NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Immunosuppressive therapy for kidney transplant in children and young people

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

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
- Are there any outstanding clinical and commissioning issues that arise during immunosuppressive therapy for kidney transplant for which further guidance is needed? Is there sufficient evidence available that could support the development of additional technology appraisal recommendations to address these issues? Would additional NICE technology appraisal guidance add value, or would other routes be more appropriate to eliminate these issues, such as other NICE programmes or NHS England commissioning policies?

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

After consultation:

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 22 May 2017

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

This guidance makes recommendations on using basiliximab, rabbit anti-human thymocyte immunoglobulin, tacrolimus (immediate-release and prolonged-release), mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept after kidney transplant in children and young people. The recommendations apply only to the initial immunosuppressive therapy (induction and maintenance therapy) started around the time of kidney transplant.

The guidance does not make recommendations on using the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid after kidney

transplant in children and young people.

Under an exceptional directive from the Department of Health, the appraisal committee was allowed to make recommendations about using drugs outside the terms of their marketing authorisations if there was compelling evidence of their safety and effectiveness.

1.1 Basiliximab, when used as part of an immunosuppressive regimen that includes a calcineurin inhibitor, is recommended as an initial option to prevent organ rejection in children and young people having a kidney transplant.[1,2]

1.2 Immediate-release tacrolimus, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in children and young people having a kidney transplant. Treatment should normally be started with the least expensive product.[3] However, treatment can be started with an alternative dosage form if the child or young person is not able to swallow capsules. Tacrolimus granules for oral suspension (Modigraf) should be used only if the company provides it at the same price or lower than that agreed with the Commercial Medicines Unit.

[1] April 2017: the use of basiliximab (in combination with tacrolimus) and mycophenolate mofetil (in combination with tacrolimus) is outside the terms of the marketing authorisations for basiliximab and for mycophenolate mofetil. If these combinations are prescribed, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. For further information, see the General Medical Council's guidance on Good practice in prescribing and managing medicines and devices.

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

[3] The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that to maintain therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only. If a prescriber considers that switching to a different brand of oral tacrolimus would be of benefit, the change requires careful supervision and therapeutic monitoring by an appropriate specialist. See the MHRA's advice on oral tacrolimus products.

1.3 Mycophenolate mofetil, when used as part of an immunosuppressive regimen, is recommended as an initial option to prevent organ rejection in children and young people having a kidney transplant. Treatment should normally be started with the least expensive product. However, treatment can be started with an alternative dosage form if the child or young person is not able to swallow capsules.[1,2]

1.4 Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as initial treatments to prevent organ rejection in children and young people having a kidney transplant.

1.5 The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in children or young people who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes children and young people who:

- are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or
- have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable, for example because of contraindications or intolerance.

1.6 These recommendations are not intended to affect treatment with any of the technologies considered in this appraisal that was started in the NHS before this guidance was published. Children

and young people having treatment outside these recommendations, or for whom the committee were unable to make a recommendation, may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person or their parents or carers.

2 Clinical need and practice

2.1 Kidney transplant is used to treat established kidney failure, which is severe and irreversible impairment of kidney function. After a kidney transplant, immunosuppressive therapy is used to reduce the risk of rejection of the transplanted kidney (or 'graft') and prolong its survival. Between April 2015 and March 2016, 129 kidney transplants were done in the UK for children and young people under 18 years.

2.2 Kidney transplant in children and young people can differ from adults in several important aspects including the cause of kidney failure, the pharmacokinetic properties of immunosuppressive therapies and how they are metabolised, the immune response after transplant, the measures of success of the transplant procedure, the susceptibility to post-transplant complications, and the degree of adherence to treatment.

2.3 Immunosuppressive therapy aims to prevent acute rejection and optimise the function of the transplanted kidney, while minimising the adverse effects of immunosuppression (such as increased risk of infection, cancer, diabetes and cardiovascular disease). Immunosuppressive therapy can be categorised as induction therapy or maintenance therapy. Induction therapy is an intensive immunosuppression regimen that is used for up to 2 weeks around the time of transplant and may include polyclonal or monoclonal

antibodies. Maintenance therapy starts immediately after transplant and continues for life.

2.4 NICE's technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and adolescents was published in 2006. It recommended basiliximab, daclizumab, tacrolimus, mycophenolate mofetil and sirolimus, in certain circumstances, as options for immunosuppressive therapy for kidney transplant in children and young people. Since that appraisal, the marketing authorisation for daclizumab has been withdrawn, new technologies (rabbit anti-human thymocyte immunoglobulin, mycophenolate sodium, belatacept, a prolonged-release formulation of tacrolimus, and everolimus) have received marketing authorisations, but some of the marketing authorisations exclude children and young people. In addition, some of the technologies are available as generics.

3 The technologies

Induction therapy

Basiliximab

3.1 Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody that acts as an interleukin-2 receptor antagonist. It has a marketing authorisation in the UK for the prophylaxis of acute organ rejection in people having a kidney transplant. The indication includes children and young people aged 1–17 years. The summary of product characteristics states that basiliximab is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel-reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for

microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

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

3.3 Basiliximab is available in 10 mg and 20 mg vials at a price of £758.69 and £842.38 respectively (excluding VAT; British National Formulary [BNF] online [accessed April 2017]), equating to £1,517 per course of treatment for a patient weighing under 35 kg and £1,685 for a patient weighing 35 kg or more.

Rabbit anti-human thymocyte immunoglobulin

3.4 Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline, Sanofi) is made by injecting human thymus cells into rabbits. The drug contains immunoglobulins (antibodies) that attach to and destroy some of the cells of the immune system. It has a marketing authorisation in the UK for the prevention of graft rejection in kidney transplant. The summary of product characteristics states that it is usually used in combination with other immunosuppressive drugs, but does not state whether the indication includes children and young people. It also advises that no recommendation about dosage for children and young people can be made, but that available information indicates that they do not need a different dosage to adults.

3.5 r-ATG is administered intravenously, at a dose of 1–1.5 mg/kg/day for 3–9 days after a kidney transplant (a cumulative dose of 3–13.5 mg/kg).

3.6 r-ATG is available in 25 mg vials at a price of £158.77 (excluding VAT; BNF online [accessed April 2017]). The assessment group (AG) estimated that the cost of induction therapy with r-ATG for a 10-year-old boy is £2,101 (assuming vials are shared so that there is no wastage).

Maintenance therapy

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

Immediate-release tacrolimus

3.8 Brands of immediate-release tacrolimus include Adoport (Sandoz), Capexion (Mylan), Modigraf (Astellas Pharma), Perixis (Accord Healthcare), Prograf (Astellas Pharma), Tacni (Teva) and Vivadex (Dexcel Pharma). All of these formulations have marketing authorisations in the UK for the prophylaxis of transplant rejection in people having a kidney transplant. Adoport, Capexion, Perixis, Prograf, Tacni and Vivadex are administered orally as capsules, twice a day. Prograf can also be administered intravenously. Modigraf consists of granules for oral suspension.

3.9 For all brands of immediate-release tacrolimus, the summary of product characteristics recommends an initial dose for children (age range not specified) of 0.3 mg/kg/day orally or 0.075–0.100 mg/kg/day intravenously and states that the dosage is usually reduced in the period after the transplant.

3.10 Modigraf (tacrolimus granules for oral suspension) is available in sachets of 0.2 mg and 1 mg at a price of £7.13 per mg (excluding VAT; BNF online [accessed April 2017]). The company has agreed

a nationally available price reduction for Modigraf with the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence. The price of tacrolimus capsules varies by brand. The AG calculated that the average cost paid by the NHS for immediate-release tacrolimus capsules is £0.52 per mg (excluding VAT; data from the Electronic Market Information Tool [eMIT], Commercial Medicines Unit). The AG estimated that the weekly cost of maintenance therapy with immediate-release tacrolimus capsules for a 10-year-old boy is £34. Adoport is available to the NHS with a nationally available price reduction agreed between the company and the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

Prolonged-release tacrolimus

3.11 Prolonged-release tacrolimus (Advagraf, Astellas Pharma) is administered orally as a capsule, once a day. It has a marketing authorisation in the UK for the prophylaxis of transplant rejection in adults having a kidney transplant. The summary of product characteristics recommends an initial dose for adults of 0.2–0.3 mg/kg/day. The dosage is usually reduced in the period after the transplant. It also states that the safety and efficacy of prolonged-release tacrolimus in children under 18 years have not yet been established and that limited data are available but no recommendation on dosage can be made.

3.12 Prolonged-release tacrolimus (Advagraf) is available as 0.5 mg, 1 mg, 3 mg and 5 mg capsules at a price of £1.07–£1.43 per mg (excluding VAT; BNF online [accessed April 2017]). The AG estimated that the weekly cost of maintenance therapy with prolonged-release tacrolimus for a 10-year-old boy is £47 (using the list price and the dosage for adults). Advagraf is available to the NHS with a nationally available price reduction agreed between the

company and the Commercial Medicines Unit. The prices agreed through the framework are commercial in confidence.

3.13 Another brand of prolonged-release tacrolimus, Envarsus (Chiesi) obtained a marketing authorisation for adults after the scope for this appraisal was finalised. The brand name Envarsus was not included in the assessment group's (AG's) search for evidence and Chiesi was not asked to submit evidence for the appraisal.

Belatacept

3.14 Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T-cells. Belatacept, in combination with corticosteroids and a mycophenolic acid, has a marketing authorisation in the UK for prophylaxis of graft rejection in adults having a kidney transplant. The summary of product characteristics recommends that an interleukin-2 receptor antagonist is added to this belatacept-based regimen. It also states that the safety and efficacy of belatacept in children and adolescents under 18 years have not yet been established and that no data are available.

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

3.16 Belatacept is available in 250 mg vials at a price of £354.52 (excluding VAT; BNF online [accessed April 2017]). The AG estimated that the weekly cost of maintenance therapy with belatacept for a 10-year-old boy is £56 (using the dosage for adults and assuming vials are shared so that there is no wastage).

Mycophenolate mofetil

3.17 Mycophenolate mofetil (generic) has a marketing authorisation in the UK, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute transplant rejection in people having a kidney transplant. Mycophenolate mofetil can be administered orally (capsules or an oral suspension) or intravenously. The summary of product characteristics states that the recommended daily dose for children and young people (aged 2–18 years) is 1,200 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.

3.18 The price of mycophenolate mofetil varies by brand. The oral suspension (CellCept) is available in 175 ml containers of 1 g/5 ml suspension at a price of £3.29 per g (excluding VAT; BNF online [accessed April 2017]). At the time of the initial committee discussion (July 2015), the average cost paid by the NHS for mycophenolate mofetil capsules was £0.38 per g (excluding VAT; data from eMIT, Commercial Medicines Unit). The AG estimated that the weekly cost of maintenance therapy with mycophenolate mofetil capsules for a 10-year-old boy is between £1.74 and £3.48.

Mycophenolate sodium

3.19 Mycophenolate sodium (Myfortic, Novartis Pharmaceuticals), in combination with ciclosporin and corticosteroids, has a marketing authorisation in the UK for the prophylaxis of acute transplant rejection in adults having a kidney transplant. The summary of product characteristics states that insufficient data are available to support the efficacy and safety of mycophenolate sodium in children and adolescents. It is administered orally, at a recommended dose for adults of 1.44 g per day.

3.20 Mycophenolate sodium is available in 180 mg and 360 mg tablets at a price of £4.48 per g (excluding VAT; BNF online [accessed April 2017]). The AG estimated that the weekly cost of maintenance therapy with mycophenolate sodium for a 10-year-old boy is £50 (using the dosage for adults).

Sirolimus

3.21 Sirolimus (Rapamune, Pfizer) is an antiproliferative that blocks a protein called mammalian target of rapamycin (mTOR). It has a marketing authorisation in the UK for the prophylaxis of organ rejection in adults having a kidney transplant, who are at low to moderate immunological risk. It is recommended to be used initially in combination with ciclosporin and corticosteroids for 2–3 months, and may be continued only if ciclosporin can be progressively discontinued. The summary of product characteristics states that the safety and efficacy of sirolimus in children and adolescents under 18 years have not been established.

3.22 Sirolimus is administered orally as a tablet or solution. The recommended dose for adults is 6 mg initially, followed by 2 mg per day for 2-3 months, then adjusted to obtain blood trough levels of 4–12 nanograms/ml.

3.23 Sirolimus is available as 0.5 mg, 1 mg and 2 mg tablets and a 1 mg/ml oral solution, at a net price of £2.71–£4.60 per mg (excluding VAT; BNF online [accessed April 2017]). The AG estimated that the weekly cost of maintenance therapy with sirolimus for a 10-year-old boy is £40 (using the dosage for adults).

Everolimus

3.24 Everolimus (Certican, Novartis Pharmaceuticals) is an antiproliferative that blocks mTOR. It has a marketing authorisation for the prophylaxis of organ rejection in adults having a kidney transplant, who are at low to moderate immunological risk. The

summary of product characteristics states that everolimus should be used in combination with ciclosporin and corticosteroids. Everolimus is administered orally as a tablet. The recommended initial dose for adults is 1.5 mg/day. The summary of product characteristics states that there is insufficient experience to recommend the use of everolimus in children and adolescents.

3.25 Everolimus is available in 0.25 mg, 0.5 mg and 0.75 mg tablets at a net price of £9.90 per mg (excluding VAT; BNF online [accessed April 2017]). The AG estimated that the weekly cost of maintenance therapy with everolimus for a 10-year-old boy is £104 (using the dosage for adults).

3.26 Costs for all of the technologies may vary in different settings because of negotiated procurement discounts.

4 Committee discussion

The appraisal committee (section 7) considered evidence from a number of sources. See the committee papers for full details of the evidence. The appraisal included 9 drugs for immunosuppression after kidney transplant in children and young people. Basiliximab and rabbit anti-human thymocyte immunoglobulin (r-ATG) are both induction therapies. The other drugs are maintenance therapies: immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept.

The appraisal committee reviewed the data available on the clinical and cost effectiveness of the technologies, having considered evidence on the nature of kidney transplant and organ rejection and the value placed on the benefits of immunosuppressive therapy by people with a kidney transplant, those who represent them, and

clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee discussed aspects of immunosuppression that are especially important for children and young people. It heard from clinical experts that quality of life is better with a transplant than while having dialysis, so the aim of immunosuppression treatment is to prolong survival of the transplanted kidney (or 'graft'). The committee also heard that it is important to minimise the side effects of immunosuppressive therapies, such as reduced growth and an increased risk of new-onset diabetes. Several submissions from consultees advised that poor adherence (that is, not taking the prescribed medication) is a major cause of graft loss, especially in young people. The committee heard that different people have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.

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

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

The committee was aware that there are several brands of oral tacrolimus, and that inadvertent switching between products has been associated with toxicity and graft rejection. It heard from clinical experts that, to minimise the risk of accidental switching, UK

clinicians follow advice from the Medicines and Healthcare products Regulatory Agency to prescribe and dispense oral tacrolimus products by brand name. It heard from clinical experts that, for the same reason, brand names are used when prescribing ciclosporin. The committee concluded that the immunosuppressive regimens most commonly used by children and young people in the UK were: induction without antibodies then maintenance therapy with tacrolimus and azathioprine; or basiliximab induction then maintenance therapy with tacrolimus and mycophenolate mofetil.

4.3 The committee discussed the decision problem addressed by the assessment report. For induction therapy, the committee agreed that it was appropriate to compare the interventions with each other and against treatment without induction. For maintenance therapy, the committee agreed that it was appropriate to compare the interventions with each other and against ciclosporin and azathioprine. The committee noted that the final guidance would apply to the interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and a corticosteroid (the standard triple therapy regimen), which were included as comparators only. A clinical expert suggested that the appraisal should also consider alemtuzumab as an induction therapy. The committee was aware that alemtuzumab does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and is not routinely available for transplant patients (it is available on a 'named patient' basis). It heard from clinical experts that alemtuzumab is not currently used for children and young people having a kidney transplant in the UK. The committee agreed that alemtuzumab should not be included as either an intervention or a comparator. Regarding the population for the appraisal, the committee agreed with the assessment group (AG) that there were insufficient data to permit analyses of subgroups such as children and young people with different levels

of immunological risk. The committee concluded that the assessment report included the appropriate population, interventions and comparators.

Clinical effectiveness

4.4 The AG's systematic review found 3 RCTs and 10 non-randomised studies of children and young people, of which 1 RCT and 6 non-randomised were identified in the updated systemic review for the current appraisal. The committee acknowledged that the number of studies in children and young people was low. It noted that the 3 RCTs were likely to be generalisable to the NHS because the trials were done in Europe, the patient and donor characteristics were largely representative of people using the NHS, and the drug doses were similar to current recommendations. However, the committee acknowledged that the evidence is quite old. The AG did not find any studies of children and young people comparing the following drugs with the comparators in the scope: r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus and belatacept. In addition, only 1 small study of children and young people assessed sirolimus. The clinical experts advised that, given the lack of evidence for children and young people, NHS practice is informed by evidence from adults and by clinical experience. The AG stated that data from the UK Transplant Registry provides useful information on graft and patient survival, but cannot be used to compare the effectiveness of different treatments. The committee concluded that it should consider all of the evidence about the effectiveness of immunosuppressive regimens, including randomised and non-randomised studies in children and young people and randomised controlled trials (RCTs) in adults.

4.5 The committee discussed whether it had considered all of the relevant evidence. Consultees and clinical experts advised that it

was important to consider TWIST, an international RCT that recruited patients of 2–18 years having a kidney transplant (Grenda et al. 2010). Patients randomised to the TWIST regimen (daclizumab induction, immediate-release tacrolimus and mycophenolate mofetil maintenance, with corticosteroids that are withdrawn after 4 days) showed greater height gain after 6 months than patients randomised to the comparator regimen (no induction, immediate-release tacrolimus and mycophenolate mofetil with long-term corticosteroids). The committee noted that the UK marketing authorisation for daclizumab has been withdrawn, so daclizumab was not included in this appraisal and as a result TWIST was not included in the assessment report. The committee heard from the clinical experts that basiliximab and daclizumab have the same mechanism of action (both are interleukin-2 receptor antagonists) and trials in adults show that they have similar effectiveness. The committee acknowledged that, according to patients and clinicians, limiting exposure to corticosteroids is an important aim of treatment. The committee concluded that it was appropriate to consider TWIST when making its recommendations.

4.6 The committee discussed the evidence for the clinical effectiveness of basiliximab. Three studies showed that basiliximab reduced acute rejection compared with treatment without induction (Cransberg et al. 2008; Offner et al. 2008 and the network meta-analysis of RCTs in adults). The committee acknowledged that, in 2 RCTs of children and young people, most outcome measures did not differ significantly between basiliximab and treatment without induction (Offner et al. 2008; Grenda et al. 2006). However, it noted that these trials may have been statistically underpowered to detect differences in graft loss and mortality. The committee was aware that TWIST showed increased height gain in children and young people treated with a regimen that included an interleukin-2 receptor antagonist. The committee heard from clinical experts that

basiliximab is currently used by several NHS paediatric transplant centres and is well tolerated by patients. The marketing authorisation for basiliximab states that it should be used in combination with ciclosporin. However, the committee noted that NHS transplant centres often use basiliximab plus tacrolimus and that this combination was used in 2 RCTs in children and young people (TWIST and Grenda at al. 2006). Taking all of the evidence into account, the committee concluded that basiliximab, plus either ciclosporin or tacrolimus, is clinically effective in children and young people.

4.7 The committee discussed the evidence for the clinical effectiveness of r-ATG, noting that the AG did not find any studies in children and young people that compared r-ATG with the comparators in the scope. Sanofi's response to the assessment report identified 2 non-randomised studies in children and young people that compared r-ATG with basiliximab or treatment without induction. These studies were excluded from the AG's review because the clinicians chose which maintenance therapy to use for each patient (Baron et al. 2008) and it was not clear what type of anti-human thymocyte immunoglobulin was used (Vilalta et al. 2009). The committee noted that Sanofi did not provide numerical results or detailed information about study design. The committee noted that the network meta-analysis of RCTs in adults showed that r-ATG reduces acute rejection compared with treatment without induction. It heard from clinical experts that the treatment regimen with r-ATG is longer and more complex than with basiliximab, and that adults having r-ATG have more adverse events (including post-transplant lymphoproliferative disorder) than those having basiliximab. The committee noted that it had not been presented with evidence about adverse events in children and young people. It heard from clinical experts that it was very rare for children and young people in the UK to have r-ATG. Overall, the committee concluded that

there was not enough evidence to establish whether r-ATG is clinically effective in children and young people.

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

4.9 The committee discussed the evidence for the clinical effectiveness of prolonged-release tacrolimus, noting that the AG did not find any studies in children and young people that compared prolonged-release tacrolimus with the comparators in the scope. The submission from Astellas referred to non-randomised studies in children and young people, but these studies were excluded from the AG's review. The committee noted that Astellas did not provide numerical results or detailed information about study design. Astellas advised that additional studies were ongoing but it was not known when they would finish. The committee noted that the AG's meta-analysis of RCTs in adults found no significant differences between prolonged-release and immediate-release tacrolimus for mortality, graft loss, graft function and acute rejection. The committee also noted that the summary of product characteristics states that 'the safety and efficacy of Advagraf [prolonged-release tacrolimus] in children under 18 years of age have not yet been established'. The committee concluded that there was not enough

evidence to establish whether prolonged-release tacrolimus is clinically effective in children and young people.

4.10 The committee considered whether prolonged-release tacrolimus could improve adherence to treatment. Patient experts advised that taking several tablets at set times each day was challenging, especially for young people who do not have a fixed daily routine, and regimens with fewer tablets may improve adherence. The committee acknowledged the importance of adherence to treatment in children and young people, and it was aware that poor adherence can cause graft loss. The committee referred to the Astellas submission for the related NICE technology appraisal for adults, which included adult studies suggesting that once-daily prolonged-release tacrolimus improves adherence, and may reduce graft loss, compared with twice-daily immediate-release tacrolimus. The committee was concerned that most of these studies measured self-reported adherence, which may be less accurate than electronic monitoring. The committee agreed that there was no robust evidence showing that improved adherence leads to lower rates of mortality, graft loss and acute rejection. It noted that switching from immediate-release to prolonged-release tacrolimus would remove only 1 tablet a day, and it was uncertain whether this would substantially improve adherence to the overall immunosuppressive regimen. The committee heard from a clinical expert that if a person forgot to take their prolonged-release tacrolimus tablet, this would leave them without tacrolimus for 24 hours. The expert advised that, potentially, this could have a greater impact than missing a tablet of immediate-release tacrolimus and being without the drug for 12 hours. The committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people.

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

4.12 The committee discussed the evidence for the clinical effectiveness of sirolimus. The only evidence in children and young people in the AG's review was a small non-randomised study that did not find any significant differences between sirolimus and immediate-release tacrolimus (Hymes et al. 2011). NICE's technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and adolescents published in 2006 did not recommend sirolimus except when proven intolerance to calcineurin inhibitors (including nephrotoxicity) necessitates the complete withdrawal of these treatments. During the present appraisal, none of the submissions and none of the experts provided evidence that sirolimus would be clinically effective for children and young people who cannot tolerate calcineurin inhibitors. Clinical experts advised that some adults taking sirolimus have adverse events, and the committee noted that it had not been

presented with data about adverse events in children and young people. The committee referred to the summary of product characteristics, which states that 'the safety and efficacy of Rapamune (sirolimus) in children and adolescents less than 18 years of age has not been established'. The committee heard from a clinical expert that, by adjusting the dose of mycophenolate mofetil, it may be possible to reduce or even stop calcineurin inhibitors for patients who cannot tolerate them. The committee considered that this strategy provided a treatment option for children and young people who cannot tolerate calcineurin inhibitors. Overall, the committee concluded that there was not enough evidence to establish whether sirolimus is clinically effective in children and young people.

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

Cost effectiveness

4.14 The AG's systematic review did not find any published cost-effectiveness evidence that had emerged since the previous NICE technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and young people. The AG developed a new model informed by the systematic review of clinical evidence. The committee noted that the AG's model included 2 types of analysis: using effectiveness estimates from RCTs in children and young people and using effectiveness

estimates from a network meta-analysis of RCTs in adults. Given the limited number of clinical trials in children and young people, the committee agreed that it was reasonable to consider the results of both analyses. Similarly, given the lack of data on the health-related quality of life of children and young people with a kidney transplant, the committee agreed that it was reasonable to use utility values estimated from adults. The committee concluded that the AG's model provided a suitable basis for decision-making.

4.15 The committee discussed the economic model submitted by Astellas. It noted that the analysis did not follow the NICE scope (because it excluded ciclosporin as a comparator) and did not follow the NICE reference case (because it did not present incremental analyses and it used list prices for drugs that are in the Electronic Market Information Tool [eMIT]). The Astellas analysis also did not include effectiveness estimates from studies in children and young people. The Astellas model assumed that prolonged-release tacrolimus improved adherence to treatment, which the committee had decided was not an appropriate assumption (see section 4.10). The committee concluded that it preferred to use the AG's model as the basis for its recommendations.

4.16 The committee noted Novartis' comments on the assessment report, advising that quality of life decreases as graft function declines. Novartis asked the AG to amend its model so that quality of life depends on graft function. The committee had discussed this issue in the related appraisal for adults. It agreed that the AG's model may underestimate total quality-adjusted life years (QALYs) for all treatments, because in the model quality of life is independent of graft function. The committee considered that the QALY underestimate would be greatest for treatments with the largest beneficial effect on graft function (such as belatacept with mycophenolate mofetil and tacrolimus with azathioprine), but that

amending the model in the way suggested by Novartis was unlikely to substantially alter the incremental cost-effectiveness ratios (ICERs). The committee concluded that it was not necessary to amend the AG's model.

4.17 The committee discussed the drug costs used in the AG's model and agreed that it was appropriate to use prices from eMIT, if available, because these reflect the prices paid by the NHS (see NICE's guide to the methods of technology appraisal section 5.5.2). The committee agreed that it was appropriate to consider the prices agreed with the Commercial Medicines Unit for Advagraf (prolonged-release tacrolimus capsules), Modigraf (tacrolimus granules for oral suspension) and Adoport (immediate-release tacrolimus) when making its recommendations, because these prices are nationally available to the NHS. The committee concluded that its preferred analysis used eMIT prices when available and the prices agreed with the Commercial Medicines Unit for Modigraf and Advagraf.

Basiliximab

4.18 The committee discussed the cost-effectiveness evidence for basiliximab, noting that all analyses assessed basiliximab plus a calcineurin inhibitor. The AG's model based on Grenda et al. (2006), and the model using data from adults, showed that treatment with basiliximab was cheaper and more effective than treatment without induction. For these 2 analyses, the incremental costs were between −£5,700 and −£11,100 and the incremental QALYs were between 0.12 and 0.18. However, the analysis based on Offner et al. (2008) gave the opposite result (treatment without induction cost £8,530 less and gained 0.55 more QALYs than basiliximab). The committee noted that the discrepancy may have arisen because the odds ratio for graft loss was more favourable to basiliximab in Grenda et al. than in Offner et al. The committee

accepted that the Offner et al. trial was probably underpowered to detect differences in mortality and graft loss, meaning that the estimates of treatment effect were uncertain. It also recalled that the TWIST trial demonstrated the effectiveness of a regimen including an interleukin-2 receptor antagonist, but the TWIST data were not included in the modelling. On balance, the committee accepted the results of the AG's analyses using Grenda et al. (2006) and the adult data, and concluded that basiliximab, when used as part of an initial immunosuppressive regimen that includes a calcineurin inhibitor, was a cost-effective option for preventing organ rejection in children and young people having a kidney transplant.

Rabbit anti-human thymocyte immunoglobulin

4.19 The committee discussed the cost-effectiveness evidence for r-ATG. The AG's model using data from adults showed that treatment with r-ATG was dominated by treatment without induction (incremental costs between £6,020 and £9,920; incremental QALYs between −0.03 and −0.06). The model assumed that vials were shared so that there was no wastage, but the committee heard from clinical experts that vial sharing was unlikely to happen in practice. The committee noted that the modelled costs of r-ATG would increase if wastage was included. Based on the evidence presented, the committee concluded that r-ATG could not be considered to be a cost-effective option for preventing organ rejection in children and young people having a kidney transplant.

Tacrolimus

4.20 The committee discussed the cost-effectiveness evidence for immediate-release tacrolimus. The AG's model using data from Trompeter et al. (2002), and the model using data from adults, showed that treatment with immediate-release tacrolimus was cheaper and more effective than treatment with ciclosporin. For

these 2 analyses, the incremental costs were between −£19,500 and −£44,500; the incremental QALYs were between 0.11 and 0.55. The AG's model using data from adults also showed that treatment with immediate-release tacrolimus was cheaper and more effective than prolonged-release tacrolimus and sirolimus. The committee concluded that immediate-release tacrolimus was a cost-effective option for preventing organ rejection in children and young people having a kidney transplant and that treatment should normally be started with the least expensive product.

4.21 The committee discussed the cost-effectiveness evidence for prolonged-release tacrolimus. The AG's model using data from adults showed that treatment with prolonged-release tacrolimus was dominated by treatment with immediate-release tacrolimus (the incremental costs are confidential, the incremental QALYs were −0.05). Astellas' response to the assessment report consultation stated that adherence to treatment was better with prolonged-release tacrolimus and that this benefit was not included in the AG's model. The committee accepted that adherence to treatment was important for children and young people, and it was plausible that a regimen with fewer tablets could improve adherence. However, the committee agreed that it had not been presented with robust data to show better adherence with prolonged-release tacrolimus (see section 4.10) and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model. Even taking into account the price agreed with the Commercial Medicines Unit, the committee did not consider prolonged-release tacrolimus to be cost effective, based on the evidence it had seen.

Mycophenolic acid, everolimus, sirolimus and belatacept

4.22 The committee discussed the cost-effectiveness evidence for mycophenolate mofetil. The AG's model using data from adults

showed that, in regimens that included ciclosporin, treatment with mycophenolate mofetil was cheaper and more effective than treatment with azathioprine (incremental costs between −£7,020 and −£10,200; incremental QALYs between 0.10 and 0.12). However, in regimens that included immediate-release tacrolimus, treatment with azathioprine was cheaper and more effective than treatment with mycophenolate mofetil (incremental costs between £4,730 and £6,450; incremental QALYs between −0.06 and −0.07). The committee noted that, in the regimens that included tacrolimus, there was only a small difference in QALYs gained between mycophenolate mofetil and azathioprine. It also noted that TWIST demonstrated the effectiveness of mycophenolate mofetil plus tacrolimus, but these data were not included in the model. The committee accepted that patients and clinicians preferred to have a choice of treatments, and the use of mycophenolate mofetil with tacrolimus was well established in the NHS. Taking all of the evidence into account, the committee concluded that mycophenolate mofetil was a cost-effective use of NHS resources for preventing organ rejection in children and young people having a kidney transplant and that treatment should normally be started with the least expensive product.

4.23 The committee discussed the cost-effectiveness evidence for mycophenolate sodium, everolimus, sirolimus and belatacept, noting that the AG's analyses used data from adults because no data from children and young people were available. It noted that, compared with mycophenolate mofetil, the ICER for mycophenolate sodium was £51,800 per QALY gained and the ICER for everolimus was £632,000 per QALY gained. Sirolimus was dominated by ciclosporin, immediate-release tacrolimus, azathioprine and mycophenolate mofetil. Belatacept had an ICER of £533,000 per QALY gained compared with immediate-release tacrolimus. The committee considered that, based on the evidence

it had seen, mycophenolate sodium, everolimus, sirolimus and belatacept were not cost-effective options for preventing organ rejection in children and young people having a kidney transplant.

Additional considerations

4.24 Following an appeal, the committee considered in detail the scope of the appraisal and the populations and clinical situations to which its recommendations would apply. It noted that its intention at the time of the first final appraisal determination was that the recommendations would apply to the initial treatments for children and young people having kidney transplants, and explained that this was based on its interpretation of the scope at that time and the evidence available from the systematic review and economic modelling. However, on further review the committee recognised that the scope included immunosuppressive treatments given immediately after transplant and at subsequent stages, in children and young people having a kidney transplant and in children and young people who have had a re-transplant in the last 2 years. The committee therefore acknowledged that the scope for this appraisal includes, in addition to initial treatments, subsequent therapies during the life of a graft and treatments for children and young people having second and subsequent transplants. The committee concluded that the scope was broader than its original recommendations, and discussed the recommendations it could make for these additional clinical scenarios.

4.25 The committee noted that the protocol and systematic review did not include the use of subsequent treatments during the life of the graft and only included studies in which randomisation took place at the time of the transplant. As a result, none of the studies considered during the appraisal investigated the effect of switching regimens during the life of a functioning graft. It also noted that the AG's economic model did not provide estimates of the cost

effectiveness of switching to alternative interventions during the life of a graft. The committee considered that the systematic review and economic modelling were suitable to provide evidence on the initial treatments started around the time of transplant. The committee heard from the clinical experts that between 10% and 20% of people cannot continue on their initial immunosuppressive treatments. This may result from intolerance because of nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy associated with ciclosporin, tacrolimus, sirolimus or everolimus, for example. The clinical and patient experts highlighted the need for other treatments to be available to ensure continued immunosuppressive therapy for children and young people unable to continue taking their initial treatment. The committee noted that sirolimus could be a cost-effective option for children and young people with calcineurin inhibitor nephrotoxicity because the only alternative would be haemodialysis, although it understood that sirolimus is currently routinely commissioned by NHS England for nephrotoxicity. The committee also heard that although thrombotic microangiopathy is rare, it results in graft loss and the person needing haemodialysis. The clinical experts noted that belatacept is the only immunosuppressant that can be given in these circumstances. The committee recognised the need for urgency in this situation and that individual funding requests might not be suitable or approved quickly enough. It also recognised that belatacept could potentially be a cost-effective use of NHS resources when thrombotic microangiopathy develops because the only alternative would be haemodialysis. The committee heard from the clinical experts and the AG that there is some limited evidence for treatment switching, but was aware that such evidence had not been searched for within a systematic review. The committee recalled that the limited analysis it had seen on treatment switching, submitted by Novartis, was highly uncertain. In addition, it heard

that it would be difficult to obtain sufficient robust evidence to inform a full consideration of the clinical and cost effectiveness of all possible treatment switching scenarios and permutations, within the context of a technology appraisal. The committee noted that any outstanding clinical and commissioning issues may be better addressed through other routes, such as other NICE programmes or clinical commissioning policies. The committee concluded that it was unable to make recommendations on the technologies as subsequent treatments during the life of a graft when initial therapies become unsuitable, and that the recommendations only apply to the initial treatment started around the time of kidney transplant.

4.26 The committee understood that the systematic review was not restricted to children and young people having their first kidney transplant, and heard from the AG that some of the trials included in the clinical and economic evaluation included people who were having a second or subsequent transplant. However, it recalled that there was insufficient evidence for subgroup analysis. The committee concluded that it was unable to make recommendations on these technologies for second or subsequent transplants when particular therapies had previously been found to be inappropriate.

4.27 The committee discussed providing immunosuppressive therapy for children and young people who cannot swallow capsules as a potential equality issue. It heard from clinical experts that young children, and some children and young people with disabilities, cannot swallow capsules and need oral suspensions instead. The committee noted that oral suspensions are available for immediate-release tacrolimus (Modigraf) and mycophenolate mofetil (CellCept), and that these products have a marketing authorisation in the UK. The suspensions are more expensive than the capsules (see sections 3.10 and 3.18). The committee was aware that there

is a nationally available price agreed with the Commercial Medicines Unit for Modigraf (see section 3.10). The committee agreed that it would be unfair if people who cannot swallow capsules were not able to have immediate-release tacrolimus and mycophenolate mofetil because these treatments are clinically effective in children and young people. It noted that restricting access in this way might discriminate against young children, or against children and young people with disabilities. The committee concluded that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. It further concluded that treatment could be started with an alternative dosage form if the child or young person is not able to swallow capsules. The committee agreed that Modigraf should be used only if the company provides Modigraf at the price agreed with the Commercial Medicines Unit.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Immunosuppressive therapy for kidney transplant in children and young people**	**Section**
Key conclusion		

Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as initial options to prevent organ rejection in children and young people having a kidney transplant.	1.1–1.3
• The committee concluded that basiliximab is clinically effective, and provided more quality-adjusted life years (QALYs) at a lower cost than treatment without induction.	4.5, 4.18
• The committee concluded that immediate-release tacrolimus is clinically effective and provided more QALYs at a lower cost than ciclosporin.	4.8, 4.20
• The committee concluded that mycophenolate mofetil is clinically effective and it is cost effective in regimens that include ciclosporin. Although there was uncertainty about cost effectiveness in regimens that included tacrolimus, the committee was prepared to accept that mycophenolate mofetil was cost effective in both regimens.	4.11, 4.22
Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as initial treatments to prevent organ rejection in children and young people having a kidney transplant.	1.4
• The committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people.	4.7, 4.9, 4.12, 4.13
• Using effectiveness estimates from adults, these drugs were either dominated or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained.	4.19, 4.21, 4.23
The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for	1.5

preventing organ rejection in children or young people who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid (for example, because of contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes children and young people who: • are unable to continue having their initial therapy and need to switch to another therapy during the life of their graft or • have a second or subsequent transplant, having previously found that 1 or more of the recommended initial treatments or standard treatments are clinically unsuitable, for example because of contraindications or intolerance.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	People have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments. The immunosuppressive regimens most commonly used by children and young people in the UK are: induction without antibodies, then maintenance therapy with tacrolimus and azathioprine; or basiliximab induction, then maintenance therapy using tacrolimus and mycophenolate mofetil.	4.1 4.2

The technologies		
Proposed benefits of the technologies How innovative are the technologies in their potential to make a significant and substantial impact on health-related benefits?	Quality of life is better with a transplant than while having dialysis, so the aim of treatment is to prolong survival of the transplanted kidney. There were no specific committee considerations about innovation, because many of these technologies have been available for some time. The committee considered whether prolonged-release tacrolimus could improve adherence to treatment. It concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes.	4.1 4.10
What are the positions of the treatments in the pathway of care for the condition?	Immunosuppressive therapy can be categorised as induction therapy or maintenance therapy. Induction therapy is an intensive immunosuppression regimen that is used for up to 2 weeks around the time of transplant. Maintenance therapy starts immediately after transplant and continues for life. Basiliximab and r-ATG are induction therapies. The remaining 7 drugs in the appraisal are maintenance therapies.	2.3

Adverse reactions	Clinical experts advised that adults having r-ATG have more adverse events than those having basiliximab. The committee was not presented with evidence about adverse events associated with r-ATG in children and young people. Clinical experts advised that some adults taking sirolimus have adverse events. The committee was not presented with data about adverse events associated with sirolimus in children and young people.	4.7 4.12
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The assessment group (AG)'s systematic review found few studies in children and young people. The committee concluded that it should consider all of the evidence, including randomised and non-randomised studies in children and young people, and randomised controlled trials (RCTs) in adults. Consultees and clinical experts advised that it was important to consider TWIST, an RCT that assessed the effectiveness of daclizumab induction then maintenance with immediate-release tacrolimus and mycophenolate mofetil, with corticosteroids that are withdrawn	4.4 4.5

	after 4 days. TWIST was not in the AG's review because daclizumab is not part of this appraisal (its marketing authorisation has been withdrawn). The committee heard from the clinical experts that basiliximab and daclizumab have the same mechanism of action and have similar effectiveness. The committee concluded that it was appropriate to consider TWIST when making its recommendations.	
Relevance to general clinical practice in the NHS	The 3 RCTs in children and young people were likely to be generalisable to the NHS because the trials were done in Europe, the patient and donor characteristics were largely representative of people using the NHS, and the drug doses were similar to current recommendations. However, the evidence is quite old.	4.4

Uncertainties generated by the evidence	The AG did not find any studies of children and young people comparing the following drugs with the comparators in the scope: r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus and belatacept. Only 1 small study of children and young people assessed sirolimus. Consequently, the committee was uncertain whether these drugs were clinically effective in children and young people.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	There were insufficient data to permit analyses of subgroups. The committee heard from the clinical experts that 10 to 20% of people cannot continue on their initial immunosuppressive treatments. This may be because of intolerance or complications requiring withdrawal, for example. The committee heard that there is some available evidence for treatment switching, but was aware that such evidence had not been systematically reviewed, and the limited analysis it had seen on treatment switching was highly uncertain. The committee concluded that it was unable to make recommendations on the technologies as subsequent treatments during the life of a graft when initial therapies become unsuitable, and that	4.3 4.25

	the recommendations only apply to the initial treatment around the time of kidney transplant. The committee understood that some of the trials included in the clinical and economic evaluation included people who were having a second or subsequent transplant. However, it recalled that there was insufficient evidence for subgroup analysis. The committee concluded that it was unable to make recommendations on these technologies for second or subsequent transplants when particular therapies had previously been found to be inappropriate.	4.26

Estimate of the size of the clinical effectiveness including strength of supporting evidence	Three studies showed that basiliximab reduced acute rejection compared with no induction. Also, TWIST showed increased height gain in children and young people who had a corticosteroid-sparing regimen that included an interleukin-2 receptor antagonist.	4.6
	Immediate-release tacrolimus improved graft function and reduced the incidence of acute rejection compared with ciclosporin.	4.8
	A non-randomised study in children and young people found lower rates of graft loss with mycophenolate mofetil than with azathioprine. The network meta-analysis of adult RCTs showed a lower incidence of acute rejection with mycophenolate mofetil than with azathioprine.	4.11

How has the new clinical evidence that has emerged since the original appraisal (TA99) influenced the current (preliminary) recommendations?	For children and young people, the new evidence includes the TWIST RCT, the Offner et al. RCT, and 6 non-randomised studies. There are also several new RCTs in adults. TWIST and Offner et al. showed that an interleukin-2 receptor antagonist (such as basiliximab) is clinically effective. The recommendation for basiliximab is consistent with NICE technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and adolescents. A non-randomised study in children and young people, and RCTs in adults, suggest that mycophenolate mofetil is clinically effective. In NICE technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and young people, mycophenolate mofetil is recommended only for certain groups of patients.	4.4–4.5 4.6 4.11
Evidence for cost effectiveness		

Availability and nature of evidence	The AG's analyses used effectiveness estimates from RCTs in children and young people and, separately, from adult RCTs. The committee agreed that it was reasonable to consider both analyses. The model submitted by Astellas did not follow the NICE scope and NICE reference case, nor did it include effectiveness estimates from children and young people. The committee preferred to use the AG's model.	4.14 4.15
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Offner et al. trial was probably underpowered to detect differences in mortality and graft loss, meaning that the estimates of treatment effect were uncertain. Astellas stated that adherence to treatment was better with prolonged-release tacrolimus but this benefit was not included in the AG's model. The committee agreed that it had not been presented with robust data to show better adherence and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model.	4.18 4.21 4.10

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Given the lack of data on the health-related quality of life of children and young people with a kidney transplant, the committee agreed that it was reasonable to use utility values from adults. No significant and substantial health-related benefits have been identified that were not included in the economic model.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	There were insufficient data to permit analyses of subgroups. The committee heard from the clinical experts that 10 to 20% of people cannot continue on their initial immunosuppressive treatments. The committee recalled that the limited analysis it had seen on treatment switching was highly uncertain, and was aware that it would be difficult to obtain sufficient robust evidence to inform a full consideration of the cost effectiveness of all possible treatment switching scenarios and permutations, within the context of a technology appraisal. The	4.3 4.25

	committee concluded that it was unable to make recommendations on the technologies as subsequent treatments during the life of a graft when initial therapies become unsuitable. The committee understood that the systematic review was not restricted to people having their first kidney transplant, but there was insufficient evidence for subgroup analysis. The committee concluded that it was unable to make recommendations on these technologies for second or subsequent transplants, in people for whom particular therapies had previously been found to be inappropriate.	4.26
What are the key drivers of cost effectiveness?	There were no specific committee considerations on the key drivers of cost effectiveness. The committee was aware that, in the AG's model, the differences between treatments in total costs were mainly because of differences in time having dialysis.	–

Most likely cost-effectiveness estimate (given as an ICER)	• Basiliximab was cheaper and more effective than treatment without induction (incremental costs between −£5,700 and −£11,100; incremental QALYs between 0.12 and 0.18).	4.18
	• Immediate-release tacrolimus was cheaper and more effective than ciclosporin (incremental costs between −£19,500 and −£44,500; incremental QALYs between 0.11 and 0.55).	4.20
	• In regimens that included ciclosporin, mycophenolate mofetil was cheaper and more effective than azathioprine (incremental costs between −£7,020 and −£10,200; incremental QALYs between 0.10 and 0.12).	4.22
	• r-ATG was dominated by treatment without induction.	4.19
	• Prolonged-release tacrolimus was dominated by immediate-release tacrolimus.	4.21
	• Compared with mycophenolate mofetil, the ICER for mycophenolate sodium was £51,800 per QALY gained and the ICER for everolimus was £632,000 per QALY gained.	4.23
	• Sirolimus was dominated by all comparators.	4.23
	• Belatacept had an ICER of £533,000 per QALY gained compared with immediate-release tacrolimus.	4.23

How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA99) influenced the current (preliminary) recommendations?	The AG's review did not find any published cost-effectiveness evidence that had emerged since the previous NICE technology appraisal guidance on immunosuppressive therapy for kidney transplantation in children and young people. Since the original appraisal, some of the technologies have become available as generics. The AG developed a new model informed by the systematic review of clinical evidence.	2.4, 4.14
Additional factors taken into account		
Patient access schemes (PPRS)	None. Astellas advised that there are nationally available discounted contract prices for Modigraf (tacrolimus granules for oral suspension) and Advagraf (prolonged-release tacrolimus).	3.10, 3.12
End-of-life considerations	Not applicable.	–

Equalities considerations and social value judgements	The committee agreed that it would be unfair if children and young people who cannot swallow capsules were not able to have immediate-release tacrolimus and mycophenolate mofetil because these treatments are clinically effective. It noted that restricting access in this way might be discriminatory. The committee concluded that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. It further concluded that treatment can be started with an alternative dosage form if the child or young person is not able to swallow capsules.	4.27

5 Implementation

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

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology,

the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a child or young person is having a kidney transplant and the doctor responsible for their care thinks that basiliximab, immediate-release tacrolimus or mycophenolate mofetil is the right treatment, these drugs should be available for use, in line with NICE's recommendations.

5.4 The NHS procures Modigraf at a confidential discounted contract price agreed through a national tender with Astellas Pharma. The prices used for decision-making in this appraisal are the relevant prices the NHS pays for Modigraf. These prices are based on pricing arrangements between the company and the Commercial Medicines Unit. The contract prices agreed through the framework are commercial in confidence. Any enquiries from NHS organisations about the prices used in this appraisal should be directed to the Commercial Medicines Unit.

6 Proposed date for review of guidance

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

Gary McVeigh
Chair, Appraisal Committee
April 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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

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

NICE project team

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

Rosie Lovett and Helen Powell
Technical Leads

Christian Griffiths and Ian Watson
Technical Lead/Technical Adviser

Sally Doss
Technical Adviser

Kate Moore
Project Manager