NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on immunosuppressive therapy for kidney transplant in children and young people (review of technology appraisal guidance 99)

Decision of the Panel		
Introduction		
1.		An Appeal Panel was convened on 30th March 2016 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on Immunosuppressive therapy for kidney transplant in children and young people (review of technology appraisal guidance 99) This appeal immediately followed the hearing of the appeal relating to the Final Appraisal Determination for immunosuppressive therapy for kidney transplants in adults (review of technology appraisal guidance 85). The Appeal Panel, Appellants and the Appraisal Committee agreed that there was no need to repeat points made at the earlier hearing relating to adults. Points made in the course of the adult hearing that are relevant to the children's appeal are recorded here so that this decision letter may stand alone.
2.		The Appeal Panel consisted of: Mr Patrick Storrie Chair Prof Robin Ferner NHS Representative Dr Mercia Page Industry Representative Mr Colin Standfield Lay Representative Mr Jonathan Tross Non-Executive Director
3.		Professor Ferner declared that he was a Fellow of the Royal

		College of Physicians, one of the Consultees. All other members declared that they had no conflict of interests.
4.		The panel considered appeals submitted by– The British Kidney Patient Association The British Transplantation Society, the Renal Association, the British Renal Society and the British Association of Paediatric Nephrology, who appealed jointly ESPRIT NHS England
5.		The British Kidney Patient Association was represented by: Ms Fiona Loud Mr Nick Palmer
6.		The British Transplantation Society, Renal Association, British Renal Society and the British Association of Paediatric Nephrology, who appealed jointly, were represented by: Dr David Hughes Dr Stephen Marks Dr Nicholas Torpey
7.		ESPRIT was represented by: Ms Julia Cook Prof Atholl Johnston
8.		NHS England was represented by: Mr Malcolm Qualie Mr Keith Rigg
9.		In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:

		Prof Gary McVeigh Mr Meindert Boysen Dr Sally Doss Ms Marcela Haasova Ms Tracey Jones-Hughes Ms Helen Knight Dr Tristan Snowsill Mr Ian Watson
10.		All the above declared no conflicts of interest.
11.		The Institute's legal adviser, Eleanor Tunnicliffe of DAC Beachcroft LLP, was also present and was accompanied by her assistant Sophie Devlin.
12.		Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this Appeal.
13.		There are two grounds under which an appeal can be lodged: **Ground One: In making the assessment that preceded the recommendation, NICE has** **a) Failed to act fairly** **b) Exceeded its powers.** **Ground Two: The recommendation is unreasonable in the light of the evidence submitted to NICE.**
14.		No appeal was lodged under Ground 1. The Vice Chair of NICE (Mr Andy McKeon) in preliminary correspondence had confirmed that: • British Association of Paediatric Nephrology, the British Transplant Society, the Renal Association

		and the British Renal Society who appealed jointly • British Kidney Patient Association • ESPRIT • NHS England had valid appeal points under Ground 2.
15.		Induction therapy is treatment at the time of transplant to prevent organ rejection. Two drugs used in induction therapy were considered in this appraisal. • Basiliximab (Simulect, Novartis Pharmaceuticals) is a monoclonal antibody that acts as an interleukin-2 receptor antagonist. It is used to prevent acute rejection of a kidney after transplant. The marketing authorisation is for use with the drug ciclosporin. • Rabbit anti-human thymocyte immunoglobulin (r-ATG; Thymoglobuline, Sanofi) is an antibody made by injecting human thymus cells into rabbits and which destroys immune cells (T-cells) involved in acute organ rejection. It is used to prevent acute rejection of a kidney after transplant. Maintenance therapy is used to prevent rejection of a transplant in the longer term. The Appraisal Committee considered several drugs used in maintenance therapy. • Tacrolimus is a calcineurin inhibitor. The Appraisal Committee considered preparations of immediate-release tacrolimus and of prolonged-release tacrolimus. Brands of immediate-release tacrolimus with marketing authorisations in the United Kingdom include Adoport (Sandoz), Capexion (Mylan), Perixis (Accord Healthcare), Tacni (Teva) and Vivadex (Dexcel Pharma). Astellas Pharma Ltd markets immediate-release tacrolimus as Modigraf and prolonged-release

		tacrolimus as Advagraf. • Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T cells. • Mycophenolic acid inhibits the enzyme inosine monophosphate dehydrogenase required by immune cells and is therefore an immunosuppressant. The Appraisal Committee considered both mycophenolate mofetil and mycophenolate sodium. • Sirolimus (Rapamune, Pfizer) is an antiproliferative agent that blocks a protein called mammalian target of rapamycin (mTOR).
16.		Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements: Dr David Hughes on behalf of the British Association of Paediatric Nephrology, the Renal Association, British Transplant Society and the British Renal Society, who appealed jointly Professor Atholl Johnson on behalf of ESPRIT Fiona Loud on behalf of The National Kidney Federation Mr Keith Rigg on behalf of NHS England and Professor Gary McVeigh on behalf of the Appraisal Committee.
17.		The appraisal that is the subject of the current Appeal provided advice to the NHS on immunosuppressive therapy for kidney transplant in children and young adults (review of technology appraisal guidance 99).
18.		A concern that arose during the Appeal was uncertainty regarding the treatment scenarios covered by the Final Appraisal Determination. This issue came to prominence during

		the Panel's questioning of the Appraisal Committee on the impact of the Guidance in limiting clinician choice. The Appraisal Committee chair explained that the 'decision problem' considered by the Committee was the use of the treatments under assessment in 'de novo' renal transplant patients and did not look at the 'downstream' sequencing of treatment if the recommended treatment was not appropriate. Although issues about the scope had not been raised as a separate ground of appeal in the appellants' appeal letters, the Appeal Panel considered that this issue was integral to and impliedly contained within other grounds of appeal that had been raised, for example regarding the appropriateness of dialysis as a comparator and the reduction of treatment options for patients. The Panel therefore considered the question of the clarity of the Final Appraisal Determination and whether it accurately stated the reasoning of the Committee as presented in the Appeal. Following questioning of the Appraisal Committee, the Appeal Panel understood that the recommendations in the Final Appraisal Determination covered treatment of 'de novo' patients and did not cover the treatment of patients for whom the recommended cost-effective treatment stated in the Final Appraisal Determination was not clinically appropriate. (The terms 'initial treatment' and 'inception treatment' were also used during the Appeal hearing to describe the treatments given to de novo patients.) The objective of the Appraisal was stated in the Final Scope as being '*To appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation in*

		children and adolescents.' [National Institute for Health and Care Excellence Final scope for the appraisal of immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99) Issue Date: July 2014]. This was further amplified (in footnote 1 to the final scope) as follows: *'The Department of Health and Welsh Assembly Government remit to the Institute was to advise on the clinical and cost-effectiveness of immunosuppressive regimes for renal transplantation, both immediately after transplantation and as far as the evidence allows at subsequent stages, including those using the newer agents.'* The Table at page 5 onwards of the final scope stated that the population to be considered was *'Children and adolescents undergoing kidney transplantation.*' Possible subgroups to be considered, if evidence allowed, were patients who had had a re-transplant within 2 years and patients with previous acute rejection. The Appeal Panel concluded that the consideration of 'downstream' treatments (i.e. use of the treatments under assessment if the most cost-effective treatment was not appropriate) was not excluded by the scope. It was therefore important that the Final Appraisal Determination made clear whether its recommendations extended to such usage. The Panel also noted that the Appraisal Committee had explicitly commented at paragraphs 1.4 and 4.77 of the Final Appraisal Determination on two circumstances in which patients were unable to continue recommended initial treatment. In those circumstances—where patients developed thrombotic

		microangiopathy or calcineurin-inhibitor induced nephrotoxicity— the Appraisal Committee stated that it was unable to make a recommendation. This appeared inconsistent with the view stated by the Committee at Appeal that the scope of the appraisal did not extend to patients in whom initial treatment had proved clinically inappropriate. The Panel's view was that the Final Appraisal Determination did not make this clear, and there was a risk that it would mislead patients, clinicians and those funding treatment. In particular, it was not clear: - whether the Final Appraisal Determination recommendations covered only the initial induction and maintenance treatment given to patients who had just received a kidney transplant, or whether it extended to subsequent ('second-line') treatments in patients who suffered adverse reactions to or were unable to take the initial treatment for reasons other than those set out at paragraph 1.4; - whether the Final Appraisal Determination recommendations covered patients receiving a subsequent kidney transplant after the failure of one or more earlier transplanted kidneys including patients for whom it had already been established, prior to re-transplant, that the recommended treatment was not clinically appropriate. The Panel concluded that the Appraisal Committee had not acted fairly because the Final Appraisal Determination did not properly explain to which patients the recommendations applied and/or did not reflect the reasoning of the Committee. If it is the case that the Appraisal Committee has decided that it

		is unable to make recommendations on uses that fall within the scope, this decision should be explained clearly in the appraisal documents and consultees given an opportunity to comment. The population and treatment scenarios covered by the Final Appraisal Determination should be clearly identified. The Panel did not make any ruling on whether or not it would be reasonable for the Committee to decide to 'not recommend' some of the appraised treatments for second-line use. This is because it understood from the Appraisal Committee that the Final Appraisal Determination was not intended to express any conclusions on second-line use.
Appeal Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE.		
19.		**Appeal by the British Transplant Society, the Renal Association, the British Association for Paediatric Nephrology and the British Renal Society ('the Joint Appeal')** **Appeal Point 2.1** **Recommendation 1.4 is unreasonable in light of the evidence presented to NICE or lack thereof.**
20.		The points made by the Joint Appeal were unnumbered. The points have been numbered here for clarity.
21.		Dr David Hughes, for the Joint Appeal, told the Appeal Panel that the evidence was important. It was very difficult to undertake adequate trials in children, and in consequence the Appraisal Committee had found only three relevant randomised control trials. The decisions on treatment in children and

		adolescents therefore had to rely on evidence extrapolated from trials in adults and on clinical experience. There were just over 800 children and adolescents with kidney transplants in the United Kingdom, cared for in 13 centres, of which 10 performed transplant surgery. The majority of patients took the regimen recommended by the Appraisal Committee. However, paediatric nephrologists delivered personalised care to those patients who encountered difficulties: one in eight took a drug that the Appraisal Committee had designated 'not recommended.' This meant that, while usage was not commonplace, it could not be considered exceptional. Loss of a transplanted kidney had a high cost for children and adolescents, because it reduced the chances of a subsequent successful graft.
22.		Dr Nicholas Torpey, for the Joint Appeal, stated that the recommendations in paragraphs 1.1–1.3 of the Final Appraisal Determination represented current practice for the majority of transplant patients. This may not be appropriate for all patients throughout the life of the transplanted kidney. If the recommendations referred to initial treatment only, then in Dr Torpey's view they were consistent with current practice.
23.		Dr Torpey told the Appeal Panel that 10% of patients in clinical trials were unable to tolerate the treatment to which they were allocated. When this happened in clinical practice alternative treatment was required. If the Appraisal Committee's decision not to recommend rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept applied to this circumstance, then the appellants believed that it unreasonably prohibited the use of

		these drugs.
24.		Dr Ball, for the Joint Appeal, stated that the difficulty did not arise in considering the Appraisal Committee's inferences from trial data across the broader population of patients who have transplants, but in considering the 15–20% of patients who are unable to tolerate the recommended treatments.
25.		Dr Snowsill stated that, as the scope did not include a population intolerant of the recommended drugs, it referred effectively to initial treatment.
26.		Professor McVeigh explained that the Final Appraisal Determination's recommendations applied only to *de novo* patients. The Committee had not made recommendations for 'downstream' treatment i.e. for treatment of those patients who were intolerant of the first-line treatment. Nor did the recommendations apply to patients receiving a re-transplant. Professor McVeigh agreed that there was less evidence in children and adolescents than in adults, and that there were only three relevant randomised controlled trials. The Committee had tried to find all of the appropriate data. When the Committee was told of the TWIST study, for example, it amended the provisional guidance to take the results of that trial into account. In the absence of evidence, he said, the Appraisal Committee could generally not make recommendations. Where evidence existed, then as far as possible the Appraisal Committee wished to decide clearly whether a treatment was recommended or not recommended for use in the NHS. Where there was evidence regarding treatments that led to

		worse outcomes and cost more than the reference case treatment, or where the incremental cost-effectiveness ratio was extremely high, then the Appraisal Committee stated that those treatments should not be recommended. The Committee decided that if there were no data in children it was appropriate to use data from adults to inform its decision. It had been advised by the clinical expert that in the absence of child data, it was necessary to extrapolate from adult data, imperfect as it may be.
27.		Dr Stephen Marks, for the British Association of Paediatric Nephrology and British Transplantation Society, emphasised that children differed from adults, that children evolved through infancy to childhood to adolescence to adulthood, and that the immune system and physiology develop and change. Clinical studies were very difficult, and if they were undertaken it was often necessary to use surrogate outcomes, since the number of events such as graft loss was very low.
28.		Dr Hughes added that those who were recruited to trials were usually the 'easy' patients who had not received other treatments. The most challenging patients were excluded from trials.
29.		In response to a question from the Panel, Professor McVeigh accepted that there was a lack of evidence regarding children. He also accepted that children were not adolescents, and adolescents differed from adults (that is, adults over the age of 18 years, when adult guidance applied), and that the Committee had found it necessary to rely on adult data.
30.		Dr Tristan Snowsill, from the Technology Appraisal Group,

		explained that in the absence of outcome data from clinical trials there were uncertainties in judging efficacy in children. The model used had not incorporated extra uncertainty for specific scenarios. However, there was not much uncertainty about drug costs, albeit that children needed smaller doses.
31.		Professor McVeigh was asked by the Appeal Panel whether, given the paucity of evidence from clinical trials in children, it was right to give more weight to clinical experience and less weight to published evidence. He thought that this was fair comment: it was very difficult to come to a definite view on treatment for children based on data from adults.
32.		The Appeal Panel understood that the Appraisal Committee could make firm decisions only on matters that it had considered. The Panel was uncertain what the Committee had considered. At the start of the hearing, having read the Final Appraisal Determination, the Panel's understanding was that the Committee's recommendations at paragraph 1.1–1.4 applied to all patients other than the two groups identified at paragraph 1.4, in relation to which 'no recommendation' was made. The Panel understood that the recommendations would apply to patients who had had one or more previous transplants and also to those for whom the recommended treatment was clinically inappropriate (this decision letter will refer to treatment in both instances as 'second-line treatment'). This is because there was no indication in the Final Appraisal Determination that it related only to 'first-line' treatment and because, as discussed above, these groups were not excluded by the scope. This also appeared to be the understanding of the appellants attending

		the hearing. The Final Appraisal Determination explains the lack of evidence for recommending treatments for particular subgroups (see e.g. the Final Appraisal Determination at 4.56). At the start of the Appeal hearing the Panel understood that this was the reason why separate recommendations had not been made regarding 'second-line' treatments, e.g. for those who had had the recommended treatment and were intolerant of it. There was not the evidence to support such recommendations. The 'not recommended' conclusions set out in the Final Appraisal Determination applied equally to these groups. It was also the Appeal Panel's understanding that there were two instances in which the Committee thought that its conclusion not to recommend particular treatments should not apply. These are the scenarios are set out at the bullet points at paragraph 1.4 of the Final Appraisal Determination. Both scenarios appear to involve 'second-line' treatment after a patient has been found to be intolerant of treatment with the recommended regimen. See paragraph 4.77 of the Final Appraisal Determination. Over the course of the hearing, both the Appraisal Committee and the Assessment Group referred to second-line recommendations being outside the scope for this appraisal. The Panel considered that this did not reflect what was said in the Final Appraisal Determination and was concerned about the inconsistency. The position as set out in the Final Appraisal Determination was that second-line treatments had been appraised and were 'not recommended' apart from in the circumstances set out in the bullet points at 1.4 of the Final

		Appraisal Determination, which identified two second-line treatment scenarios which had been considered and where 'no recommendation' was made. The position as set out during the Appeal was that second-line treatments were outside the scope. The difference between these two positions was highly relevant for patients, clinicians, and funders of care. The Panel's view was that, having heard the arguments of the Appraisal Committee at the Appeal hearing, the Final Appraisal Determination was not sufficiently clear. There was a risk that it would mislead patients, clinicians and those funding treatment. In particular, it was not clear: - whether the Final Appraisal Determination recommendations covered only the initial induction and maintenance treatment given to patients who had just received a kidney transplant, or whether it extended to subsequent (second-line) treatments in patients who suffered adverse reactions to or were unable to take the initial treatment other than those patients described in paragraph 1.4; - whether the Final Appraisal Determination recommendations covered patients receiving a subsequent kidney transplant after the failure of one or more earlier transplanted kidneys including patients for whom it had already been established, prior to transplant, that the recommended treatment was not clinically appropriate. The Panel concluded that the Appraisal Committee had not acted fairly because the Final Appraisal Determination did not properly explain to which patients the recommendations applied. If it is the case that the Appraisal Committee has decided that is

		unable to make recommendations on uses that fall within the scope, this decision should be explained clearly in the appraisal documents and consultees given an opportunity to comment. The population and treatment scenarios covered by the Final Appraisal Determination should be clearly identified.
33.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. Any updated guidance will need to be clear whether patients who have previously been found to be intolerant of the recommended initial treatment, e.g. as a result of an adverse drug reaction to a relevant medicinal product, are covered by the recommendations. The Panel noted that the scope specifically stated that recommendations could be made for a subgroup of patients who had had a re-transplant, if the evidence allowed. This suggested to the Panel that patients who had had a previous transplant were within the scope, although the scope recognised that it might not be possible to make recommendations specifically relating to such patients. Any updated guidance will need to be clear which patients are covered and whether patients not covered by the guidance have been excluded because of the wording of the scope or because of the paucity of evidence.
Joint Appeal **Appeal Point 2.2** **Recommendation 1.4 disadvantages patients who are intolerant of mycophenolate mofetil and experience gastrointestinal disturbances.**		

34.		Dr David Hughes explained that nationally 40 paediatric patients across several centres were treated with mycophenolate sodium. Mycophenolate sodium was very useful in paediatric patients if adjustments to the dose of mycophenolate mofetil did not relieve adverse effects.
35.		In answer to a question from the Appeal Panel, Dr Hughes stated his view that the relevant question in judging whether the decision of the Appraisal Committee was reasonable was to what extent clinical expert opinion should inform the decision when other evidence was absent. While there was a lack of evidence from clinical trials, many clinicians in different centres when faced with a difficult clinical problem had applied similar judgment in using mycophenolate sodium.
36.		In Dr Hughes's view it would have been appropriate for the Appraisal Committee to borrow the Scottish legal verdict 'not proven' in respect of the cost-effectiveness of mycophenolate sodium in children and adolescents – that is, they should not have concluded definitely that it was not recommended.
37.		Professor McVeigh, for the Appraisal Committee, stated that the Committee had considered whether mycophenolate sodium was better tolerated than mycophenolate mofetil. He said that this was a clinical impression. Mycophenolate sodium was developed specifically to try to avoid adverse gastrointestinal effects, but clinical trial data in adults failed to show any significant benefit for mycophenolate sodium over mycophenolate mofetil with regard to gastrointestinal adverse effects. Many adult patients intolerant of mycophenolate mofetil were also intolerant of mycophenolate sodium and were subsequently switched to sirolimus.

38.		Professor McVeigh noted that dose-splitting and dosage reduction were recommended by NHS England as ways of reducing the gastrointestinal adverse effects of mycophenolate mofetil. There was also the option of using azathioprine in place of mycophenolic acid.
39.		The Appraisal Committee did understand that there were special circumstances in children, such as problems in swallowing tablets, and had taken these into account. They had not heard that mycophenolate sodium was commonly used in children, and had understood that azathioprine was used more commonly than mycophenolic acid formulations.
40.		The Panel noted that mycophenolate sodium had a marketing authorisation only in adult patients, and asked Dr Hughes about off-label use. He answered that there was a long history of using products off-label when treating children: approximately 20% of all medicines use in children would be outside the terms of the marketing authorisation.
41.		Professor McVeigh maintained that it could have caused difficulties if the Appraisal Committee had reached different conclusions on the use of mycophenolate sodium in paediatric and adult patients when the Committee had considered the same evidence base.
42.		The Appeal Panel considered that the need to extrapolate further from the evidence when making recommendations for children and young people could mean that different conclusions could be reached in the different appraisals. They would not be unreasonable simply because they were different, although it should be clear why a different conclusion was reached.

		The Appeal Panel understood clearly that mycophenolate mofetil can cause unpleasant and sometimes intolerable diarrhoea. It was thought by clinicians and patient groups that mycophenolate sodium might be less prone to causing gastrointestinal adverse effects. However, mycophenolate sodium had similar effects, and no appreciable difference was found in clinical trials in adults.
43.		It was not unreasonable for the Committee to prefer to base its conclusion on the evidence extrapolated from clinical trials in adults. As outlined above, the Appeal Panel noted the Committee's position that the recommendations in the Final Appraisal Document applied only to first-line treatment, and the Panel accepted that the Appraisal Committee was not unreasonable in concluding that mycophenolate sodium was 'not recommended' for first-line treatment. The Appeal Panel did not consider whether it was reasonable to reach firm conclusions regarding the value of mycophenolate sodium for second-line treatment.
44.		The Appeal Panel therefore dismissed the appeal on this point.
Joint Appeal **Appeal Point 2.3** **Recommendation 1.4 does not account for drug variability and non-adherence**		
45.		Dr Hughes told the Panel that poor outcomes in children and adolescents were often associated with non-adherence. Prolonged-release tacrolimus had the advantage over immediate-release tacrolimus that it needed to be taken only once a day. Thirty-three patients in nine paediatric centres were receiving treatment with prolonged-release tacrolimus.

46.		Dr Marks reiterated that adherence was an important issue for young people. It was often difficult to ascertain the reason for non-adherence.
47.		Ms Loud told the Appeal Panel that patient representatives 'had not been fully listened to' when they expressed their views to the Appraisal Committee. There were difficulties with adherence. Tacrolimus doses had to be taken at a consistent time in relation to meals. This made matters difficult for teenagers, for example, if they wished to go to a night-club.
48.		Mr Nick Palmer, for the British Kidney Patient Association, reminded the Appeal Panel that the NICE guidance on Medicines Adherence recommended a series of medical and psycho-social interventions to improve adherence. One of these was to reduce the number of tablets that a patient needed to take.
49.		Professor McVeigh confirmed that young people had given evidence to the Appraisal Committee and had told the Committee of the complex regimen of medication that had to be followed. The Committee had noted this was a particular problem.
50.		Dr Snowsill referred to a study in adults by Kuypers *et al 2013.* He explained that the study had been reviewed after the Technology Assessment Group had read a response to the Appraisal Consultation Document that drew attention to it. Its design had both strengths and weaknesses. It was randomised, but it recruited only stable adult patients, and it did not examine of any of the outcomes pre-specified in this assessment. It did not provide information on the whole group of adult patients or on those in whom there were problems of adherence.
51.		Professor McVeigh explained that it was difficult to define in advance a subgroup of patients in whom there would be problems of adherence. It was not possible to find a study in adults or children that compared relevant outcomes (such as

		episodes of acute rejection) in patients who had been randomised to treatment with prolonged-release tacrolimus or with immediate-release tacrolimus. This meant the clinical effectiveness was uncertain.
52.		In considering this ground of appeal the Panel was mindful of the Institute's duties under the Equality Act 2010, in particular the requirement of the public sector equality duty to promote equality of opportunity between different age groups. The Appeal Panel considered that the Appraisal Committee had carefully examined evidence on adherence and that evidence did not show that a change from immediate-release tacrolimus to prolonged-release tacrolimus in patients with poor adherence either improved adherence or led to better outcomes. The Appeal Panel considered that the need to extrapolate further from the evidence when making recommendations for children and young people could mean that different conclusions could be reached in the different appraisals. They would not be unreasonable simply because they were different, although it should be clear why a different conclusion was reached. The Committee had sought but failed to find a clearly defined subgroup with poor adherence that could be predicted prior to treatment. It had not reached an unreasonable conclusion.
53.		The Appeal Panel therefore dismissed the appeal on this point. As outlined above, the Appeal Panel noted the Committee's position that the recommendations in the Final Appraisal Document only applied to first-line treatment. The Appeal Panel therefore did not consider whether it was reasonable to reach firm conclusions regarding the value of mycophenolate sodium for second-line treatment.

Joint Appeal **Appeal Point 2.4** **Recommendation 1.4 prevents the use of rabbit anti-human thymocyte globulin in 'high immunological risk' patients**		
54.		Dr Hughes told the Appeal Panel that the large majority of patients received the induction therapy recommended in the Final Appraisal Determination. Rabbit anti-human thymocyte globulin had been used as induction therapy only three times in the last five years, and that was in complex patients deemed at high risk of rejection. It was also required in cases of transplant rejection that did not respond to corticosteroid treatment. The Appraisal Committee, he said, had taken some evidence from adult treatment, but he did not see how the Committee could be sufficiently confident to state that the treatment was 'not recommended.'
55.		Dr Marks said he had used rabbit anti-human thymocyte globulin for induction in re-transplanted patients.
56.		The marketing authorisation for basiliximab (Simulect) stipulates that it 'is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years). It 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.'
57.		Professor McVeigh stated that basiliximab was cost-effective, and was the induction treatment most commonly used in the United Kingdom.
58.		He agreed, in response to a question from the Appeal Panel, that it was long-established custom and practice to use it outside the strict terms of the marketing authorisation, and this was

		uncontroversial.
59.		The Appeal Panel heard from several appellants that the Appraisal Committee's recommended regimen, which included basiliximab but not ciclosporin, was the standard regimen. No appellant suggested that the regimen favoured by the Appraisal Committee was unreasonable.
60.		Professor McVeigh explained that the Appraisal Committee had heard that rabbit anti-human thymocyte globulin was almost never used in children, because it requires a more complex regimen, is given over long periods, and has more significant adverse effects than basiliximab.
61.		Professor McVeigh stated that the Appraisal Committee had discussed rabbit anti-human thymocyte globulin at some length. The Committee knew that some clinicians wished to use it as the induction treatment in patients at high immunological risk. In the absence of data on children, Professor McVeigh said, the Committee had once again relied on data from adults. They had considered the study by Brennan *et al* (2006), which was a randomised controlled trial of basiliximab against rabbit anti-human thymocyte globulin. However, only 18% of the recruited patients were at high risk. It had been included in the Technology Assessment Group's network analysis. The Appraisal Committee sought other evidence but none was identified.
62.		When the Technology Assessment Group compared basiliximab with rabbit anti-human thymocyte globulin in adults, they found that basiliximab was always more effective and less expensive. The probability that rabbit anti-human thymocyte globulin would be cost-effective was less than 7%. The benefits would have to be very different for the treatment to be cost-effective in children and adolescents, because the costs were the same. There were uncertainties. Appraisal Committees were very experienced in dealing with uncertainty.

63.		Mr Boysen made it clear that the Appraisal Committee had not formally considered patients having a second transplant.
64.		The Appeal Panel noted the reference in the Final Appraisal Determination (page 1) that there needed to be 'compelling evidence of their safety and effectiveness' for the Appraisal Committee to recommend the use of drugs outside of the terms of their marketing authorisation. The Appeal Panel considered whether NICE had been unreasonable in considering the use of basiliximab outside the terms of its marketing authorisation. The regimen recommended by the Appraisal Committee was routinely used in the NHS. Its safety profile was therefore well understood. It was clinically effective and cost-effective according to a model that incorporated data from a randomised controlled trial, and none of the appellants had suggested that basiliximab should not be recommended for use in the NHS. The Appeal Panel could not see how the actions of the Appraisal Committee could be characterised as unreasonable. The Appeal Panel therefore dismissed the appeal on this point insofar as it referred to use of basiliximab outside its marketing authorisation. With regard to the use of rabbit anti-human thymocyte globulin in those who were not suitable for basiliximab, the Appeal Panel again noted the position adopted by the Appraisal Committee and the Technology Assessment Group in the Appeal. This was that second-line treatment was outside the scope of the appraisal and therefore the Committee's decision not to recommend certain treatments did not apply to patients who were not able to take the recommended initial regimen.

		For the reasons outlined above, the Appeal Panel concluded that the inconsistency between the position as set out in the Final Appraisal Determination and as explained by the Appraisal Committee and the Technology Appraisal Group at the Appeal was unfair. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
Joint Appeal **Appeal Point 2.5** **Recommendation 1.4 prevents the use of sirolimus as a calcineurin-inhibitor sparing agent or in patients with mycophenolate intolerance and those with malignancy**		
65.		Dr Hughes stated that 24 paediatric transplant patients in six centres were treated with sirolimus. It was not used as an induction agent in children or adolescents.
66.		Professor McVeigh reminded the Appeal Panel that patients treated with sirolimus 'to prevent further malignancy' were receiving it for an indication other than the prevention of transplant rejection, and so the Appraisal Committee had not considered its cost-effectiveness in that circumstance.
67.		Professor McVeigh told the Appeal Panel that the Appraisal Committee had explicitly considered treatment for what he called '*de novo*' transplant patients. It had not considered what treatments were suitable for patients unable to tolerate one or more components of the preferred initial regimen.

68.		He told the Appeal Panel that the Appraisal Committee had been unable to establish how many patients who were intolerant of mycophenolate mofetil would tolerate mycophenolate sodium, nor how many who failed to tolerate mycophenolate sodium would be treated with sirolimus. It was clear, however, that sirolimus was much more expensive and less cost-effective than azathioprine. Professor McVeigh reminded the Appeal Panel that the Appraisal Committee had not considered whether regimens containing sirolimus were effective, but whether they were cost-effective, and they were not.
69.		The Appeal Panel considered whether the Appraisal Committee had been unreasonable to state that sirolimus was not recommended, except in two well-defined and rare circumstances. The Panel understood clearly that the incremental cost-effectiveness ratio of sirolimus was very high compared with the preferred regimen of basiliximab with tacrolimus and mycophenolate mofetil. It therefore dismissed this ground of appeal, insofar as it related to the use of sirolimus for first-line treatment.
70.		The scope of the appraisal was again important. As discussed above, the Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. It was not clear to the Panel that second-line treatment was outside the scope. The Panel acknowledged that at face value it appeared unlikely that sirolimus would be recommended given the high incremental cost-effectiveness ratios. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations

		on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
British Kidney Patient Association **Appeal Point 2.1** **Recommendation 1.4 that 'Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in children and young people having a kidney transplant' is unreasonable as it has not taken into account the resultant reduction in transplants, which would lead to more dialysis.**		
71.		Ms Fiona Loud, for the British Kidney Patient Association, stated that the model used by the Technology Assessment Group failed to adequately consider dialysis as a comparator. The conclusion that several treatments were not recommended was made without taking into account the costs of failed transplants and wasted kidneys.
72.		Dr Snowsill stated that the Technology Assessment Group's model had not considered the costs associated with dialysis in patients who, as a consequence of the Appraisal Committee's decision that certain drugs were not recommended, would be unable to undergo a future transplant, because those patients were outside the scope. The clinical advisor to the Technology Assessment Group provided guidance that the Group should be wary of downstream evidence because of problems of bias. Such evidence would also be going beyond the scope. The Assessment Group had been clear about its approach and consultees and commentators had had an opportunity to comment.
73.		Professor McVeigh stated that the Appraisal Committee had

		considered clinical and cost-effectiveness evidence in what he called '*de novo*' transplant patients, and had considered evidence from clinicians, patients and consultees. The Committee had requested relevant evidence (for patients for whom the recommended treatments were not clinically appropriate) but none was provided. In the absence of evidence, the Appraisal Committee could generally not make recommendations. Where evidence existed, then as far as possible the Appraisal Committee wished to decide clearly whether a treatment was recommended or not recommended for use in the NHS. Where there was evidence regarding treatments that led to worse outcomes and cost more than the reference case treatment, or where the incremental cost-effectiveness ratio was extremely high, then the Appraisal Committee stated that those treatments should not be recommended. Following consultee comments on the Appraisal Consultation Document, the Appraisal Committee had accepted in two specific circumstances, namely patients who suffered kidney damage from calcineurin inhibitors (such as tacrolimus) and those rare patients who developed thrombotic microangiopathy and required urgent treatment to save the graft, that there was very little evidence, and that it would be very difficult to conduct a clinical trial. They therefore made 'no recommendation' for the otherwise 'not recommended' treatments in those unusual circumstances. The Appraisal Committee had not considered 'downstream switching,' that is, a change in treatment made in response to

		failure of initial treatment or the occurrence of adverse reactions.
74.		Professor McVeigh was asked by the Panel whether the Final Appraisal Determination referred only to the initial treatment. (The terms ‘initial treatment’ and ‘inception treatment’ were used during the Appeal hearing to describe the treatments given to *de novo* patients.) He stated that there was no doubt that that was the scope of the Appraisal: ‘there was no mystery'. The population was the patients undergoing new transplants. This was also confirmed by the Technology Assessment Group, who explained that the population under consideration was that undergoing first-line treatment for their first transplant. There was no evidence regarding switching treatments. The Committee had asked for evidence to identify sub-groups at higher risk of rejection but these patients could not be identified prospectively.
75.		The Panel asked if there was any evidence regarding second-line treatment. Dr Torpey commented that there was a wealth of evidence of second-line use, including randomized controlled trials. Professor McVeigh responded that this did not quite answer the Panel's question. The Committee was not saying that alternative regimens were not effective. It was saying that they were not cost-effective compared to the (recommended) cost-effective regimen.
76.		Dr Snowsill explained that the costs of dialysis were included in the model in two ways: as the cost of providing dialysis, and as the loss of quality of life, expressed as a decrease in utility of

		approximately 0.25.
77.		Marcela Haasova, for the Technology Assessment Group, stated that studies in which patients changed treatments after transplantation were excluded. However, if the studies examined a subgroup at high risk or who had suffered a special toxicity, they would have been included.
78.		The Appeal Panel understood that in respect of initial treatment the costs of dialysis had been included in the model. It therefore dismissed this appeal point insofar as it related to first-line treatment. However, the Appraisal Committee had not examined second-line treatments, as discussed above.
79.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. Any updated guidance will need to be clear whether patients who have previously been found to be intolerant of the recommended initial treatment, e.g. as a result of an adverse drug reaction to a relevant medicinal product, and who therefore might be precluded from having a transplant in the future if alternative treatments were not recommended, are covered by the recommendations. The Panel noted that the scope specifically stated that recommendations could be made for a subgroup of patients who had had a re-transplant, if the evidence allowed. This suggested to the Panel that patients who had had a previous transplant were within the scope, although the scope recognised that it might not be possible to make recommendations specifically relating to such patients.

		Any updated guidance will need to be clear which patients are covered and whether patients not covered by the guidance have been excluded because of the wording of the scope or because of the paucity of evidence.
British Kidney Patient Association **Appeal Point 2.3** **Recommendation 1.4 does not take into account the quality of life impact resulting from lost transplants for children and young people who are unable to tolerate immediate-release tacrolimus, basiliximab or mycophenolate mofetil, who experience acute rejection at initiation or chronic rejection over time and who are then unable to access alternative agents.**		
80.		Ms Loud had already explained to the Panel that the Appraisal Committee's conclusion that several treatments were not recommended was made without taking into account the costs when transplants failed and kidneys were wasted. She stated this was true of those unable to tolerate immediate-release tacrolimus, basiliximab or mycophenolate mofetil. The Appeal Panel understood that in respect of initial treatment the costs of dialysis had been included in the model. (See above British Kidney Patient Association Appeal Point 2.1.).
81.		Professor McVeigh reminded the Appeal Panel that the regimen of ciclosporin, azathioprine and a corticosteroid, which was not considered within this appraisal, was a cost-effective regimen for patients with renal transplants. It constituted an alternative to the three drugs suggested as initial therapy.
		The Appeal Panel accepted that there were patients in whom the use of ciclosporin, azathioprine and a corticosteroid was likely to provide a cost-effective alternative to the preferred initial regimen. It had not, however, seen analysis of the cost-

		effectiveness of switching to different regimens. The Appeal Panel again noted the position adopted by the Appraisal Committee and the Technology Assessment Group in the Appeal. This was that second-line treatment was outside the scope of the appraisal and therefore the Committee's decision not to recommend certain treatments did not apply to patients who were not able to take the recommended initial regimen. For the reasons outlined above, the Appeal Panel concluded that the inconsistency between the position as set out in the Final Appraisal Determination and as explained by the Appraisal Committee and the Technology Appraisal Group at the Appeal was unfair. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
British Kidney Patient Association **Appeal Point 2.4** **Recommendation 1.4 does not take into account the increased mortality of those who will be unable to access transplantation and are taken off the transplant waiting list because alternative treatments are not available.**		
82.		Fiona Loud told the Appeal Panel that paragraph 1.4 of the Final Appraisal Determination, which listed a series of treatments that were not recommended, failed to take account of the mortality those who had already lost a transplant and were now unable to have a second transplant.

83.		She said that patients with a transplant were likely to live longer than those having dialysis, in whom the risk of dying below the age of 40 was 19 times the risk in the general population.
84.		Professor McVeigh stated that no subgroup could be identified that was unable to have treatment as a consequence of the Final Appraisal Determination. The Appraisal Committee had tried to identify subgroups at higher risk, but was unable to find evidence on which to base such an identification. The Appraisal Committee asked for further evidence, and it did not hear that there was evidence that it had failed to consider.
85.		Ms Haasova told the Appeal Panel that if a study had been performed in a population of special interest, such as patients suffering acute rejection, and if it had been randomized at the time of transplantation, then the Technology Assessment Group would have included it. (Emphasis supplied.)
86.		Dr Snowsill stated that the increased risk of death for patients on dialysis was included in the model. The data used came from the UK Renal Register.
87.		Professor McVeigh was asked by the Appeal Panel whether the advice extended to re-transplantation. He answered that he honestly thought that it did not, although he was aware that some trials the Technology Assessment Group had used to inform the model had included a small number of re-transplanted patients.
88.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. The Panel noted that the scope specifically stated that recommendations could be made for a subgroup of patients who had had a re-transplant, if the evidence allowed. This suggested to the Panel that patients who had had a previous transplant

		were within the scope, although the scope recognised that it might not be possible to make recommendations specifically relating to such patients. Any updated guidance will need to be clear which patients are covered and whether patients not covered by the guidance have been excluded because of the wording of the scope or because of the paucity of evidence.
British Kidney Patient Association **Appeal Point 2.5** **The cost comparator does not take into account the additional costs of dialysis and/or failed transplant operations as a result of the inability to prescribe alternative therapies. As we pointed out in our original submission the true comparator is the costs of dialysis (at approximately £30,000 pa not including patient transport and certain drugs) and the costs of a failed transplant at approximately £17,000.**		
89.		Ms Loud stated that dialysis was anyway costly and patients with a transplant were likely to live longer than those having dialysis, in whom the risk of dying below the age of 40 was 19 times the risk in the general population.
90.		Dr Snowsill acknowledged that the assessment had not directly considered the scenario where a patient proved to be unable to take tacrolimus. While assessment groups were sometimes instructed to consider a subgroup defined by intolerance to prior treatment, that was not the case on this occasion.
91.		The Appeal Panel understood that in respect of initial treatment the costs of dialysis had been included in the model. (See above British Kidney Patient Association Appeal Point 2.1.)
92.		However, the Appraisal Committee had not examined second-line treatments (treatments used after the patient became intolerant of or developed adverse reactions to initial treatment). It had not therefore compared the cost of dialysis and failed

		transplantation against the cost of regimens used when the initial cost-effective regimen could no longer be given.
93.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
British Kidney Patient Association **Appeal Point 2.8** **Recommendation 1.4 reduces effective options for patients who are intolerant of mycophenolate mofetil by not recommending mycophenolate sodium (section 1.3). Gastrointestinal adverse reactions to mycophenolate mofetil are common and disabling despite dose modification and are less for mycophenolate sodium. For those patients who have already experienced a rejection episode there is also a risk of further rejection and poor outcomes.**		
94.		The Appeal Panel noted that this ground of appeal raised similar issues to Joint Appeal Ground 2.2.
95.		With regard to the specific issue of whether mycophenolate sodium was better tolerated than mycophenolate mofetil, Professor McVeigh had told the Appeal Panel that this was a clinical impression. Mycophenolate sodium was developed for that reason, but clinical trial data failed to show any significant benefit of mycophenolate sodium over mycophenolate mofetil in

		adult patients. Many patients intolerant of mycophenolate mofetil were also intolerant of mycophenolate sodium and were subsequently switched to sirolimus.
96.		It was not unreasonable for the Committee to prefer to base its conclusion on the evidence extrapolated from clinical trials in adults. As outlined above, the Appeal Panel noted the Committee's position that the recommendations in the Final Appraisal Document applied only to first-line treatment, and the Panel accepted that the Appraisal Committee was not unreasonable to prefer to base its conclusion on the evidence from clinical trials and conclude that mycophenolate sodium was 'not recommended' for first-line treatment. The Appeal Panel did not consider whether it was reasonable to reach firm conclusions regarding the value of mycophenolate sodium for second-line treatment.
97.		The Appeal Panel therefore dismissed the appeal on this point.

British Kidney Patient Association **Appeal Point 2.9** **Recommendation 1.4 reduces effective options for the subgroup of patients (particularly adolescents and young people) who have poor adherence or marked variability of drug levels with immediate release tacrolimus (1.2) by not recommending prolonged release tacrolimus. There is plenty of evidence that non-adherence and high variability are associated with worse outcomes, generally graft loss. Evidence given to the Appraisal Committee on this by patient representatives has not been accounted for.**		
98.		The Appeal Panel had already considered this question of adherence (Joint Appeal, Ground 2.3 above). The Panel found

		that the Appraisal Committee had carefully examined evidence on adherence and that evidence did not show whether a change from immediate-release tacrolimus to prolonged-release tacrolimus in patients with poor adherence either improved adherence or led to better outcomes. The Committee had sought but failed to find a clearly defined subgroup with poor adherence that could be predicted prior to treatment. It had not reached an unreasonable conclusion.
99.		The Appeal Panel therefore dismissed the appeal on this point.
British Kidney Patient Association **Appeal Point 2.10** **Recommendation 1.4 reduces effective options for future patients who would benefit from sirolimus treatment. The Committee has not taken into consideration the current ways in which sirolimus is used e.g. to prevent further malignancy or to alleviate the gastro-intestinal effects of mycophenolate mofetil if mycophenolate sodium is also not tolerated.**		
100.		Professor McVeigh reminded the Appeal Panel that the Appraisal Committee had not considered whether regimens containing sirolimus were effective, but whether they were cost-effective, and they were not.
101.		The Appeal Panel was clear that the Appraisal Committee had considered the use of sirolimus in initial regimens after transplantation. Their conclusion on the evidence before them was that those regimens were not cost-effective. That was reasonable.
102.		However, as set out above, it became clear during the Appeal hearing that the Appraisal Committee did not consider second-line treatments (as defined above) as within the scope. This was problematic as it was not clear from the Final Appraisal Determination which treatment scenarios the 'not recommended' conclusion at 1.4 applied to.

103.		The Appeal Panel noted that it had already upheld arguments regarding the clarity of the Final Appraisal Determination and the populations covered. It did not consider that this ground added further to those arguments and therefore this ground of appeal was dismissed.
British Kidney Patient Association **Appeal Point 2.11** **Recommendation 1.4 reduces effective options for future patients who are not suitable for basiliximab induction therapy (section 1.1) by not recommending rabbit anti-human thymocyte globulin. There was no compelling evidence presented showing the safety and effectiveness of using Basiliximab outside the marketing authorisation and NICE is being inconsistent in the use of evidence, as it uses lack of evidence as a reason not to recommend other drugs.**		
104.		The Appeal Panel had already considered whether the Appraisal Committee had acted reasonably in deciding that rabbit anti-human thymocyte globulin was not recommended. (See Joint Appeal, Appeal Point 2.4.)
105.		The Appeal Panel noted the reference in the Final Appraisal Determination (page 1) that there needed to be 'compelling evidence of their safety and effectiveness' for the Appraisal Committee to recommend the use of drugs outside of the terms of their marketing authorization. The Appeal Panel considered whether NICE had been unreasonable in considering the use of basiliximab outside the terms of its marketing authorisation. The regimen recommended by the Appraisal Committee was routinely used in the NHS. Its safety profile was therefore well understood. It was clinically effective and cost-effective according to a model that incorporated data from a randomised controlled trial, and none of the

		appellants had suggested that basiliximab should not be recommended for use in the NHS. The Appeal Panel could not see how the actions of the Appraisal Committee could be characterised as unreasonable.
106.		The Appeal Panel therefore dismissed the appeal on this point insofar as it referred to use of basiliximab outside its marketing authorisation.
107.		With regard to the use of rabbit anti-human thymocyte globulin in those who were not suitable for basiliximab, the Appeal Panel's conclusion is as set out under British Kidney Patient Association ground 2.3.
British Kidney Patient Association **Appeal Point 2.12** **The Appraisal Committee acknowledge that there are limitations in the available evidence and of the consequent clinical and cost-effectiveness analysis which raises concerns about the robustness of the recommendations. Nevertheless the risks in this process are disregarded and a set of recommendations, which we believe will lead to extremely poor outcomes for transplanted kidney patients and result in significantly increased cost, has been made.**		
108.		Over the course of the hearing, the Appellants had made many references to the importance of clinical experience and the ability of clinicians to choose from a range of treatments, particularly where the recommended regimen was not clinically appropriate. The task of the Appraisal Committee was difficult because data regarding clinical experience (e.g. observational data on patient treatment and outcomes) had not been collected in a systematic way and presented to the Committee. The Panel had not been presented with any arguments that persuaded it that the recommendations set out at paragraphs 1.1

		to 1.3 were unreasonable. It believed that the Appraisal Committee had made reasonable decisions about initial therapy that took into account clinical and cost-effectiveness, bearing in mind all the evidence that they had heard.
109.		However, as set out above, it became clear during the Appeal hearing that the Appraisal Committee did not consider either second-line treatments (as defined above) as within the scope. This was problematic as it was not clear from the Final Appraisal Determination which treatment scenarios the 'not recommended' conclusion at 1.4 applied to.
110.		The Appeal Panel noted that it had already upheld arguments regarding the clarity of the Final Appraisal Determination and the populations covered. It did not consider that this ground added further to those arguments and therefore this ground of appeal was dismissed.
ESPRIT **Appeal Point 2.1** **The blanket 'not recommended' in section 1.4 of the Final Appraisal Determination is contrary to current best clinical practice, based on hands-on experience of transplant specialists over many years of managing individual patients' immunosuppression**		
111.		Professor Atholl Johnston, for ESPRIT, stated that the Appraisal Committee's decision that some drugs were 'not recommended' in section 1.4 of the Final Appraisal Determination was contrary to best clinical practice. Clinical experience showed that 20–30% of patients were unsuitable for or intolerant of the therapies recommended in the Final Appraisal Determination.
112.		Professor McVeigh had indicated that the Final Appraisal Determination was intended to refer to initial treatment.
113.		The Panel noted that similar points raised by other appellants had already been considered. The Panel considered that the FAD

		recommendations were reasonable, insofar as they related to first-line treatment. It therefore dismissed this point of appeal. The Appeal Panel understood that the question of changing to a second-line regimen in those who were intolerant of the preferred initial treatment had not been explicitly considered.
114.		As discussed above, the Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
ESPRIT **Appeal Point 2.2** **We question how the Assessment Committee arrived at the active 'not recommended' statement in section 1.4 of the Final Appraisal Determination**		
115.		Professor Johnston questioned how the Appraisal Committee had arrived at a decision that some drugs were not recommended, when the Committee acknowledged that there were limitations to the evidence. In the absence of formal evidence, it was more logical to state that the Appraisal Committee was unable to make a recommendation.
116.		Professor McVeigh described how the Appraisal Committee had reached its decisions. The Committee had listened to the

		evidence presented to it, whether that was from clinicians, patients or consultees.
117.		Where there was no evidence, the Appraisal Committee felt unable to make any recommendation. That had been the case for patients suffering from calcineurin-inhibitor nephrotoxicity or from thrombotic microangiopathy, circumstances in which there was currently no evidence, and where it would be very difficult to gather evidence.
118.		However, in other circumstances, there was evidence, and that evidence on cost-effectiveness showed that the 'not recommended' treatment was less effective than other treatments and cost more (that is, it was 'dominated' by other treatments), or at least that it had a very high incremental cost-effectiveness ratio (that is, what improvements it brought came at very high cost). Since the Appraisal Committee was expected to provide clear guidance, it had made decisions to recommend or not recommend treatment where it was possible to do so.
119.		The Appeal Panel noted that this ground of appeal raised similar issues to British Kidney Patient Association Ground 2.12 and Joint Appeal Ground 2.1. The Panel had not been presented with any arguments that persuaded it that the recommendations set out at paragraphs 1.1 to 1.4 were unreasonable insofar as they related to first-line treatment. It believed that the Appraisal Committee had made reasonable decisions about initial therapy that took into account clinical and cost-effectiveness, bearing in mind all the evidence that they had heard.
120.		The Appeal Panel noted that it had already upheld arguments regarding the clarity of the Final Appraisal Determination and the populations covered. It did not consider that this ground added

		further to those arguments and therefore this ground of appeal was dismissed.
ESPRIT **Appeal Point 2.3** **The economic analysis has apparently neglected a pivotal comparator, namely the cost of graft failure as a consequence of inadequate immunosuppression, and the resulting return to costly dialysis.**		
121.		This point had been discussed when the Appeal Panel had considered British Kidney Patient Association appeal point 2.5.
122.		The Appeal Panel understood that in respect of initial treatment the costs of dialysis had been included in the model. (See above British Kidney Patient Association Appeal Point 2.1.) It therefore dismissed this appeal point insofar as it related to first-line treatment. However, the Appraisal Committee had not examined second-line treatments, as discussed above.
123.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. Any updated guidance will need to be clear whether patients who have previously been found to be intolerant of the recommended initial treatment, e.g. as a result of an adverse drug reaction to a relevant medicinal product, and who therefore might be precluded from having a transplant in the future if alternative treatments were not recommended, are covered by the recommendations. The Panel noted that the scope specifically stated that recommendations could be made for a subgroup of patients who

		had had a re-transplant, if the evidence allowed. This suggested to the Panel that patients who had had a previous transplant were within the scope, although the scope recognised that it might not be possible to make recommendations specifically relating to such patients. Any updated guidance will need to be clear which patients are covered and whether patients not covered by the guidance have been excluded because of the wording of the scope or because of the paucity of evidence.
NHS England **Appeal Point 2.1** **Recommendation 1.4 would be at variance with much of current clinical practice in the absence of sufficient trial data for or against the recommendations, thereby reducing effective options for future patients who are intolerant of, or unsuitable for, the interventions recommended in sections 1.1–1.3 of the Final Appraisal Determination.**		
124.		Mr Keith Rigg, for NHS England, told the Appeal Panel that he supported the recommendations in paragraphs 1.1–1.3 of the Final Appraisal Determination. Every transplant unit would start with the treatments recommended in paragraphs 1.1–1.3 of the Final Appraisal Determination, that is basiliximab, immediate-release tacrolimus, and mycophenolate mofetil (or sometimes azathioprine, which was not included in this technology assessment).
125.		The Appeal Panel had already heard that it was not possible to identify subgroups of patients prior to first transplant who were unable to have agents used in the preferred regimen specified in paragraphs 1.1–1.3. It was therefore not unreasonable for the Appraisal Committee to state that agents other than the preferred agents were not recommended as initial treatment. This ground of

		appeal was therefore dismissed insofar as it relates to first-line treatment.
126.		However, difficulties arose when the recommended regimen was used and patients became intolerant of one or more component. The agents that the Appraisal Committee had stated were not recommended are used currently, although all are used only in subgroups of patients. If the agents were unavailable, then patients would require dialysis, which was expensive.
127.		The Appeal Panel had already confirmed that the decisions of the Appraisal Committee relating to initial treatment were reasonable, and noted that NHS England endorsed those decisions. What was again at issue was the extent to which the scope of the appraisal covered those in whom it was necessary for clinical reasons not to administer the recommended treatments because intolerance or inefficacy had been established earlier in treatment for the current transplant or in relation to a previous transplant.
128.		The Appeal Panel again noted the position adopted by the Appraisal Committee and the Technology Assessment Group in the Appeal. This was that second-line treatment was outside the scope of the appraisal and therefore the Committee's decision not to recommend certain treatments did not apply to patients who were not able to take the recommended initial regimen. For the reasons outlined above, the Appeal Panel concluded that the inconsistency between the position as set out in the Final Appraisal Determination and as explained by the Appraisal Committee and the Technology Appraisal Group at the Appeal was unfair. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will

		need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
NHS England **Appeal Point 2.2** **Recommendation 1.4 reduces effective options for future patients who are intolerant of mycophenolate mofetil by not recommending mycophenolate sodium (section 1.3). Gastrointestinal side effects were not considered in the analysis and are less for mycophenolate sodium in the published SPC.**		
129.		Mr Rigg stated that sometimes switching from mycophenolate mofetil to mycophenolate sodium might alleviate symptoms of gastrointestinal disturbance, although sometimes it might not. He also explained that while dose reduction could mitigate the adverse effects of mycophenolate mofetil, it might also increase the risk of rejection.
130.		The Appeal Panel had already considered similar arguments under British Kidney Patient Association Appeal Point 2.8. It had heard that clinicians believed mycophenolate sodium could be helpful in patients with gastrointestinal adverse reactions to mycophenolate mofetil. The Appraisal Committee had examined the evidence from clinical trials in adults and found no important difference in gastrointestinal effects between the two formulations of mycophenolic acid.
131.		The Appeal Panel therefore dismissed the appeal on this point.
NHS England **Appeal Point 2.3** **Recommendation 1.4 reduces effective options for the subgroup of future patients who have poor adherence or marked variability of drug levels with immediate-release tacrolimus (1.2) by not recommending prolonged release**		

tacrolimus. This is despite there being evidence that non-adherence and high within-patient variability are associated with worse outcomes, generally graft loss.		
132.		The Appeal Panel had considered this question above (see Joint Appeal Point 2.3 and British Kidney Patient Association Appeal Point 2.9). It concluded that the Appraisal Committee had not acted unreasonably in stating that prolonged-release tacrolimus was not recommended.
133.		The Appeal Panel therefore dismissed the appeal on this point.
NHS England **Appeal Point 2.4** **Recommendation 1.4 reduces effective options for future patients who would benefit from sirolimus treatment. The Committee has not taken into consideration the current ways in which sirolimus is used.**		
134.		The Appeal Panel had considered the appraisal of sirolimus above (see Joint Appeal Point 2.5 and British Kidney Patient Association Appeal Point 2.10).
135.		As discussed above, the Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
NHS England		

Appeal Point 2.5 **Recommendation 1.4 reduces effective options for future patients who are not suitable for basiliximab induction therapy (section 1.1) by not recommending rabbit anti-human thymocyte globulin. No compelling evidence has been presented showing the safety and effectiveness of using basiliximab outside the marketing authorisation.**		
136.		The Appeal Panel had already discussed the use of rabbit anti-human thymocyte globulin (see Joint Appeal Point 2.4 and British Kidney Patient Association Appeal Point 2.11).
137.		The Appeal Panel understood that most (though not all) patients in whom rabbit anti-human thymocyte globulin was used were at high immunological risk by virtue of having previously received one or more transplants. The Appraisal Committee had said that patients undergoing re-transplantation were not considered because they were outside the scope of the appraisal.
138.		With regard to the use of basiliximab, the Appeal Panel noted that all the clinicians present, including Mr Rigg for NHS England, endorsed the use of basiliximab for initial treatment with agents other than ciclosporin. In addition, the trial evidence from Brennan *et al* 2006 had been taken into account, and that included some patients at high immunological risk.
139.		The Appeal Panel believed that the Appraisal Committee had found sufficient evidence to support its recommendation for the use of basiliximab outside the terms of the marketing authorization, and that its recommendation for the use of basliximab was not unreasonable.
140.		The Appeal Panel dismissed the appeal on this point as it related to the recommendation for basiliximab for first-line treatment.
141.		The Appeal Panel again noted the position adopted by the Appraisal Committee and the Technology Assessment Group in the Appeal. This was that second-line treatment was outside the

		scope of the appraisal and therefore the Committee's decision not to recommend certain treatments did not apply to patients who were not able to take the recommended initial regimen. For the reasons outlined above, the Appeal Panel concluded that the inconsistency between the position as set out in the Final Appraisal Determination and as explained by the Appraisal Committee and the Technology Appraisal Group at the Appeal was unfair. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
NHS England **Appeal Point 2.6** **The Appraisal Committee acknowledge that there are limitations in the available evidence and of the consequent clinical and cost-effectiveness analysis which raises concerns about the robustness of the recommendations.**		
142.		The Appeal Panel had already understood from Professor McVeigh that, where possible, the Appraisal Committee sought to make a clear statement that an agent was, or was not, recommended for use in the NHS. [British Kidney Patient Association Appeal Point 2.1].
143.		With regard to the strength of evidence required for the Appraisal Committee to reach a decision that a treatment was 'not

		recommended,' the Appeal Panel had already heard from Professor McVeigh that the Appraisal Committee had considered evidence from a wide range of sources regarding the clinical and cost-effectiveness of regimens in '*de novo'* transplant patients. [British Kidney Patient Association Appeal Point 2.1].
144.		NHS England also contended that clinical trials predominantly provided evidence only in the short and medium term, with outcomes up to three years. This raised concerns that extrapolation to 50 years in the economic models was unreliable.
145.		Dr Snowsill stated that it was reasonable to be concerned that the model extrapolated from results at one year to results at 50 years. The Technology Assessment Group had examined the effects of using different time horizons in the model. No treatment that was cost-ineffective at 50 years became cost-effective at a shorter time horizon. Some treatments, including basiliximab, only became cost-effective if the time horizon was extended beyond the duration of the trials.
146.		Dr Snowsill confirmed that the Technology Assessment Group had not explicitly considered the cost-effectiveness of treatments in those who were unable to tolerate tacrolimus.
147.		The Appeal Panel was clear that the approach regarding what Professor McVeigh had termed '*de novo*' patients was reasonable.
148.		However, as set out above, it became clear during the Appeal hearing that the Appraisal Committee did not consider either second-line treatment (as defined above) as within the scope. This was problematic as it was not clear from the Final Appraisal Determination which treatment scenarios the 'not recommended' conclusion at 1.4 applied to. The Appeal Panel noted that it had already upheld arguments regarding the clarity of the Final Appraisal Determination and the populations covered. It did not consider that this ground added

		further to those arguments and therefore this ground of appeal was dismissed.
NHS England **Appeal Point 2.7** **The recommendations are based on the wrong comparator used in the economic analysis**		
149.		Mr Rigg told the Appeal Panel that it was not always necessary to use rabbit anti-human thymocyte globulin at full dose, and that therefore the costs attributed to it were an overestimate.
150.		Dr Snowsill reassured the Appeal Panel that the Technology Assessment Group had considered the question of dosage, examining the latest randomised trials to allow for changes in dosage as a result of the adoption of lower target concentrations, for example. The dosage calculations for basiliximab and rabbit anti-human thymocyte globulin were based on the doses actually administered to trial patients in the study by Brennan *et al.*
151.		Professor McVeigh stated that the model had not taken into account the reduced cost that came from vial-sharing, and he did not believe that it should have done so.
152.		NHS England also noted that the cost of second-line treatments had not been compared with the costs of dialysis. The Appeal Panel had already considered this point. (See appeal Point British Kidney Patient Association Appeal Points 2.1, 2.5 and ESPRIT Appeal Point 2.3.)
153.		Regarding the costs assigned to rabbit anti-human thymocyte globulin and other drugs in the model, the Appeal Panel was clear that the approach of the Appraisal Committee was reasonable.
154.		The Appeal Panel therefore dismissed the appeal point insofar as

		it related to costs used in the economic analysis.
155.		The Appeal Panel also considered the matter of the cost of dialysis as a comparator for second-line treatments. This had been considered under British Kidney Patient Association point 2.5.
156.		The Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee. It was not clear to the Panel that second-line treatment was outside the scope. Any updated guidance would need to deal with this point. In particular, if the Appraisal Committee decides not to provide recommendations on second-line treatment it will need to be clear whether that is because it is outside the scope of the appraisal or because there is insufficient evidence to make a recommendation.
Conclusion and effect of the Appeal Panel's decision		
157.		Given the length of this decision it may assist the Appellants and the Institute if the Appeal Panel summarises its conclusions. The recommendations made by the Appraisal Committee were reasonable insofar as they went. The calculation of prices was carried out fairly. The Panel heard from the Appraisal Committee and the Technology Appraisal Group that the recommendations did not extend to what the Panel has termed 'second-line' use i.e. use in patients for whom the recommended treatment was not clinically appropriate and/or in patients who had previously received a transplant. This was not clear to the Panel from the Final Appraisal Determination, even when read in conjunction with the

		scope, and for this reason it held that the Final Appraisal Determination was unfair. The Panel had some reservations about the Committee's interpretation of the scope as the Committee described it at the Panel hearing, in particular the conclusion that it did not apply to re-transplant patients. The Panel did not uphold the appeal on this basis but in order to assist the Institute it has highlighted its concerns in this decision letter. Where the Panel has dismissed a challenge to the reasonableness of the Committee's recommendations, it has done so on the basis that the recommendation applies to first-line treatment, as explained by the Committee during the Appeal hearing. Those points cannot be re-opened on any subsequent appeal. However, the Panel's ruling on those reasonableness points does not extend to use beyond first-line treatment. Therefore, any conclusions set out in any future Final Appraisal Determination on recommending treatments for second-line use could be the subject of a further appeal.
158.		The following appeal points are **dismissed**: • British Kidney Patient Association 2.8, 2.9, 2.10, 2.12 • Joint Appeal 2.1, 2.2, 2.3, 2.4, 2.5 • ESPRIT 2.2 • NHS England 2.2, 2.3, 2.4, 2.6
159.		The following appeal points are **allowed**: • British Kidney Patient Association 2.1, 2.3, 2.4, 2.5 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment) • ESPRIT 2.1, 2.3 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment)
160.		The following appeals points are **allowed in part**:

		• British Kidney Patient Association 2.11 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment) • NHS England 2.1, 2.5, 2.7 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment)
161.		The following appeal points are **dismissed in part**: • British Kidney Patient Association 2.11 (insofar as it relates to use of basiliximab outside the terms of its marketing authorisation) • NHS England 2.1 (insofar as it relates to the unreasonableness of recommendations for first-line treatment) • NHS England 2.5 (insofar as it relates to use of basiliximab outside the terms of its marketing authorisation) • NHS England 2.7 (insofar as it relates to dosage and costs)
162.		The Panel considered whether it should refer the appraisal to the Guidance Executive for editorial corrections to reflect the intended scope of the recommendations. The Panel concluded that the impact of the changes was too significant for this to be an appropriate step for the Panel to take.