic review for the current appraisal. The AG highlighted that the identified clinical studies were of varying quality; all appeared to have limitations and most had reporting omissions. It considered that only 11 trials adequately matched the population and current practice in the NHS in England.

Induction therapies

4.2 The AG found 8 studies that compared basiliximab with placebo or treatment without induction. Pooled results showed that basiliximab was associated with a statistically significant reduction in acute rejection compared with placebo or treatment without induction at 1 year (odds ratio [OR] 0.53, 95% confidence interval [CI] 0.40 to 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 treatment without induction, but statistical significance was not reached. No statistically significant differences between basiliximab and treatment without induction

were seen in pooled analyses of mortality at 1 year and graft function at 6 months and 1 year. Longer-term outcomes were reported in 1 study, Sheashaa et al. (2013), and the findings were broadly consistent with the pooled results. Statistically significant reductions in acute rejection with basiliximab compared with treatment without induction were seen at 3 and 10 years. There were no statistically significant differences between basiliximab and treatment without induction in mortality or graft function at 3, 5, 7 and 10 years.

4.3 The AG's network meta-analysis (see Table 1) showed that basiliximab was statistically significantly more effective than treatment without induction for acute rejection (OR 0.52, 95% credible interval [CrI] 0.41 to 0.65). The AG stated that there is little evidence to suggest that basiliximab is more effective than treatment without induction for reducing graft loss or mortality.

4.4 The AG found 2 relevant studies that compared rabbit anti-human thymocyte immunoglobulin (r-ATG) with treatment without induction. Charpentier et al. (2001 and 2003) found a statistically significant reduction in acute rejection associated with r-ATG compared with treatment without induction at 6 months and 1 year (1 year: OR 0.41, 95% CI 0.24 to 0.72). The AG noted that the reporting of time to acute rejection varied between studies. No statistically significant differences between r-ATG and treatment without induction were seen in mortality or graft loss. The AG's network meta-analysis (see Table 1) showed that r-ATG was statistically significantly more effective than treatment without induction for preventing acute rejection (OR 0.36, 95% CrI 0.24 to 0.54). The AG stated that there was little evidence to suggest that r-ATG is more effective than treatment without induction for reducing graft loss or mortality or improving graft function.

4.5 The AG found 3 randomised controlled trials that provided head-to-head comparisons between basiliximab and r-ATG. Pooled analyses found 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 time points assessed. The AG highlighted that studies by Lebranchu et al. (2002) and Mourad et al. (2004) reported differences in graft function and time to acute rejection in favour of basiliximab, although the results were not statistically significant. The AG's network meta-analysis (see Table 1) suggested that r-ATG may be more effective than basiliximab for acute rejection, although the 95% credible interval for the odds ratio crossed 1 (OR 0.70, 95% CrI 0.47 to 1.03). There was no evidence to suggest a statistically significant difference between r-ATG and basiliximab for mortality, graft loss or graft function.

Table 1 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 versus placebo/treatment without 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 versus placebo/treatment without 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 versus 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 less than 1 favours the first treatment in the comparison; a mean difference greater than 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; CrI, credible interval.

Maintenance therapies

- 4.6 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.

Tacrolimus

- 4.7 Pooled comparisons suggested that, when used with azathioprine, tacrolimus was associated with fewer episodes of acute rejection after 1–4 years and less severe acute rejection after 1–2 years, compared with ciclosporin. When used 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 plus sirolimus, than with ciclosporin plus sirolimus.
- 4.8 Tacrolimus plus mycophenolate mofetil was associated with statistically significantly lower acute rejection, compared with sirolimus plus mycophenolate mofetil. Similarly, for tacrolimus plus mycophenolate sodium, the odds ratio for acute rejection appeared to favour tacrolimus compared with sirolimus, although this did not reach statistical significance.
- 4.9 Comparison of immediate-release and prolonged-release tacrolimus (plus mycophenolate mofetil) showed no consistent statistically significant differences. In 1 study, immediate-release tacrolimus was associated with statistically significantly greater graft function at 6 months, although the difference was not statistically significant at 1 year in a pooled analysis. Analysis of 2 studies suggested that immediate-release tacrolimus was associated with 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 statistically significant difference was seen at 1 year.

Belatacept

4.10 Belatacept plus mycophenolate mofetil was associated with statistically significant improvements in graft loss at 5 years and graft function at 1, 3 and 5 years, compared with ciclosporin plus mycophenolate mofetil (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 statistically significantly greater acute rejection than ciclosporin at 5 years.

Mycophenolate mofetil and mycophenolate sodium

4.11 Mycophenolate mofetil plus ciclosporin was associated with fewer acute rejections than azathioprine at 6 months. Mycophenolate mofetil plus sirolimus was associated with statistically significantly greater graft function than tacrolimus at 2 years.

4.12 Mycophenolate mofetil and mycophenolate sodium were compared in 2 trials. The AG noted that there appeared to be no noticeable difference between arms for any of the reported outcomes; although a statistically 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

4.13 Sampaio et al. (2008) reported a statistically significantly greater mean time to acute rejection with sirolimus than with mycophenolate mofetil (both plus tacrolimus). Sirolimus plus mycophenolate mofetil was associated with statistically significantly

reduced graft function compared with ciclosporin plus mycophenolate mofetil after 2–5 years. However, sirolimus plus azathioprine appeared to statistically significantly improve graft function at 6 months and 1 year compared with ciclosporin plus azathioprine (1 study).

Everolimus

- 4.14 Mjornstedt et al. (2012) compared everolimus with ciclosporin (both plus mycophenolate sodium), and saw a statistically significant increase in the odds of acute rejection at 1 year with everolimus.

Network meta-analyses

- 4.15 The AG noted that there was substantial heterogeneity in all of the network meta-analyses. It stated that none of the maintenance regimens performed consistently well across all 4 outcomes assessed in the network meta-analysis (mortality, graft loss, acute rejection and graft function), although some differences between regimens were seen for some outcomes (see Table 2). The AG stated that because of wide confidence intervals, there was a great deal of uncertainty associated with the results and limited conclusions could be drawn.

- Mortality: Belatacept plus mycophenolate mofetil was more effective at reducing mortality than tacrolimus and sirolimus (both plus mycophenolate mofetil).
- Graft loss: There was no evidence to suggest that any of the treatments were better than the others for this outcome.
- Acute rejection: Ciclosporin plus azathioprine was statistically significantly worse than 5 regimens (tacrolimus plus azathioprine, mycophenolate mofetil or sirolimus, and ciclosporin plus mycophenolate mofetil or everolimus). Everolimus plus mycophenolate mofetil was statistically significantly worse than

3 regimens (tacrolimus or ciclosporin plus mycophenolate mofetil, and tacrolimus plus sirolimus).

- Graft function: A number of regimens (specifically tacrolimus plus azathioprine or sirolimus, ciclosporin plus everolimus, and ciclosporin or tacrolimus plus mycophenolate mofetil) were better than ciclosporin plus azathioprine. Tacrolimus or belatacept plus mycophenolate mofetil were better than ciclosporin plus mycophenolate mofetil. Tacrolimus plus azathioprine was better than 3 regimens (tacrolimus plus sirolimus, and ciclosporin plus mycophenolate mofetil or sirolimus).

Table 2 Summary of the Assessment Group’s network meta-analyses for maintenance therapy; median treatment effects (and 95% credible intervals) compared with ciclosporin plus azathioprine

Regimen	Odds ratios <i>Lower is better</i>			Graft function (mean difference in eGFR) <i>Higher is better</i>
	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 (in ml/min/1.73 m ²). Evidence suggesting a difference between the regimen and the comparator (ciclosporin and azathioprine) is in bold text.				

Adverse events

- 4.16 The AG summarised adverse event data from all the identified clinical trials. The AG focused in particular on 6 groups of adverse events: new-onset diabetes, malignancy, post-transplant lymphoproliferative disorders, infections, cytomegalovirus (CMV) infections and dyslipidaemia.
- 4.17 The AG found evidence to suggest that r-ATG may be associated with an increase in CMV infections. In the AG's pooled analysis, r-ATG was associated with a statistically significant increase in CMV infections compared with treatment without induction, although there was no statistically significant difference between r-ATG and basiliximab. No statistically significant differences between r-ATG, basiliximab and treatment without induction were seen in the incidence of infections, new-onset diabetes or malignancy, in the pooled analyses.
- 4.18 The AG's meta-analysis of adverse events with maintenance therapies found a number of statistically significant differences between treatments in the incidence of diabetes, all infections and CMV infections. In particular, tacrolimus and sirolimus increased the rate of new-onset diabetes compared with ciclosporin, whereas belatacept reduced the rate of this event. Sirolimus and everolimus were both associated with statistically significantly reduced rates of CMV infection, compared with ciclosporin and mycophenolate respectively. Tacrolimus was associated with a statistically significantly reduced rate of all infections compared with sirolimus. There were no other statistically significant differences between treatments in the incidence of adverse events.
- 4.19 The AG found that, based on a fixed-effect meta-analysis of 10 studies, everolimus and sirolimus statistically significantly

increased the risk of dyslipidaemia, compared with regimens that do not contain these drugs.

Comments from other consultees

4.20 Consultees highlighted that each of the technologies under consideration may have benefits for particular groups of people. In particular, they stated that:

- r-ATG may be valuable in people with high immunological risk of rejection.
- Once-daily (prolonged-release) tacrolimus and the once-monthly regimen for belatacept may help improve adherence.
- Belatacept may benefit people who cannot take or cannot digest oral therapies, and may reduce the long-term adverse effects of calcineurin inhibitors.
- Sirolimus and everolimus may improve graft function and may be particularly valuable in people with a history of cancer (although they are thought to have adverse effects on wound healing).
- Mycophenolate mofetil and mycophenolate sodium may help reduce steroid use.
- Mycophenolate sodium may benefit people who have gastrointestinal adverse reactions with mycophenolate mofetil.
- Everolimus may be an option for people at high risk of CMV infection.
- Older people have a different risk–benefit balance to younger people and so should be considered separately.

Consultees highlighted that the availability of additional drugs and combinations for particular groups may help increase access to transplants. The AG emphasised that there was not enough evidence available for robust subgroup analyses.

- 4.21 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. Consultees stated that mycophenolate mofetil and tacrolimus are often used at lower doses than specified in their marketing authorisations, and doses may be adjusted during treatment, which may affect their costs.
- 4.22 In their responses to the assessment report, consultees noted that the AG's systematic review had focused 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. The AG acknowledged the limitations in the evidence available.

Cost effectiveness

- 4.23 Economic analyses were presented by the AG, Astellas, Bristol-Myers Squibb and Novartis.

The Assessment Group's economic model

- 4.24 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. The AG stated that its model was independent of that built for the appraisal of [immunosuppressive therapy for renal transplantation in adults](#). It highlighted that the previous analysis had not fully accounted for uncertainty and had not taken into account the recently identified effect of kidney function on clinical and economic outcomes.
- 4.25 The model comprised 7 states. Throughout the model, patients were assumed to have a functioning kidney transplant ('functioning

graft' states), to depend on dialysis ('graft loss' states) or to have died ('death' state). At the start of the model, most patients entered the first functioning graft state. The remaining patients started the model in the first graft loss state because their transplant did not work (called 'primary non-function'). From the first functioning graft state, patients could either move to the first graft loss state when the transplanted kidney stopped working, or they may have a second transplant before the graft stopped working (called 'pre-emptive re-transplant') and would enter one of the subsequent states. From the first graft loss state, patients had a second transplant ('re-transplant') and entered one of the subsequent states. When patients had a second transplant, they could move to the second functioning graft state and then, when the second transplant stopped working, to the second graft loss state. If the second transplant was not successful (primary non-function), patients moved directly to the second graft loss state. From the second graft loss state, a third transplant was modelled similarly to the second transplant. Mortality was modelled by moving to the 'death' state (referred to as 'death with functioning graft' and 'death following graft loss').

4.26 Movement between health states was determined by 3 key factors: mortality, graft loss, and rates of transplant. 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.

4.27 In the AG's model, death could occur either before graft loss (that is, from the functioning graft states; called 'death with a functioning graft') or after graft loss.

- 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. In subsequent years, the rate was adjusted based on a surrogate relationship between new-onset diabetes and death.

- The rate of death after graft loss was based on mortality associated with dialysis, taken from the UK Renal Registry. This was not adjusted according to the immunosuppressive regimen.

4.28 Graft loss was modelled using 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 of graft loss was adjusted for each immunosuppressive regimen to match the rates 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.

4.29 The AG modelled health-related quality of life using an age- and sex-dependent baseline utility score, combined with a utility decrease (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 (0.06).

4.30 The model calculated the costs associated with each immunosuppressive regimen, including: drug acquisition, drug administration and monitoring, patient follow-up, dialysis and re-

transplant, preventing and managing adverse events, and treating acute rejection. The AG stated that immunosuppressive therapy is prescribed in hospitals; therefore, 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, preventing and treating infections (including 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 the same for all regimens. Cost estimates were based on NHS reference costs when available, and from costing studies presented by Bristol-Myers Squibb and data from University Hospital Wales and the Royal Devon and Exeter Hospital.

- 4.31 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. Induction agents and maintenance regimens were combined, assuming independence. The AG assumed that all regimens included corticosteroids. Because the AG's network meta-analysis did not distinguish between mycophenolate mofetil and mycophenolate sodium or between immediate- and prolonged-release tacrolimus, clinical effectiveness estimates and adverse event rates were calculated by adjusting results from the network meta-analyses using head-to-head comparisons. For all regimens, the model assumed that after re-transplant, all patients switched to the same regimen

(basiliximab, tacrolimus and mycophenolate mofetil) for the second and subsequent transplant.

The Assessment Group’s economic model: results

4.32 For the induction treatments, the AG presented comparisons between basiliximab, r-ATG and treatment without induction, for combinations with 3 different maintenance regimens (see Table 3). In all analyses, basiliximab dominated (that is, was more effective and less costly than) both r-ATG and treatment without induction. r-ATG was more costly and more effective than treatment without induction, and was associated with incremental cost effectiveness ratios (ICERs) of £63,150 to £332,971 per quality-adjusted life year (QALY) gained.

Table 3 The Assessment Group’s economic analysis for induction therapies: summary of pairwise cost-effectiveness comparisons (deterministic results)

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)	
	Total	Incremental	Total	Incremental	Incremental	Versus no induction
<i>With ciclosporin + azathioprine</i>						
No induction	£101,595	–	10.7711	–	Dominated	
r-ATG	£104,570	£2975	10.8182	0.0471	Dominated	£63,150
Basiliximab	£98,244	–£6326	10.9029	0.0848	–	Dominant
<i>With ciclosporin + mycophenolate mofetil</i>						
No induction	£97,429	–	10.9145	–	Dominated	
r-ATG	£101,940	£4511	10.9281	0.0135	Dominated	£332,971
Basiliximab	£95,219	–£6720	11.0247	0.0966	–	Dominant
<i>With tacrolimus + mycophenolate mofetil</i>						
No induction	£92,226	–	10.8884	–	Dominated	
r-ATG	£97,146	£4920	10.9047	0.0163	Dominated	£301,516
Basiliximab	£90,405	–£6741	10.988	0.0832	–	Dominant
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin Dominated: provides fewer QALYs at greater cost than the comparator Dominant: provides more QALYs at lower cost than the comparator						

4.33 For the maintenance treatments, the AG presented results for all 7 drugs, compared with each other and with ciclosporin and

azathioprine when possible (see Table 4). The AG stated that, 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 4 The Assessment Group’s economic analysis for maintenance therapies: summary of incremental cost-effectiveness comparisons (deterministic results)

	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
<i>With mycophenolate mofetil</i>					
Tacrolimus-PR	£106,529	–	10.7920	–	Dominated
Tacrolimus-IR	£92,226	-£14,303	10.8884	+0.0964	–
Ciclosporin	£97,429	+£5203	10.9145	+0.0261	£199,118
<i>With azathioprine</i>					
Ciclosporin	£101,595	–	10.7711	–	Dominated
Tacrolimus	£93,319	-£8276	10.8696	+0.0986	–
<i>With basiliximab+mycophenolate mofetil</i>					
Sirolimus	£114,549	–	10.9010	–	Dominated
Tacrolimus-IR	£90,405	-£24,144	10.9880	+0.0869	–
Ciclosporin	£95,219	+£4815	11.0247	+0.0367	£131,035
Belatacept	£209,409	+£114,189	11.2941	+0.2694	£423,890
<i>With r-ATG+mycophenolate mofetil</i>					
Tacrolimus-IR	£97,146	–	10.9047	–	–

Ciclosporin	£101,940	+£4794	10.9281	+0.0234	£205,214
With ciclosporin					
Azathioprine	£101,595	–	10.7711	–	Dominated
Mycophenolate mofetil	£97,429	–£4166	10.9145	+0.1435	–
Everolimus	£176,154	+£78,725	10.9659	+0.0514	£1,532,379
With tacrolimus-IR					
Sirolimus	£125,539	–	10.6023	–	Dominated
Azathioprine	£93,319	–£32,220	10.8696	+0.2674	Dominated
Mycophenolate mofetil	£92,226	–£1093	10.8884	+0.0188	–
With basiliximab+ciclosporin					
Azathioprine	£98,244	–	10.9029	–	Dominated
Mycophenolate mofetil	£95,219	–£3025	11.0247	+0.1218	–
Mycophenolate sodium	£111,540	+£16,321	11.1377	+0.1130	£144,449
With r-ATG+ciclosporin					
Azathioprine	£104,570	–	10.8182	–	Dominated
Mycophenolate mofetil	£101,940	–£2631	10.9281	+0.1099	–
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin Dominated: provides fewer QALYs at greater cost than the comparator					

4.34 In the simultaneous comparison of the 16 regimens, all except 4 regimens were dominated or extendedly dominated (that is, a combination of 2 comparators provided equal health at a lower cost). The 4 regimens (tacrolimus plus mycophenolate mofetil, ciclosporin plus mycophenolate mofetil, ciclosporin plus mycophenolate sodium and belatacept plus mycophenolate mofetil, all with basiliximab induction) were therefore compared in an incremental analysis. Of these, basiliximab plus tacrolimus and mycophenolate mofetil was the least costly and least effective; the remaining regimens were associated with ICERs much greater than £100,000 per QALY gained compared with the next, less costly alternative.

4.35 The AG presented a probabilistic sensitivity analysis, and the results were mostly similar to the deterministic analysis. The largest

difference between the deterministic and probabilistic analyses was for the regimen of basiliximab, ciclosporin and mycophenolate sodium: the probabilistic analysis predicted 0.1133 fewer QALYs. This led to some changes in the ICERs in the pairwise comparison of maintenance drugs, and led to basiliximab plus ciclosporin and mycophenolate sodium becoming dominated in the simultaneous comparison of regimens. However, the AG's conclusions remained unchanged compared with the deterministic analysis.

- 4.36 The AG explored uncertainties in the model structure using 5 scenario analyses. These analyses explored the effect of the surrogate relationship between graft survival and clinical variables, the effect of possible nephrotoxicity associated with ciclosporin and tacrolimus, and the costs of treatment. In particular, the costs of immunosuppressive therapies were explored using the list prices for all drugs (rather than the eMIT prices) and a discount for prolonged-release tacrolimus available through a national tender.
- 4.37 Consultees raised a number of queries about the AG's economic analysis.
- Consultees expressed concerns about the drug acquisition costs used in the model. The AG emphasised that the prices used in the model closely match the costs to NHS hospitals.
 - Novartis suggested an alternative approach for modelling quality of life, whereby utilities are adjusted based on graft function. The AG noted uncertainties in the evidence to support this approach.
 - Sanofi queried the costs associated with CMV infections. The AG noted that this is not a major driver of the model results.
 - The British Transplantation Society queried the use of a Weibull model to extrapolate survival. The AG considered that the Weibull model was unlikely to have overestimated survival, and was not expected to affect the overall conclusions.

- Astellas noted that the model did not consider the effect of adherence. 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. The AG stated that malignancy would only affect the cost-effectiveness conclusions if different agents were associated with different rates of this outcome.

Company economic models: Astellas

4.38 Astellas presented a Markov model with 6 states, a 1-year cycle length and a 25-year time horizon. The model represented the clinical pathway of patients having immunosuppressive therapy, based on the rates of acute rejection, graft loss, re-transplant and mortality taken from the company's clinical effectiveness review, NHS Blood and Transplant and the UK Renal Registry. 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. 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 done at the University Hospital of Wales. Costs and QALYs were discounted at a rate of 3.5% per year in the base case.

4.39 The company presented the results for each immunosuppressive drug compared with immediate-release tacrolimus. 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 £170,681 to

£1,651,801 and per QALY lost. The model results were similar in all sensitivity analyses, except for 1 scenario analysis in which sirolimus was dominated by immediate-release tacrolimus.

- 4.40 The AG highlighted a number of concerns about the Astellas model. The AG noted that the company had omitted ciclosporin as a comparator, which affected 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. The AG 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.

Company economic models: Bristol-Myers Squibb

- 4.41 Bristol-Myers Squibb presented an analysis of the cost effectiveness of belatacept compared with tacrolimus and ciclosporin. This was based on a 36-month initial phase followed by a longer-term Markov model with a lifetime time horizon. Health-related quality of life was estimated by applying utility estimates to the functioning graft state (split by estimated glomerular filtration rate [eGFR]) and graft loss state and utility decrements associated with 3 complications after transplant (new-onset diabetes, post-transplant lymphoproliferative disorders and acute rejection). Resource use was estimated using an observational database study (PORTRAIT), combined with separate costs for immunosuppressive regimens (based on list prices) and complications after transplant. All costs and QALYs were discounted at a rate of 3.5% per year.

- 4.42 The base-case analysis showed 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.
- 4.43 The company also presented a subgroup analysis of people whose graft survival was expected to be short (people with an eGFR of less than 30 ml/min/1.73 m² at 1 year after transplant). In this analysis, belatacept dominated both ciclosporin and tacrolimus.
- 4.44 The AG commented that the Bristol-Myers Squibb model captured the key clinical outcomes and incorporated the effects of kidney function and acute rejection on costs and quality of life. It highlighted that using the results of the cost study presented by Bristol-Myers Squibb was a major strength of the model. However, the AG considered that the model had methodological limitations relating to the generalisability of the transition probabilities to the UK population, the application of efficacy differences between drugs and the assumption of a linear decline in eGFR after 3 years. The AG also noted important limitations in the subgroup analyses.

Company economic models: Novartis

- 4.45 Novartis presented a patient-level simulation model, in which individual patients were followed through a pathway based on acute rejection, graft failure, re-transplant and death. The model used 1-month cycles and a lifetime time horizon to capture the cost effectiveness of everolimus plus reduced-dose ciclosporin and mycophenolate sodium plus standard-dose ciclosporin, compared with mycophenolate mofetil plus standard-dose ciclosporin or tacrolimus. The model captured health-related quality of life by applying published EQ-5D data to each patient according to their eGFR. After consultation, Novartis submitted additional economic analyses, and corrected errors in the programming of the model.

- 4.46 In the base-case analysis (uncorrected results), everolimus plus ciclosporin dominated tacrolimus plus mycophenolate mofetil. After correcting errors in the model, everolimus plus ciclosporin was associated with an ICER of £17,182 per QALY gained compared with mycophenolate mofetil plus ciclosporin. Mycophenolate sodium dominated mycophenolate mofetil (both plus ciclosporin). The company noted that the results were sensitive to the utility score for people with stage 3 chronic kidney disease, the time to re-transplant and the effect of treatment discontinuation.
- 4.47 Novartis's additional economic analyses matched the costs, efficacy parameters and key assumptions in the model to the AG's model, and explored the effect of utility assumptions on the results. In the revised base case, everolimus plus ciclosporin was associated with an ICER of £100,459 per QALY gained compared with ciclosporin plus mycophenolate mofetil. Mycophenolate sodium was associated with an ICER of £27,327 per QALY gained, compared with mycophenolate mofetil (both plus ciclosporin). The company noted that the methods of utility estimation had a large effect on the results.
- 4.48 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, although new-onset diabetes had been omitted. 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 the assumption that graft failure occurs independently of graft function and acute rejection was flawed. The AG 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 kidney function to be confident that Novartis's approach is better. The AG questioned whether the subgroup analysis of mycophenolate sodium as a second-line therapy was robust enough to support the cost effectiveness of this treatment.

Summary

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

- Basiliximab dominated both r-ATG and treatment without induction.
- r-ATG was more costly and more effective than treatment without induction, with ICERs of £63,100 to £333,000 per QALY gained.

4.50 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 (in 3 of 4 comparisons), with ICERs of £131,000 to £389,000 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.

4.51 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.

4.52 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.
- Bristol-Myers Squibb: 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 (plus ciclosporin) dominated mycophenolate mofetil (plus tacrolimus), and was associated with an ICER of £17,200 per QALY gained compared with mycophenolate mofetil (plus ciclosporin). Mycophenolate sodium dominated mycophenolate mofetil (both plus ciclosporin).

4.53 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. The AG commented that the less favourable results seen in its own model (compared with the company models) was mainly a result of using a systematic review and meta-analysis rather than specific

randomised controlled trials, differences in the use of surrogate end points 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. 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 of clinical effectiveness differences between drugs (relative to the company models) on the QALYs.

- 4.54 The AG acknowledged that there were limitations and uncertainties in its analysis. It stated that its analysis did not consider changes in graft function over time, the effect of steroid reduction, differences in the severity of acute rejection, stopping or switching treatment (including delayed introduction of sirolimus) or the effect of medication adherence, and did not fully model all adverse events. The AG also noted that there was not enough evidence to support subgroup analyses. The AG highlighted that the calculation of costs did not include transport costs for haemodialysis or continuing immunosuppressive therapy after graft loss. Its 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. The AG highlighted that there are a number of uncertainties remaining in its analysis, in particular the predicted survival differences between regimens (because there is limited long-term evidence from randomised controlled trials), the effects of immunosuppressive therapy 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.

Consideration of the evidence

The appraisal included 9 drugs for immunosuppression after kidney transplant in adults. Basiliximab and r-ATG are both induction therapies. The other drugs are maintenance therapies: immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept. The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of these technologies, having considered evidence on the nature of kidney transplant and organ rejection and the value placed on the benefits of the technologies by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.55 The Committee heard from the clinical experts that the key priority for clinicians is to prolong graft survival for as long as possible, while minimising adverse effects, with the ultimate goal of allowing people to return to normal life. The clinical experts considered that both quality of life and survival are better with a functioning kidney transplant than with dialysis. The patient experts described their experiences of kidney transplants and immunosuppressive regimens, and emphasised the value of maintaining a functioning kidney transplant. The Committee understood that effective immunosuppressive therapies are important to prevent organ rejection in adults having kidney transplants.
- 4.56 The Committee heard from the clinical experts that the choice between immunosuppressive therapies is affected by a number of factors, including the characteristics and preferences of the person having treatment. The Committee heard that the side effect profiles of each drug and the risk profile of the kidney donor and recipient may be particularly important considerations. In particular, the risks of new-onset diabetes, delayed graft function and nephrotoxicity

may be key priorities for some people (for example, people of African-Caribbean and Asian family origins have a higher risk of developing diabetes), whereas the level of immunological risk may be a priority for others. The clinical and patient experts therefore emphasised the importance of having access to a choice of treatment options to meet the needs of different people. The Committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people. The Committee understood the value of having a choice of immunosuppressive therapies.

- 4.57 The Committee discussed the technologies included in the assessment report. A clinical expert suggested that the appraisal should consider alemtuzumab as an induction therapy. The Committee was aware that alemtuzumab does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and is not routinely available for transplant patients (it is available on a 'named patient' basis), and was therefore not included in the scope for this appraisal. The Committee concluded that alemtuzumab should not be included as either an intervention or a comparator.
- 4.58 The Committee considered the clinical effectiveness evidence presented by the AG and companies. It noted that the AG's systematic review was comprehensive and found a large number of randomised controlled trials. The Committee heard from the clinical experts that additional observational evidence is available in the UK Transplant Registry. The AG stated that this evidence had been used in its economic model to inform the natural history of the condition. However, the Committee heard from the AG that there were some challenges with the recording of immunosuppressive regimens in the registry. Also there were relatively few patients

having the newer drugs in the registry than in the clinical trials, and so there were limitations to the clinical effectiveness evidence available from this source. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness evidence had been taken into account.

- 4.59 The Committee discussed the findings of the pooled head-to-head analyses and network meta-analyses of the induction therapies. It understood that both basiliximab and r-ATG were associated with statistically significant reductions in the incidence of acute rejection compared with placebo or treatment without induction. The Committee saw no evidence of a statistically significant difference between basiliximab and r-ATG, either in head-to-head comparisons or in the network meta-analysis. The Committee concluded that basiliximab and r-ATG are effective induction therapies, but there was no evidence of a difference in clinical effectiveness between them.
- 4.60 The Committee discussed the findings of the clinical effectiveness analyses for the maintenance therapies. It noted that head-to-head comparisons suggested that calcineurin inhibitors (tacrolimus and ciclosporin) were associated with statistically significant reductions in acute rejection compared with belatacept, everolimus and sirolimus. It also noted that tacrolimus reduced the incidence of acute rejection compared with ciclosporin. The Committee noted that both belatacept and mycophenolate mofetil were associated with improved graft function compared with calcineurin inhibitors. The Committee noted that there were no consistent differences between immediate- and prolonged-release tacrolimus, or between mycophenolate mofetil and mycophenolate sodium. The Committee highlighted that the AG's network meta-analysis presented a systematic comparison of maintenance regimens across

4 outcomes (mortality, graft loss, acute rejection and graft function). It noted that all regimens except belatacept plus mycophenolate mofetil showed evidence of improvement in acute rejection compared with ciclosporin plus azathioprine. However, belatacept plus mycophenolate mofetil statistically significantly increased graft function compared with ciclosporin plus azathioprine. The Committee understood that there was substantial heterogeneity in the AG's network meta-analysis, and none of the maintenance regimens performed consistently well across all 4 outcomes. The Committee concluded that the maintenance therapies included in this appraisal are effective options for immunosuppression in adults having a kidney transplant, although limited conclusions on differences between these options can be drawn from the AG's network meta-analysis.

4.61 The Committee reviewed the economic models presented by the AG and 3 companies. It heard from the clinical experts that they considered the AG's model to be believable, reliable and to represent current practice. The Committee considered in particular the modelling of quality of life, kidney donor types and maintenance therapy dosing:

- The Committee noted that the AG modelled quality of life using fixed utility decrements for each health state, whereas Novartis assumed that quality of life would decrease as graft function decreased. The Committee heard from the clinical experts that people with kidney disease often have few symptoms until their kidney function (eGFR) reaches about 25 ml/min/1.73 m². Similarly, the patient experts reported good quality of life until they approached the end stages of kidney disease. The Committee understood that the Novartis model suggested that the cost-effectiveness results were very sensitive to the utility assumptions. It considered that Novartis's analyses implied that

the benefits had been underestimated for all treatments, and would be most underestimated for treatments with the largest beneficial effect on eGFR (such as belatacept plus mycophenolate mofetil and tacrolimus plus azathioprine).

- The Committee heard from the clinical experts that a major factor influencing graft survival is the type of organ donor and their age. The experts stated that kidney transplants from living donors have become more common in recent years, and are associated with longer graft survival than kidneys from deceased donors. The AG confirmed that its model included a mix of kidney donor types, and the Committee heard that the patterns of graft survival predicted by the model were consistent with the clinical experts' expectations.
- The Committee noted comments from consultees stating that the dosage of maintenance therapies used in clinical practice is often lower than is recommended in their marketing authorisations, and often decreases over time. It heard that the lower doses may be associated with a decrease in the incidence of new-onset diabetes. The AG stated that the model included a reduction in maintenance dosing over time, with the dosage stabilising after 1 to 3 years. The Committee highlighted that the maintenance therapy dosages and the clinical outcomes associated with them in the AG's model were based on clinical trials.

The Committee concluded that the AG's model provided a robust analysis of cost effectiveness and was the most informative model for decision-making.

4.62 The Committee understood that in clinical practice, some treatments may be considered particularly valuable for certain groups of people (see section 4.56). It therefore considered whether there was any clinical and cost-effectiveness evidence for

specific subgroups. The Committee noted that there were very little subgroup data for any of the interventions, and highlighted that the AG had not found enough evidence in its systematic review to inform robust subgroup analyses. The clinical experts acknowledged that there is limited evidence in this area. The Committee considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. Therefore the Committee concluded that it was unable to make recommendations for any of the interventions in specific subgroups.

- 4.63 The Committee understood that some treatments are associated with complications and so must be avoided or withdrawn for some people. In particular, calcineurin inhibitors are associated with nephrotoxicity, and the Committee heard from the clinical specialists that about 5% of people develop nephrotoxicity soon after transplant and more develop it over a longer period. In addition, a small number of people develop microangiopathic haemolytic anaemia during treatment with tacrolimus, ciclosporin, sirolimus or everolimus, and there are very few treatment options in this situation. The Committee recognised that there is a particular need for additional treatment options when these complications arise. However, it was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations. It further considered that microangiopathy is likely to be sufficiently rare that this complication could be effectively managed through individual funding requests. The Committee concluded that it was not able to make recommendations for people whose treatment needs to be withdrawn because of complications.

4.64 The Committee considered the effect of adherence on the clinical and cost effectiveness of immunosuppressive regimens. The Committee heard from patient experts that, although it took some adjustment, taking the medicines could be fitted into a daily routine. The patient experts described some people who may find adherence more difficult, such as people at university and those who need to take a lot of other medicines for concomitant conditions. The clinical experts also noted that it is the evening dose of tacrolimus that is most often missed. The clinical experts stated that once-daily dosing of tacrolimus (using the prolonged-release formulation) is likely to be helpful for some people, although there are others for whom it makes little difference. The Committee understood that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes, and that it would be difficult to identify people who would benefit. The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. It highlighted that this model was based on a single trial demonstrating the effect of once-daily tacrolimus on adherence, combined with a meta-analysis showing the effect of improved adherence on clinical outcomes. The Committee noted that the quality of the evidence informing this meta-analysis varied. The Committee also highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas's approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. Therefore the Committee considered that there were limitations in Astellas's analysis. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, it concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain.

Basiliximab

4.65 The Committee considered that basiliximab is a clinically effective treatment option. It noted that the AG's economic model showed that basiliximab dominated (that is, provides more QALYs at a lower cost than) both treatment without induction and r-ATG, when used in combination with either tacrolimus-based or ciclosporin-based maintenance regimens. Therefore the Committee concluded that basiliximab was cost effective and could be recommended as part of a calcineurin-inhibitor-based immunosuppressive regimen, as an option to prevent organ rejection in adults having a kidney transplant. The Committee was aware that treatment with basiliximab plus tacrolimus was outside the terms of the marketing authorisation, and noted the exceptional directive from the Department of Health for this appraisal regarding this situation. It was convinced that there was sufficient evidence to support this recommendation.

Rabbit anti-human thymocyte immunoglobulin

4.66 The Committee considered r-ATG to be a clinically effective induction therapy. It noted that in the AG's economic model, r-ATG was dominated by basiliximab and was associated with ICERs compared with treatment without induction of £63,200 to £333,000 per QALY gained. The Committee understood that the AG's model had assumed vials of r-ATG would be shared and there was no wastage of partially used vials. It heard from the clinical experts that this was unlikely, so considered that the costs of r-ATG had been underestimated. The Committee also heard from the clinical experts that r-ATG causes short-term side effects and so can be unpleasant to take. The Committee acknowledged that there may be some subgroups of people, such as people with high immunological risk or delayed graft function, for whom r-ATG may provide additional benefits. However, it considered that there was

not enough evidence to support recommendations in specific subgroups. Therefore the Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant.

Tacrolimus

- 4.67 The Committee heard from the clinical experts that tacrolimus is a potent immunosuppressive therapy, and noted that the immediate-release formulation was cost effective in all comparisons presented by the AG. Therefore the Committee concluded that immediate-release tacrolimus could be recommended as an option as part of an immunosuppressive regimen for preventing organ rejection in adults having a kidney transplant.
- 4.68 The Committee heard that there were no consistent statistically significant differences in clinical effectiveness between prolonged-release and immediate-release tacrolimus. It noted that prolonged-release tacrolimus was dominated by both immediate-release tacrolimus and ciclosporin in the AG's economic analyses. Therefore the Committee did not consider prolonged-release tacrolimus to be cost effective. The Committee noted that Astellas's submission stated that its formulation of prolonged-release tacrolimus (Advagraf) is available at a discount through a national tender, and discussed a scenario analysis presented by the AG using this discount. The discount and the results of the scenario analysis are commercial in confidence and so cannot be reported here. The Committee considered that this scenario did not affect its conclusion about the cost effectiveness of prolonged-release tacrolimus. Therefore the Committee concluded that prolonged-release tacrolimus is not a cost-effective use of NHS resources.

Belatacept

4.69 The Committee noted that belatacept was likely to be a clinically effective treatment, and in particular that belatacept plus mycophenolate mofetil increased graft function compared with ciclosporin plus azathioprine in the AG's network meta-analysis. It was also aware that belatacept may be an option for people with nephrotoxicity or microangiopathy. The Committee acknowledged that there may be some subgroups of people for whom belatacept may provide additional benefits, but considered that there was not enough evidence to support recommendations in specific subgroups. The Committee highlighted that belatacept was associated with ICERs ranging from £241,000 to £424,000 per QALY gained, compared with immediate-release tacrolimus, sirolimus and ciclosporin, and that these ICERs were substantially higher than the range normally considered cost effective. The Committee concluded that belatacept is not a cost-effective use of NHS resources.

Mycophenolic acid

4.70 The Committee noted that in the AG's economic analysis, mycophenolate mofetil dominated both sirolimus and azathioprine, and was less costly and less effective than mycophenolate sodium and everolimus; it noted that the ICERs for these comparisons were £144,000 and £1,530,000 per QALY lost respectively. The Committee considered that mycophenolate mofetil was a clinically effective option, and was cost effective in all the comparisons presented. The Committee concluded that mycophenolate mofetil was a cost-effective use of NHS resources and could be recommended as an option as part of an immunosuppressive regimen to prevent organ rejection in adults having a kidney transplant.

4.71 The Committee heard that there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium. It noted that mycophenolate sodium was associated with an ICER of £56,600 per QALY gained compared with azathioprine, and £144,000 per QALY gained compared with mycophenolate mofetil. The Committee concluded that mycophenolate sodium is not a cost-effective use of NHS resources.

Sirolimus

4.72 The Committee heard from the clinical experts that treatment with sirolimus can be difficult to manage in clinical practice, and may be associated with a range of adverse effects including peripheral oedema and bone marrow suppression. It also heard that anaemia may be more common with sirolimus and everolimus than with other immunosuppressive therapies (although the AG had assumed the rate would be equal across all regimens). The Committee noted that in the AG's base-case economic analyses, sirolimus was dominated by immediate-release tacrolimus and mycophenolate mofetil. The Committee considered that this suggested that sirolimus was not cost effective, and noted that the cost effectiveness of sirolimus would worsen if the incidence of anaemia increased. The Committee concluded that sirolimus is not a cost-effective use of NHS resources.

Everolimus

4.73 The Committee noted that the AG's economic model suggested that everolimus may be more effective than mycophenolate mofetil and azathioprine, although it was also associated with higher costs. The Committee noted that the ICERs were £1,530,000 and £383,000 per QALY gained respectively, and were well above the range normally considered cost effective. The Committee was also aware that anaemia may be more common with sirolimus and

everolimus than with other immunosuppressive therapies, and that this would worsen the cost effectiveness of everolimus in these comparisons. The Committee concluded that everolimus is not a cost-effective use of NHS resources.

Additional considerations

- 4.74 The Committee considered the bioequivalence of generic immunosuppressive therapies. It noted that calcineurin inhibitors have a narrow therapeutic index. It understood that the Commission on Human Medicines recommends that oral tacrolimus should be prescribed by brand name, and that care is needed when switching between drugs with a narrow therapeutic index. The Committee heard from the clinical experts that these concerns primarily apply to the drugs that are dosed based on plasma levels, such as tacrolimus, and that clinicians are aware of the risks associated with generic prescribing and switching formulations. The Committee understood that guidance on good practice in prescribing generic immunosuppressive therapies is routinely followed in clinical practice. The Committee also heard that clinicians are aware of cost differences between the different brands of immunosuppressive therapies, and take into account local-level costs in their prescribing decisions. The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the product with the lowest acquisition cost.
- 4.75 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising immunosuppressive therapies. The Committee noted NICE's position statement in this regard, and accepted the

conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was irrelevant for the consideration of cost effectiveness of immunosuppressive therapies for kidney transplant in adults.

4.76 The Committee noted the potential equality issue raised by consultees during scoping, in submissions and during the Committee meeting. It understood that some Jehovah’s Witnesses are unwilling to have human blood products, but noted that none of the recommended technologies are based on human blood products. The Committee understood that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and noted that a number of effective treatment options are available. The Committee also heard that mycophenolate mofetil cannot be taken by women who are pregnant and noted that alternative treatment options are available. The Committee concluded that no changes to the recommendations were needed to take account of equality issues.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as options to prevent organ rejection in adults having a kidney transplant.		1.1–1.3
<ul style="list-style-type: none"> The Committee considered that basiliximab is a clinically 		4.65

<p>effective treatment option, and provided more quality-adjusted life years (QALYs) at a lower cost than treatment without induction and rabbit anti-human thymocyte immunoglobulin (r-ATG).</p>	
<ul style="list-style-type: none"> The Committee heard that tacrolimus is a potent immunosuppressive therapy, and considered that immediate-release tacrolimus was cost effective. 	4.67
<ul style="list-style-type: none"> The Committee considered that mycophenolate mofetil was a clinically effective option, and was cost effective in all the comparisons presented. 	4.70
<p>r-ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended.</p>	1.4
<ul style="list-style-type: none"> The Committee considered that r-ATG was clinically effective, but concluded that it was not cost effective. 	4.66
<ul style="list-style-type: none"> The Committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. 	4.68
<ul style="list-style-type: none"> The Committee noted that belatacept was likely to be clinically effective, but was associated with incremental cost-effectiveness ratios (ICERs) substantially higher than the range normally considered cost effective. 	4.69
<ul style="list-style-type: none"> The Committee heard that there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium, and concluded that mycophenolate sodium was not cost effective. 	4.71
<ul style="list-style-type: none"> The Committee noted that sirolimus was not a cost-effective treatment option. 	4.72
<ul style="list-style-type: none"> The Committee noted the economic modelling suggested that everolimus may be more effective than mycophenolate 	4.73

mofetil and azathioprine, although it was not cost effective.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee understood that effective immunosuppressive therapies are important to prevent organ rejection in adults having kidney transplants.	4.55
	The Committee heard that the choice between immunosuppressive therapies is affected by a number of factors, including the characteristics and preferences of the person having treatment. The Committee understood the value of having a choice of immunosuppressive therapies.	4.56
The technologies		
Proposed benefits of the technologies How innovative are the technologies in their potential to make a significant and substantial impact on health-related benefits?	The Committee heard that the key priority for immunosuppressive therapy is to prolong graft survival for as long as possible, while minimising adverse effects. The clinical experts considered that both quality of life and survival are better with a functioning kidney transplant than with dialysis, and the patient experts emphasised the value of maintaining a functioning kidney transplant.	4.55
What are the positions of the	Immunosuppressive therapy can be categorised as induction therapy and	2.3

<p>treatments in the pathway of care for the condition?</p>	<p>maintenance therapy. Induction therapy is an intensive immunosuppression regimen that is used for up to 2 weeks around the time of transplant and may include polyclonal or monoclonal antibodies. Maintenance therapy starts immediately after transplant and continues for life.</p> <p>Basiliximab and r-ATG are options for induction therapy. Tacrolimus, belatacept, mycophenolate mofetil, mycophenolate sodium, sirolimus and everolimus are options for maintenance therapy.</p> <p>The Committee understood that in clinical practice, some treatments may be considered particularly valuable for certain groups of people.</p>	<p>–</p> <p>4.62</p>
<p>Adverse reactions</p>	<p>The AG summarised adverse event data focusing on 6 groups of adverse events: new-onset diabetes, malignancy, post-transplant lymphoproliferative disorders, infections, cytomegalovirus (CMV) infections and dyslipidaemia.</p> <p>The AG found evidence to suggest that r-ATG may be associated with an increase in CMV infections, and found a number of significant differences between maintenance treatments in the incidence of diabetes and CMV</p>	<p>4.16</p> <p>4.17, 4.18</p>

	<p>infections.</p> <p>The AG also found evidence to suggest that everolimus and sirolimus may be associated with an increased risk of dyslipidaemia and anaemia, and consultees stated that sirolimus and everolimus may have adverse effects on wound healing. The Committee heard that sirolimus may be associated with a range of adverse effects including peripheral oedema and bone marrow suppression.</p>	<p>4.19, 4.20, 4.72, 4.73</p>
Evidence for clinical effectiveness		
<p>Availability, nature and quality of evidence</p>	<p>The AG’s systematic review found 86 randomised controlled trials, including 11 studies of induction therapies, 73 studies of maintenance therapies and 2 studies examining both induction and maintenance therapies.</p> <p>The Committee noted that the AG’s systematic review was comprehensive and found a large number of randomised controlled trials. It concluded that all the relevant clinical effectiveness evidence had been taken into account.</p>	<p>4.1</p> <p>4.58</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The AG considered that only 11 trials adequately matched the population and current practice in the NHS in England.</p>	<p>4.1</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The AG’s network meta-analysis showed that basiliximab and r-ATG were significantly more effective than treatment without induction for acute rejection (odds ratios 0.52 and OR 0.36 respectively). The Committee concluded that basiliximab and r-ATG are effective induction therapies, but there was no evidence of a difference in clinical effectiveness between them.</p> <p>The AG’s network meta-analysis showed a number of statistically significant differences between regimens, although none of the maintenance regimens performed consistently well across all 4 outcomes assessed. The Committee saw that all regimens except 1 showed evidence of improvement in acute rejection compared with ciclosporin plus azathioprine, although this regimen significantly increased graft function. The Committee concluded that the maintenance therapies are effective options.</p>	<p>4.2–4.5, 4.59</p> <p>4.15, 4.60</p>
<p>How has the new clinical evidence that has emerged since the original appraisal (TA85) influenced the current (preliminary)</p>	<p>The AG’s systematic review found 86 randomised controlled trials, of which 23 were included in the original appraisal of immunosuppressive therapy for kidney transplantation in adults, and 63 were identified in the updated systematic review for the current appraisal. The</p>	<p>4.1, 4.58–4.60</p>

<p>recommendations?</p>	<p>Committee noted that the AG’s systematic review was comprehensive and found a large number of randomised controlled trials, and discussed the findings of the clinical effectiveness analyses for the induction and maintenance therapies.</p> <p>Since the original appraisal of immunosuppressive therapy for kidney transplantation in adults, the marketing authorisation for daclizumab has been withdrawn and 5 new technologies have received marketing authorisations.</p>	<p>2.4</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>Economic analyses were presented by the AG, Astellas, Bristol-Myers Squibb and Novartis.</p> <ul style="list-style-type: none"> • The AG presented an economic model based on a discrete-time state transition structure. • Astellas submitted a Markov model and presented results for each immunosuppressive drug compared with immediate-release tacrolimus. • Bristol-Myers Squibb 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 	<p>4.23</p> <p>4.24</p> <p>4.38, 4.39</p> <p>4.41</p>

	<p>Markov model.</p> <ul style="list-style-type: none"> Novartis presented a patient-level simulation model to capture the cost effectiveness of everolimus plus reduced-dose ciclosporin and mycophenolate sodium plus standard-dose ciclosporin, compared with mycophenolate mofetil plus standard-dose ciclosporin or tacrolimus. 	4.45
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that the AG and Novartis modelled quality of life differently. It understood that the Novartis model suggested that the cost-effectiveness results were very sensitive to the utility assumptions.</p> <p>The Committee concluded that the AG's model provided a robust analysis of cost effectiveness.</p>	4.61
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in</p>	<p>The Committee noted that the AG modelled quality of life using fixed utility decrements for each health state.</p> <p>The Committee noted that Novartis assumed that quality of life would decrease as graft function decreased. It considered that Novartis's analyses implied that the benefits had been underestimated for all treatments, and would be most underestimated for treatments with the largest beneficial</p>	4.61

<p>the economic model, and how have they been considered?</p>	<p>effect on graft function.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups.</p> <p>The Committee understood that some treatments are associated with complications and so must be avoided or withdrawn for some people. The Committee was conscious that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations.</p>	<p>4.62</p> <p>4.63</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The Committee understood that the cost-effectiveness results were very sensitive to the utility assumptions.</p> <p>The AG explored uncertainties in the model structure using 4 scenario analyses and a probabilistic sensitivity analysis. Scenario analyses explored the effect of the surrogate relationship between graft survival and clinical variables, possible nephrotoxicity</p>	<p>4.61</p> <p>4.35, 4.36</p>

	associated with calcineurin inhibitors, and the costs of treatment.	
Most likely cost-effectiveness estimate (given as an ICER)	<ul style="list-style-type: none"> • Basiliximab: dominated (provided more QALYs at a lower cost than) treatment without induction and r-ATG 	4.65
	<ul style="list-style-type: none"> • r-ATG: dominated by basiliximab and was associated with ICERs compared with treatment without induction of £63,200 to £333,000 per QALY gained. 	4.66
	<ul style="list-style-type: none"> • Immediate-release tacrolimus: dominated prolonged-release tacrolimus, sirolimus and ciclosporin (in 1 of 4 comparisons); less costly and less effective than belatacept and ciclosporin, with ICERs ranging from £131,035 to £388,740 per QALY lost. 	4.33
	<ul style="list-style-type: none"> • Prolonged-release tacrolimus was dominated by both immediate-release tacrolimus and ciclosporin. 	4.68
	<ul style="list-style-type: none"> • Belatacept was associated with ICERs of £241,000 to £424,000 per QALY gained, compared with immediate-release tacrolimus, sirolimus and ciclosporin. 	4.69
	<ul style="list-style-type: none"> • Mycophenolate mofetil dominated both sirolimus and azathioprine, and was less costly and less effective than mycophenolate sodium and everolimus with ICERs of £144,000 and £1,530,000 per QALY lost 	4.70

	<p>respectively.</p> <ul style="list-style-type: none"> • Mycophenolate sodium was associated with an ICER of £56,600 per QALY gained compared with azathioprine, and £144,000 per QALY gained compared with mycophenolate mofetil. • Sirolimus was dominated by mycophenolate mofetil and immediate-release tacrolimus. • Everolimus was associated with ICERs of £1,530,000 and £383,000 per QALY gained, compared with mycophenolate mofetil and azathioprine respectively. 	<p>4.71</p> <p>4.72</p> <p>4.73</p>
<p>How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA85) influenced the current (preliminary) recommendations?</p>	<p>Economic analyses were presented by the AG, Astellas, Bristol-Myers Squibb and Novartis. The AG's model was independent of that built for the appraisal of immunosuppressive therapy for renal transplantation in adults. The AG highlighted that the previous analysis had not fully accounted for uncertainty and had not taken into account the effect of kidney function on clinical and economic outcomes. Since the original appraisal, some of the technologies have become available generically.</p> <p>The Committee concluded that the AG's model provided a robust analysis of cost effectiveness and was the most</p>	<p>2.4, 4.23, 4.24</p> <p>4.61</p>

	informative model for decision-making.	
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	–
End-of-life considerations	Not applicable	–
Equalities considerations and social value judgements	<p>The Committee understood that some Jehovah’s Witnesses are unwilling to have human blood products, that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and that mycophenolate mofetil cannot be taken by women who are pregnant.</p> <p>The Committee concluded that no changes to the recommendations were needed to take account of equality issues.</p>	4.76

5 Implementation

5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient is having a kidney transplant and the doctor responsible for their care thinks that basiliximab, immediate-release tacrolimus and/or mycophenolate mofetil is the right treatment, these drugs should be available for use, in line with NICE’s recommendations.
- 5.4 NICE has developed tools [[link to www.nice.org.uk/guidance/TAXXX](#)] to help organisations put this guidance into practice (listed below). [**NICE to amend list as needed at time of publication**]
- Slides highlighting key messages for local discussion.
 - Costing template and report to estimate the national and local savings and costs associated with implementation.
 - Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
 - A costing statement explaining the resource impact of this guidance.
 - Audit support for monitoring local practice.

6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

Published

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

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, publication expected January 2016.

NICE pathways

- There is a NICE pathway on [chronic kidney disease](#).

7 Proposed date for review of guidance

- 7.1 NICE proposes that the guidance on these technologies is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technologies should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
July 2015

8 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Gary McVeigh (Chair)

Professor of Cardiovascular Medicine, Queen's University Belfast and
Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)

GP, West Coker Surgery, Somerset

Dr Andrew Black

GP, Mortimer Medical Practice, Herefordshire

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS Trust

Dr Matthew Bradley

Vice President, Value Evidence and Outcomes, GlaxoSmithKline

National Institute for Health and Care Excellence

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Appraisal consultation document – Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

Issue date: July 2015

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Mrs Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Mrs Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Dr Warren Linley

Independent Pharmacist and Health Economist

Dr Malcolm Oswald

Lay Member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ian Watson

Technical Lead

Sally Doss

Technical Adviser

Kate Moore

Project Manager

9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG):

- Jones-Hughes T, et al. Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85); a systematic review and economic model, March 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies:

- Astellas Pharma
- Bristol-Myers Squibb
- Novartis Pharmaceuticals
- Roche Products
- Sandoz
- Sanofi
- Teva

II. Professional/expert and patient/carer groups:

- British Kidney Patient Association
- Kidney Research UK
- National Kidney Federation
- British Association of Urological Surgeons
- British Renal Society
- British Transplantation Society
- ESPRIT
- Renal Association
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Intraparm Laboratories

- Novartis Pharmaceuticals
- Sandoz
- Teva
- National Institute for Health Research Health Technology Assessment Programme
- Peninsula Technology Assessment Group

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on immunosuppressive therapy for kidney transplantation in adults by attending the initial Committee discussion and/or providing a written statement to the Committee. They are invited to comment on the ACD.

- Professor Christopher Watson, Professor of Transplantation and Honorary Consultant Surgeon, nominated by Bristol-Myers Squibb – clinical expert
- Mr Colin Wilson, Consultant Transplant and Hepatobiliary Surgeon, nominated by Cochrane Renal Group – clinical expert
- Jason Clark, nominated by Kidney Research UK – patient expert
- Keith Pennington, nominated by the British Kidney Patient Association

D. Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Astellas
- Bristol-Myers Squibb
- Novartis
- Sandoz
- Sanofi
- Teva