NICE National Institute for Health and Care Excellence

NICE guidance

Immunosuppressive therapy for kidney transplant in adults

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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This guidance replaces TA85.

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 adults. The recommendations apply only to the initial immunosuppressive therapy (induction and maintenance therapy) started around the time of kidney transplant.

It was outside the scope of the appraisal to make recommendations on using the standard triple therapy regimen of ciclosporin, azathioprine and a corticosteroid after kidney transplant in adults.

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 adults 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 adults 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 least expensive product is not suitable (for example, if the person is not able to swallow capsules as a result of a disability or they are unable to have a particular ingredient because of allergy or religious reasons). 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.

1.3 Mycophenolate mofetil, when used as part of an immunosuppressive

regimen, is recommended as an initial option to prevent organ rejection in adults 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 least expensive product is not suitable (for example, if the person is not able to swallow capsules as a result of a disability or they are unable to have a particular ingredient because of allergy or religious reasons).[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 adults 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 adults who are, or become, unable to have the technologies recommended in sections 1.1 to 1.3 or standard triple therapy with ciclosporin, azathioprine and a corticosteroid (for example, because of treatment failure, contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults 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 treatment failure, contraindications or intolerance.

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

[1] August 2017: the use of basiliximab (with tacrolimus) and mycophenolate mofetil (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 Department of Health has stated that 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.

2 Clinical need and practice

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

2.2 Between April 2016 and March 2017, 3,042 kidney transplants were done in adults in the UK; 2,682 of these were in England. At the end of 2014, approximately 31,150 people in the UK were having immunosuppressive therapy after a kidney transplant, including 26,100 people in England.

2.3 Immunosuppressive therapy aims to prevent acute rejection and optimise the function of the transplanted kidney, while minimising the adverse effects of immunosuppression (such as increased risk of infection, cancer, diabetes and cardiovascular disease). Immunosuppressive therapy can be categorised as induction therapy 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 adults was published in 2004. It recommended basiliximab, daclizumab, tacrolimus, mycophenolate mofetil and sirolimus, in certain circumstances, as options for immunosuppressive therapy for kidney transplant in adults. Since that appraisal, the marketing authorisation for daclizumab has been withdrawn, new technologies (rabbit anti-human thymocyte immunoglobulin, mycophenolate sodium, belatacept, a prolonged-release formulation of tacrolimus, and everolimus) have received marketing authorisations, and some of the technologies 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 adults having a kidney transplant. 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 2 doses of 20 mg each (one 2 hours before the surgery and the second 4 days after).

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 August 2017]), equating to £1,685 per course of treatment (2 doses of 20 mg).

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 with other immunosuppressive drugs.

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

3.6 r-ATG is available in 25 mg vials, at a price of £158.77 (excluding VAT; BNF online [accessed August 2017]), equating to £1,428.93 to £7,144.65 per course for a 70-kg person.

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 adults 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 of 0.2 to 0.3 mg/kg/day orally or 0.05 to 0.1 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 August 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. Tacrolimus immediate-release capsules are available as 0.5-mg, 0.75-mg, 1-mg, 2-mg and 5-mg capsules (depending on the brand), the price of which varies by brand. The assessment group (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). This equates to £50.96 to £76.44 per week for an initial dose of 0.2 to 0.3 mg/kg/day in a 70-kg person. 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 to 0.3 mg/kg/day. The dosage is usually reduced in the period after the transplant.

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 to £1.43 per mg (excluding VAT; BNF online [accessed August 2017]). This equates to £112.11 to £210.47 per week for an initial dose of 0.2 to 0.3 mg/kg/day in a 70-kg person. 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 after the scope for this appraisal was finalised. The brand name Envarsus was not included in the AG's search for evidence and Chiesi was not asked to submit evidence for the appraisal.

Belatacept

3.14 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.

3.15 Belatacept is administered intravenously. The recommended dose 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 August 2017]). For a 70-kg person, this equates to £6,381.36 for the first 12 weeks and £709.04 every 4 weeks from week 16 onwards.

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. It can be administered orally (capsules or an oral suspension) or intravenously, at a recommended dose of 2 g/day.

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 August 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), equating to £5.28 per week.

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. It is administered orally, at a recommended dose 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 August 2017]), equating to £45.13 per week.

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 with ciclosporin and corticosteroids for 2 to 3 months, and may be continued only if ciclosporin can be progressively discontinued.

3.22 Sirolimus is administered orally as a tablet or solution. The recommended dose is 6 mg initially, followed by 2 mg per day for 2 to 3 months, then adjusted to obtain blood trough levels of 4 to 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 to £4.60 per mg (excluding VAT; BNF online [accessed August 2017]), equating to £16.24 to £27.60 initially, followed by £37.90 to £64.40 per week.

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 with ciclosporin and corticosteroids. Everolimus is administered orally at an initial dose of 1.5 mg/day.

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 August 2017]). This equates to £103.95 per week.

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 6) 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 adults. 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 heard from the clinical experts that the key priority for clinicians is to prolong graft survival for as long as possible, while minimising adverse effects, with the ultimate goal of allowing people to return to normal life. The clinical experts considered that both quality of life and survival are better with a functioning kidney transplant than with dialysis. The patient experts described their experiences of kidney transplants and immunosuppressive regimens, and emphasised the value of maintaining a functioning kidney transplant. The committee understood that effective immunosuppressive therapies are important to prevent organ rejection in adults having kidney transplants.

4.2 The committee heard from the clinical experts that the choice of immunosuppressive therapy is affected by a number of factors, including the characteristics and preferences of the person having treatment. The committee heard that the side-effect profiles of each drug and the risk profile of the kidney donor and recipient are important considerations. In particular, the risks of new-onset diabetes, delayed graft function and nephrotoxicity may be key priorities for some people (for example, people of African-Caribbean and Asian family origins have a higher risk of developing diabetes), whereas the level of immunological risk may be a priority for others. The clinical and patient experts therefore emphasised the importance of having access to a choice of treatment

options to meet the needs of different people. The committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people.

4.3 The committee discussed the technologies included in the assessment report. It 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 prednisolone (the standard triple therapy regimen), which were included as comparators only. A clinical expert suggested that the appraisal should consider alemtuzumab as an induction therapy. The committee was aware that alemtuzumab does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and is not routinely available for transplant patients (it is available on a 'named patient' basis). It was therefore not included in the scope for this appraisal.

Clinical effectiveness

4.4 The committee considered the clinical effectiveness evidence presented by the AG and companies. The AG's systematic review found 86 randomised controlled trials, of which 23 were included in NICE's technology appraisal guidance on immunosuppressive therapy for kidney transplantation in adults, and 63 were identified in the updated systematic review for the current appraisal. The systematic review included 11 studies of induction therapies, 73 studies of maintenance therapies and 2 studies examining both induction and maintenance therapies. The AG considered that only 11 trials adequately matched the population and current practice in the NHS in England. The committee accepted that the AG's systematic review was comprehensive and concluded that all the relevant clinical effectiveness randomised controlled trials had been taken into account. The committee heard from the clinical experts that additional observational evidence is available from the UK Transplant Registry. The AG stated that this evidence had been used in its economic model to inform the natural history of the condition. However, the committee heard from the AG that there were some challenges with the recording of immunosuppressive regimens in the registry. Also there were relatively fewer people having the newer

drugs in the registry than in the clinical trials, and so the clinical effectiveness evidence available from this source was limited. The committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account.

4.5 The committee discussed the findings of the pooled head-to-head analyses and network meta-analyses for the induction therapies. It understood that both basiliximab and r-ATG were associated with statistically significant reductions in the incidence of acute rejection compared with placebo or treatment without induction. The committee saw no evidence of a statistically significant difference between basiliximab and r-ATG, either in head-to-head comparisons or in the network meta-analysis. The committee concluded that basiliximab and r-ATG are effective induction therapies, but there was no evidence of a difference in clinical effectiveness between them.

4.6 The committee discussed the findings of the clinical effectiveness analyses for the maintenance therapies. It noted that head-to-head comparisons suggested that calcineurin inhibitors (tacrolimus and ciclosporin) were associated with statistically significant reductions in the incidence of acute rejection compared with belatacept, everolimus and sirolimus. It also noted that tacrolimus reduced the incidence of acute rejection compared with ciclosporin. The committee noted that both belatacept and mycophenolate mofetil were associated with improved graft function compared with calcineurin inhibitors. The committee noted that there were no consistent differences between immediate- and prolonged-release tacrolimus, or between mycophenolate mofetil and mycophenolate sodium. The committee noted that the AG's network meta-analysis presented a systematic comparison of maintenance regimens across 4 outcomes (mortality, graft loss, acute rejection and graft function). It noted that all regimens except belatacept plus mycophenolate mofetil showed evidence of improvement in acute rejection compared with ciclosporin plus azathioprine. However, belatacept plus mycophenolate mofetil statistically significantly increased graft function compared with ciclosporin plus azathioprine. The committee understood that there was substantial heterogeneity in the AG's network meta-analysis, and none of the maintenance regimens

performed consistently well across all 4 outcomes. The committee concluded that the maintenance therapies included in this appraisal are effective options for immunosuppression in adults having a kidney transplant, although limited conclusions on differences between these options can be drawn from the AG's network meta-analysis.

Cost effectiveness

4.7 The committee reviewed the economic models presented by the AG and 3 companies, Astellas, Bristol-Myers Squibb and Novartis. The AG presented an economic model based on a discrete-time state transition structure. The model was independent of that built for NICE's technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults. The AG highlighted that the previous analysis had not fully accounted for uncertainty and had not taken into account the effect of kidney function on clinical and economic outcomes. Since the original appraisal, some of the technologies have become available as generics. Astellas submitted a Markov model and presented results for each immunosuppressive drug compared with immediate-release tacrolimus. Bristol-Myers Squibb presented an analysis of the cost effectiveness of belatacept compared with tacrolimus and ciclosporin, based on a 36-month initial phase followed by a longer-term Markov model. Novartis presented a patient-level simulation model to capture the cost effectiveness of everolimus plus reduced-dose ciclosporin and mycophenolate sodium plus standard-dose ciclosporin, compared with mycophenolate mofetil plus standard-dose ciclosporin or tacrolimus. The committee heard from the clinical experts that they considered the AG's model to represent current practice. The committee considered in particular the modelling of quality of life, kidney donor types and maintenance therapy dosing.

- The committee noted that the AG modelled quality of life using fixed utility decrements for each health state, whereas Novartis assumed that quality of life would decrease as graft function decreased. The committee heard from the clinical experts that people with kidney disease often have few symptoms until their kidney function (estimated glomerular filtration rate; eGFR) reaches about 25 ml/min/1.73 m^2. Similarly, the patient experts reported good quality of life until they approached the end stages of kidney disease. The committee understood that the Novartis model suggested that the cost-effectiveness results were very sensitive to the utility assumptions. It considered that Novartis's analyses implied that the benefits had been underestimated for all treatments, and would be most underestimated for treatments with the largest beneficial effect on eGFR (such as belatacept plus mycophenolate mofetil and tacrolimus plus azathioprine).

- The committee heard from the clinical experts that a major factor influencing graft survival is the type of organ donor and their age. The experts stated that kidney transplants from living donors have become more common in recent years, and are associated with longer graft survival than kidneys from donors who have died. The AG confirmed that its model included a mix of kidney donor types, and the committee heard that the patterns of graft survival predicted by the model were consistent with the clinical experts' expectations.

- The committee noted comments from consultees stating that the dosage of maintenance therapies used in clinical practice is often lower than is recommended in their marketing authorisations, and often decreases over time. It heard from the clinical experts that the lower doses may be associated with a decrease in the incidence of new-onset diabetes. The AG stated that the model included a reduction in maintenance dosing over time, with the dosage stabilising after 1 to 3 years. The committee accepted that the maintenance therapy dosages and the clinical outcomes associated with them in the AG's model were based on clinical trials.

- The committee discussed the drug costs used in the AG's model and agreed that it was appropriate to use prices from the Electronic Market Information Tool (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 Advagraf, Modigraf and Adoport.

  The committee concluded that the AG's model was the most informative model for decision-making.

4.8 The committee understood that in clinical practice, some treatments may be considered particularly valuable for certain groups of people (see section 4.2). It therefore considered whether there was any clinical and cost-effectiveness evidence for specific subgroups. The committee noted that there were very little subgroup data for any of the interventions, and highlighted that the AG had not found enough evidence in its systematic review to inform robust subgroup analyses. The clinical experts acknowledged that there is limited evidence in this area. The committee considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. Therefore the committee concluded that it was unable to make recommendations for any of the interventions in specific subgroups (see sections 4.20 and 4.21).

4.9 The committee considered the effect of adherence on the clinical and cost effectiveness of immunosuppressive regimens. The committee heard from patient experts that, although it took some adjustment, taking the medicines could be fitted into a daily routine. The patient experts described some people who may find adherence more difficult, such as people at university and those who need to take a lot of medicines for other conditions. The clinical experts also noted that it is the evening dose of tacrolimus that is most often missed. The clinical experts stated that once-daily dosing of tacrolimus (using the prolonged-release

formulation) is likely to be helpful for some people, although there are others for whom it makes little difference. The committee understood that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes, and that it would be difficult to identify people who would benefit. The committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. It noted that this model was based on a single trial demonstrating the effect of once-daily tacrolimus on adherence, combined with a meta-analysis showing the effect of improved adherence on clinical outcomes. The committee considered that the quality of the evidence informing this meta-analysis varied. The committee also highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas's approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. Therefore, the committee considered that there were limitations in Astellas's analysis. The committee noted the additional evidence received from Astellas during consultation. The company highlighted a randomised controlled study by Kuypers et al. (2013) that had been included in its original submission, which compared adherence between tacrolimus once-daily and twice-daily regimens. The company stated that non-randomised evidence was also available, which suggested that prolonged-release tacrolimus improved adherence and reduced within-patient variation in blood levels of tacrolimus. The company stated that these outcomes were associated with graft survival. The AG highlighted that the study by Kuypers et al. (2013) had a number of strengths, but also weaknesses, which limited its generalisability. The committee noted that the study did not report patient-related outcomes such as graft survival. It also noted the AG's view that people had more contact with clinicians when they were transferred from immediate-release tacrolimus to prolonged-release tacrolimus, which could be a potential reason for better adherence. The committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However considering all the evidence, the committee concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain.

Basiliximab

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

Rabbit anti-human thymocyte immunoglobulin

4.11 The committee considered r-ATG to be a clinically effective induction therapy. It noted that in the AG's economic model, r-ATG was dominated by basiliximab and was associated with incremental cost-effectiveness ratios (ICERs) of £63,200 to £333,000 per QALY gained compared with treatment without induction. The committee understood that the AG's model had assumed vials of r-ATG would be shared and there was no wastage of partially used vials. It heard from the clinical experts that this was unlikely, so considered that the costs of r-ATG could have been underestimated. The committee also heard from the clinical experts that r-ATG causes short-term side effects and so can be unpleasant to take. The committee acknowledged that there may be some subgroups of people, such as people with high immunological risk or delayed graft function, for whom r-ATG may provide additional benefits. The committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk and its effect on the incidence of antibody-treated acute rejection. The committee noted the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The committee

recognised that immunological risk is influenced by a number of factors as well as panel-reactive antibody levels, but questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The committee concluded that the evidence it had seen showed that r-ATG is not cost effective for preventing organ rejection in adults having a kidney transplant.

Tacrolimus

4.12 The committee heard from the clinical experts that tacrolimus is a potent immunosuppressive therapy, and noted that the immediate-release formulation was cost effective in all comparisons presented by the AG. Therefore the committee concluded that immediate-release tacrolimus could be recommended as an option as part of an immunosuppressive regimen for preventing organ rejection in adults having a kidney transplant.

4.13 The committee heard that there were no consistent statistically significant differences in clinical effectiveness between prolonged-release and immediate-release tacrolimus. It noted that prolonged-release tacrolimus was dominated by both immediate-release tacrolimus and ciclosporin in the AG's economic analyses. Therefore the committee did not consider prolonged-release tacrolimus to be cost effective, based on the evidence it had seen. The committee noted that Astellas's submission stated that its formulation of prolonged-release tacrolimus (Advagraf) is available at a discount through an agreement with the Commercial Medicines Unit, and discussed a scenario analysis presented by the AG using this discount. The discount and the results of the scenario analysis are commercial in confidence and so cannot be reported here. The committee considered that this scenario analysis did not affect its conclusion about the cost effectiveness of prolonged-release tacrolimus.

Belatacept

4.14 The committee acknowledged that belatacept was likely to be a clinically effective treatment, based on the evidence it had seen. In particular, it

noted that belatacept plus mycophenolate mofetil increased graft function compared with ciclosporin plus azathioprine in the AG's network meta-analysis. The committee accepted that belatacept was associated with ICERs ranging from £241,000 to £424,000 per QALY gained, compared with immediate-release tacrolimus, sirolimus and ciclosporin, and that these ICERs were substantially higher than the range normally considered cost effective. The committee acknowledged that there may be some subgroups of people for whom belatacept may provide additional benefits, for example, people with nephrotoxicity or microangiopathy resulting from previous immunosuppressive treatment. However, it considered that there was limited evidence to support recommendations in specific subgroups (see sections 4.20 and 4.21).

Mycophenolic acid

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

4.16 The committee heard that there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium. It noted that mycophenolate sodium was associated with an ICER of £56,600 per QALY gained compared with azathioprine, and £144,000 per QALY gained compared with mycophenolate mofetil. The committee concluded that mycophenolate sodium was not cost effective, based on the evidence it had seen.

Sirolimus

4.17 The committee heard from the clinical experts that treatment with

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

Everolimus

4.18 The committee noted that the AG's economic model suggested that everolimus may be more effective than mycophenolate mofetil and azathioprine, although it was also associated with higher costs. The committee noted that the ICERs were £1,530,000 and £383,000 per QALY gained respectively, and were well above the range normally considered cost effective. The committee was also aware that anaemia may be more common with sirolimus and everolimus than with other immunosuppressive therapies, and that this would worsen the cost effectiveness of everolimus in these comparisons.

Additional considerations

4.19 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 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 people having a kidney transplant and in 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 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.

4.20 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 people unable to continue taking their initial treatment. They also highlighted recent studies which showed that tacrolimus withdrawal should be avoided. They therefore emphasised the need for alternative immunosuppressants if tacrolimus has to be stopped. The committee was aware that returning to dialysis if a transplant fails can have a significant effect on quality of life as well as incurring costs to the NHS. It noted that sirolimus could be a cost-effective option for people with calcineurin inhibitor nephrotoxicity because the only alternative would be dialysis, 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 dialysis. 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 dialysis. 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 in 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 considered that any outstanding clinical and commissioning issues would be better addressed through other routes, such as other NICE programmes or clinical commissioning policies. They noted that the consultees agreed with this approach. 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.

4.21 The committee understood that the systematic review was not restricted to people having their first kidney transplant, and heard from the AG that about 30% 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 also heard from the AG that the economic model gives the same results whether it considers the first or second transplant. It was aware that the conclusions from the economic model might change if individual interventions were removed because, at the time of the second transplant, they had previously been found to be clinically inappropriate. However, it had not seen evidence for this situation, and considered that it was unlikely that sufficient evidence to inform a robust analysis could be obtained. 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.

4.22 The committee considered the bioequivalence of generic immunosuppressive therapies. It noted that calcineurin inhibitors have a narrow therapeutic index. It understood that the Commission on Human Medicines recommends that oral tacrolimus should be prescribed by brand name, and that care is needed when switching between drugs with a narrow therapeutic index (see the Medicines and Healthcare products Regulatory Agency's drug safety update on oral tacrolimus products). The committee heard from the clinical experts that this primarily applies to the drugs that are dosed based on plasma levels, such as tacrolimus, and that clinicians are aware of the risks associated with generic prescribing and switching formulations. The committee understood that guidance on good practice in prescribing generic immunosuppressive therapies is routinely followed in clinical practice. The committee also heard that clinicians are aware of cost differences between the different brands of immunosuppressive therapies, and take into account local costs in their prescribing decisions. The committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least expensive product when starting treatment.

4.23 The committee noted the potential equality issue raised by consultees during scoping, in submissions and during the committee meeting. It understood that some Jehovah's Witnesses are unwilling to have human blood products, but noted that none of the recommended technologies are based on human blood products. The committee understood that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and noted that a number of effective treatment options are available. The committee also heard that mycophenolate mofetil cannot be taken by women who are pregnant and noted that alternative effective treatment options are available.

4.24 The committee discussed providing immunosuppressive therapy for adults who cannot swallow capsules as a result of a disability, or who cannot take a particular preparation of tacrolimus or mycophenolate mofetil for religious reasons because it contains gelatine of animal origin. The committee noted that these people might need alternative

formulations (such as oral suspensions or gelatine-free formulations) instead. The committee noted that oral suspensions and gelatine-free formulations are available for both immediate-release tacrolimus and mycophenolate mofetil, and that these products have marketing authorisations in the UK. The suspensions are more expensive than the capsules, although there is a nationally available price agreed with the Commercial Medicines Unit for Modigraf (see section 3.10 and section 3.18). The committee recognised that, given its recommendations (see section 4.12 and section 4.15) covered all formulations of immediate-release tacrolimus and mycophenolate mofetil, it might be considered unfair to allow access to only the least expensive formulations because people who cannot take a particular formulation as a result of a disability or other characteristic protected under equality legislation would then be unable to have the recommended treatments. It noted that restricting access in this way might discriminate against adults with protected characteristics. The committee reiterated that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product (see section 4.22), but concluded that it could be started with an alternative dosage form if the least expensive product is not suitable. 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

TA481	Appraisal title: Immunosuppressive therapy for kidney transplant in adults	Section
Key conclusion		

Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as initial options to prevent organ rejection in adults having a kidney transplant. • The committee considered that basiliximab is a clinically effective treatment option, and provided more quality-adjusted life years (QALYs) at a lower cost than treatment without induction and rabbit anti-human thymocyte immunoglobulin (r-ATG). • The committee heard that tacrolimus is a potent immunosuppressive therapy, and considered that immediate-release tacrolimus was cost effective. • The committee considered that mycophenolate mofetil was a clinically effective option, and was cost effective in all the comparisons presented. r-ATG, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as initial treatments to prevent organ rejection in adults having a kidney transplant. • The committee considered that r-ATG was clinically effective, but concluded that it was not cost effective. • The committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. • The committee noted that belatacept was likely to be clinically effective, but was associated with incremental cost-effectiveness ratios (ICERs) substantially higher than the range normally considered cost effective. • The committee heard that there were no noticeable differences in clinical effectiveness between mycophenolate mofetil and mycophenolate sodium, and concluded that mycophenolate sodium was not cost effective. • The committee noted that sirolimus was not a cost-effective treatment option.	1.1–1.3, 4.10, 4.12, 4.15, 1.4, 4.11, 4.13, 4.14, 4.16–4.18, 1.5

• The committee noted the economic modelling suggested that everolimus may be more effective than mycophenolate mofetil and azathioprine, although it was not cost effective. The committee was unable to make recommendations on any of the technologies considered in this appraisal as options for preventing organ rejection in adults 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 treatment failure, contraindications, or intolerance such as nephrotoxicity associated with calcineurin inhibitors, or thrombotic microangiopathy). This includes adults 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 treatment failure, contraindications or intolerance.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee understood that effective immunosuppressive therapies are important to prevent organ rejection in adults having kidney transplants. The committee heard that the choice of immunosuppressive therapy is affected by a number of factors, including the characteristics and preferences of the person having treatment. The committee understood the value of having a choice of immunosuppressive therapies.	4.1, 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?	The committee heard that the key priority for immunosuppressive therapy is to prolong graft survival for as long as possible, while minimising adverse effects. The clinical experts considered that both quality of life and survival are better with a functioning kidney transplant than with dialysis, and the patient experts emphasised the value of maintaining a functioning kidney transplant.	4.1
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 and may include polyclonal or monoclonal antibodies. Maintenance therapy starts immediately after transplant and continues for life. Basiliximab and r-ATG are options for induction therapy. Tacrolimus, belatacept, mycophenolate mofetil, mycophenolate sodium, sirolimus and everolimus are options for maintenance therapy. The committee understood that in clinical practice, some treatments may be considered particularly valuable for certain groups of people.	2.3, 4.8
Adverse reactions	The committee heard that sirolimus may be associated with a range of adverse effects including peripheral oedema and bone marrow suppression and that sirolimus and everolimus may be associated with an increased risk of anaemia.	4.17, 4.18
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The AG's systematic review found 86 randomised controlled trials, including 11 studies of induction therapies, 73 studies of maintenance therapies and 2 studies examining both induction and maintenance therapies. The committee noted that the AG's systematic review was comprehensive and concluded that all the relevant clinical effectiveness randomised controlled trial evidence had been taken into account.	4.4
Relevance to general clinical practice in the NHS	The committee noted that the AG considered that only 11 trials adequately matched the population and current practice in the NHS in England.	4.4
Uncertainties generated by the evidence	The committee understood that there was substantial heterogeneity in the AG's network meta-analysis, and none of the maintenance regimens performed consistently well across all 4 outcomes. The committee considered that limited conclusions on differences between these options can be drawn from the AG's network meta-analysis. The committee understood that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes, and that it would be difficult to identify people who would benefit. It concluded that the effect on clinical outcomes was uncertain.	4.6, 4.9

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. 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 limited evidence for treatment switching, but was aware that such evidence had not been searched for in a systematic review, 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 the recommendations only apply to the initial treatment around the time of kidney transplant. The committee understood that about 30% 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.	4.8, 4.20, 4.21

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The AG's network meta-analysis showed that basiliximab and r-ATG were significantly more effective than treatment without induction for acute rejection. The committee concluded that basiliximab and r-ATG are effective induction therapies, but there was no evidence of a difference in clinical effectiveness between them. The AG's network meta-analysis showed a number of statistically significant differences between regimens, although none of the maintenance regimens performed consistently well across all 4 outcomes assessed. The committee saw that all regimens except belatacept plus mycophenolate mofetil showed evidence of improvement in acute rejection compared with ciclosporin plus azathioprine, although belatacept plus mycophenolate mofetil statistically significantly increased graft function. The committee concluded that the maintenance therapies are effective options.	4.5, 4.6
How has the new clinical evidence that has emerged since the original appraisal (TA85) influenced the current (preliminary) recommendations?	The AG's systematic review found 86 randomised controlled trials, of which 23 were included in NICE's original technology appraisal guidance on immunosuppressive therapy for kidney transplantation in adults, and 63 were identified in the updated systematic review for the current appraisal. The committee noted that the AG's systematic review was comprehensive and included all relevant clinical effectiveness randomised controlled trial evidence. Since the NICE technology appraisal guidance on immunosuppressive therapy for kidney transplantation in adults was published in 2004, the marketing authorisation for daclizumab has been withdrawn and new technologies have received marketing authorisations.	4.4–4.6, 2.4
Evidence for cost effectiveness		

Availability and nature of evidence	Economic analyses were presented by the AG, Astellas, Bristol-Myers Squibb and Novartis. • The AG presented an economic model based on a discrete-time state transition structure. • Astellas submitted a Markov model and presented results for each immunosuppressive drug compared with immediate-release tacrolimus. • Bristol-Myers Squibb presented an analysis of the cost effectiveness of belatacept compared with tacrolimus and ciclosporin, based on a 36-month initial phase followed by a longer-term Markov model. • Novartis presented a patient-level simulation model to capture the cost effectiveness of everolimus plus reduced-dose ciclosporin and mycophenolate sodium plus standard-dose ciclosporin, compared with mycophenolate mofetil plus standard-dose ciclosporin or tacrolimus.	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee noted that the AG and Novartis modelled quality of life differently. It understood that the Novartis model suggested that the cost-effectiveness results were very sensitive to the utility assumptions. The committee concluded that the AG's model was the most informative model for decision-making.	4.7

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?	The committee noted that the AG modelled quality of life using fixed utility decrements for each health state. The committee noted that Novartis assumed that quality of life would decrease as graft function decreased. It considered that Novartis's analyses implied that the benefits had been underestimated for all treatments, and would be most underestimated for treatments with the largest beneficial effect on graft function.	4.7

Are there specific groups of people for whom the technology is particularly cost effective?	The committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. 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 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 heard from the AG the that economic model gives the same results whether it considers the first or second transplant, but was aware that the conclusions might change if individual interventions were removed because, at the time of the second transplant, they had previously been found to be clinically inappropriate. However, it had not seen evidence for this situation, and considered that it was unlikely that sufficient evidence to inform a robust analysis could be obtained. 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.	4.8, 4.20, 4.21

What are the key drivers of cost effectiveness?	The committee understood that the cost-effectiveness results were very sensitive to the utility assumptions.	4.7
Most likely cost-effectiveness estimate (given as an ICER)	• Basiliximab dominated (provided more QALYs at a lower cost) treatment without induction and r-ATG. • r-ATG was dominated by basiliximab and was associated with ICERs of £63,200 to £333,000 per QALY gained compared with treatment without induction. • Immediate-release tacrolimus was cost effective in all comparisons presented by the AG. • Prolonged-release tacrolimus was dominated by both immediate-release tacrolimus and ciclosporin. • Belatacept was associated with ICERs of £241,000 to £424,000 per QALY gained, compared with immediate-release tacrolimus, sirolimus and ciclosporin. • Mycophenolate mofetil dominated both sirolimus and azathioprine, and was less costly and less effective than mycophenolate sodium and everolimus with ICERs of £144,000 and £1,530,000 per QALY lost respectively. • Mycophenolate sodium was associated with an ICER of £56,600 per QALY gained compared with azathioprine, and £144,000 per QALY gained compared with mycophenolate mofetil. • Sirolimus was dominated by mycophenolate mofetil and immediate-release tacrolimus. • Everolimus was associated with ICERs of £1,530,000 and £383,000 per QALY gained, compared with mycophenolate mofetil and azathioprine respectively.	4.10–4.18

How has the new cost-effectiveness evidence that has emerged since the original appraisal (TA85) influenced the current (preliminary) recommendations?	Economic analyses were presented by the AG, Astellas, Bristol-Myers Squibb and Novartis. The AG's model was independent of that built for NICE's technology appraisal guidance on immunosuppressive therapy for renal transplantation in adults. The AG highlighted that the previous analysis had not fully accounted for uncertainty and had not taken into account the effect of kidney function on clinical and economic outcomes. Since the original appraisal, some of the technologies have become available as generics. The committee concluded that the AG's model was the most informative model for decision-making.	4.7
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 understood that some Jehovah's Witnesses are unwilling to have human blood products, that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and that mycophenolate mofetil cannot be taken by women who are pregnant. The committee understood that some adults may not be able to swallow capsules as a result of a disability, or cannot take a particular preparation of tacrolimus or mycophenolate mofetil for religious reasons because it contains gelatine of animal origin. It recognised that, given its recommendations covered all formulations of immediate-release tacrolimus and mycophenolate mofetil, it might be considered unfair to allow access to only the least expensive formulations because people who cannot take a particular formulation as a result of a disability or other characteristic protected under equality legislation would then be unable to have the recommended treatments. It noted that restricting access in this way might be discriminatory. The committee noted that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. However, treatment could be started with an alternative dosage form if the least expensive product is not suitable.	4.23, 1.2, 4.24

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 ministers have 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 2 months of the first publication of the final appraisal determination.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient is having a kidney transplant and the doctor responsible for their care thinks that basiliximab, immediate-release tacrolimus 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 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.

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