

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Immunosuppressive therapy for kidney
transplant in children and young people
(review of technology appraisal guidance
99)**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using immunosuppressive regimens for kidney transplant in children and young people in the NHS in England. The interventions include basiliximab, rabbit anti-human thymocyte immunoglobulin, immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept. 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 basiliximab, rabbit anti-human thymocyte immunoglobulin, immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept 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: 27 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 children and young people 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 children and young people having a kidney transplant. Treatment should normally be started with the least expensive product. However, an alternative product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension. Modigraf (tacrolimus granules for oral suspension) should be used only when the company provides Modigraf at the contract price.
- 1.3 Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an option to prevent organ rejection in children and young people having a kidney transplant.^{2,3} Treatment should normally be started with the least expensive product. However, an alternative product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension.
- 1.4 Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and

belatacept are not recommended to prevent organ rejection in children and young people having a kidney transplant.

- 1.5 Children and young people 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. This decision should be made jointly by the clinician and the child or young person and/or their parents or carers.

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. Between April 2013 and March 2014, 127 kidney transplants were done in the UK for children and young people aged under 18 years.
- 2.2 Kidney transplant in children and young people can differ from adults in several important aspects including the cause of kidney failure, the metabolisation and pharmacokinetic properties of

immunosuppressive therapies, the immune response after transplant, the measures of success of the transplant procedure, the susceptibility to post-transplant complications, and the degree of adherence to treatment.

- 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 children and adolescents](#) was published in 2006. It recommended basiliximab, daclizumab, tacrolimus, mycophenolate mofetil and sirolimus, in certain circumstances, as options for immunosuppressive therapy for kidney transplant in children and young people. Some of the recommended treatments are now available as generic products, and the marketing authorisation for daclizumab has been withdrawn. Since the publication of the guidance, new technologies have obtained marketing authorisations (rabbit anti-human thymocyte immunoglobulin, belatacept, prolonged-release tacrolimus, everolimus and an oral suspension of immediate-release tacrolimus), but some of the marketing authorisations exclude children and young people.

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 people having a kidney transplant. The indication includes children and young people aged 1–17 years. 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 children and young people weighing less than 35 kg, the recommended total dose is 20 mg given in 2 doses of 10 mg each. In children and young people weighing 35 kg or more, the recommended dose is 40 mg given in 2 doses of 20 mg each.
- 3.3 The summary of product characteristics states that the following adverse reactions occur in at least 20% of children and young people treated with basiliximab: urinary tract infection, excessive hair growth, rhinitis (inflammation of the mucous membrane of the nose), fever, hypertension, upper respiratory tract infection, viral infection, sepsis and constipation. 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 price of £758.69 and £842.38, respectively (excluding VAT; British national formulary [BNF] online [accessed May 2015]), equating to £1517 per course of treatment for a patient weighing under 35 kg and £1685 for a patient weighing 35 kg or more.

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 does not state whether the indication includes children and young people. The summary of product characteristics states that 'currently available [paediatric] data are described in section 4.8 and 5.1 but no recommendation on a posology can be made. Available information indicates that paediatric patients do not require a different dosage than adult patients.' The summary of product characteristics states that r-ATG 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 price of £158.77 (excluding VAT; BNF online, accessed May 2015). The Assessment Group (AG) estimated that the cost of induction therapy with r-ATG for a 10-year-old boy is £2101 (assuming vials are shared so that there is no wastage).

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 drugs have marketing authorisations in the UK for the prophylaxis of transplant rejection in people having a kidney transplant. Adoport, Capexion, Perixis, Prograf, Tacni and Vivadex are administered orally as capsules twice a day. Prograf can also be administered intravenously. Modigraf consists of granules for oral suspension.
- 3.11 For all brands of immediate-release tacrolimus, the summary of product characteristics recommends an initial dose for children (age range not specified) of 0.3 mg/kg/day orally or 0.075–0.100 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 Modigraf is available in sachets of 0.2 mg and 1 mg at a price of £7.13 per mg (excluding VAT; BNF online [accessed May 2015]). Modigraf is available to the NHS at a discounted contract price that has been agreed until 30 April 2016. The level of discount is commercial in confidence, so cannot be reported here. The price of capsules varies by brand. The AG calculated that 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). The AG estimated that, from a hospital pharmacy, the weekly cost of maintenance therapy with immediate-release tacrolimus capsules for a 10-year-old boy is £34.

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 price of £1.07–£1.43 per mg (excluding VAT; BNF online [accessed May 2015]). The AG estimated that the weekly cost of maintenance therapy with prolonged-release tacrolimus for a 10-year-old boy is £47 (using the list price and the posology for adults). Advagraf is available to the NHS at a discounted contract price that has been agreed until 30 April 2016. The level of discount is commercial in confidence, so cannot be reported here.
- 3.17 Another brand of prolonged-release tacrolimus, Envarsus (Chiesi) obtained a marketing authorisation for adults 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 for the appraisal.

Belatacept

- 3.18 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.
- 3.19 Belatacept is administered intravenously. The recommended dose for adults is 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.

- 3.20 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.
- 3.21 Belatacept is available in 250 mg vials at a price of £354.52 (excluding VAT; BNF online [accessed May 2015]). The AG estimated that the weekly cost of maintenance therapy with belatacept for a 10-year-old boy is £56 (using the posology for adults and assuming vials are shared so that there is no wastage).

Mycophenolate mofetil

- 3.22 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. Mycophenolate mofetil can be administered orally (in capsules or an oral suspension) or intravenously. The summary of product characteristics states that the recommended daily dose for children and young people (aged 2–18 years) is 1200 mg/m² up to a maximum of 2 g per day. See the summary of product characteristics for dosage recommendations for patients with a body surface area below 1.5 m².
- 3.23 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. The summary of product characteristics states that adverse reactions in children are generally similar to those in adults, although the following are more frequent in children: sepsis, infection, leukopenia, anaemia and diarrhoea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 3.24 The price of mycophenolate mofetil varies by brand. The oral suspension of CellCept is available in 175 ml containers of 1 g/5 ml suspension at a price of £3.29 per g (excluding VAT; BNF online, accessed July 2015). The AG calculated that the average cost paid by the NHS for mycophenolate mofetil capsules is £0.38 per g (excluding VAT; data from eMIT, Commercial Medicines Unit). The AG estimated that, from a hospital pharmacy, the weekly cost of maintenance therapy with mycophenolate mofetil capsules for a 10-year-old boy is between £1.74 and £3.48.

Mycophenolate sodium

- 3.25 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 as a tablet, at a recommended dose for adults of 1.44 g per day.
- 3.26 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.

- 3.27 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 May 2015]). The AG estimated that the weekly cost of maintenance therapy with mycophenolate sodium for a 10-year-old boy is £50 (using the posology for adults).

Sirolimus

- 3.28 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.
- 3.29 Sirolimus is administered orally as a tablet or solution. The recommended dose for adults is 6 mg initially, followed by 2 mg per day then adjusted to obtain blood trough levels of 4–12 ng/ml.
- 3.30 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.
- 3.31 Sirolimus is available as 0.5 mg, 1 mg and 2 mg tablets and a 1 mg/ml oral solution, at a price of £2.71–£4.60 per mg (excluding VAT; BNF online [accessed May 2015]). The AG estimated that the

weekly cost of maintenance therapy with sirolimus for a 10-year-old boy is £40 (using the posology for adults).

Everolimus

- 3.32 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 as a tablet. The recommended initial dose for adults is 1.5 mg/day.
- 3.33 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.
- 3.34 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). The AG estimated that the weekly cost of maintenance therapy with everolimus for a 10-year-old boy is £104 (using the posology for adults).
- 3.35 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 included studies that recruited children and young people aged 0–18 years (inclusive) having a kidney transplant. It excluded studies of patients who had a transplant previously and were switching from 1 immunosuppressive regimen to another. The review addressed the population, interventions, comparators and outcomes specified in the scope. It included randomised controlled trials (RCTs) and non-randomised studies with a control group. In its original report, the AG searched directly for RCTs and systematic reviews only. It identified non-randomised studies from the bibliographies of systematic reviews. Before the first Committee meeting, the AG submitted an addendum presenting an additional search for non-randomised studies with a control group.

Quantity and quality of research

4.2 The AG's review found 3 RCTs of children and young people. Offner et al. (2008) compared basiliximab induction therapy (n=100) with placebo (n=92). Grenda et al. (2006) compared basiliximab induction therapy (n=99) against treatment without induction (n=93). Trompeter et al. (2002) compared maintenance therapy using either immediate-release tacrolimus (n=103) or ciclosporin (n=93).

- 4.3 The AG's additional search found 10 non-randomised studies of children and young people. Cransberg et al. (2008) compared basiliximab induction therapy against treatment without induction. Mosaad et al. (2012) compared a regimen of basiliximab induction therapy then maintenance therapy with immediate-release tacrolimus and mycophenolate mofetil, against a regimen of treatment without induction then maintenance therapy with ciclosporin and azathioprine. The remaining 8 studies compared maintenance regimens. Four studies compared mycophenolate mofetil with azathioprine (Antoniadis et al. 1998; Benfield et al. 1999; Chavers et al. 2009; Staskewitz et al. 2001). Hymes et al. (2011) compared sirolimus with immediate-release tacrolimus. Garcia et al. (2002) compared a regimen of immediate-release tacrolimus and azathioprine with a regimen of ciclosporin and mycophenolate mofetil. Two studies compared a regimen of immediate-release tacrolimus plus mycophenolate mofetil with a regimen of ciclosporin plus azathioprine (Delucchi et al. 2007; Valenzuela et al. 2008).
- 4.4 Compared with the previous assessment report in 2006, the present review found 1 new RCT of children and young people (Offner et al. 2008) and 6 new non-randomised studies of children and young people (Chavers et al. 2009; Cransberg et al. 2008; Delucchi et al. 2007; Hymes et al. 2011; Mosaad et al. 2012; Valenzuela et al. 2008).
- 4.5 The AG assessed the quality of the RCTs in children and young people. Offner et al. (2008) used an adequate method of randomisation and was double-blinded (meaning patients and care providers did not know which treatment patients received). The other 2 trials used an unclear method of randomisation and were not blinded. The AG advised that all 3 RCTs were likely to be generalisable to the NHS because the trials were done in Europe,

the patient and donor characteristics were largely representative of people using the NHS, and the drug doses were similar to current recommendations. However, the evidence is quite old (for example, Trompeter et al. began recruiting patients in 1996).

- 4.6 The AG assessed the quality of the non-randomised studies. Six studies did not report whether treatment groups were similar at baseline, while 4 reported statistically significant differences between groups at baseline (Chavers et al. 2009; Garcia et al. 2002; Staskewitz et al. 2001; Valenzuela et al. 2008). Nine studies could not be blinded because of the study design; the remaining study did not report whether blinding was used (Antoniadis et al. 1998). The AG advised that, for 7 studies, it was not clear if the results were generalisable to the NHS. For the remaining 3 studies, the donor characteristics were not representative of the NHS (Antoniadis et al. 1998; Mosaad et al. 2012; Staskewitz et al. 2001).

Assessment Group's network meta-analysis of RCTs in adults

- 4.7 There was a lack of evidence from children and young people, so some of the AG's economic analyses used estimates of effectiveness from a network meta-analysis of 86 RCTs in adults. The analyses of induction therapy compared each drug with a reference regimen of treatment without antibody induction. The analyses of maintenance therapy compared the effectiveness of immunosuppressive regimens rather than individual drugs; the reference regimen was ciclosporin and azathioprine.

Outcome measures

- 4.8 The AG's review focused on 3 key outcomes plus mortality.
- Graft function is measured by estimated glomerular filtration rate (eGFR), in which lower values indicate poorer function.
 - Acute rejection happens when the immune system identifies the transplanted kidney as foreign tissue and tries to destroy it.

When confirmed by a biopsy, it is known as biopsy-proven acute rejection (BPAR). The severity of acute rejection is graded using the Banff criteria (grades I–III, in which grade III indicates the most severe).

- Graft loss happens when the transplanted kidney stops working and the person needs long-term dialysis or a new transplant.

Evidence of clinical effectiveness: induction therapy

4.9 The review of studies in children and young people found 2 RCTs and 1 non-randomised study of basiliximab. One additional non-randomised study included rabbit anti-human thymocyte immunoglobulin (r-ATG; Chavers et al. 2009). However, because it was given to all patients, the effectiveness of r-ATG could not be assessed.

RCTs in children and young people

4.10 Two RCTs found no statistically significant difference between the basiliximab group and the no-induction group in mortality, incidence of graft loss, incidence of BPAR, and graft function (Grenda et al. 2006; Offner et al. 2008; table 1). The odds ratio for mortality was below 1 for Grenda et al. (indicating lower mortality with basiliximab) and above 1 for Offner et al., although the difference between groups was not statistically significant in either study. The odds ratio for graft loss was more favourable to basiliximab in Grenda et al. (0.50) than in Offner et al. (0.92). Regarding the severity of acute rejection, Offner et al. reported fewer severe BPAR (Banff grade IIA) in the basiliximab group than the placebo group (odds ratio [OR] 0.05, 95% confidence interval [CI] 0.003 to 0.87). The AG's meta-analysis of the 2 trials showed no statistically significant differences between treatment groups in graft loss, BPAR and graft function at 6 months.

Table 1. Results of RCTs of basiliximab in children and young people.

Outcome measure	Offner et al. (2008): 1-year follow-up			Grenda et al. (2006) : 2-year follow-up		
	Basiliximab	Placebo	Odds ratio (95% CI)	Basiliximab	No induction	Odds ratio (95% CI)
Mortality n/N, %	3/100, 3%	0/92, 0%	6.64 (0.34; 130.3)	0/99, 0%	1/93, 1%	0.33 (0.01; 8.20)
Graft loss n/N, %	1/100, 1%	1/92, 1%	0.92 (0.06; 14.9)	5/99, 5%	9/93, 10%	0.50 (0.16; 1.54)
BPAR n/N, %	13/100, 13%	21/92, 23%	0.51 (0.24; 1.08)	23/99, 23%	27/93, 29%	0.74 (0.39; 1.40)
Graft function mean eGFR (SD)	79 (23)	82 (24)	t test = -0.88, p=0.38	66.7 (NR)	65.8 (NR)	t test = 0.22, p=0.82
<p>Note: an odds ratio <1 means fewer events with basiliximab. Abbreviations: BPAR, biopsy proven acute rejection; CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m²); NR, not reported; SD, standard deviation.</p>						

4.11 For adverse events, Offner et al. (2008) reported more infections in the basiliximab group (95%) than the placebo group (90%; OR 2.23; 95% CI 1.03 to 4.68). Grenda et al. (2006) found that the incidence of kidney damage caused by a toxin (toxic nephropathy) was higher in the basiliximab group than the no-induction group (14.1% and 4.3% respectively; p=0.03); similarly, the incidence of abdominal pain was higher in the basiliximab group (11.1% and 2.2% respectively; p=0.02).

Non-randomised studies in children and young people

4.12 Cransberg et al. (2008) reported that, after 1-year follow-up, 21% (23/110) of patients who had basiliximab had experienced BPAR compared with 36% (44/123) of patients who had treatment without induction; this difference was statistically significant (OR 0.47; 95% CI 0.27 to 0.85). There were no statistically significant

differences between treatment groups in mortality, graft loss or graft function.

- 4.13 Sanofi's response to consultation on the assessment report identified 2 non-randomised studies of an anti-human thymocyte immunoglobulin in children and young people. Baron et al. (2008) compared 3 groups of patients treated with low-dose r-ATG, basiliximab or without induction. The AG advised that Baron et al. was excluded from its review because the clinicians chose which maintenance therapy to use for each patient. Vilalta et al. (2009) compared an anti-human thymocyte immunoglobulin with basiliximab; the AG excluded this study because it was not clear what type of anti-human thymocyte immunoglobulin was used.

RCTs in adults

- 4.14 The AG's network meta-analysis of induction therapy included 12 RCTs in adults with a follow-up time of 1 year. Both basiliximab and r-ATG were more effective than treatment without induction in reducing BPAR (table 2). There was no evidence that basiliximab and r-ATG were more effective than treatment without induction in reducing mortality, graft loss or graft function. There was no evidence that either treatment was more effective than the other (all credible intervals included zero).

Table 2. Results of the Assessment Group's network meta-analysis (fixed-effects model) of adult RCTs of induction therapy with a follow-up of 1 year.

Outcome	Basiliximab versus placebo/no induction	r-ATG versus placebo/no induction	r-ATG versus basiliximab
Mortality, OR (95% CrI)	0.99 (0.53 to 1.85)	0.84 (0.33 to 2.07)	0.84 (0.36 to 1.96)
Graft loss, OR (95% CrI)	0.82 (0.56 to 1.18)	0.77 (0.39 to 1.47)	0.94 (0.50 to 1.75)
BPAR, OR (95% CrI)	0.52 (0.41 to 0.65)	0.36 (0.24 to 0.54)	0.70 (0.47 to 1.03)
Graft function, mean eGFR (95% CrI)	2.11 (-0.45, 4.68)	-3.95 (-11.8, 3.94)	-6.06 (-13.5, 1.37)

Notes: an odds ratio <1 means fewer events with the first treatment in the comparison. Evidence suggesting a difference between treatments is in bold text. Abbreviations: BPAR, biopsy proven acute rejection; CrI, credible interval; OR, odds ratio; r-ATG, rabbit anti-human thymocyte immunoglobulin.

4.15 The AG did meta-analyses of adverse events in RCTs in adults with a follow-up of 1 year. The analyses assessed new-onset diabetes, post-transplant lymphoproliferative disorder, malignancy, infections and cytomegalovirus infections. There were no statistically significant differences between basiliximab and treatment without induction, or between basiliximab and r-ATG. A single study compared r-ATG against treatment without induction; it reported that there was no statistically significant difference in the incidence of new-onset diabetes but there were more incidences of cytomegalovirus infection with r-ATG (OR 2.11; 95% CI 1.26 to 3.52).

Evidence of clinical effectiveness: maintenance therapy

4.16 The AG's review of studies in children and young people found 1 RCT of immediate-release tacrolimus and 9 non-randomised studies of immediate-release tacrolimus, mycophenolate mofetil or sirolimus. The review did not find any studies (either randomised or

non-randomised) of prolonged-release tacrolimus, belatacept, mycophenolate sodium or everolimus in children and young people.

RCT in children and young people

4.17 Trompeter et al. (2002) reported that there were no statistically significant differences between the immediate-release tacrolimus group and the ciclosporin group for mortality and graft loss (table 3). Graft function was statistically significantly better in the immediate-release tacrolimus group than in the ciclosporin group. At 6-month follow-up, BPAR was experienced by fewer patients in the immediate-release tacrolimus group (17/94 patients, 18%) than the ciclosporin group (37/86 patients, 43%); the difference was statistically significant (OR 0.29; 95% CI 0.15 to 0.57).

Table 3. Results at 4-year follow-up for an RCT comparing immediate-release tacrolimus with ciclosporin in children and young people (Trompeter et al. 2002).

Outcome measure	Immediate-release tacrolimus	Ciclosporin	Odds ratio (95% CI)
Mortality n/N, %	5/103, 5%	4/93, 4%	1.14 (0.30; 4.36)
Graft loss n/N, %	9/103, 9%	17/93, 18%	0.43 (0.18; 1.01)
Graft function mean eGFR (SD) [N]	71.5 (22.9) [51]	53.0 (21.6) [44]	t-test=4.03; p<0.01
Note: an odds ratio <1 favours tacrolimus; evidence suggesting a difference between treatments is in bold text. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m ²); SD, standard deviation.			

4.18 Trompeter et al. (2002) found that the following adverse events were more common with tacrolimus than with ciclosporin: a deficiency of magnesium in the blood (34.0% compared with 12.9%; p=0.001) and diarrhoea (13.6% compared with 3.2%; p<0.05). However, the following events were less common with tacrolimus than with ciclosporin: excessive hair growth (0.0% compared with 7.5%; p<0.05), flu syndrome (0.0% compared with

5.4%; $p < 0.05$) and swollen gums (0.0% compared with 5.4%; $p < 0.05$).

Non-randomised studies in children and young people

- 4.19 Four non-randomised studies compared mycophenolate mofetil with azathioprine. Staskewitz et al. (2001) found that, 1 year after transplant, 2% (2/86) of patients in the mycophenolate mofetil group had experienced graft loss compared with 15% (8/54) of patients in the azathioprine group; the difference was statistically significant (OR 0.14; 95% CI 0.03 to 0.68). Chavers et al. (2009) reported that, 1 year after transplant, patients in the mycophenolate mofetil group were taller than patients in the azathioprine group. However, this difference between the groups was also present before transplant. Across all 4 studies, there were no further statistically significant differences between the mycophenolate mofetil and azathioprine groups.
- 4.20 Valenzuela et al. (2008) reported better graft function after 6 months with ciclosporin and azathioprine (mean eGFR 98 ml/min/1.73 m²) than with immediate-release tacrolimus and mycophenolate mofetil (mean eGFR 76 ml/min/1.73 m²); the difference between groups was statistically significant. Delucchi et al. (2007) compared the same regimens but did not find a statistically significant difference between groups for graft function. In both studies, there were no further significant differences between treatment groups.
- 4.21 The remaining non-randomised studies did not find any statistically significant differences between treatment groups (Garcia et al. 2002; Hymes et al. 2011; Mosaad et al. 2012).

RCTs in adults

- 4.22 The AG's network meta-analysis of maintenance therapies included 32–42 RCTs in adults, depending on the outcome measure. The

follow-up time was 1 year. None of the maintenance regimens performed consistently well on all outcomes. A regimen of ciclosporin and azathioprine was associated with poorer graft function, and higher risk of BPAR, than the other regimens (table 4). For all comparisons, there was a great deal of heterogeneity and the credible intervals were wide, indicating uncertainty in the results.

- 4.23 The network meta-analysis assumed that mycophenolate mofetil and mycophenolate sodium were the same drug. To supplement this analysis, the AG identified 2 RCTs in adults that compared mycophenolate mofetil with mycophenolate sodium. Ciancio et al. (2008) found that graft function was statistically significantly better in the mycophenolate sodium group at 6 months and at 1 year, but the difference was reversed at 3 years when graft function was better in the mycophenolate mofetil group. Salvadori et al. (2004) reported no statistically significant differences between treatment groups.
- 4.24 The network meta-analysis did not include prolonged-release tacrolimus, so the AG identified 4 RCTs in adults that compared immediate-release tacrolimus with prolonged-release tacrolimus. A meta-analysis showed no statistically significant differences between treatment groups for mortality, graft loss, graft function or BPAR.

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

Regimen	Odds ratios <i>Lower is better</i>			Mean difference in eGFR <i>Higher is better</i>
	Mortality	Graft loss	BPAR	
IR 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 mycophenolate mofetil	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)
IR tacrolimus and mycophenolate mofetil	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 mycophenolate mofetil	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)
IR 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 mycophenolate mofetil	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)
Abbreviations: BPAR, biopsy proven acute rejection; eGFR, estimated glomerular filtration rate (ml/min/1.73 m ²); IR, immediate release. Evidence suggesting a difference between treatments is in bold text.				

4.25 The AG did meta-analyses of adverse events in RCTs in adults with a follow-up of 1 year. Immediate-release tacrolimus and sirolimus increased the incidence of new-onset diabetes compared with ciclosporin, whereas belatacept reduced the incidence of new-onset diabetes. Sirolimus and everolimus both reduced the incidence of cytomegalovirus infection compared with ciclosporin and mycophenolate mofetil, respectively. Immediate-release

tacrolimus reduced the incidence of infection compared with sirolimus.

Cost effectiveness

Assessment Group's economic model

4.26 The AG presented 2 types of economic analysis.

- In the first analysis, a decision tree was used to model the expected costs and quality-adjusted life years (QALYs) accrued during an RCT of children and young people. Beyond that time point, costs and QALYs were extrapolated using a Markov model informed by data from RCTs of children and young people. This approach provided 2 analyses of basiliximab and 1 of tacrolimus.
- In the second analysis, only the Markov model was used to calculate expected costs and QALYs. The effectiveness estimates came from the network meta-analysis of RCTs in adults. This approach allowed the cost-effectiveness of all interventions to be assessed.

The AG advised that neither approach was preferred because both had limitations. The following paragraphs (sections 4.27 to 4.30) describe the aspects of modelling that were the same in both approaches.

4.27 The AG's analyses had a time horizon of 50 years and took the perspective of the NHS and personal social services. Costs and health effects were discounted at a rate of 3.5% per year. The model compared treatment regimens rather than individual drugs, because immunosuppressive therapies are used in combination and in sequence. The AG advised that the cost effectiveness of an individual drug can be assessed by comparing regimens that are identical except for the use of the intervention drug and the

comparator. The modelling assumed that the treatment effect of induction therapy was independent of the effect of maintenance therapy.

- 4.28 The modelled population was children and young people aged under 18 years having a kidney transplant. People who had a transplant some time before were excluded. The model calculated costs and QALYs separately for patients in each 1-year age group between 1 and 18 years, then calculated weighted-average costs and QALYs based on the age distribution of kidney transplant recipients in the UK. For many drugs, dosing is based on weight or body surface area. In the base case, patients' weight followed the median curve for children and young people in the UK. A scenario analysis used the 9th centile curve because young people with kidney transplants may have impaired growth. Body surface area was calculated based on weight.
- 4.29 The model estimated the resources used for immunosuppression treatment (including drug acquisition, drug administration and regular outpatient visits) and for managing a failed transplant (including dialysis, dialysis-access surgery, explant surgery and re-transplantation). The model also estimated the resources used to treat the following adverse events: cytomegalovirus infection, anaemia, dyslipidaemia and new-onset diabetes. Dosages were based on RCTs of children and young people when possible. For belatacept, the AG assumed that partially-used vials were not shared between patients. In contrast, for r-ATG it assumed that vials were shared and there was no wastage; this may underestimate the costs of r-ATG.
- 4.30 The AG advised that immunosuppressive therapies are usually prescribed in hospital. It took drug costs from the Electronic Market Information Tool (eMIT; Commercial Medicines Unit) when possible, because this represents the prices paid by NHS hospitals.

For drugs not included in eMIT, list prices were taken from the BNF or from company submissions. The AG's main analyses used the list price for Advagraf (prolonged-release tacrolimus) and its supplementary analysis used the nationally available contract price. For immediate-release tacrolimus, the AG used the cost of capsules and did not assess Modigraf separately. For procedures, costs were taken from NHS reference costs when available.

Assessment Group's decision tree

- 4.31 For each of the 3 RCTs in children and young people, a decision tree was used to calculate the following outcomes for each treatment over the duration of the trial: costs, time with a functioning graft, time on dialysis, and QALYs. In addition, the trial results (such as the probability of BPAR and new-onset diabetes within 12 months, and graft function at 12 months) were used to inform the Markov model. The discounted costs and QALYs from the decision tree and the Markov model were summed to estimate the total discounted costs and QALYs over a 50-year time horizon.
- 4.32 For each decision tree, the characteristics of the modelled population matched the participants in the RCT of children and young people. For all 3 trials, the mean patient age was between 10 and 11 years and approximately 60% were male. The decision trees included the costs of some adverse events that were not in the Markov model (post-transplant lymphoproliferative disorder, hypomagnesaemia and hypertension). The utility values for the decision trees were the same as for the Markov model (see section 4.40).

Assessment Group's Markov model

- 4.33 The Markov model used a cycle length of 3 months and included a half-cycle correction. The model had 3 main states: functioning graft, graft loss and death. The states were further defined by

whether it was the patient's first, second, third or fourth transplant. At the start of the model, most patients were in the first functioning graft state. The remaining patients were in the first graft loss state because their transplant never worked (known as 'primary non-function'). From the functioning graft state, patients moved to the graft loss state if the transplanted kidney stopped functioning; these patients had dialysis. From the graft loss state, patients who had a further transplant moved to either a functioning graft state or, if they had primary non-function, a subsequent graft loss state. Patients whose first graft started to fail could have a second transplant before starting dialysis – this is called 'pre-emptive re-transplantation' and was only possible from the first functioning graft state. Death could occur from any state.

- 4.34 In the base case, the modelled population was aged 10 years and 60% were male. The AG chose to model 18 regimens, which were selected because they were either currently used in the NHS or could plausibly be used in the NHS and sufficient clinical evidence was available. All maintenance regimens included corticosteroids.
- 4.35 The time in each health state was determined by the rate of 3 events: mortality, graft loss and re-transplantation. The rate of re-transplantation was the same for all regimens and was calculated from the UK Transplant Registry. The underlying rates of mortality and graft loss were derived from registry data (the UK Transplant Registry and UK Renal Registry) and adjusted to reflect the characteristics of the modelled population. The rates of mortality and graft loss were further adjusted to reflect the effectiveness of each regimen, as described in sections 4.36 and 4.37.
- 4.36 In the AG's model, death could occur from the functioning graft state or the graft loss state.

- For the first 12 months, the rate of death with functioning graft was calculated using regimen-specific odds ratios from the network meta-analysis. After 12 months with the first graft, a surrogate relationship was used to predict the rate of death with functioning graft, based on age, time since transplant and the regimen-specific incidence of new-onset diabetes. For subsequent grafts, the surrogate relationship was based only on age and new-onset diabetes.
- The rate of death from the graft loss state (that is, the rate of death while having dialysis) was estimated using data from the UK Renal Registry, adjusted for age. This rate was the same for all regimens.

4.37 Graft loss was modelled separately for the first graft and subsequent grafts.

- For the first graft, the rate of graft loss over the first 12 months was calculated using regimen-specific odds ratios from the network meta-analysis. For later time points, a surrogate relationship was used to predict the rate of graft loss based on: time since transplant, a regimen-specific estimate of graft function, and the regimen-specific incidence of BPAR and new-onset diabetes. A sensitivity analysis removed BPAR from the list of variables used to predict graft loss.
- For subsequent grafts, the rate of graft loss was based on an exponential distribution fitted to data from the UK Transplant Registry. This rate was the same for all regimens.

4.38 The model included 4 adverse events: anaemia, new-onset diabetes, cytomegalovirus infection and dyslipidaemia. The incidence of anaemia was the same for all regimens. For the other adverse events, the regimen-specific incidence was based on a

network meta-analysis of RCTs in adults. All adverse events incurred costs but only new-onset diabetes had a utility decrement.

- 4.39 The network meta-analysis did not include mycophenolate sodium. Clinical effectiveness estimates and adverse event rates for mycophenolate sodium were taken from the mycophenolate mofetil group in the network meta-analyses and adjusted using head-to-head comparisons between mycophenolate mofetil and mycophenolate sodium. Similarly, for prolonged-release tacrolimus the AG adjusted the results for immediate-release tacrolimus using head-to-head comparisons.
- 4.40 The AG did not find any studies of the health-related quality of life of children and young people with a kidney transplant, so data from adults were used instead. The average EQ-5D utility value for the general population was calculated and adjusted to reflect the age and sex of the modelled population (Health Survey for England, 2002). The AG then applied utility decrements for each health state. The functioning graft state had a utility decrement of 0.053, based on a published meta-analysis of EQ-5D data for adults with a kidney transplant. The same meta-analysis was used to calculate the decrements associated with haemodialysis (0.277) and peritoneal dialysis (0.264), which were applied to the graft loss state. The proportion of patients receiving each type of dialysis depended on age. New-onset diabetes was associated with a decrement of 0.06, based on EQ-5D values from a US study.

Results of the Assessment Group's modelling using data from RCTs of children and young people

- 4.41 The model that used data from the RCT of Grenda et al. (2006) showed that treatment with basiliximab dominated treatment without induction. 'Dominated' means that basiliximab was less costly and more effective than treatment without induction

(incremental costs –£5697, incremental QALYs 0.18; see table 5). The cost difference arose because treatment with basiliximab resulted in lower predicted expenditure on dialysis after the end of the trial. A probabilistic sensitivity analysis showed that, with a threshold of £20,000 per QALY gained, basiliximab was predicted to be cost effective in 67% of simulations.

- 4.42 In contrast, the model that used data from Offner et al. (2008) showed that treatment without induction dominated treatment with basiliximab (incremental costs –£8528, incremental QALYs 0.55; see table 5). The cost difference arose because induction therapy with basiliximab cost more and also led to higher predicted expenditure on dialysis after the end of the trial. The total QALYs were slightly lower for basiliximab because it had poorer patient survival and graft survival. A probabilistic sensitivity analysis showed that, with a threshold of £20,000 per QALY gained, basiliximab was predicted to be cost effective in 10% of simulations.
- 4.43 The model based on Trompeter et al. (2002) showed that treatment with immediate-release tacrolimus dominated treatment with ciclosporin (incremental costs –£44,543, incremental QALYs 0.55; see table 5). The cost difference arose because tacrolimus was associated with lower expenditure on dialysis, both during the trial and afterwards. A probabilistic sensitivity analysis showed that, with a threshold of £20,000 per QALY gained, tacrolimus was predicted to be cost effective in 100% of simulations.

Table 5. Results of the Assessment Group’s model using data from RCTs of children and young people (deterministic analysis).

Regimen	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incr.	Total	Incr.	
<i>Grenda et al. (2006) – all patients had tacrolimus and azathioprine</i>					
No induction	£141,012	-	17.49	-	-
Basiliximab	£135,315	-£5697	17.67	0.18	Dominant
<i>Offner et al. (2008) – all patients had ciclosporin and mycophenolate mofetil</i>					
Basiliximab	£135,212	-	17.83	-	-
Placebo	£126,684	-£8528	18.38	0.55	Dominant
<i>Trompeter et al. (2002) – all patients had azathioprine</i>					
Ciclosporin	£221,489	-	16.17	-	-
Immediate-release tacrolimus	£176,946	-£44,543	16.72	0.55	Dominant
Regimens are sorted in order of ascending total QALYs. The incremental values were calculated by the NICE technical team. ‘Dominant’ means treatment with the intervention cost less and was more effective than treatment with the comparator. Abbreviations: Incr, incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.					

4.44 For all 3 analyses using data from children and young people, the probabilistic results were similar to the deterministic results. The AG did one-way sensitivity analyses assuming that patients had below-average body weight and, separately, removing BPAR from the variables used to predict graft loss. The results of the sensitivity analyses were similar to the base case.

Results of the Assessment Group’s modelling using adult data: induction treatments

4.45 The AG compared basiliximab, r-ATG and treatment without induction in 4 analyses, each with a different maintenance regimen (table 6). In all analyses treatment without induction dominated r-ATG (incremental costs between -£6017 and -£9918; incremental QALYs between 0.03 and 0.06). Basiliximab dominated both r-ATG and treatment without induction (compared

with no induction, incremental costs between –£9053 and –£11,055; incremental QALYs between 0.12 and 0.13).

- 4.46 The results of probabilistic analyses were similar to those of deterministic analyses. A probabilistic sensitivity analysis showed that, with a threshold of £20,000 per QALY gained, basiliximab was predicted to be cost effective in approximately 92% of simulations compared with about 7% for r-ATG. The results of one-way sensitivity analyses were similar to the base case.

Table 6. Assessment Group’s cost-effectiveness results for induction treatments, using effectiveness estimates from adult RCTs (deterministic analysis).

Induction drug	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
<i>Regimens with ciclosporin and azathioprine</i>					
r-ATG	£216,114	—	17.97	—	—
No induction	£210,097	-£6017	18.00	0.03	Dominates r-ATG
Basiliximab	£199,042	-£11,055	18.13	0.13	Dominates r-ATG and no induction
<i>Regimens with ciclosporin and mycophenolate mofetil</i>					
r-ATG	£209,097	—	18.07	—	—
No induction	£199,910	-£9188	18.13	0.06	Dominates r-ATG
Basiliximab	£190,856	-£9053	18.25	0.12	Dominates r-ATG and no induction
<i>Regimens with tacrolimus and azathioprine</i>					
r-ATG	£183,191	—	18.25	—	—
No induction	£174,989	-£8202	18.30	0.05	Dominates r-ATG
Basiliximab	£164,316	-£10,673	18.43	0.13	Dominates r-ATG and no induction
<i>Regimens with tacrolimus and mycophenolate mofetil</i>					
r-ATG	£189,637	—	18.18	—	—
No induction	£179,719	-£9918	18.24	0.06	Dominates r-ATG
Basiliximab	£170,182	-£9537	18.36	0.12	Dominates r-ATG and no induction
Regimens are sorted in order of ascending total QALYs. ‘Dominates’ means treatment with the intervention cost less and was more effective than treatment with the comparator. Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin.					

Results of the Assessment Group’s modelling using adult data: maintenance treatments

4.47 The maintenance regimens all resulted in similar total discounted QALYs (table 7 and table 8), so the incremental QALY gain was under 0.3 for all comparisons. The results for each intervention were as follows:

- **Immediate-release tacrolimus** dominated treatment with ciclosporin, prolonged-release tacrolimus and sirolimus in all regimens. The cost savings associated with immediate-release

tacrolimus were at least £19,460 compared with ciclosporin and £28,449 compared with sirolimus. The cost savings compared with prolonged-release tacrolimus are confidential and cannot be reported here.

- **Prolonged-release tacrolimus** (using the contract price) dominated ciclosporin. However, prolonged-release tacrolimus was dominated by immediate-release tacrolimus (incremental QALYs -0.05; the incremental costs are confidential and cannot be reported here).
- **Belatacept** had an incremental cost-effectiveness ratio (ICER) of £533,449 per QALY gained compared with immediate-release tacrolimus.
- **Mycophenolate mofetil** dominated azathioprine when it was used in a regimen containing ciclosporin (incremental costs between -£7017 and -£10,188; incremental QALYs between 0.10 and 0.12). However, mycophenolate mofetil was dominated by azathioprine when it was used in a regimen containing tacrolimus (incremental costs between £4730 and £6446; incremental QALYs between -0.06 and -0.07).
- **Mycophenolate sodium** dominated azathioprine, but had an ICER of £51,770 per QALY gained compared with mycophenolate mofetil.
- **Sirolimus** was dominated by ciclosporin, immediate-release tacrolimus, azathioprine and mycophenolate mofetil. The incremental cost of sirolimus was £7775 compared with ciclosporin, £28,449 compared with immediate-release tacrolimus, £47,311 compared with azathioprine and £42,581 compared with mycophenolate mofetil.
- **Everolimus** had an ICER of £632,246 per QALY gained compared with mycophenolate mofetil.

- 4.48 The AG advised that, at a threshold of £20,000 or £30,000 per QALY gained, the only cost-effective interventions were immediate-release tacrolimus and mycophenolate mofetil, provided mycophenolate mofetil was used with ciclosporin.
- 4.49 The results of probabilistic analyses were similar to those of deterministic analyses. An exception was mycophenolate sodium: compared with mycophenolate mofetil, the probabilistic ICER was £130,080 per QALY gained and the deterministic ICER was £51,770 per QALY gained.
- 4.50 The AG did one-way sensitivity analyses assuming that patients had below-average body weight and, separately, removing BPAR from the variables used to predict graft loss. For most maintenance treatments, the results of the sensitivity analyses were similar to the base case. For mycophenolate sodium, the ICER compared with mycophenolate mofetil reduced to £27,006 per QALY gained in the lower body weight scenario and to £33,157 per QALY gained in the scenario without BPAR as a predictor of graft loss.

Table 7. Assessment Group’s deterministic cost-effectiveness results for the following maintenance treatments: immediate-release tacrolimus, prolonged-release tacrolimus, sirolimus and belatacept. The analysis used effectiveness estimates from adult RCTs.

Maintenance treatment	Discounted total costs	Discounted total QALYs	ICER (cost per QALY)
<i>Regimens with mycophenolate mofetil</i>			
Ciclosporin	£199,910	18.13	—
PR tacrolimus (at contract price)	Confidential	18.19	Dominates ciclosporin
IR tacrolimus	£179,719	18.24	Dominates ciclosporin and PR tacrolimus
<i>Regimens with azathioprine</i>			
Ciclosporin	£210,097	18.00	—
IR tacrolimus	£174,989	18.30	Dominates ciclosporin
<i>Regimens with basiliximab and mycophenolate mofetil</i>			
Sirolimus	£198,631	18.24	—
Ciclosporin	£190,856	18.25	Dominates sirolimus
IR tacrolimus	£170,182	18.36	Dominates sirolimus and ciclosporin
Belatacept	£293,175	18.59	£533,449 compared with IR tacrolimus
<i>Regimens with basiliximab and azathioprine</i>			
Ciclosporin	£199,042	18.13	—
IR tacrolimus	£164,316	18.43	Dominates ciclosporin
<i>Regimens with r-ATG and mycophenolate mofetil</i>			
Ciclosporin	£209,097	18.07	—
IR tacrolimus	£189,637	18.18	Dominates ciclosporin
<i>Regimens with r-ATG and azathioprine</i>			
Ciclosporin	£216,114	17.97	—
IR tacrolimus	£183,191	18.25	Dominates ciclosporin
Regimens are sorted in order of ascending total QALYs. ‘Dominates’ means treatment with the intervention cost less and was more effective than treatment with the comparator. Abbreviations: ICER, incremental cost-effectiveness ratio; IR, immediate-release; PR, prolonged-release; QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin.			

Table 8. Assessment Group’s deterministic cost-effectiveness results for the following maintenance treatments: mycophenolate mofetil, mycophenolate sodium, everolimus and sirolimus. The analysis used effectiveness estimates from adult RCTs.

Maintenance treatment	Discounted total costs	Discounted total QALYs	ICER (cost per QALY)
<i>Regimens with ciclosporin</i>			
Azathioprine	£210,097	18.00	—
Myc. mofetil	£199,910	18.13	Dominates azathioprine
Everolimus	£259,327	18.22	£632,246 compared with myc. mofetil
<i>Regimens with immediate-release tacrolimus</i>			
Sirolimus	£222,300	17.96	—
Myc. mofetil	£179,719	18.24	Dominates sirolimus
Azathioprine	£174,989	18.30	Dominates both sirolimus and myc.mofetil
<i>Regimens with basiliximab and ciclosporin</i>			
Azathioprine	£199,042	18.13	—
Myc. mofetil	£190,856	18.25	Dominates azathioprine
Myc. sodium	£198,303	18.39	£51,770 compared with myc. mofetil
<i>Regimens with basiliximab and immediate-release tacrolimus</i>			
Myc. mofetil	£170,182	18.36	—
Azathioprine	£164,316	18.43	Dominates myc. mofetil
<i>Regimens with r-ATG and ciclosporin</i>			
Azathioprine	£216,114	17.97	—
Myc. mofetil	£209,097	18.07	Dominates azathioprine
<i>Regimens with r-ATG and immediate-release tacrolimus</i>			
Myc. mofetil	£189,637	18.18	—
Azathioprine	£183,191	18.25	Dominates myc. mofetil
Regimens are sorted in order of ascending total QALYs. ‘Dominates’ means treatment with the intervention cost less and was more effective than treatment with the comparator. Abbreviations: ICER, incremental cost-effectiveness ratio; IR, immediate-release; Myc, mycophenolate; PR, prolonged-release QALY, quality-adjusted life year; r-ATG, rabbit anti-human thymocyte immunoglobulin.			

Astellas' economic model

- 4.51 Astellas submitted a Markov model that compared a subset of the maintenance therapies in the scope. Patients entered the model aged 8 years and the time horizon was 10 years. Astellas used effectiveness estimates from adult studies. It assumed that adherence to treatment was better with prolonged-release tacrolimus than with immediate-release tacrolimus (based on data from Kuypers et al. 2013) and that this improved graft survival. The utility values were based on EQ-5D data from UK adults. Drug costs were from the BNF.
- 4.52 Astellas presented the results as pairwise comparisons with Prograf (a brand of immediate-release tacrolimus capsules).
- Prograf dominated belatacept, everolimus and sirolimus (when sirolimus was used in a regimen without calcineurin inhibitors).
 - Prolonged-release tacrolimus dominated Prograf.
 - All preparations of immediate-release tacrolimus were assumed to have similar effectiveness but Modigraf was the most expensive.
 - Prograf had an ICER of over £1.5 million per QALY gained compared with sirolimus (when sirolimus was used in a regimen that minimised the use of calcineurin inhibitors).
- 4.53 The AG advised that the Astellas model omitted ciclosporin as a comparator so the results may be misleading. The AG's model showed that prolonged-release tacrolimus (at the contract price) was more costly and less effective than immediate-release tacrolimus, whereas the Astellas model showed that prolonged-release tacrolimus (at list price) was cheaper and more effective than Prograf. There are several possible reasons for the difference in results:

- The models used different time horizons, utility values and clinical trial data.
- Astellas used the list price for immediate-release tacrolimus, whereas the AG used the eMIT price.
- In the Astellas model adherence was better with prolonged-release tacrolimus and this was assumed to improve graft survival. In contrast, the AG's model did not include a surrogate relationship linking adherence to longer-term outcomes.

Consideration of the evidence

The appraisal included 9 drugs for immunosuppression after kidney transplant in children and young people. 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 immunosuppression after kidney transplant and the value placed on the benefits of immunosuppressive therapy by people with a kidney transplant, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.54 The Committee discussed aspects of immunosuppression that are especially important for children and young people. It heard from clinical experts that quality of life is better with a transplant than while having dialysis, so the aim of immunosuppression treatment is to prolong survival of the transplanted kidney (or 'graft'). The Committee also heard that it is important to minimise the side effects of immunosuppressive therapies, such as reduced growth and an increased risk of new-onset diabetes. Several submissions from consultees advised that poor adherence (that is, not taking the prescribed medication) is a major cause of graft loss, especially in

young people. The Committee heard that different people have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The Committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.

4.55 The Committee discussed the immunosuppressive regimens currently used in the NHS for children and young people with a kidney transplant. The clinical experts advised that most paediatric transplant centres use:

- induction without antibodies then maintenance therapy with tacrolimus and azathioprine (based on Trompeter et al. 2002); **or**
- basiliximab induction then maintenance therapy with tacrolimus and mycophenolate mofetil (based on the TWIST trial, Grenda et al. 2010).

The Committee was aware that there are several brands of oral tacrolimus, and that inadvertent switching between products has been associated with toxicity and graft rejection. It heard from clinical experts that, to minimise the risk of accidental switching, UK clinicians follow advice from the [Medicines and Healthcare Products Regulatory Agency](#) to prescribe and dispense oral tacrolimus products by brand name. It heard from clinical experts that, for the same reason, brand names were used when prescribing ciclosporin. The Committee concluded that the immunosuppressive regimens most commonly used by children and young people in the UK were: induction without antibodies then maintenance therapy with tacrolimus and azathioprine; or basiliximab induction then maintenance therapy with tacrolimus and mycophenolate mofetil.

4.56 The Committee discussed the decision problem addressed by the assessment report. For induction therapy, the Committee agreed

that it was appropriate to compare the interventions with each other and against treatment without induction. For maintenance therapy, the Committee agreed that it was appropriate to compare the interventions with each other and against ciclosporin and azathioprine. A clinical expert suggested that the appraisal should also consider alemtuzumab as an induction therapy. The Committee was aware that alemtuzumab was not included in the final scope because it does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and it is not routinely available for transplant patients (it is available on a 'named patient' basis). It heard from clinical experts that alemtuzumab is not currently used for children and young people having a kidney transplant in the UK. The Committee agreed that alemtuzumab should not be included as either an intervention or a comparator. Regarding the population for the appraisal, the Committee agreed with the AG that there were insufficient data to permit analyses of subgroups such as children and young people with different levels of immunological risk. The Committee concluded that the assessment report included the appropriate population, interventions and comparators.

Clinical effectiveness

4.57 The Committee considered the results of the AG's systematic review, noting that it found few studies of children and young people. The clinical experts advised that, given the lack of evidence for children and young people, NHS practice is informed by evidence from adults and by clinical experience. The AG stated that data from the UK Transplant Registry provides useful information on graft and patient survival, but cannot be used to compare the effectiveness of different treatments. The Committee concluded that it should consider all of the evidence about the effectiveness of immunosuppressive regimens, including randomised and non-

randomised studies in children and young people and RCTs in adults.

4.58 The Committee discussed whether it had considered all of the relevant evidence. Consultees and clinical experts advised that it was important to consider TWIST, an international RCT that recruited patients aged 2–18 years having a kidney transplant (Grenda et al. 2010). Patients randomised to the TWIST regimen (daclizumab, immediate-release tacrolimus and mycophenolate mofetil, with steroids that are withdrawn after 4 days) showed greater height gain after 6 months than patients randomised to the comparator regimen (no induction, immediate-release tacrolimus and mycophenolate mofetil with long-term steroids). The Committee noted that the UK marketing authorisation for daclizumab has been withdrawn, so daclizumab was not included in the appraisal and consequently TWIST was not included in the assessment report. The Committee heard from clinical experts that basiliximab and daclizumab have the same mechanism of action (both are interleukin-2 receptor antagonists) and adult trials show that they have similar effectiveness. The Committee acknowledged that patients and clinicians view a reduction in the side effects of steroids as an important aim of treatment. The Committee concluded that it was appropriate to consider TWIST when making its recommendations.

4.59 The Committee discussed the evidence for the clinical effectiveness of basiliximab. Three studies showed that basiliximab reduced acute rejection compared against treatment without induction (Cransberg et al. 2008; Offner et al. 2008 and the network meta-analysis of RCTs in adults). The Committee acknowledged that, in 2 RCTs of children and young people, most outcome measures did not differ significantly between basiliximab and treatment without induction (Offner et al. 2008; Grenda et al. 2006).

However, it noted that these trials may have been statistically underpowered to detect differences in graft loss and mortality. The Committee was aware that TWIST showed increased height gain in children and young people treated with a regimen that included an interleukin-2 receptor antagonist. The Committee heard from clinical experts that basiliximab is currently used by several NHS paediatric transplant centres and is well tolerated by patients. The marketing authorisation for basiliximab states that it should be used in combination with ciclosporin. However, the Committee noted that NHS transplant centres often use basiliximab plus tacrolimus and that this combination was used in 2 RCTs of children and young people (TWIST and Grenda *et al.* 2006). Taking all of the evidence into account, the Committee concluded that basiliximab, plus either ciclosporin or tacrolimus, is clinically effective in children and young people.

- 4.60 The Committee discussed the evidence for the clinical effectiveness of r-ATG, noting that the AG did not find any studies of children and young people that compared r-ATG with the comparators in the scope. Sanofi's response to the assessment report consultation identified 2 non-randomised studies of children and young people that compared r-ATG with basiliximab or treatment without induction. These studies were excluded from the AG's review (see section 4.13). The Committee noted that Sanofi did not provide numerical results or detailed information about study design. The Committee noted that the network meta-analysis of RCTs in adults showed that r-ATG reduces acute rejection compared against treatment without induction. It heard from clinical experts that the treatment regimen with r-ATG is longer and more complex than with basiliximab, and that adults having r-ATG experience more adverse events (including post-transplant lymphoproliferative disorder) than those having basiliximab. The Committee noted that it had not been presented with evidence

about adverse events in children and young people. The Committee heard from clinical experts that it was very rare for children and young people in the UK to have r-ATG. Overall, the Committee concluded that there was not enough evidence to establish whether r-ATG is clinically effective in children and young people.

4.61 The Committee discussed the evidence for the clinical effectiveness of immediate-release tacrolimus. It noted that an RCT of children and young people (Trompeter et al. 2002), and the network meta-analysis of RCTs in adults, showed better graft function and lower incidence of acute rejection with immediate-release tacrolimus than with ciclosporin. The Committee was aware that in Trompeter et al. (2002) tacrolimus was used with azathioprine, whereas TWIST used tacrolimus with mycophenolate mofetil. It heard from clinical experts that both of these regimens are currently used by NHS paediatric transplant centres and both are usually well tolerated by patients. The Committee concluded that immediate-release tacrolimus is clinically effective in children and young people.

4.62 The Committee discussed the evidence for the clinical effectiveness of prolonged-release tacrolimus, noting that the AG did not find any studies of children and young people that compared prolonged-release tacrolimus with the comparators in the scope. The submission from Astellas referred to non-randomised studies in children and young people, but these studies were excluded from the AG's review. The Committee noted that Astellas did not provide numerical results or detailed information about study design. Astellas advised that additional studies were ongoing but it was not known when they would finish. The Committee noted that the AG's meta-analysis of RCTs in adults found no significant differences between prolonged-release and immediate-release

tacrolimus for mortality, graft loss, graft function and acute rejection. The Committee also noted that the summary of product characteristics states that 'the safety and efficacy of Advagraf [prolonged-release tacrolimus] in children under 18 years of age have not yet been established'. The Committee concluded that there was not enough evidence to establish whether prolonged-release tacrolimus is clinically effective in children and young people.

- 4.63 The Committee considered whether prolonged-release tacrolimus could improve adherence to treatment. Patient experts advised that taking several tablets at set times each day was challenging, especially for young people who do not have a fixed daily routine, and regimens with fewer tablets may improve adherence. The Committee acknowledged the importance of adherence to treatment in children and young people, and it was aware that poor adherence can cause graft loss. The Committee referred to the Astellas submission for the related [adult appraisal](#), which included adult studies suggesting that once-daily prolonged-release tacrolimus improves adherence, and may reduce graft loss, compared with twice-daily immediate-release tacrolimus. The Committee was concerned that most of these studies measured self-reported adherence, which may be less accurate than electronic monitoring. The Committee agreed that there was no robust evidence showing that improved adherence leads to lower rates of mortality, graft loss and acute rejection. It noted that switching from immediate-release to prolonged-release tacrolimus would remove only 1 tablet a day, and it was uncertain whether this would substantially improve adherence to the overall immunosuppressive regimen. The Committee heard from a clinical expert that, if a person forgot to take their prolonged-release tacrolimus tablet, this would leave them without tacrolimus for 24 hours. The expert advised that, potentially, this could have a

greater impact than missing a tablet of immediate-release tacrolimus and being without the drug for 12 hours. The Committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people.

4.64 The Committee discussed the evidence for the clinical effectiveness of mycophenolate mofetil. It noted that a non-randomised study in children and young people found lower rates of graft loss with mycophenolate mofetil than with azathioprine (Staskewitz et al. 2001), but 3 other studies did not replicate this result. It noted that the network meta-analysis of RCTs in adults showed a lower incidence of acute rejection with mycophenolate mofetil than with azathioprine. The Committee also noted that the TWIST regimen included mycophenolate mofetil. It heard from clinical experts that mycophenolate mofetil is currently used by several NHS paediatric transplant centres and is well tolerated by patients. The marketing authorisation for mycophenolate mofetil states that it should be used in combination with ciclosporin. However, the Committee noted that NHS transplant centres often use mycophenolate mofetil plus tacrolimus and that this combination was used in the TWIST trial. The Committee concluded that mycophenolate mofetil is clinically effective in children and young people.

4.65 The Committee discussed the evidence for the clinical effectiveness of sirolimus. The only evidence in children and young people in the AG's review was a non-randomised study that did not find any significant differences between sirolimus and immediate-release tacrolimus (Hymes et al. 2011). NICE guidance on [immunosuppressive therapy for kidney transplantation in children and adolescents](#) did not recommend sirolimus except when a proven intolerance to calcineurin inhibitors (including

nephrotoxicity) necessitates the complete withdrawal of these treatments. During the present appraisal, none of the submissions and none of the experts provided evidence that sirolimus would be clinically effective for children and young people who cannot tolerate calcineurin inhibitors. Clinical experts advised that some adults having sirolimus experience adverse events, and the Committee noted that it had not been presented with data about adverse events in children and young people. The Committee referred to the summary of product characteristics, which states that 'the safety and efficacy of Rapamune [sirolimus] in children and adolescents less than 18 years of age have not been established'. The committee heard from a clinical expert that, by adjusting the dose of mycophenolate mofetil, it may be possible to reduce or even stop calcineurin inhibitors for patients who cannot tolerate them. The Committee considered that this strategy provided a treatment option for children and young people who cannot tolerate calcineurin inhibitors. Overall, the Committee concluded that there was not enough evidence to establish whether sirolimus is clinically effective in children and young people.

- 4.66 The Committee discussed the evidence for the clinical effectiveness of mycophenolate sodium, everolimus and belatacept, noting that the AG's review did not identify any studies of these technologies for children and young people. For all 3 drugs, the summary of product characteristics states that safety and efficacy in children and young people has not been established. The Committee concluded that there was not enough evidence to establish whether mycophenolate sodium, everolimus and belatacept were clinically effective in children and young people.

Cost effectiveness

- 4.67 The Committee noted that the AG's model included 2 types of analysis: using effectiveness estimates from RCTs of children and young people and using effectiveness estimates from a network meta-analysis of RCTs in adults. Given the limited number of clinical trials in children and young people, the Committee agreed that it was reasonable to consider the results of both analyses. Similarly, given the lack of data on the health-related quality of life of children and young people with a kidney transplant, the Committee agreed that it was reasonable to use utility values estimated from adults. The Committee concluded that the AG's model provided a suitable basis for decision-making.
- 4.68 The Committee discussed the economic model submitted by Astellas. It noted that the analysis did not follow the NICE scope (because it excluded ciclosporin as a comparator) and did not follow the NICE reference case (because it did not present incremental analyses and it used list prices for drugs that are in eMIT). The Astellas analysis also did not include effectiveness estimates from studies in children and young people. The Astellas model assumed that prolonged-release tacrolimus improved adherence to treatment, which the Committee had decided was not an appropriate assumption (see section 4.63). The Committee concluded that it preferred to use the AG's model as the basis for its recommendations.
- 4.69 The Committee noted Novartis' comments on the assessment report, advising that quality of life decreases as graft function declines. Novartis asked the AG to amend its model so that quality of life depends on graft function. The Committee had discussed this issue in the related appraisal for adults. The Committee agreed that the AG's model may underestimate total QALYs for all treatments, because in the model quality of life is independent of graft function.

The Committee considered that the QALY underestimate would be greatest for treatments with the largest beneficial effect on graft function (such as belatacept with mycophenolate mofetil and tacrolimus with azathioprine), but that amending the model in the way suggested by Novartis was unlikely to substantially alter the ICERs. The Committee concluded that it was not necessary to amend the AG's model.

- 4.70 The Committee discussed the drug costs used in the AG's model and agreed that it was appropriate to use prices from eMIT, if available, because these reflect the prices paid by the NHS (see NICE's [guide to the methods of technology appraisal](#) section 5.5.2). The Committee agreed that it was appropriate to consider the contract prices for Advagraf and Modigraf when making its recommendations, because these prices are nationally available. It noted that the contract prices were guaranteed for only a limited time, so it chose a proposed review date of the guidance (see section 7) based on this time period. The Committee concluded that its preferred analysis used eMIT prices when available and the contract prices for Modigraf and Advagraf.
- 4.71 The Committee discussed the cost-effectiveness evidence for basiliximab, noting that all analyses assessed basiliximab in combination with a calcineurin inhibitor. The AG's model based on Grenda et al. (2006), and the model using data from adults, showed that treatment with basiliximab was cheaper and more effective than treatment without induction. For these 2 analyses, the incremental costs were between -£5700 and -£11,100 and the incremental QALYs were between 0.12 and 0.18. However, the analysis based on Offner et al. (2008) gave the opposite result (treatment without induction cost £8530 less and gained 0.55 more QALYs than basiliximab). The Committee noted that the discrepancy may have arisen because the odds ratio for graft loss

was more favourable to basiliximab in Grenda et al. than in Offner et al. (see table 1). The Committee accepted that the Offner et al. trial was probably underpowered to detect differences in mortality and graft loss, meaning that the estimates of treatment effect were uncertain. It also recalled that the TWIST trial demonstrated the effectiveness of a regimen including an interleukin-2 receptor antagonist, but the TWIST data were not included in the modelling. On balance, the Committee accepted the results of the AG's analyses using Grenda et al. (2006) and the adult data, and concluded that basiliximab in combination with a calcineurin inhibitor was a cost-effective use of NHS resources.

4.72 The Committee discussed the cost-effectiveness evidence for r-ATG. The AG's model using data from adults showed that treatment with r-ATG was dominated by treatment without induction (incremental costs between £6020 and £9920; incremental QALYs between -0.03 and -0.06). The model assumed that vials were shared so that there was no wastage, but the Committee heard from clinical experts that vial sharing was unlikely to happen in practice. The Committee noted that the modelled costs of r-ATG would increase if wastage was included. Based on the evidence presented, the Committee concluded that r-ATG could not be considered a cost-effective use of NHS resources.

4.73 The Committee discussed the cost-effectiveness evidence for immediate-release tacrolimus. The AG's model using data from Trompeter et al. (2002), and the model using data from adults, showed that treatment with immediate-release tacrolimus was cheaper and more effective than treatment with ciclosporin. For these 2 analyses, the incremental costs were between -£19,500 and -£44,500; the incremental QALYs were between 0.11 and 0.55. The AG's model using data from adults also showed that treatment with immediate-release tacrolimus was cheaper and

more effective than prolonged-release tacrolimus and sirolimus.

The Committee concluded that immediate-release tacrolimus was a cost-effective use of NHS resources and that treatment should normally be started with the least expensive product.

4.74 The Committee discussed the cost-effectiveness evidence for prolonged-release tacrolimus. The AG's model using data from adults, and including the contract price for Advagraf, showed that treatment with prolonged-release tacrolimus was dominated by treatment with immediate-release tacrolimus (the incremental costs are confidential, the incremental QALYs were -0.05). Astellas' response to the assessment report consultation stated that adherence to treatment was better with prolonged-release tacrolimus and that this benefit was not included in the AG's model. The Committee accepted that adherence to treatment was important for children and young people, and it was plausible that a regimen with fewer tablets could improve adherence. However, the Committee agreed that it had not been presented with robust data to show better adherence with prolonged-release tacrolimus (see section 4.63) and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model. Even taking into account the contract price, the Committee concluded that prolonged-release tacrolimus could not be considered a cost-effective use of NHS resources.

4.75 The Committee discussed the cost-effectiveness evidence for mycophenolate mofetil. The AG's model using data from adults showed that, in regimens that included ciclosporin, treatment with mycophenolate mofetil was cheaper and more effective than treatment with azathioprine (incremental costs between -£7020 and -£10,200; incremental QALYs between 0.10 and 0.12). However, in regimens that include immediate-release tacrolimus, treatment with azathioprine was cheaper and more effective than

treatment with mycophenolate mofetil (incremental costs between £4730 and £6450; incremental QALYs between -0.06 and -0.07). The Committee noted that, in the regimens that included tacrolimus, there was only a small difference in QALYs gained between mycophenolate mofetil and azathioprine. It also noted that TWIST demonstrated the effectiveness of mycophenolate mofetil plus tacrolimus, but these data were not included in the model. The Committee accepted that patients and clinicians preferred to have a choice of treatments, and the use of mycophenolate mofetil with tacrolimus was well established in the NHS. Taking all of the evidence into account, the Committee concluded that mycophenolate mofetil was a cost-effective use of NHS resources and that treatment should normally be started with the least expensive product.

4.76 The Committee discussed the cost-effectiveness evidence for mycophenolate sodium, everolimus, sirolimus and belatacept, noting that the AG's analyses used data from adults because no data from children and young people were available. It noted that, compared with mycophenolate mofetil, the ICER for mycophenolate sodium was £51,800 per QALY gained and the ICER for everolimus was £632,000 per QALY gained. Sirolimus was dominated by ciclosporin, immediate-release tacrolimus, azathioprine and mycophenolate mofetil. Belatacept had an ICER of £533,000 per QALY gained compared with immediate-release tacrolimus. The Committee concluded that mycophenolate sodium, everolimus, sirolimus and belatacept could not be considered a cost-effective use of NHS resources.

4.77 The Committee discussed the provision of immunosuppressive therapy for children and young people who cannot swallow tablets. It heard from clinical experts that young children, and some children and young people with disabilities, cannot swallow tablets

and need oral suspensions instead. The Committee noted that oral suspensions are available for immediate-release tacrolimus (Modigraf) and mycophenolate mofetil (CellCept), and that these products have a marketing authorisation in the UK. The suspensions are more expensive than capsules (see sections 3.13 and 3.24). The Committee was aware that there is a nationally available contract price for Modigraf (see section 3.13). The Committee agreed that it would be unfair if people who cannot swallow capsules were not able to have immediate-release tacrolimus and mycophenolate mofetil because these treatments were clinically effective in children and young people. It noted that restricting access in this way might discriminate against young children, or against children and young people with disabilities. The Committee had concluded that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. It further concluded that an alternative product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension. The Committee agreed that Modigraf should be used only when the company provides Modigraf at the contract price.

- 4.78 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 for kidney transplant. 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 of immunosuppressive

therapies for kidney transplant. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of cost effectiveness of immunosuppressive therapies for kidney transplant.

- 4.79 The Committee agreed that basiliximab, immediate-release tacrolimus and mycophenolate mofetil were clinically effective and cost effective as part of immunosuppressive therapy for kidney transplant in children and young people. Accordingly, basiliximab, immediate-release tacrolimus and mycophenolate mofetil were recommended as options for use in the NHS. The Committee agreed that it had not been presented with robust evidence that the following drugs were clinically effective and cost effective, and therefore they were not recommended for use in the NHS: r-ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept.

Summary of Appraisal Committee’s key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		

<p>Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as options to prevent organ rejection in children and young people having a kidney transplant.</p>	<p>1.1–3</p>
<ul style="list-style-type: none"> • The Committee concluded that basiliximab is clinically effective, and provided more quality-adjusted life years (QALYs) at a lower cost than treatment without induction. 	<p>4.59, 4.71</p>
<ul style="list-style-type: none"> • The Committee concluded that immediate-release tacrolimus is clinically effective and provided more QALYs at a lower cost than ciclosporin. 	<p>4.61, 4.73</p>
<ul style="list-style-type: none"> • The Committee concluded that mycophenolate mofetil is clinically effective and it is cost effective in regimens that included ciclosporin. Although there was uncertainty about cost effectiveness in regimens that included tacrolimus, the Committee was prepared to accept that mycophenolate mofetil was cost effective in both regimens. 	<p>4.64, 4.75</p>
<p>Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended.</p>	<p>1.4</p>
<ul style="list-style-type: none"> • The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people. 	<p>4.60, 4.62, 4.65, 4.66</p>
<ul style="list-style-type: none"> • Using effectiveness estimates from adults, these drugs were either dominated or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained. 	<p>4.72, 4.74, 4.76</p>
<p>Current practice</p>	

Clinical need of patients, including the availability of alternative treatments	People have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The Committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.	4.54
	The immunosuppressive regimens most commonly used by children and young people in the UK are: induction without antibodies then maintenance therapy with tacrolimus and azathioprine; or basiliximab induction therapy then maintenance therapy using tacrolimus and mycophenolate mofetil.	4.55
The technology		

Adverse reactions	Clinical experts advised that adults having r-ATG experience more adverse events than those having basiliximab. The Committee was not presented with evidence about adverse events associated with r-ATG in children and young people.	4.60
	Clinical experts advised that some adults having sirolimus experience adverse events. The Committee was not presented with data about adverse events associated with sirolimus in children and young people.	4.65
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Assessment Group (AG)'s systematic review found few studies of children and young people. The Committee concluded that it should consider all of the evidence, including randomised and non-randomised studies in children and young people, and RCTs in adults.	4.57
	Consultees and clinical experts advised that it was important to consider TWIST, an RCT that assessed the effectiveness of daclizumab induction then maintenance with immediate-release tacrolimus and mycophenolate mofetil, with steroids that are withdrawn after 4 days. TWIST was not in the AG's review	4.58

	<p>because daclizumab is not part of the appraisal (its marketing authorisation has been withdrawn). The Committee heard from clinical experts that basiliximab and daclizumab have the same mechanism of action and have similar effectiveness. The Committee concluded that it was appropriate to consider TWIST when making its recommendations.</p>	
<p>Relevance to general clinical practice in the NHS</p>	<p>The 3 RCTs in children and young people were likely to be generalisable to the NHS because the trials were done in Europe, the patient and donor characteristics were largely representative of people using the NHS, and the drug doses were similar to current recommendations. However, the evidence is quite old.</p>	<p>4.5</p>
<p>Uncertainties generated by the evidence</p>	<p>The AG did not find any studies of children and young people comparing the following drugs with the comparators in the scope: r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus and belatacept. Only 1 small study of children and young people assessed sirolimus. Consequently, the Committee was uncertain whether these drugs were clinically effective in children and young people.</p>	<p>4.60, 4.62, 4.65, 4.66</p>

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>There were insufficient data to permit analyses of subgroups.</p>	<p>4.56</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Three studies showed that basiliximab reduced acute rejection compared with no induction. Also, TWIST showed increased height gain in children and young people who had a steroid-sparing regimen that included an interleukin-2 receptor antagonist.</p> <p>Immediate-release tacrolimus improved graft function and reduced the incidence of acute rejection compared with ciclosporin.</p> <p>A non-randomised study of children and young people found lower rates of graft loss with mycophenolate mofetil than with azathioprine. The network meta-analysis of adult RCTs showed a lower incidence of acute rejection with mycophenolate mofetil than with azathioprine.</p>	<p>4.59</p> <p>4.61</p> <p>4.64</p>

<p>How has the new clinical evidence that has emerged since the original appraisal (TA99) influenced the current (preliminary) recommendations?</p>	<p>For children and young people, the new evidence includes the TWIST RCT, the Offner et al. RCT, and 6 non-randomised studies. There are also several new RCTs in adults.</p> <p>TWIST and Offner et al. showed that an interleukin-2 receptor antagonist (such as basiliximab) is clinically effective. The preliminary recommendation of basiliximab is consistent with previous NICE guidance on immunosuppressive therapy for kidney transplantation in children and adolescents.</p> <p>A non-randomised study of children and young people, and RCTs in adults, suggest that mycophenolate mofetil is clinically effective. In previous NICE guidance on immunosuppressive therapy for kidney transplantation in children and young people, mycophenolate mofetil was recommended only for restricted groups of patients.</p>	<p>4.4, 4.58</p> <p>4.59</p> <p>4.64</p>
<p>Evidence for cost effectiveness</p>		

<p>Availability and nature of evidence</p>	<p>The AG’s analyses used effectiveness estimates from RCTs of children and young people and, separately, from adult RCTs. The Committee agreed that it was reasonable to consider both analyses.</p> <p>The model submitted by Astellas did not follow the NICE scope and NICE reference case, nor did it include effectiveness estimates from children and young people. The Committee preferred to use the AG’s model.</p>	<p>4.67</p> <p>4.68</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Offner et al. trial was probably underpowered to detect differences in mortality and graft loss, meaning that the estimates of treatment effect were uncertain.</p> <p>Astellas stated that adherence to treatment was better with prolonged-release tacrolimus but this benefit was not included in the AG’s model. The Committee agreed that it had not been presented with robust data to show better adherence and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model.</p>	<p>4.71</p> <p>4.74</p> <p>4.63</p>

<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 the economic model, and how have they been considered?</p>	<p>Given the lack of data on the health-related quality of life of children and young people with a kidney transplant, the Committee agreed that it was reasonable to use utility values from adults.</p> <p>No significant and substantial health-related benefits have been identified that were not included in the economic model.</p>	<p>4.67</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>There were insufficient data to permit analyses of subgroups.</p>	<p>4.56</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>There were no specific Committee considerations on the key drivers of cost effectiveness. The Committee was aware that, in the AG's model, the differences between treatments in total costs were mainly due to differences in time having dialysis.</p>	<p>4.41–3</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<ul style="list-style-type: none"> • Basiliximab was cheaper and more effective than treatment without induction (incremental costs between -£5700 and -£11,100; incremental QALYs between 0.12 and 0.18). 	4.71
	<ul style="list-style-type: none"> • Immediate-release tacrolimus was cheaper and more effective than ciclosporin (incremental costs between -£19,500 and -£44,500; incremental QALYs between 0.11 and 0.55). 	4.73
	<ul style="list-style-type: none"> • In regimens that included ciclosporin, mycophenolate mofetil was cheaper and more effective than azathioprine (incremental costs between -£7020 and -£10,200; incremental QALYs between 0.10 and 0.12). 	4.75
	<ul style="list-style-type: none"> • r-ATG was dominated by treatment without induction. 	4.72
	<ul style="list-style-type: none"> • Prolonged-release tacrolimus was dominated by immediate-release tacrolimus. 	4.74
	<ul style="list-style-type: none"> • Compared with mycophenolate mofetil, the ICER for mycophenolate sodium was £51,800 per QALY gained and the ICER for everolimus was £632,000 per QALY gained. 	4.76
	<ul style="list-style-type: none"> • Sirolimus was dominated by all comparators. 	4.76
	<ul style="list-style-type: none"> • Belatacept had an ICER of £533,000 per QALY gained compared with immediate-release tacrolimus. 	4.76

<p>How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA99) influenced the current (preliminary) recommendations?</p>	<p>The AG’s review did not find any published cost-effectiveness evidence that had emerged since previous NICE guidance on immunosuppressive therapy for kidney transplantation in children and young people. Since the original appraisal, some of the technologies have become available generically. The AG developed a new model informed by the systematic review of clinical evidence.</p>	<p>4.67</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>None. Astellas advised that there are nationally available discounted contract prices for Modigraf (tacrolimus granules for oral suspension) and Advagraf (prolonged-release tacrolimus).</p>	<p>3.13, 3.16</p>
<p>End-of-life considerations</p>	<p>Not applicable.</p>	

<p>Equalities considerations and social value judgements</p>	<p>The Committee noted the potential equality issue raised by consultees for the related adult appraisal, that some Jehovah’s Witnesses are unwilling to be treated with human blood products. The Committee noted that none of the recommended technologies are based on human blood products.</p> <p>The Committee agreed that it would be unfair if children and young people who cannot swallow capsules were not able to have immediate-release tacrolimus and mycophenolate mofetil because these treatments were clinically effective. It noted that restricting access in this way might be discriminatory. The Committee had concluded that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. It further concluded that an alternative product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension.</p>	<p align="center">4.77</p>
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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 child or young person 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 The NHS procures Modigraf at a confidential discounted contract price agreed through a national tender with Astellas Pharma. The contract price is agreed until April 2016. [NICE to add details at time of publication]
- 5.5 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 kidney transplantation in adults \(review of technology appraisal guidance 85\)](#). NICE technology appraisal, publication expected November 2015.

NICE pathways

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

7 Proposed date for review of guidance

7.1 NICE proposes that recommendation 1.2 is considered for review by the Guidance Executive in April 2016. This date reflects the period for which the contract price for Modigraf has been guaranteed. NICE proposes that the remaining recommendations are considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on the proposed dates. 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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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.

Dr Rosie Lovett

Technical Lead

Dr 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 the Peninsula Technology Assessment Group (PenTAG):

- Haasova M, et al. Immunosuppressive therapy for kidney transplantation in children and young people (review of technology appraisal 99); a systematic review and economic model, April 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
- British Association of Paediatric Nephrology
- ESPRIT
- Royal College of Paediatric and Child Health
- 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
- Novartis Pharmaceuticals
- Sandoz
- Teva
- Cochrane Renal Group

- 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 transplant in children and young people by attending the initial Committee discussion and/or providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Paul Harden, Consultant Nephrologist and Transplant Physician, nominated by Royal College of Physicians – clinical expert
- Dr David Milford, Consultant Paediatric Nephrologist, nominated by British Association of Paediatric Nephrology – clinical expert
- Michael Beswick, nominated by British Kidney Patient Association – patient expert
- Sarah-Louise Harwood, nominated by the Kidney Research UK – patient expert

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 Pharma
- Novartis
- Sanofi