NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99)

This premeeting briefing is a summary of:

- the evidence and views submitted by the companies, the consultees and their nominated clinical experts and patient experts and
- the assessment report and
- the responses to consultation on the assessment report.

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

Key issues for consideration

Clinical effectiveness

- The assessment report included:
  - 2 paediatric randomised controlled trials (RCTs), and 1 paediatric non-randomised study, that compared basiliximab with no induction or placebo;
  - 1 paediatric RCT that compared immediate-release tacrolimus with ciclosporin;
  - 4 paediatric non-randomised studies that compared mycophenolate mofetil with azathioprine;
  - 1 paediatric non-randomised study that compared sirolimus with immediate-release tacrolimus.

  Are basiliximab, immediate-release tacrolimus, mycophenolate mofetil and sirolimus clinically effective in children and adolescents?

- The assessment report did not include any paediatric comparative studies (either randomised or non-randomised) of rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, belatacept, mycophenolate sodium and everolimus. Evidence from RCTs in adults is presented in the assessment report for the parallel appraisal of immunosuppressive therapy in adults (ID 456). Is the adult evidence generalisable to children and adolescents?
- Under an exceptional directive from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their marketing authorisation, where there is compelling evidence of their safety and effectiveness. Is such evidence available for the following drugs which do not have a marketing authorisation for children and adolescents?
  - Prolonged-release tacrolimus
  - Belatacept
  - Mycophenolate sodium
  - Sirolimus
  - Everolimus

  Note that it is not clear if the marketing authorisation for r-ATG includes children (see section 2.5).
- Some children and adolescents do not take their prescribed dose of immunosuppressants (that is, they have poor adherence) and this may increase the risk of graft loss. The submission from Astellas stated that prolonged-release tacrolimus may improve adherence compared with immediate-release tacrolimus, because the former drug has a simpler and less frequent dosing schedule. Is there evidence that prolonged-release tacrolimus is associated with improved adherence, and improved outcomes, in children and adolescents?

Cost effectiveness

- The Assessment Group presented 2 types of economic analysis. The first used effectiveness estimates from paediatric randomised trials but, because of a lack of trial data, only assessed the cost effectiveness of basiliximab and tacrolimus. The second analysis used effectiveness estimates from adult trials, allowing the cost-

effectiveness of all interventions to be assessed. Does the Committee have a preferred approach?

- The results regarding basiliximab were contradictory. The Assessment Group's model based on the paediatric trial of Grenda et al. (2006), and the model using data from adults, showed that basiliximab dominated no induction (meaning basiliximab cost less and was more effective). In contrast, the model based on the paediatric trial of Offner et al. (2008) showed that basiliximab was dominated by placebo. Which of these analyses is most representative of the cost-effectiveness of basiliximab?
- The Assessment Group's model using data from adults showed that, in regimens that include ciclosporin, mycophenolate mofetil dominated azathioprine. Conversely, in regimens that include tacrolimus, mycophenolate mofetil was dominated by azathioprine. What is the Committee's view of the cost-effectiveness of mycophenolate mofetil?
- Using data from adults, the Assessment Group's model showed that prolonged-release tacrolimus was dominated by immediate-release tacrolimus. Astellas also used data from adults but obtained the opposite result: prolonged-release tacrolimus dominated immediate-release tacrolimus. There were several differences between the 2 models (see section 6.40). Which of these analyses is most representative of the cost-effectiveness of prolonged-release tacrolimus?

1 Background: clinical need and practice

1.1 Kidney transplantation is used to treat established renal failure, which is severe and irreversible impairment of kidney function. After a kidney transplant, immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney (or 'graft') and prolong its survival. Between April 2013 and March 2014, 127 kidney transplant operations were performed in the UK for children and adolescents under 18 years of age. In 2013, approximately 715 children and adolescents in the UK were receiving immunosuppressive therapy after kidney transplantation.

1.2 Kidney transplantation in children and adolescents can differ from adults in several important aspects, including the cause of organ failure, the metabolism and pharmacokinetic properties of immunosuppressants, the immune response following organ transplantation, the measures of success of the transplant procedure, the susceptibility to post-transplant complications, and the degree of adherence to treatment.

1.3 Immunosuppressive therapy can be categorised as induction therapy, initial maintenance therapy, and long-term maintenance therapy (**Error! Reference source not found.**). The aim of treatment is to prevent acute rejection and optimise the function of the transplanted kidney, while minimising the adverse consequences of immunosuppression such as an increased risk of infection, cancer and cardiovascular disease.

Table 1. Categories of immunosuppressive therapy.

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

1.4 The Assessment Group consulted clinical experts, who advised that 4 of the 10 paediatric transplant centres in the UK routinely use basiliximab for induction therapy. Six centres do not routinely use antibody induction therapy. For maintenance therapy, 6/10 centres routinely use tacrolimus plus azathioprine and 4/10 use tacrolimus plus mycophenolate mofetil.

1.5 The choice of immunosuppressive therapy is informed by the level of immunological risk, which is determined by factors such as age and antibody reactivity. Antibody reactivity indicates the likelihood that the recipient's immune system will identify the transplanted kidney as 'foreign' tissue and attempt to destroy it.

1.6 NICE technology appraisal 99, published in April 2006, provides guidance on immunosuppressive therapy for kidney transplantation in children and adolescents. The recommendations are shown in Table 2. Since the publication of technology appraisal 99, new technologies have received relevant marketing authorisations (rabbit anti-human thymocyte immunoglobulin, belatacept, prolonged-release tacrolimus, everolimus and an oral suspension of immediate-release tacrolimus). Note that some of the technologies have a marketing authorisation that excludes children and adolescents (Table 2). Some of the treatments in NICE technology appraisal 99 are now available generically, and the marketing authorisation for daclizumab has been withdrawn.

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

2 The technologies

Table 2. Summary of technologies in the appraisal.

Technology	Recommendation in TA99	Marketing authorisation for renal transplantation in children and adolescents?
For induction therapy		
Basiliximab (Simulect, Novartis Pharmaceuticals)	Basiliximab, used as part of a ciclosporin-based immunosuppressive regimen, is recommended as an option… irrespective of immunological risk.	Yes, age range 1–17 years
Rabbit anti-human thymocyte immunoglobulin (Thymoglobuline, Sanofi)	Not included in TA99.	Indication is not restricted to adults. The summary of product characteristics (SPC) states that 'currently available [paediatric] data are described…but no recommendation on a posology can be made. Available information indicates that paediatric patients do not require a different dosage than adult patients.'
For maintenance therapy		

Immediate-release tacrolimus (see section 2.10 for list of brands and companies)	Tacrolimus is recommended as an alternative option to ciclosporin when a calcineurin inhibitor is indicated…The initial choice of tacrolimus or ciclosporin should be based on the relative importance of their side-effect profiles for the individual patient.	Indication is not restricted to adults. The SPC includes dosage recommendations for children, age range not specified.
Prolonged-release tacrolimus (Advagraf, Astellas Pharma)	Not included in TA99.	No – the indication is restricted to adults.
Belatacept (Nulojix, Bristol-Myers Squibb)	Not included in TA99.	No – the indication is restricted to adults.
Mycophenolate mofetil (non-proprietary)	Recommended only when: - there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity which could lead to **risk** of chronic allograft dysfunction, or - there is a very high risk of nephrotoxicity necessitating the minimisation or avoidance of a calcineurin inhibitor until the period of high risk has passed. The use of mycophenolate mofetil in corticosteroid reduction or withdrawal strategies…is recommended only within the context of randomised clinical trials.	The indication is not restricted to adults. The SPC includes dosage recommendations for people aged 2–18 years.
Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals)	Not recommended.	No – the indication is restricted to adults.
Sirolimus (Rapamune, Pfizer)	Not recommended…except when proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitates the complete withdrawal of these treatments.	No – the indication is restricted to adults.
Everolimus (Certican, Novartis Pharmaceuticals)	Not included in TA99.	No – the indication is restricted to adults.

Source: final scope and SPCs.

Induction therapy

Basiliximab

2.1 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 de novo allogeneic renal transplantation. The indication includes children and adolescents 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'. Higher panel reactive antibodies mean there is a higher risk of transplant rejection.

2.2 Basiliximab is administered intravenously. In children and adolescents weighing less than 35 kg, the recommended total dose is 20 mg given in 2 doses of 10 mg each. In children and adolescents weighing 35 kg or more, the recommended dose is 40 mg given in 2 doses of 20 mg each.

2.3 The summary of product characteristics states that the following adverse reactions occur in at least 20% of children and adolescents treated with basiliximab: urinary tract infection, excess 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.

2.4 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 online, accessed May 2015). The Assessment Group estimated that the cost of induction therapy with basiliximab is £1517 for a patient weighing

under 35 kg and £1685 for a patient weighing over 35 kg. Costs may vary in different settings because of negotiated procurement discounts.

Rabbit anti-human thymocyte immunoglobulin

2.5 Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline, Sanofi) is a gamma immune globulin, generated by immunising rabbits with human thymocytes. It has a marketing authorisation in the UK for the prevention of graft rejection in renal transplantation. The summary of product characteristics does not state whether the indication includes children and adolescents. 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 rATG is usually used in combination with other immunosuppressive drugs.

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

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

2.8 R-ATG is available in 25-mg vials at a price of £158.77 (excluding VAT; British national formulary online, accessed May 2015). The Assessment Group 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). Costs may vary in different settings because of negotiated procurement discounts.

Maintenance therapy

2.9 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. The Commission on Human Medicines advises that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only. 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

2.10 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 a marketing authorisation in the UK for the prophylaxis of transplant rejection in kidney allograft recipients. Adoport, Capexion, Perixis, Prograf, Tacni and Vivadex are oral capsules. Prograf is also available as a concentrate for intravenous infusion. Modigraf contains granules for oral suspension.

2.11 For all brands of immediate-release tacrolimus, the summary of product characteristics recommends an initial dose for children (age range not specified) of 0.30 mg/kg/day orally or 0.075–0.100 mg/kg/day intravenously. The dosage is usually reduced in the post-transplant period.

2.12 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.

2.13 Prograf is available in 1-ml ampoules containing 5 mg/ml concentrate for intravenous infusion at a price of £11.69 per mg (excluding VAT; British national formulary online, accessed May 2015). Modigraf is available in sachets of 0.2 mg and 1 mg at a price of £71.30 and £356.65, respectively, for a 50-sachet pack (excluding VAT; British national formulary online, accessed May 2015). This is equivalent to £7.13 per mg for Modigraf. The price of capsules varies by brand. The Assessment Group 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 Assessment Group 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. Costs may vary in different settings because of negotiated procurement discounts.

Prolonged-release tacrolimus

2.14 Prolonged-release tacrolimus (Advagraf, Astellas Pharma) is an oral capsule. It has a marketing authorisation in the UK for the prophylaxis of transplant rejection in **adult** kidney allograft recipients. The summary of product characteristics recommends an initial dose for adults of 0.20–0.30 mg/kg/day. The dosage is usually reduced in the post-transplant period.

2.15 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.

2.16 Prolonged-release tacrolimus is available as 0.5 mg, 1 mg, 3 mg and 5 mg capsules at a price of £1.07 to £1.43 per mg (excluding VAT; British national formulary online, accessed May 2015). The Assessment Group

estimated that the weekly cost of maintenance therapy with prolonged-release tacrolimus for a 10-year-old boy is £47 (using the posology for adults). Costs may vary in different settings because of negotiated procurement discounts.

Belatacept

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

2.18 Belatacept is administered intravenously. The recommended dose for adults is 10 mg/kg on the day of transplantation, followed by 10 mg/kg on days 5, 14, 28, 56 and 84 and 5 mg/kg every 4 weeks from then on.

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

2.20 Belatacept is available in 250-mg vials at a price of £354.52 (excluding VAT; British national formulary online, accessed May 2015). The Assessment Group 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). Costs may vary in different settings because of negotiated procurement discounts.

Mycophenolate mofetil

2.21 Mycophenolate mofetil (non-proprietary) has a marketing authorisation in the UK, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute transplant rejection in people undergoing kidney transplantation. 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 adolescents (aged 2–18 years) is 1200 mg/m^2 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 m^2.

2.22 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with mycophenolate mofetil: viral, bacterial and fungal infections; leukopenia; thrombocytopenia; anaemia; vomiting; abdominal pain; diarrhoea and nausea. 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 the paediatric population: sepsis, infection, leukopenia, anaemia and diarrhoea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.23 The price of mycophenolate mofetil varies by brand. The Assessment Group 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 Assessment Group 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. Costs may vary in different settings because of negotiated procurement discounts.

Mycophenolate sodium

2.24 Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals), in combination with ciclosporin and corticosteroids, has a marketing

authorisation in the UK for the prophylaxis of acute transplant rejection in **adults** receiving an allogeneic kidney transplant. It is administered as an oral tablet at a recommended dose for adults of 1.44 g per day.

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

2.26 Mycophenolate sodium is available in 180-mg and 360-mg tablets at a price of £96.72 and £193.43, respectively, for a pack of 120 tablets (excluding VAT; British national formulary online, accessed May 2015). The Assessment Group estimated that the weekly cost of maintenance therapy with mycophenolate sodium for a 10-year-old boy is £50 (using the posology for adults). Costs may vary in different settings because of negotiated procurement discounts.

Sirolimus

2.27 Sirolimus (Rapamune, Pfizer) is an antiproliferative that blocks a protein called mammalian target of rapamycin (mTOR). Sirolimus has a marketing authorisation in the UK for the prophylaxis of organ rejection in **adults** at low to moderate immunological risk receiving a renal transplant. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2 to 3 months, and may be continued only if ciclosporin can be progressively discontinued.

2.28 Sirolimus is administered orally as a tablet or solution. The recommended dose for adults is 6 mg initially, followed by 2 mg per day; subsequent doses are adjusted to achieve the desired level of sirolimus in the blood.

2.29 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with sirolimus: fever; hypertension; decreased levels of platelets, red blood cells, potassium or

phosphates in the blood; increased levels of cholesterol, sugar, triglycerides, creatinine or lactate dehydrogenase in the blood; urinary tract infection; pain; lymphocele; peripheral oedema; acne; diarrhoea; constipation and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.30 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 to £4.60 per mg (excluding VAT; British national formulary online, accessed May 2015). The Assessment Group estimated that the weekly cost of maintenance therapy with sirolimus for a 10-year-old boy is £40 (using the posology for adults). Costs may vary in different settings because of negotiated procurement discounts.

Everolimus

2.31 Everolimus (Certican, Novartis Pharmaceuticals) is an antiproliferative that blocks a protein called mammalian target of rapamycin (mTOR). Everolimus has a marketing authorisation for the prophylaxis of organ rejection in **adults** at low to moderate immunological risk receiving an allogeneic renal transplant. The summary of product characteristics states that everolimus should be used in combination with ciclosporin for microemulsion and corticosteroids. Everolimus is administered as an oral tablet. The recommended initial dose for adults is 1.5 mg/day.

2.32 The summary of product characteristics states that the following adverse reactions occur in at least 10% of adults treated with everolimus: infections; diabetes; insomnia; anxiety; pain; pericardial or pleural effusion (fluid in the space around the heart or lungs); hypertension; venous thromboembolic events; cough; dyspnoea; gastrointestinal disorders; peripheral oedema; impaired healing; fever; decreased levels of platelets, red blood cells, white blood cells or potassium in the blood; and increased levels of cholesterol or triglycerides in the blood. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.33 Everolimus is available in 0.1-mg, 0.25-mg, 0.5-mg, 0.75-mg and 1-mg tablets at a net price of £9.90 per mg (from the Novartis submission for the ongoing appraisal of immunosuppression in adults). The Assessment Group estimated that the weekly cost of maintenance therapy with everolimus for a 10-year-old boy is £104 (using the posology for adults). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The objective is to appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation in children and adolescents.

Table 3. Summary of the decision problem.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Population	Children and adolescents undergoing kidney transplantation	The protocol specified an age range of <18 years. In the final report this was changed to 0–18 years (inclusive), to match the age criteria in 3 randomised trials. The report included evidence from 'new' transplant recipients. People who previously received transplant(s) and immunosuppression were excluded.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Intervention	*Induction therapy* For prevention of organ rejection, regimens containing: - Basiliximab - Rabbit anti-human thymocyte immunoglobulin *Initial and long-term maintenance therapy* For prevention of organ rejection, regimens containing: - Immediate-release tacrolimus - Prolonged-release tacrolimus - Belatacept - Mycophenolate mofetil - Mycophenolate sodium - Sirolimus - Everolimus	As per the scope. Immunosuppressive drugs are used in combination and in sequence. Accordingly, the network meta-analysis and economic model compared regimens rather than individual drugs.
Comparators	*Induction therapy* - Regimens without monoclonal or polyclonal antibodies, for example regimens that include methylprednisolone - Interventions should also be compared with each other *Initial and long-term maintenance therapy* - A calcineurin inhibitor with or without an antiproliferative agent and/or corticosteroids - Interventions should also be compared with each other Where appropriate the interventions will be appraised as part of combination regimens.	As per the scope.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Outcomes	The outcome measures to be considered include: - patient survival - graft survival - graft function - time to and incidence of acute rejection - severity of acute rejection - growth - adverse effects of treatment - health-related quality of life.	The review did not identify any studies of children and adolescents that measured health related quality-of-life.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Two types of economic analysis were presented: 1) Using effectiveness data from paediatric randomised trials; 2) Using effectiveness data from randomised trials in adults.
Other considerations	If evidence allows, subgroups … will be considered, including: - Different age groups - Level of immunological risk (including human leukocyte antigen compatibility and blood group compatibility) - People at high risk of rejection within the first 6 months - People who have had a retransplant within 2 years - Previous acute rejection - People at high risk of complications from immunosuppression (including new-onset diabetes).	Due to a lack of evidence, no subgroups were assessed in the clinical-effectiveness section of the report. The Assessment Group presented a cost-effectiveness analysis in which age at transplantation was varied. No other subgroups were assessed.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Other considerations	If evidence allows, the appraisal will consider treatment regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors. If evidence allows, adherence to treatment will be considered.	Due to a lack of evidence, the report did not consider treatment regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors, or regimens that aim to improve adherence.
Other considerations	The use of immunosuppressive drugs in patients receiving multiple organ transplants (for example, combined kidney and pancreas transplantation) is excluded from this appraisal.	As per the scope.

4 Clinical-effectiveness evidence

4.1 The Assessment Group conducted a systematic review of evidence published between 2002 and January 2015. Studies published before 2002 were identified using the assessment report for technology appraisal 99. The systematic review included studies that recruited children and adolescents aged 0–18 years (inclusive). Studies that recruited both adults and children were included only if a subgroup analysis for children and adolescents was reported (no such studies were found). The review included studies that addressed the population, interventions, comparators and outcomes specified in the scope (see Table 3).

4.2 Randomised controlled trials (RCTs) and non-randomised studies with a control group were included in the review. In its original report, the Assessment Group searched directly for RCTs and systematic reviews only. It identified non-randomised studies via the bibliographies of systematic reviews. After discussions with NICE, the Assessment Group submitted an addendum presenting an additional search for non-randomised studies with a control group. The additional search used the

same inclusion criteria as the main review (see section 4.1 and Table 3) except the outcomes were restricted to graft function, graft survival, mortality, acute rejection and growth at 1 year's follow-up. Adverse effects and health-related quality of life were not included in the additional search.

4.3 The results of the systematic review were presented as a narrative summary. A random-effects meta-analysis of RCTs was conducted where possible.

Quantity and quality of research

4.4 The Assessment Group's review found 3 RCTs of children and adolescents. Offner et al. (2008) compared basiliximab (n=100) with placebo (n=92); all patients received maintenance therapy with ciclosporin, mycophenolate mofetil and corticosteroids. Grenda et al. (2006) compared basiliximab (n=99) with no induction (n=93); all patients received maintenance therapy with immediate-release tacrolimus, azathioprine and corticosteroids. Trompeter et al. (2002) compared immediate-release tacrolimus (n=103) with ciclosporin (n=93); all patients received azathioprine and corticosteroids. The baseline characteristics of patients in each trial are presented in section 4.2.5 of the assessment report.

4.5 The review found 10 non-randomised studies of children and adolescents (

4.6 Table 4). The baseline characteristics of patients in the studies are reported in Table 6 of the assessment report addendum. The studies by Delucchi et al. (2007) and Valenzuela et al. (2008) were conducted at the same centre, shared some co-authors, and reported similar study designs, so the Assessment Group advised that these articles may be reporting the same study.

Table 4. Non-randomised studies in the Assessment Group's review.

Study	Design	N	Treatment group 1		Treatment group 2	
			Induction	Mainten-ance	Induction	Mainten-ance
Comparison of induction therapies						
Cransberg et al. 2008	Retrospective cohort study	233	**BAS**	CSA + MMF	**None**	CSA + MMF
Comparison of maintenance therapies: mycophenolate mofetil versus azathioprine						
Antoniadis et al. 1998	Non-randomised controlled trial	14	Methyl-prednis-olone	**MMF** + CSA	Methyl-prednis-olone	**AZA** + CSA
Benfield et al. 1999	Historical control group	67	OKT3 or CSA	**MMF** + CSA	OKT3 or CSA	**AZA** + CSA
Chavers et al. 2009	Historical control group	60	r-ATG (5–7 days)	**MMF** + CSA[a]	r-ATG (6–15 days)	**AZA** + CSA
Staskewitz et al. 2001	Historical control group	139	Pred-nisone/ methyl-prednis-olone	**MMF** + CSA	Not reported	**AZA** + CSA
Comparison of maintenance therapies: sirolimus versus immediate-release tacrolimus						
Hymes et al. 2011	Retrospective cohort study	48	BAS	**TAC for 3 months then SRL** (plus MMF)	BAS	**TAC** + MMF
Comparison of maintenance regimens: immediate-release tacrolimus plus azathioprine versus ciclosporin plus mycophenolate mofetil						
Garcia et al. 2002	Retrospective cohort study	24	BAS	**TAC** + **AZA**	BAS	**CSA** + **MMF**
Comparison of maintenance regimens: immediate-release tacrolimus plus mycophenolate mofetil versus ciclosporin plus azathioprine						
Delucchi et al. 2007	Historical control group	46	BAS	**TAC** + **MMF**[a]	BAS	**CSA** + **AZA**
Valen-zuela et al. 2008	Historical control group	23	BAS	**TAC** + **MMF**[a]	BAS	**CSA** + **AZA**
Comparison of regimens that differed in both induction and maintenance therapy						
Mosaad et al. 2012	Retrospective cohort study	32	**BAS**	**TAC + MMF**	**None**	**CSA + AZA**

Notes. All maintenance regimens included corticosteroids. OKT3 is also known as muromonab-CD3 – this monoclonal antibody does not have a UK marketing authorisation.
a. Corticosteroids used for only 6 days.
Abbreviations: AZA, azathioprine; BAS, basiliximab; CSA, ciclosporin, MMF; mycophenolate mofetil; r-ATG, rabbit anti-human thymocyte immunoglobulin.

Study	Design	N	Treatment group 1		Treatment group 2	
			Induction	Mainten-ance	Induction	Mainten-ance
Source: assessment report addendum, Tables 3 and 6.						

4.7 Compared with the previous assessment report in 2006, the present review found 1 new paediatric RCT (Offner et al. 2008) and 6 new paediatric non-randomised studies (Chavers et al. 2009; Cransberg et al. 2008; Delucchi et al. 2007; Hymes et al. 2011; Mosaad et al. 2012; Valenzuela et al. 2008). The present review excluded 1 paediatric RCT, and 5 paediatric non-randomised studies, that were included in the 2006 assessment report. The reasons for the exclusions are in section 4.2.3 of the assessment report.

4.8 The review did not identify any studies of children and adolescents that measured:

- health related quality-of-life
- adherence to treatment
- outcomes for treatment regimens that aim to reduce or withdraw corticosteroids or calcineurin inhibitors.

4.9 The Assessment Group assessed the quality of the RCTs using a 10-point checklist. For all 3 trials, at least 5 items were rated as ‘inadequate’ or ‘unclear’. Offner et al. (2008) used an adequate method of random allocation and the trial was double-blind (meaning patients and care providers did not know which treatment patients received). The other 2 trials used an unclear method of random allocation and were not blinded. None of the trials reported an adequate intention-to-treat analysis. The Assessment Group advised that all 3 RCTs were likely to be generalisable to the NHS because the trials were conducted in Europe, the patient and donor characteristics were largely representative of the NHS, and the drug doses were similar to current recommendations. On the other hand, the

results may not be generalisable because the evidence is quite old. For example, Trompeter et al. (2002) began recruiting patients in 1996.

4.10 The Assessment Group assessed the quality of the non-randomised studies using a 10-point checklist (see Table 5 of the assessment report addendum). For all 10 studies, 5 or fewer items were rated as adequate. Nine studies described how patients were allocated to treatment groups, but only 2 stated that selection bias was minimised by enrolling all eligible patients (Cransberg et al. 2008; Mosaad et al. 2012). Six studies did not report whether treatment groups were similar at baseline, whilst 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). None of the studies used blinding. The Assessment Group 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).

Systematic review of adult RCTs

4.11 There were only 3 RCTs of children and adolescents and these trials did not include all of the interventions in the appraisal. Accordingly, some of the Assessment Group's economic analyses used estimates of clinical effectiveness from RCTs in adults. The Assessment Group's review of adult trials found 10 RCTs of induction therapy, 73 RCTs of maintenance therapy, and 2 RCTs that assessed both induction and maintenance therapies. The quality assessment of the adult RCTs is in section 4.2.2 of the assessment report for adults. Overall, the adult RCTs were of variable quality and the quality assessment was hampered by poor reporting. The Assessment Group conducted a network meta-analysis of the adult trials (the methods are described in section 4.1.8 of the adult assessment report). The analyses of induction therapy compared each drug with a reference treatment of no induction/placebo. The analyses of maintenance therapy compared the effectiveness of immunosuppressive

regimens rather than individual drugs; the reference regimen was ciclosporin and azathioprine. In the network meta-analyses, mycophenolate mofetil and mycophenolate sodium were assumed to be the same drug. Similarly, immediate-release and prolonged-release tacrolimus were assumed to be the same drug.

Outcome measures

4.12 Although the Assessment Group's systematic review included all outcomes in the scope, it focused on 3 key outcomes plus mortality. **Graft function** is measured by estimated glomerular filtration rate (eGFR); 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 to III, where 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. In its analyses of graft loss, the Assessment Group excluded graft loss due to death. The rationale was, firstly, to avoid double counting with mortality data and, secondly, because death-censored graft survival is 'a well-established clinical outcome'.

Evidence of clinical effectiveness: induction therapy

4.13 The review of paediatric studies found 2 RCTs of basiliximab and 1 non-randomised study of basiliximab. One non-randomised study included rabbit anti-human thymocyte immunoglobulin (r-ATG; Chavers et al. 2009). However, r-ATG was given to all patients so the study could not assess the effectiveness of r-ATG. Chavers et al. (2009) did compare maintenance therapies and the results of this comparison are in section 4.23.

RCTs in children and adolescents

4.14 For most outcomes, Offner et al. (2008) reported data at 6 and 12 months and Grenda et al. (2006) reported data at 6 and 24 months. Both studies found no statistically significant difference between the basiliximab group and the placebo/no induction group in mortality, incidence of graft loss, incidence of BPAR, and graft function at any time point. Table 5 shows the results of the final assessment in each study. The odds ratios for mortality were above 1 for Offner et al. (indicating higher mortality with basiliximab) and below 1 for Grenda et al., although the difference between groups was not statistically significant in either study. The odds ratios for BPAR were below 1 for both studies, indicating lower rates of acute rejection with basiliximab, but the difference was not statistically significant. 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 Assessment Group'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 5. Summary of results from RCTs of basiliximab in children and adolescents.

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

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)
Note: an odds ratio <1 favours basiliximab. Abbreviations: BPAR, Biopsy proven acute rejection; CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); NR, not reported; SD, standard deviation. Source: assessment report Tables 18–21.						

4.15 Regarding 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 study in children and adolescents

4.16 Cransberg et al. (2008) reported that, after 1 year's follow-up, 21% (23/110) of patients treated with basiliximab had experienced BPAR compared with 36% (44/123) of patients treated with no 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 (OR 3.42, 95% CI 0.35 to 33.34), graft loss (OR 1.38, 95% CI 0.58 to 3.33) or graft function (mean eGFR [in ml/min/1.73 m^2] 64 with basiliximab and 62 with no induction, p=0.38). An odds ratio above 1 means higher incidence in the basiliximab group.

RCTs in adults

4.17 The Assessment Group's network meta-analysis of induction therapy included 12 adult RCTs with a follow-up time of 1 year. Seven trials compared basiliximab with placebo/no induction; 2 compared r-ATG with placebo/no induction; and 3 compared basiliximab with r-ATG. There was no evidence that basiliximab and r-ATG were more effective than placebo in reducing graft loss and mortality (Table 6). Both basiliximab and r-ATG

were more effective than placebo/no induction in reducing BPAR. For graft function, there was no evidence that basiliximab or r-ATG were more effective than placebo/no induction, and no evidence that either treatment was more effective than the other (all credibility intervals included zero).

Table 6. 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.

Treatment comparison	Odds ratio (95% credibility interval)		
	Graft loss	Mortality	BPAR
Basiliximab vs placebo/no induction	0.82 (0.56 to 1.18)	0.99 (0.53 to 1.85)	**0.52 (0.41 to 0.65)**
r-ATG vs placebo/no induction	0.77 (0.39 to 1.47)	0.84 (0.33 to 2.07)	**0.36 (0.24 to 0.54)**
r-ATG vs basiliximab	0.94 (0.50 to 1.75)	0.84 (0.36 to 1.96)	0.70 (0.47 to 1.03)

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

Abbreviations: r-ATG, rabbit anti-human thymocyte immunoglobulin; BPAR, biopsy proven acute rejection. Source: erratum to adult assessment report, Table 1.

4.18 The Assessment Group conducted meta-analyses of adverse events in adult RCTs with a follow-up of 1 year.[1] There were no statistically significant differences between basiliximab and placebo/no induction in the incidence of selected adverse events (new-onset diabetes, post-transplant lymphoproliferative disease, malignancy, infections and cytomegalovirus infections). Comparing basiliximab with r-ATG, the only statistically significant difference was a lower incidence of malignancy with basiliximab (OR 0.23, 95% CI 0.06 to 0.95). Comparing r-ATG with placebo/no induction, the only statistically significant difference was a greater incidence of cytomegalovirus infection with r-ATG (OR 1.67, 95% CI 1.05 to 2.66).

[1] The assessment report for adults included 4 trials of drugs that were similar to, but not the same as, Thymoglobuline. In an erratum, the Assessment Group removed these 4 trials from the network meta-analysis and presented revised efficacy estimates that are included in this document. However, the meta-analyses of adverse events were not updated. The meta-analyses include the 4 trials and should be interpreted with caution.

Summary

4.19 Two paediatric RCTs, and 1 paediatric non-randomised study, reported no statistically significant differences between basiliximab and placebo/no induction in mortality, graft loss and graft function. The randomised trials reported no significant difference in the incidence of BPAR, whereas the non-randomised study found that the incidence of BPAR was significantly lower with basiliximab. One randomised trial found that patients in the basiliximab group had fewer severe episodes of BPAR. In RCTs of children and adolescents, basiliximab was associated with an increased incidence of infection, toxic nephropathy and abdominal pain compared with placebo/no induction. The review did not find any paediatric studies that compared r-ATG with basiliximab or no induction.

4.20 A network meta-analysis of adult RCTs found no evidence that basiliximab and r-ATG are more effective than placebo in reducing graft loss and mortality or in improving graft function. Both basiliximab and r-ATG were more effective than placebo/no induction in reducing the incidence of BPAR.

Evidence of clinical effectiveness: maintenance therapy

4.21 The Assessment Group's review of paediatric studies found 1 RCT of immediate-release tacrolimus and 9 non-randomised studies that included immediate-release tacrolimus, mycophenolate mofetil or sirolimus. The review did not find any paediatric studies (either randomised or non-randomised) of prolonged-release tacrolimus, belatacept, mycophenolate sodium and everolimus.

RCT in children and adolescents

4.22 For most outcomes, Trompeter et al. (2002) reported data at 0.5, 1, 2 and 4 years of follow-up. At all time points, there were no statistically significant differences between the immediate-release tacrolimus group and the ciclosporin group in mortality and graft loss. Table 7 shows the 4-year results. At all assessments between 1 and 4 years, graft function was

statistically significantly better in the immediate-release tacrolimus group than the ciclosporin group (4-year results: mean eGFR 71.5 and 53.0 ml/min/1.73 m^2 respectively, p<0.01). At 6 months' 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). Subsequent assessments did not include BPAR.

Table 7. Four-year results from an RCT comparing immediate-release tacrolimus with ciclosporin in children and adolescents (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. Source: assessment report Tables 25, 27, 29.			

4.23 The assessment report stated that Trompeter et al. (2002) reported no statistically significant differences between immediate-release tacrolimus and ciclosporin for a range of adverse events including infections, new-onset diabetes, post-transplant lymphoproliferative disease and hypertension. The publication by Trompeter et al. (2002) states that the following adverse events were more common with tacrolimus than with ciclosporin: a deficiency of magnesium in the blood (34.0% versus 12.9%, p=0.001) and diarrhoea (13.6% versus 3.2%, p<0.05). Conversely, the following events were less common with tacrolimus than with ciclosporin: excessive hair growth (0.0% versus 7.5%, p<0.05), flu syndrome (0.0% versus 5.4%, p<0.05) and swollen gums (0.0% versus 5.4%, p<0.05).

Non-randomised studies in children and adolescents

4.24 Four non-randomised studies compared mycophenolate mofetil with azathioprine (see Table 8 of the Assessment Report addendum).

Staskewitz et al. (2001) found that, 1 year after transplantation, 2/86 (2%) patients in the mycophenolate mofetil group had experienced graft loss compared with 8/54 (15%) 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 transplantation, the height of patients in the mycophenolate mofetil group was closer to the average for their age group than the height of patients in the azathioprine group (on average, 0.6 and 2.0 standard deviations below the age-group mean respectively; p=0.001). However, there was a baseline difference between the groups in Chavers et al. (2009). Prior to transplantation the height of the mycophenolate mofetil group was 0.9 standard deviations below the age-group mean compared with 1.9 standard deviations for the azathioprine group. Moreover, in Chavers et al. (2009) the mycophenolate mofetil group had r-ATG for up to 7 days whereas the azathioprine group had r-ATG for up to 15 days, so there was a confounding difference in induction treatment between groups. Across all 4 studies, there were no further statistically significant differences between the mycophenolate mofetil and azathioprine groups.

4.25 Hymes et al. (2011) compared immediate-release tacrolimus (n=23) with a regimen of immediate-release tacrolimus for 3 months followed by long-term sirolimus (n=25). After 2 years, patients in both groups had similar graft function (mean eGFR [in ml/min/1.73 m^2] 69 with tacrolimus and 77 with sirolimus, p=0.32) and height (both groups were 1.6 standard deviations below the age-group mean; p=0.94). No additional outcome measures were reported.

4.26 Garcia et al. (2002) compared a regimen of immediate-release tacrolimus and azathioprine (n=12) with a regimen of ciclosporin and mycophenolate mofetil (n=12). After 3 months, there were no statistically significant differences between groups for mortality, graft loss, graft function and BPAR.

4.27 Two publications, which may come from the same study (see section 4.5), compared a regimen of immediate-release tacrolimus and mycophenolate mofetil with a regimen of ciclosporin and azathioprine (Delucchi et al. 2007; Valenzuela et al. 2008). Valenzuela et al. (2008) reported better graft function after 6 months with ciclosporin and azathioprine (mean eGFR 98 ml/min/1.73 m^2) than with immediate-release tacrolimus and mycophenolate mofetil (mean eGFR 76 ml/min/1.73 m^2); the difference between groups was statistically significant. The report by Delucchi et al. included more patients (46 compared with 23) and a longer follow-up (1 year compared with 6 months) but did not find a statistically significant difference between groups in graft function. There were no further significant differences between treatment groups.

4.28 Mosaad et al. (2012) compared a regimen of basiliximab induction, immediate-release tacrolimus and mycophenolate mofetil (n=5) with a regimen of no induction, ciclosporin and azathioprine (n=27). There were no statistically significant differences between treatment groups in graft loss and growth. Additional outcome measures were not reported.

RCTs in adults

4.29 The Assessment Group's network meta-analysis of maintenance therapy included 32–42 adult RCTs, depending on the outcome measure. The follow-up time was 1 year. The results are in section 4.3.3.2 and Tables 117–125 of the assessment report for adults. To summarise, 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. For all comparisons, there was a great deal of heterogeneity and the credibility intervals were wide, indicating uncertainty in the results. The network meta-analysis compared many regimens; Table 8 summarises the estimates of treatment effect for the regimens included in the economic analysis for children and adolescents.

Table 8. Summary of the Assessment Group's network meta-analyses of adult RCTs of maintenance therapy with a follow-up time of 1 year. The table shows median treatment effects (and 95% credibility intervals) compared with a regimen of ciclosporin and azathioprine.

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

Note. a: mean difference in ml/min/1.73 m^2.
Evidence suggesting a difference between treatments is in bold text.
Source: Tables 118, 120, 122 and 124 of assessment report.

4.30 The network meta-analysis assumed that mycophenolate mofetil and mycophenolate sodium were the same drug. To supplement this analysis, the Assessment Group identified 2 adult RCTs that compared mycophenolate mofetil with mycophenolate sodium. Patients in Ciancio et al. (2008) received the study drug in combination with tacrolimus. The only statistically significant difference between treatment groups was in graft function, which was better in the mycophenolate sodium group at 0.5 and 1 years. However, this difference was reversed at 3 years when graft function was significantly better in the mycophenolate mofetil group. Patients in Salvadori et al. (2004) received the study drug in combination

with ciclosporin; there were no statistically significant differences between treatment groups.

4.31 The network meta-analysis assumed that immediate-release and prolonged-release tacrolimus were the same drug. To supplement this analysis, the Assessment Group identified 4 adult RCTs that compared immediate-release tacrolimus with prolonged-release tacrolimus; all patients also had mycophenolate mofetil. A meta-analysis found no statistically significant differences between treatment groups in mortality, graft loss or BPAR. One trial reported significantly better graft function at 6 months in patients randomised to immediate-release tacrolimus than in patients randomised to prolonged-release tacrolimus (mean difference in eGFR 1.90 ml/min/1.73 m^2; 95% CI 1.70 to 2.10). However, a meta-analysis of 2 trials reporting graft function at 12 months showed no statistically significant differences between treatment groups (weighted mean difference in eGFR 0.21 ml/min/1.73 m^2; 95% CI −2.10 to 2.53).

4.32 The Assessment Group conducted meta-analyses of selected adverse events (listed in section 4.17) in adult RCTs with a follow-up of 1 year. Both tacrolimus and sirolimus increased the incidence of new-onset diabetes compared with ciclosporin (tacrolimus vs ciclosporin: OR 2.22, 95% CI 1.42 to 3.46; ciclosporin vs sirolimus: OR 0.60, 95% CI 0.37 to 0.98). Conversely, belatacept reduced the incidence of new-onset diabetes compared with ciclosporin (ciclosporin vs belatacept: OR 2.17, 95% CI 1.15 to 4.09). Sirolimus and everolimus both reduced the incidence of cytomegalovirus infection compared with ciclosporin and mycophenolate respectively (ciclosporin vs sirolimus: OR 2.47, 95% CI 1.42 to 4.31; mycophenolate mofetil vs everolimus: OR 5.81, 95% CI 3.25 to 10.40). Tacrolimus reduced the incidence of general infections compared with sirolimus (OR=0.68, 95% CI 0.47–0.98). There were no further statistically significant differences between treatments in the incidence of adverse events.

Summary

4.33 A single paediatric RCT found that patients treated with immediate-release tacrolimus had better graft function and a lower incidence of BPAR than patients treated with ciclosporin; there were no differences between treatments for mortality and graft loss. The immediate-release tacrolimus group had a greater incidence of magnesium deficiency and diarrhoea, whilst the ciclosporin group had a greater incidence of excessive hair growth, flu syndrome and swollen gums.

4.34 One paediatric non-randomised study found that patients treated with mycophenolate mofetil had a lower incidence of graft loss than patients treated with azathioprine. Three further non-randomised studies found no differences in outcome between mycophenolate mofetil and azathioprine (except for a possible difference in height, see section 4.23). One paediatric non-randomised study reported better graft function with ciclosporin and azathioprine than with immediate-release tacrolimus and mycophenolate mofetil, but this finding was not replicated by a larger study with longer follow-up.

4.35 In the Assessment Group's network meta-analysis of adult RCTs, none of the regimens was consistently better than any other regimen, although ciclosporin and azathioprine was associated with poorer graft function and higher risk of BPAR. Adult RCTs showed that mycophenolate mofetil and mycophenolate sodium have similar effectiveness and also that immediate-release tacrolimus and prolonged-release tacrolimus have similar effectiveness.

Evidence of clinical effectiveness: strengths and limitations

4.36 The Assessment Group's literature search did not filter by age; instead, studies of children and adolescents were identified through manual screening. The Assessment Group advised that this is a sensitive search strategy so it is unlikely that relevant paediatric RCTs have been missed. Nonetheless, the review found little paediatric evidence. No paediatric

comparative studies (either randomised or non-randomised) were identified for r-ATG, prolonged-release tacrolimus, belatacept, mycophenolate sodium and everolimus. The available paediatric evidence was of moderate or poor quality. Moreover, some of it is old and may not be generalisable to the NHS.

5 Comments from companies and other consultees

5.1 Submissions were received from David Milford (a clinical expert nominated by the British Association for Paediatric Nephrology), Astellas, the British Transplantation Society and the Efficacy and Safety of Prescribing in Transplantation (ESPRIT) group. Responses to the consultation on the assessment report were received from the British Association for Paediatric Nephrology and 3 companies (Astellas, Novartis and Sanofi). The Department of Health stated it had no comments to make on the assessment report.

Consultee submissions

5.2 Astellas stated that children and adolescents who cannot swallow capsules may be prescribed a 'specials' formulation of tacrolimus in oral solution prepared by a pharmacist. Astellas also advised that hospital staff and caregivers sometimes open capsules of tacrolimus and dissolve them in water to create an oral solution. Astellas noted that there are safety concerns for both of these practices and advised that it is preferable to use Modigraf. Similarly, the British Transplantation Society stated that Modigraf is a consistent preparation of tacrolimus that is suitable for young children, whereas 'specials' formulations may vary. Astellas referred to advice from the Medicines and Healthcare Products Regulatory Agency (MHRA, 2010) that 'before using an unlicensed medicine or a licensed medicine off-label, prescribers should satisfy themselves that an alternative, licensed medicine such as Modigraf would not meet the patient's needs'. This advice has been superseded by the MHRA's (2012) advice on oral tacrolimus products, which does not

include the statement above. However, guidance from the General Medical Council (2013) on good practice in prescribing and managing medicines and devices states that 'prescribing unlicensed medicines may be necessary where there is no suitably licensed medicine that will meet the patient's need.'

5.3 The British Transplantation Society, the clinical expert and Astellas advised that poor adherence (that is, not taking prescribed medication) is a major cause of graft loss in children and adolescents. Astellas stated that prolonged-release tacrolimus, which is taken once a day, may be associated with better adherence than immediate-release tacrolimus which is taken twice a day. Astellas referred to evidence that adherence was better with prolonged-release than immediate-release tacrolimus in both children/adolescents and adults. However, Astellas provided few details of these studies and acknowledged that randomised trials were needed. The Assessment Group advised that the adult study referred to by Astellas (Kuypers et al. 2013) did not use an intention-to-treat analysis.

5.4 The clinical expert advised that the side effects of immunosuppressants can have a substantial impact on the growth and well-being of children and adolescents. Accordingly, paediatric clinical trials often measure the reduction in the side effects of steroids and calcineurin inhibitors, rather than the acute rejection rate.

5.5 ESPRIT stated that preparations of ciclosporin, mycophenolate mofetil and tacrolimus from different manufacturers may vary in bioavailability and pharmacokinetic profiles. To avoid accidental switching between products, ESPRIT stated that it was important to prescribe these drugs using their brand name (or, in the case of mycophenolate mofetil, to specify the manufacturer). ESPRIT encouraged the Committee to make recommendations on prescribing in the final guidance.

5.6 The British Transplantation Society advised that, after transplantation, children and adolescents can spend more time in education and this may

improve their employment prospects. The British Transplantation Society also noted that caring for a child or adolescent who is having dialysis can affect the quality of life of the whole family. Consequently, kidney transplantation can benefit family members who may be more able to work and to participate in social and family life.

Responses to consultation on the assessment report

5.7 The British Association for Paediatric Nephrology stated that it was important to consider the TWIST trial, which has influenced clinical practice in the UK. TWIST compared a regimen of daclizumab induction, tacrolimus, mycophenolate mofetil and steroids for 4 days with a regimen of no induction, tacrolimus, mycophenolate mofetil and long-term steroids. The Assessment Group's review excluded the TWIST study because daclizumab is not an intervention in the appraisal (it no longer has a marketing authorisation in the UK).

5.8 Novartis advised that it would be helpful to analyse clinical and cost effectiveness separately for subgroups, such as patients with poor kidney function immediately after transplantation and those at higher risk of cytomegalovirus infection.

5.9 Sanofi identified 2 non-randomised studies of rabbit anti-human thymocyte immunoglobulin (r-ATG) in children and adolescents. Baron et al. (2008) compared low-dose r-ATG with basiliximab and no induction; this study was excluded from the Assessment Group's review because the clinicians chose which maintenance therapy to use for each patient. Vilalta et al. (2009) compared r-ATG with basiliximab; it was excluded from the Assessment Group's review because it was not clear what type of r-ATG was used.

5.10 Sanofi advised that, in clinical practice, r-ATG is mostly used for patients at moderate or high immunological risk. Sanofi commented that the Assessment Group's review included adult RCTs that recruited patients with different immunological risks, and this could affect the outcomes

observed in the trials. Moreover, some of the trials used a higher dose of r-ATG than is currently used in clinical practice, which could lead to increased rates of infection and malignancy.

6 Cost-effectiveness evidence

Assessment Group's economic model

6.1 The Assessment Group 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 the duration of a paediatric RCT. Beyond that time point, costs and QALYs were extrapolated using a Markov model informed by the paediatric trial data. This approach provided 2 analyses of basiliximab and 1 of tacrolimus, using the trials by Offner et al. (2008), Grenda et al. (2006) and Trompeter et al. (2002) respectively.
- 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 adult RCTs. This approach allowed the cost-effectiveness of all interventions to be assessed.

The Assessment Group advised that neither approach was preferred because both had limitations. The following paragraphs (sections 6.2 to 6.5) describe the aspects of modelling that were common to both approaches.

6.2 The Assessment Group'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 immunosuppressants are used in combination and in sequence. The Assessment Group 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.

6.3 The modelled population was children and adolescents aged under 18 receiving a kidney transplant. People who had received a transplant previously, and those with multi-organ transplants, 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 adolescents 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.

6.4 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 retransplantation). The model also estimated the resources used to treat the following adverse events: biopsy-proven acute rejection (BPAR), cytomegalovirus infection, anaemia, dyslipidaemia and new-onset diabetes. Dosages were based on RCTs of children and adolescents where possible. For belatacept, the Assessment Group assumed that partially used vials were not shared between patients. In contrast, for rabbit anti-human thymocyte immunoglobulin (r-ATG) it assumed that vials were shared and there was no wastage; this may underestimate the costs of r-ATG.

6.5 The Assessment Group took drug costs from the electronic market information tool (eMIT; Commercial Medicines Unit) where possible, because this represents the average costs paid by the NHS. For drugs not included in eMIT, costs were taken from the British national formulary or from company submissions. For procedures, costs were taken from NHS

reference costs where available. For immediate-release tacrolimus, the Assessment Group used the cost of capsules and did not assess Modigraf separately.

Assessment Group's decision tree

6.6 For each of the 3 RCTs in children and adolescents, a decision tree was used to calculate the following outcomes for each treatment over the trial duration:

- Costs of immunosuppression, acute rejection and adverse events
- Life years with functioning graft and with dialysis
- QALYs

In addition, for each trial the following results were used to inform the Markov model:

- Proportion of patients alive with a functioning graft at the end of the trial
- Proportion of patients on dialysis at the end of the trial
- Probability of BPAR within 12 months
- Probability of new-onset diabetes within 12 months
- Graft function (mean estimated glomerular filtration rate [eGFR]) at 12 months

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.

6.7 For each decision tree, the characteristics of the modelled population matched the participants in the paediatric RCT. 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. All 3 decision trees included post-transplant lymphoproliferative disease; the analysis based on Trompeter et al. (2002) also included hypomagnesaemia and hypertension. The

utility values for the decision trees were the same as for the Markov model (see section 6.17).

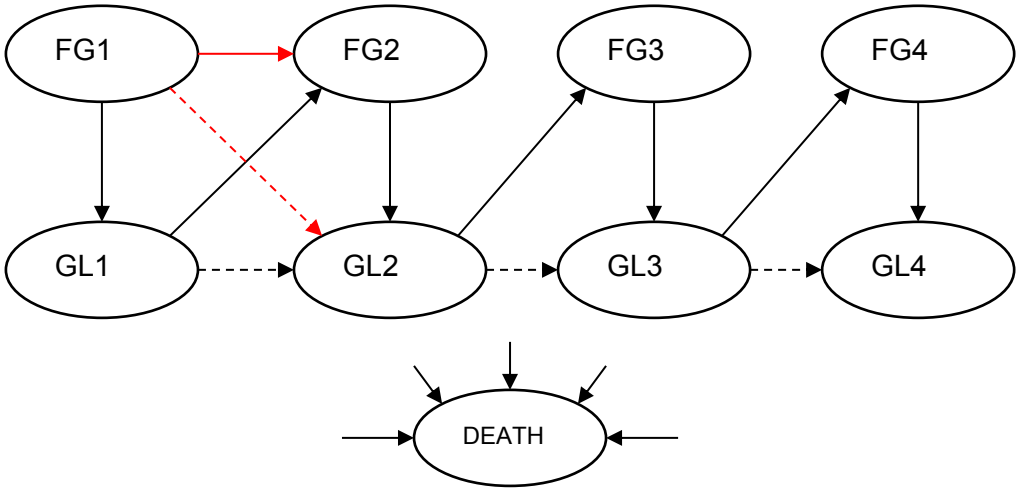
6.8 The Assessment Group assumed that no patients would be retransplanted within the trial duration. The Assessment Group advised that this was a reasonable assumption for Offner et al. (2008) which had a follow-up of 1 year, but for Grenda et al. (2006) and Trompeter et al. (2002) the assumption could lead to bias against the arm with greater graft loss. Grenda had a follow-up of 2 years and Trompeter 4 years.

6.9 The inputs to the model derived from each paediatric trial are shown in Tables 56 and 57 of the assessment report.

Assessment Group's Markov model

6.10 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 the patient was using their first, second, third or fourth transplant (Figure 1). 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 received dialysis. From the graft loss state, patients who received 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 retransplantation' and was only possible from the first functioning graft state (see red arrows in Figure 1). Death could occur from any state but the risk was higher in the graft loss states.

Figure 1. Structure of the Assessment Group's Markov model.



Key: FG, functioning graft; GL, graft loss.

Note: red arrows indicate pre-emptive retransplantation; dashed arrows signify primary non-function. Self-links are omitted for clarity (there are no tunnel states).

Source: assessment report figure 16.

6.11 In the base case, the modelled population was aged 10 years and 60% were male. The Assessment Group 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. Regardless of the regimen used for the first transplant, the same regimen was used for subsequent transplants (basiliximab, immediate-release tacrolimus and mycophenolate mofetil). The Assessment Group advised that, because subsequent transplants used the same regimen, the cost-effectiveness results were primarily driven by outcomes for the first transplant.

6.12 The time in each health state was determined by the rate of 3 events: mortality, graft loss and retransplantation. The rate of retransplantation was the same for all regimens and was calculated from the UK Transplant Registry with an adjustment to reflect shorter waiting times for children and adolescents. 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 6.13 and 6.14.

6.13 In the Assessment Group'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. For later time points with the first graft, a surrogate relationship was used to predict the rate of death with functioning graft, based on age, time since transplantation and the regimen-specific incidence of new-onset diabetes (calculated from the network meta-analysis). For subsequent grafts, the surrogate relationship was based only on age and new-onset diabetes. The hazard ratio linking new-onset diabetes to mortality, 1.41, was taken from a published study of adults (Cole et al. 2008).
- The **rate of death from the graft loss state** (that is, the rate of death whilst on dialysis) was estimated using data from the UK Renal Registry, adjusted for age. This rate was the same for all regimens.

6.14 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 transplantation, a regimen-specific estimate of graft function, and the regimen-specific incidence of BPAR and new-onset diabetes. The last 3 estimates were calculated from the network meta-analysis. The hazard ratios linking graft function to graft loss were based on paediatric data (Muscheites et al. 2009). The hazard ratios linking BPAR (hazard ratio=1.60) and new-onset diabetes (hazard ratio=1.12) to graft loss were based on adult

data (Cole et al. 2008). 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.

6.15 The model included 4 adverse events:

- New-onset diabetes within 12 months of transplantation. Based on a network meta-analysis of adult RCTs, the incidence was higher for regimens that included tacrolimus.
- Cytomegalovirus infection within 12 months of transplantation. Based on a network meta-analysis of adult RCTs, the incidence was lower for regimens that included sirolimus or everolimus.
- Dyslipidaemia within 12 months of transplantation. Based on a network meta-analysis of adult RCTs, the incidence was higher for regimens that included sirolimus or everolimus.
- Anaemia: the prevalence was the same for all regimens.

6.16 The network meta-analysis did not distinguish between mycophenolate mofetil and mycophenolate sodium. Accordingly, clinical effectiveness estimates and adverse event rates for mycophenolate sodium were taken from the mycophenolic acid arm of the network meta-analyses and adjusted using head-to-head comparisons between mycophenolate mofetil and mycophenolate sodium. Similarly, for prolonged-release tacrolimus the Assessment Group adjusted the results for immediate-release tacrolimus using head-to-head comparisons.

6.17 The Assessment Group did not find any studies of the health-related quality of life of children and adolescents 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 Assessment Group 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 (see Table 86 of the assessment report). New-onset diabetes was associated with a decrement of 0.06, based on an American study that reported EQ-5D values. The remaining adverse events did not result in a utility decrement. Appendix 8 of the assessment report summarises the parameters in the model.

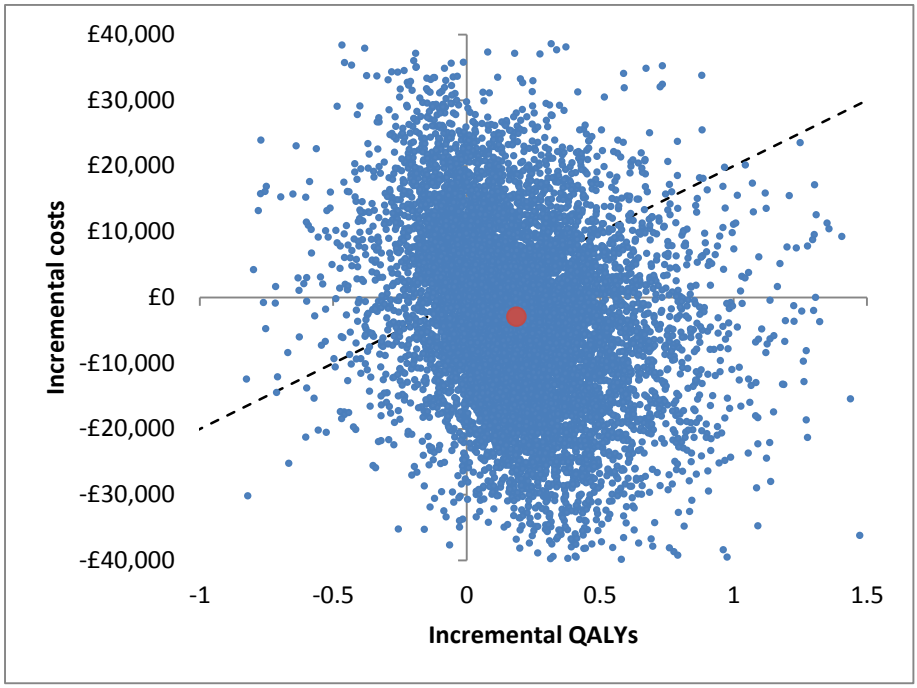
6.18 In an erratum, the Assessment Group made a number of corrections to the model including changes to: efficacy estimates for r-ATG, drug administration costs for belatacept, resource use for sirolimus, and discounting of costs. This document presents the corrected results.

Results of the Assessment Group's modelling using paediatric data

6.19 The model based on the RCT of Grenda et al. (2006) showed that treatment with basiliximab dominated treatment with no induction. 'Dominated' means that basiliximab cost less and was more effective than no induction (incremental costs −£5697, incremental QALYs 0.1817; see

6.20 Table 9). The cost difference arose because treatment with basiliximab resulted in lower predicted expenditure on dialysis after the end of the trial. The total QALYs were similar for both basiliximab and no induction. 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 (although the simulations were scattered widely, see Figure 2).

Figure 2. Probabilistic sensitivity analysis scatter cloud based on the RCT of Grenda et al. (2006), comparing basiliximab with no induction.

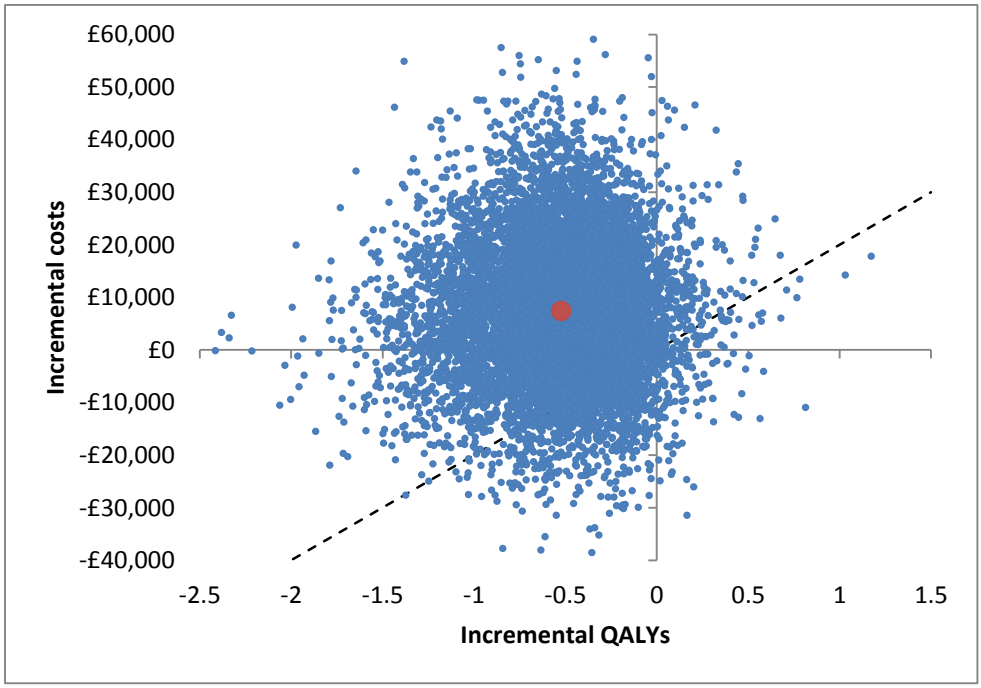


Note: The dashed line indicates a threshold of £20,000 per QALY gained. Points to the south-east of this line indicate that basiliximab is cost-effective versus placebo at £20,000 per QALY gained. The red dot shows the mean incremental costs and QALYs. Source: erratum to assessment report, figure 29.

6.21 In contrast to the results based on Grenda et al. (2006), the model based on Offner et al. (2008) showed that treatment with placebo dominated treatment with basiliximab (incremental costs −£8528, incremental QALYs 0.5457;

6.22 Table 9). 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 (Figure 3).

Figure 3. Probabilistic sensitivity analysis scatter cloud based on the RCT of Offner et al. (2008), comparing basiliximab with placebo.



Note: The dashed line indicates a threshold of £20,000 per QALY gained. Points to the south-east of this line indicate that basiliximab is cost-effective versus placebo at £20,000 per QALY gained. The red dot shows the mean incremental costs and QALYs. Source: erratum to assessment report, figure 31.

6.23 The Assessment Group's model based on the RCT of Trompeter et al. (2002) showed that treatment with immediate-release tacrolimus dominated treatment with ciclosporin (incremental costs −£44,543, incremental QALYs 0.5487). 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 9. Results of the Assessment Group's modelling using data from paediatric RCTs (deterministic analysis).

Regimen	Discounted costs		Discounted QALYs		ICER
	Total	Incr.	Total	Incr.	
Grenda et al. (2006) – all patients received tacrolimus and azathioprine					
No induction	£141,012	-	17.4928	-	-
Basiliximab	£135,315	−£5697	17.6745	0.1817	Dominant
Offner et al. (2008) – all patients received ciclosporin and mycophenolate mofetil					
Basiliximab	£135,212	-	17.8300	-	-
Placebo	£126,684	−£8528	18.3757	0.5457	Dominant
Trompeter et al. (2002) – all patients received azathioprine					
Ciclosporin	£221,489	-	16.1698	-	-
Immediate-release tacrolimus	£176,946	−£44,543	16.7185	0.5487	Dominant

Abbreviations: Incr, incremental; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

For consistency with the assessment report, regimens are sorted in order of ascending effectiveness (total discounted QALYs). The incremental values were calculated by the NICE technical team.

Source: erratum to the assessment report, Tables 108, 112 and 116.

6.24 For all 3 analyses using paediatric data, the probabilistic results were similar to the deterministic results. The Assessment Group conducted 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 all 3 analyses using paediatric data, the results of the sensitivity analyses were similar to the base case.

Results of the Assessment Group's modelling using adult data

6.25 The Assessment Group presented the results in 2 ways: firstly as a simultaneous comparison between all 18 regimens in the model, and secondly as a series of comparisons between individual drugs. When all regimens were compared simultaneously, the combination of basiliximab plus tacrolimus plus azathioprine dominated all but one of the other regimens. The exception was basiliximab plus belatacept plus mycophenolate mofetil, which had an incremental cost-effectiveness ratio

(ICER) of over £700,000 per QALY gained compared with basiliximab plus tacrolimus plus azathioprine.

Comparison of individual induction treatments

6.26 The Assessment Group compared basiliximab, r-ATG and no induction in 4 analyses, each of which used a different maintenance regimen (Table 10). In all analyses, no induction dominated r-ATG (incremental costs between −£6017 and −£9918; incremental QALYs between 0.03 and 0.06). Basiliximab dominated both r-ATG and no induction (compared with no induction, incremental costs between −£9053 and −£11,055; incremental QALYs between 0.12 and 0.13).

6.27 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 Assessment Group conducted 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.

Table 10. Assessment Group's cost-effectiveness results for induction agents, using effectiveness estimates from adult RCTs (deterministic analysis).

Induction agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Regimens with ciclosporin and azathioprine					
r-ATG	£216,114	—	17.9721	—	—
No induction	£210,097	−£6017	18.0031	0.0310	Dominant
Basiliximab	£199,042	−£11,055	18.1308	0.1277	Dominant
Regimens with ciclosporin and mycophenolate mofetil					
Rabbit ATG	£209,097	—	18.0702	—	—
No induction	£199,910	−£9188	18.1269	0.0567	Dominant
Basiliximab	£190,856	−£9053	18.2468	0.1200	Dominant
Regimens with tacrolimus and azathioprine					
Rabbit ATG	£183,191	—	18.2468	—	—
No induction	£174,989	−£8202	18.2970	0.0502	Dominant
Basiliximab	£164,316	−£10,673	18.4259	0.1288	Dominant

Regimens with tacrolimus and mycophenolate mofetil					
Rabbit ATG	£189,637	—	18.1763	—	—
No induction	£179,719	−£9918	18.2398	0.0635	Dominant
Basiliximab	£170,182	−£9537	18.3596	0.1198	Dominant
Source: erratum to assessment report Table 120.					

Comparison of individual maintenance treatments

6.28 The maintenance regimens all resulted in similar total discounted QALYs, so the incremental QALY gain was under 0.3 for all comparisons (

6.29 Table 11). The results for each intervention were as follows:

- Treatment with **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 £20,000 compared with ciclosporin, £16,446 compared with prolonged-release tacrolimus, and £28,449 compared with sirolimus.
- **Prolonged-release tacrolimus** dominated ciclosporin. However, prolonged-release tacrolimus was dominated by immediate-release tacrolimus (incremental costs £16,446; incremental QALYs −0.0544).
- **Belatacept** had an ICER of £533,449 per QALY gained compared with immediate-release tacrolimus.
- **Mycophenolate mofetil** dominated azathioprine when it was 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 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.

6.30 To summarise, 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 in combination with ciclosporin.

6.31 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. Cost-effectiveness acceptability curves are shown in section 6.3.2.2 of the erratum to the assessment report (figures 35–50).

6.32 The Assessment Group conducted 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 dropped 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.

6.33 The Assessment Group presented an analysis in which the age at transplantation was varied from 2 to 17 years. For all ages, the most cost-effective regimen was basiliximab, tacrolimus and azathioprine.

Table 11. Assessment Group's cost-effectiveness results for maintenance treatments, using effectiveness estimates from adult RCTs (deterministic analysis).

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Regimens with mycophenolate mofetil					
Ciclosporin	£199,910	—	18.1269	—	—
PR tacrolimus	£196,165	−£3744	18.1854	0.0586	Dominant
IR tacrolimus	£179,719	−£16,446	18.2398	0.0544	Dominant
Regimens with azathioprine					
Ciclosporin	£210,097	—	18.0031	—	—
IR tacrolimus	£174,989	−£35,108	18.2970	0.2940	Dominant
Regimens with basiliximab and mycophenolate mofetil					
Sirolimus	£198,631	—	18.2423	—	—
Ciclosporin	£190,856	−£7775	18.2468	0.0045	Dominant
IR tacrolimus	£170,182	−£20,674	18.3596	0.1127	Dominant
Belatacept	£293,175	£122,993	18.5901	0.2306	£533,449
Regimens with basiliximab and azathioprine					
Ciclosporin	£199,042	—	18.1308	—	—
IR tacrolimus	£164,316	−£34,726	18.4259	0.2951	Dominant
Regimens with rATG and mycophenolate mofetil					
Ciclosporin	£209,097	—	18.0702	—	—
IR tacrolimus	£189,637	−£19,460	18.1763	0.1061	Dominant
Regimens with rATG and azathioprine					
Ciclosporin	£216,114	—	17.9721	—	—
IR tacrolimus	£183,191	−£32,923	18.2468	0.2748	Dominant
Regimens with ciclosporin					
Azathioprine	£210,097	—	18.0031	—	—
Myc. mofetil	£199,910	−£10,188	18.1269	0.1238	Dominant
Everolimus	£259,327	£59,417	18.2209	0.0940	£632,246
Regimens with immediate-release tacrolimus					
Sirolimus	£222,300	—	17.9553	—	—
Myc. mofetil	£179,719	−£42,581	18.2398	0.2844	Dominant
Azathioprine	£174,989	−£4730	18.2970	0.0572	Dominant
Regimens with basiliximab and ciclosporin					
Azathioprine	£199,042	—	18.1308	—	—
Myc. mofetil	£190,856	−£8186	18.2468	0.1161	Dominant

Maintenance agent	Discounted costs		Discounted QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Myc. sodium	£198,303	£7447	18.3907	0.1438	£51,770
Regimens with basiliximab and immediate-release tacrolimus					
Myc. mofetil	£170,182	—	18.3596	—	—
Azathioprine	£164,316	−£5866	18.4259	0.0663	Dominant
Regimens with rATG and ciclosporin					
Azathioprine	£216,114	—	17.9721	—	—
Myc. mofetil	£209,097	−£7017	18.0702	0.0982	Dominant
Regimens with rATG and immediate-release tacrolimus					
Myc. mofetil	£189,637	—	18.1763	—	—
Azathioprine	£183,191	−£6446	18.2468	0.0705	Dominant

Abbreviations. Myc, myophenolate; IR, immediate-release; PR, prolonged-release.
Source: erratum to assessment report, table 122.

Responses to consultation on the Assessment Group's model

6.34 Astellas stated that the model underestimated the benefits of prolonged-release tacrolimus arising from better adherence. Novartis advised that health-related quality of life depends on graft function, but this was not reflected in the model because all patients with a functioning graft were assumed to have the same utility. Regarding drug costs, Astellas advised that the model should use discounted prices for prolonged-release tacrolimus (see section 6.34) and Sanofi advised that the dosage of r-ATG was too high.

Astellas' economic model

6.35 Astellas submitted a Markov model with 4 states: functioning graft without previous BPAR, functioning graft with previous BPAR, non-functioning graft and death. In the base case, patients entered the model aged 8 years and the time horizon was 10 years. Astellas' model evaluated the following maintenance therapies: prolonged-release tacrolimus, tacrolimus granules for oral suspension (Modigraf), tacrolimus 'specials' (that is, an oral suspension made by a pharmacist), belatacept, everolimus, sirolimus in combination with low-dose ciclosporin (a regimen that minimised

calcineurin inhibitors) and sirolimus in combination with mycophenolate mofetil (a regimen that avoided calcineurin inhibitors). The comparator was Prograf (a brand of immediate-release tacrolimus capsules).

6.36 The Astellas model used effectiveness estimates from studies of adults. For each drug, the incidence of BPAR in the first 12 months was used to predict the long-term rate of graft loss. The hazard ratio for graft loss, comparing patients who had BPAR with patients who did not, was 1.52. For the comparison between prolonged- and immediate-release tacrolimus, Astellas assumed that adherence was better with prolonged-release tacrolimus (based on data from Kuypers et al. 2013) and that this improved graft survival and patient survival. For all other comparisons, adherence was not included in the model. The utility values, based on EQ-5D data from adults in the UK, were 0.71 for health states with a functioning graft and 0.46 for the graft failure state. The model included the costs of induction with basiliximab, maintenance treatment, managing BPAR, treating adverse events, dialysis and retransplantation. Drug costs were from the British national formulary.

6.37 Astellas presented the results as pairwise comparisons with Prograf.

- Prograf dominated belatacept, everolimus and sirolimus in a calcineurin-inhibitor avoidance regimen.
- Prolonged-release tacrolimus dominated Prograf.
- All forms of immediate-release tacrolimus were assumed to have similar effectiveness but Modigraf was the most expensive (total costs were £88,915, compared with £58,471 for Prograf and £72,945 for 'specials').
- Prograf had an ICER of over £1.5 million per QALY gained compared with sirolimus in a calcineurin-inhibitor minimisation regimen.

Sensitivity analyses used a discounted price for [redacted] Prograf [redacted], Advagraf [redacted] and

Modigraf [redacted]. The total costs were reduced by [redacted] respectively.

6.38 The Assessment Group advised that the Astellas evaluation omitted ciclosporin as a comparator so the results may be misleading. Moreover, Astellas used list prices for drugs even though the NHS pays discounted prices for generic drugs including immediate-release tacrolimus, mycophenolate mofetil and steroids. For the population of children and adolescents unable to swallow tablets, Astellas compared Modigraf with a 'specials' formulation of tacrolimus. The Assessment Group commented that this analysis was inconsistent, because it assumed that patients would be able to swallow tablets containing mycophenolate mofetil and prednisolone but not tablets containing tacrolimus.

Summary of cost-effectiveness results

6.39 There were 3 main analyses:

- The Assessment Group's evaluation using data from paediatric RCTs. This provided 2 assessments of basiliximab and 1 of immediate-release tacrolimus.
- The Assessment Group's evaluation using effectiveness results from adult RCTs. This included all interventions.
- The evaluation by Astellas, which assessed a subset of the maintenance therapies and did not include ciclosporin as a comparator.

6.40 The results regarding basiliximab were contradictory. The Assessment Group's model based on Grenda et al. (2006), and the model using data from adults, showed that basiliximab was cheaper and more effective than no induction. In contrast, the model based on Offner et al. (2008) showed that basiliximab was more expensive and less effective than placebo. One possible reason for the discrepancy is that the odds ratio for graft loss was more favourable to basiliximab in Grenda et al. than in Offner et al. (see Table 5). In all the models, the difference between induction treatments in

total QALYs was small. The Assessment Group's model using adult data showed that basiliximab was cheaper and more effective than both r-ATG and placebo.

6.41 Regarding maintenance therapy, the results for immediate-release tacrolimus were consistently favourable. The Assessment Group's model based on Trompeter et al. (2002), and the model using data from adults, showed that immediate-release tacrolimus was cheaper and more effective than ciclosporin. The Assessment Group's model using data from adults also showed that immediate-release tacrolimus was cheaper and more effective than prolonged-release tacrolimus and sirolimus. The same model showed that, in regimens that include ciclosporin, mycophenolate mofetil was cheaper and more effective than azathioprine.

6.42 The Assessment Group's model using data from adults showed that the following treatments were either dominated or had an ICER above £30,000 per QALY gained: prolonged-release tacrolimus, belatacept, mycophenolate mofetil in combination with tacrolimus, mycophenolate sodium, sirolimus and everolimus.

6.43 The Assessment Group's result for prolonged-release tacrolimus was contradicted by the Astellas model, which showed that prolonged-release tacrolimus was cheaper and more effective than Prograf (a brand of immediate-release tacrolimus). The Assessment Group advised that the following differences between models could explain the discrepancy in results:

- The models used different time horizons, utility values and clinical trial data (see page 307 of the assessment report).
- Astellas used only BPAR to predict long-term outcomes, whereas the Assessment Group used BPAR, new-onset diabetes and graft function.
- Astellas used list prices for drug costs and the Assessment Group used eMIT prices.

- In the Astellas model, adherence was better with prolonged-release tacrolimus and this was assumed to improve graft survival and patient survival. The Assessment Group's model did not include a surrogate relationship linking adherence to longer-term outcomes.

6.44 The Assessment Group's economic evaluation had a number of strengths (see section 7.2.2.1 of the assessment report). The natural history of disease was based on UK registry data and the surrogate relationship between graft function and graft survival was estimated from a study of children and adolescents. The Assessment Group used effectiveness estimates from paediatric RCTs where available, and also used effectiveness estimates from adult RCTs in order to assess all interventions in the scope. The limitations of the evaluation include: graft function was not modelled over time, the cost-effectiveness of reducing corticosteroids was not assessed, adherence was not assessed, some surrogate relationships were based on adult data, it was assumed that there were no treatment interactions between induction and maintenance therapy, vial sharing was assumed for r-ATG, and only selected adverse events were included (see section 7.2.2.2 of the assessment report).

7 Equality issues

7.1 During scoping for the related appraisal for adults (Immunosuppressive therapy for kidney transplantation in adults, including a review of technology appraisal guidance 85) consultees noted that some Jehovah's Witnesses are unwilling to be treated with intravenous human immunoglobulin. Consideration should be given to the treatment options available for people who are unwilling to receive human blood products, to ensure that any recommendations do not directly or indirectly discriminate on the basis of religion.

7.2 The assessment report noted that black patients tend to have worse graft function, shorter graft survival and higher rates of nephropathy than white patients.

8 Innovation

8.1 Astellas advised that Modigraf is the only granular formulation of tacrolimus that has a marketing authorisation for paediatric use in the UK (see section 5.2). Astellas stated that, if Modigraf is not used, opening tacrolimus capsules and dissolving them in water may endanger the health of parents and healthcare providers, but this risk is not included in the calculation of quality-adjusted life years.

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Appendix A: Supporting evidence

Related NICE guidance

Published

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

Under development

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

- Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85). NICE technology appraisal. Anticipated publication date TBC.

NICE pathways

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

Appendix B: Public assessment reports

- **Basiliximab** initial marketing authorisation: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000207/WC500053538.pdf. Variation to add details of paediatric studies: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000207/WC500131049.pdf
- **Rabbit anti-human thymocyte immunoglobulin** – to access the Public Assessment Report, go to http://www.mhra.gov.uk/public-assessment-reports/, search for 'thymoglobuline', click on the link, then select 'view the item you were looking for in the UK Government Web Archive'.
- **Immediate-release tacrolimus** (Tacni): http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con103029.pdf
- **Immediate-release tacrolimus** (Modigraf): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000954/WC500030473.pdf
- **Prolonged-release tacrolimus** (Advagraf): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000712/WC500022237.pdf
- **Belatacept**: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002098/WC500108357.pdf
- **Mycophenolate mofetil** (CellCept): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000082/WC500021861.pdf
- **Mycophenolate sodium**: Not available online. SPC: https://www.medicines.org.uk/emc/medicine/14917
- **Sirolimus**: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000273/WC500046434.pdf
- **Everolimus**: Not available online. SPC: https://www.medicines.org.uk/emc/medicine/30306