

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**  
**MULTIPLE TECHNOLOGY APPRAISAL**  
**APPEAL HEARING**

**Advice on Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)**

<b>Decision of the Panel</b>	
<b>Introduction</b>	
1.	An Appeal Panel was convened on 30 <sup>th</sup> March 2016 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)
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: Astellas Pharma Ltd ('Astellas') The British Kidney Patient Association The British Transplantation Society, Renal Association, and British Renal Society, who appealed jointly ESPRIT

	NHS England The National Kidney Foundation
5.	Astellas Pharma Ltd was represented by:  Ms Amanda Fahey Dr Martin Hurst Ms Jane Shaw
6.	The British Kidney Patient Association was represented by:  Dr Patrizie Hodge Ms Fiona Loud Mr Nick Palmer
7.	The British Transplantation Society, Renal Association, and British Renal Society, who appealed jointly, were represented by:  Dr Simon Ball Dr Graham Lipkin Dr Nicholas Torpey
8.	ESPRIT was represented by:  Ms Julia Cook Prof Atholl Johnston
9.	NHS England was represented by:  Mr Malcolm Qualie Mr Keith Rigg
10.	The National Kidney Foundation was represented by:  Mr Tim Statham Ms Andrea Brown Mr David Marshall

11.	<p>In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel:</p> <p>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</p>
12.	All the above declared no conflicts of interest
13.	The Institute's legal adviser, Eleanor Tunnicliffe of DAC Beachcroft LLP, was also present and was accompanied by her assistant Sophie Devlin
14.	Dr Biba Stanton was present as an observer, and sat with the Appeal Panel, but took no part in the proceedings.
15.	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.
16.	<p>There are two grounds under which an appeal can be lodged:</p> <p><b>Ground One: In making the assessment that preceded the recommendation, NICE has</b></p> <ul style="list-style-type: none"> <li>a) <b>Failed to act fairly</b></li> <li>b) <b>Exceeded its powers.</b></li> </ul> <p><b>Ground Two: The recommendation is unreasonable in the light of</b></p>

	<b>the evidence submitted to NICE.</b>
17.	<p>The Vice Chair of NICE (Mr Andy McKeon) in preliminary correspondence had confirmed that:</p> <ul style="list-style-type: none"> <li>• Astellas had potentially valid grounds of appeal as follows: Grounds 1a and 2.</li> <li>• The British Kidney Patient Association had potentially valid grounds of appeal as follows: Ground 2</li> <li>• The British Transplantation Society, Renal Association and British Renal Society, had potentially valid grounds of appeal as follows: Ground 2</li> <li>• ESPRIT had potentially valid grounds of appeal as follows: Ground 2</li> <li>• NHS England had potentially valid grounds of appeal as follows: Ground 2</li> <li>• The National Kidney Foundation had potentially valid grounds of appeal as follows: Ground 2</li> </ul>
18.	<p>Induction therapy is treatment at the time of transplant to prevent organ rejection. Two drugs used in induction therapy were considered in this appraisal.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> </ul> <p>Maintenance therapy is used to prevent rejection of a transplant in the longer term. The Appraisal Committee considered several drugs used</p>

	<p>in maintenance therapy.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Belatacept (Nulojix, Bristol-Myers Squibb) is a soluble fusion protein designed to selectively inhibit CD28-mediated co-stimulation of T cells.</li> <li>• 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.</li> <li>• Sirolimus (Rapamune, Pfizer) is an antiproliferative agent that blocks a protein called mammalian target of rapamycin (mTOR).</li> </ul>
19.	<p>Before the Appeal Panel inquired into the detailed complaints the following made preliminary statements:</p> <p>Amanda Fahey on behalf of Astellas Pharma Ltd</p> <p>Timothy Statham on behalf of the British Kidney Patient Association</p> <p>Dr Nicholas Torpey on behalf of the British Transplantation Society, Renal Association, and British Renal Society</p> <p>Professor Atholl Johnson on behalf of ESPRIT</p> <p>Fiona Loud on behalf of The National Kidney Foundation</p> <p>Mr Keith Rigg on behalf of NHS England</p>

	<p>and</p> <p>Professor Gary McVeigh on behalf of the Appraisal Committee.</p>
20.	<p>The appraisal that is the subject of the current Appeal provided advice to the NHS on Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85).</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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-</p>

	<p>effective treatment stated in the Final Appraisal Determination was not clinically appropriate.</p> <p>(The terms ‘initial treatment’ and ‘inception treatment’ were also used during the Appeal hearing to describe the treatments given to de novo patients.)</p> <p>The objective of the Appraisal was stated in the Final Scope as being ‘<i>To appraise the clinical and cost-effectiveness of immunosuppressive regimens for kidney transplantation in adults.</i>’ [National Institute for Health and Care Excellence Final scope for the appraisal of immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85) Issue Date: July 2014].</p> <p>This was further amplified (in footnote 1 to the final scope) as follows: ‘<i>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.</i>’</p> <p>The Table at page 4 of the final scope stated that the population to be considered was ‘<i>Adults undergoing kidney transplantation.</i>’ 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.</p> <p>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</p>
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	<p>such usage.</p> <p>The Panel also noted that the Appraisal Committee had explicitly commented at paragraphs 1.4, 4.75, and 4.76 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 <u>nephrotoxicity</u>—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.</p> <p>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:</p> <ul style="list-style-type: none"><li>- 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</li><li>- 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</li></ul> <p>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</p>
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	<p>reflect the reasoning of the Committee.</p> <p>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.</p> <p>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.</p>
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#### **Appeal by Astellas Pharma Ltd**

##### **Appeal Ground 1: In making the assessment that preceded the recommendation, NICE has**

- a) Failed to act fairly
- b) Exceeded its powers.

#### **Astellas**

##### **Appeal Point 1a.1**

**Inconsistent selection of study populations during systematic review biases the results of the Assessment Group model unfairly against prolonged release tacrolimus contrary to section 3.5.3 of NICE Process Guide.**

21.		Amanda Fahey, for Astellas stated that there were four studies

	<p>relevant to the comparison of immediate-release tacrolimus with prolonged-release tacrolimus, namely: Krämer <i>et al</i> 2010; Tsuchiya <i>et al</i> 2013; Silva <i>et al</i> 2007; and Albano <i>et al</i> 2013. Krämer <i>et al</i> studied 800 patients for 24 weeks and Tsuchiya studied 100 Japanese patients. These were included in the Assessment Group's analysis. Neither study showed a statistically significant difference between immediate-release tacrolimus and prolonged-release tacrolimus, but in the Krämer study there was a small, non-significant, benefit for immediate-release tacrolimus. Astellas stated that the Appraisal Committee had placed too much reliance on this. The Appellant also questioned whether the Tsuchiya study should have been included given the subjects were Japanese and therefore it was questionable whether any findings would be applicable to the NHS.</p> <p>The Appraisal Committee had excluded the studies of Silva and Albano, even though they included over twice as many patients, and even though they would have supported the conclusion that there was no difference in efficacy between the two formulations of mycophenolic acid.</p>
22.	Professor McVeigh stated that the criteria for inclusion and exclusion of studies had been pre-specified in the systematic review protocol, and the protocol had been applied in a consistent manner.
23.	Tracey Jones-Hughes, for the Appraisal Committee, explained that only randomized controlled trials in adults were included under the protocol. Silva <i>et al</i> 2007 recruited both adults and those below the age of 18 years but did not distinguish between them. It was excluded on this basis. Albano <i>et al</i> 2013 did meet the criteria and was included. However, as it only reported outcomes up to six months they were not incorporated in to the model. Both studies included a small number of re-transplanted patients.

24.	<p>Dr Tristan Snowsill, representing the Technology Assessment Group, added that the Tsuchiya study had provided no information on either patient survival or graft loss.</p> <p>The protocol did not pre-specify race as an inclusion or exclusion criterion.</p>
25.	<p>The Appeal Panel inquired of Astellas where the unfairness lay.</p> <p>Ms Jane Shaw, for Astellas, stated that it would have been reasonable for the Appraisal Committee to go back and look at the excluded studies.</p> <p>Ms Fahey noted that the Appraisal Committee had used point estimates of the efficacy of immediate-release tacrolimus and prolonged-release tacrolimus that favoured immediate-release tacrolimus, even though when the four trials were taken together the efficacy was identical.</p>
26.	The Appeal Panel concluded that the Appraisal Committee had acted fairly in applying a pre-specified protocol in a consistent manner.
27.	The Appraisal Committee had not been unfair in its treatment of the studies by Tsuchiya, Silva, and Albano.
28.	The Appeal Panel therefore dismissed the appeal on this point.
<b>Astellas</b>	
<b>Appeal Point 1a.2</b>	
<b>Inconsistent calculation of price of tacrolimus formulations in the Assessment</b>	

**Group model that does not represent the true cost of tacrolimus to the NHS  
(NICE Process Guide 3.5.3)**

**[*Sic: See Guide to the methods of technology appraisal 2013 paragraph 5.5.3.*]**

29.	<p>Ms Fahey described how tacrolimus was prescribed in primary care. The NICE Process Guide made it clear that Drug Tariff prices should be used in that circumstance. Not to do so contradicted NICE's guidelines.</p> <p>When Drug Tariff prices were compared, immediate-release tacrolimus cost £1.51 per milligram, while prolonged-release tacrolimus cost £1.24 per milligram. This meant that, in considering cost-effectiveness, there was no reason to restrict the prescription of prolonged-release tacrolimus.</p> <p>However, the reference case used the lowest price for immediate-release tacrolimus as stated in the NHS Commercial Medicines Unit electronic Marketing Information Tool (eMIT) and the price for prolonged-release tacrolimus as quoted in the Drug Tariff.</p> <p>In fact, NHS usage figures indicated that only 4% of immediate-release tacrolimus was obtained at the lowest price, and 96% was more expensive.</p> <p>Astellas said this was unfair.</p>
30.	The Appeal Panel asked whether the 'repatriation' of prescribing to secondary care was relevant.
31.	Malcolm Qualie, for NHS England, explained that most prescriptions for the relevant drugs are written in secondary care. There was also

	<p>prescribing for stable patients in primary care. Because there were clinical concerns about switching brands, and because generic prescribing was common in primary care, NHS England had advised that all prescribing should now be in secondary care.</p>
32.	<p>Professor McVeigh stated that pricing had been thoroughly discussed. The Appraisal Committee had understood clearly that prescribing of these drugs was to be removed from primary care by the time the guidance came into effect.</p>
33.	<p>Dr Snowsill pointed out that the Assessment Group's model was for new care, not for existing patients. The Assessment Group had followed the Guide's recommendations for establishing prices for prescribing in secondary care. Where eMIT prices were not available, the list prices had been used.</p> <p>The Assessment Group had then been asked to consider the effect of a confidential discount, but when this was included in the calculations, prolonged-release tacrolimus was still not cost-effective.</p>
34.	<p>Ms Fahey said that there was no reason why guidance to use the Drug Tariff price was inapplicable. It was unclear whether the scope referred only to new patients, which made the contention that all prescribing would be in secondary care doubtful. At present, 66% of prescribing was still in Primary Care.</p>
35.	<p>Mr Meindert Boysen, on behalf of the Institute, stated that the Final Appraisal Determination only applied to future patients, and in consequence of the NHS England advice, prescribing for such patients would take place in secondary care. The costs were therefore appropriately considered.</p>

36.	<p>In response to a question from Meindert Boysen, Ms Eleanor Tunnicliffe, Legal Advisor to the Appeal Panel, agreed that his understanding of the roles of the Institute and NHS England in decisions to funding treatment was correct.</p>
37.	<p>Ms Fahey argued that if prolonged-release tacrolimus cost less than immediate-release tacrolimus and if they were of equal efficacy, then prolonged-release tacrolimus would be cost-effective.</p>
38.	<p>Professor McVeigh replied that the Appraisal Committee had not seen an analysis based on these two assumptions.</p>
39.	<p>The Appeal Panel considered whether there had been unfairness in assigning costs. They noted that the Final Appraisal Determination at paragraph 4.63 discussed the question of costs in detail. They also accepted that future patients would, following the advice from NHS England, be given prescriptions in secondary care and that the effect of paragraph 1.5 of the Final Appraisal Determination was that its recommendations would not apply to patients already receiving treatments that had not been recommended. The Panel decided that the appropriate costs were those associated with prescribing in the secondary care setting. The Committee had acted in accordance with paragraph 5.5.2 of the Methods Guide.</p> <p>Furthermore, the Committee had consulted on its approach to costs (as this approach was set out in the Assessment Report) and taken into account the appellant's representations.</p> <p>For these reasons, the Panel concluded that the Appraisal Committee had not acted unfairly.</p>
40.	<p>The Appeal Panel therefore dismissed the appeal on this point.</p>

<b>Astellas</b>		
<b>Appeal Point 2.1</b>		
<p><b>The Appraisal Committee and Assessment Group were unreasonable to conclude that prolonged-release tacrolimus is inferior to immediate-release tacrolimus.</b></p>		
41.	<p>Ms Fahey had referred to the trials comparing immediate-release tacrolimus with prolonged-release tacrolimus (see above). These were the studies of Krämer <i>et al</i> 2010; Tsuchiya <i>et al</i> 2013; Silva <i>et al</i> 2007; and Albano <i>et al</i> 2013. The Appraisal Committee had used point estimates of the efficacy of immediate-release tacrolimus and prolonged-release tacrolimus that favoured immediate-release tacrolimus, even though when the four trials were taken together the efficacy was identical.</p> <p>Ms Fahey stated it would have been reasonable for the Appraisal Committee to examine the studies of Silva and Albano, since they demonstrated that the model as constructed, which ascribed a greater benefit to immediate-release tacrolimus than to prolonged-release tacrolimus, was wrong.</p> <p>The model contradicted the assertion in the Final Appraisal Determination that '<i>Comparison of immediate-release and prolonged-release tacrolimus (plus mycophenolate mofetil) showed no consistent clinically significant differences.</i>' [Final Appraisal Determination paragraph 4.9]. It also contradicted the view of the regulators.</p>	
	<p>Dr Snowsill explained that there was no need to carry out a scenario analysis to explore the assumption that there was similar efficacy across outcomes for the two formulations of tacrolimus. Prolonged-</p>	

	<p>release tacrolimus cost more than immediate release tacrolimus, and the Committee had concluded that the two formulations were equivalent in clinical effectiveness. Therefore, it was clear that the cheaper formulation—immediate release tacrolimus—would be more cost-effective.</p>
42.	<p>The Appeal Panel considered whether the Appraisal Committee had acted unreasonably. It noted the statement at paragraph 4.69 of the Final Appraisal Determination that '<i>there were no consistent statistically significant differences in clinical effectiveness between prolonged-release and immediate-release tacrolimus</i>'.</p> <p>Given the Appraisal Committee's acceptance that the two formulations were of equivalent clinical effectiveness, and the Committee's position on appropriate costs (which the Panel found to be fair and reasonable), the Appeal Panel's view was that the Committee had drawn a reasonable conclusion about the cost-effectiveness of the two formulations of tacrolimus, a conclusion that was not altered by the Astellas submission about pricing. The Committee had not acted unreasonably in concluding that prolonged-release tacrolimus was not a cost-effective use of NHS resources.</p> <p>Astellas had also argued that the Committee's view was unreasonable because it was different from that of the Committee for Medicinal Products for Human Use (CHMP). The Panel noted that the CHMP and the Committee appeared to reach similar conclusions on the efficacy of prolonged-release tacrolimus, i.e. that it is equivalent to immediate-release tacrolimus.</p> <p>The Appeal Panel also noted that the views of the regulator refer to acceptable efficacy and safety and good quality of manufacture. The regulator does not consider cost-effectiveness in the way that the Appraisal Committee was bound to do.</p>

43.	The Appeal Panel therefore dismissed the appeal on this point.

### Astellas

#### Appeal Point 2.2

**The Appraisal Committee and Assessment Group dismissed other relevant evidence, resulting in unreasonably restrictive recommendations.**

44.	Ms Fahey referred to other evidence—a study by Kuypers <i>et al</i> 2013 and registry data on the outcome of liver transplant—that supported the contention that prolonged-release tacrolimus was as effective as, or more effective than, immediate-release tacrolimus.
45.	Regarding the Kuypers study, Dr Snowsill explained that the study had been reviewed after the Technology Assessment Group had read Astellas's response to the Appraisal Consultation Document, which drew attention to it. Its design had both strengths and weaknesses. It was randomised, but it recruited only stable patients, and it did not examine of any of the outcomes pre-specified in this assessment. It did not provide information on the whole patient group or on those in whom there were problems of adherence.
46.	Ms Fahey explained that livers were less likely to be rejected than kidneys. Registry data showed that graft survival in liver transplant patients was better with prolonged-release tacrolimus than with immediate-release tacrolimus. It was reasonable to assume that the benefit would be greater still in kidney transplant patients.
47.	Professor McVeigh stated that liver transplant patients were different from kidney transplant patients. He also pointed out that in the context of a complex regimen, a switch from prolonged-release tacrolimus to

	immediate-release tacrolimus would reduce the tablet count by only one.
48.	Dr Martin Hurst, for Astellas, explained that tacrolimus had a narrow therapeutic range (its concentration in the blood should be kept within narrow limits to ensure that it works) and adherence to treatment was critical. Adherence could be assessed by talking to patients, by validated questionnaires, and by other methods. Concentrations in blood could be used to detect excess variability.
49.	<p>In response to questions from the Panel, Dr Hurst agreed that several factors influenced tacrolimus concentrations in blood, and one important factor was when the patient had taken food in relation to taking the tablet.</p> <p>He clarified the position that the methods he described were to detect poor adherence when it existed, not to predict whether poor adherence would occur.</p> <p>He also agreed that there was no precise definition of 'excess variability.'</p>
50.	<p>The Appeal Panel considered that the Assessment Group had carefully examined the study by Kuypers when it had been drawn to their attention in Astellas's response to the Appraisal Consultation Document. They had acknowledged both its strengths and its weaknesses. The Assessment Group's view was that the study's recruitment of stable patients only and the absence of data on outcomes relevant to the assessment made it difficult to use the results. The Appeal Panel found this to be a reasonable conclusion.</p> <p>The Panel found that the Appraisal Committee had given the study of</p>

	<p>Kuypers <i>et al</i> due consideration. It was not unreasonable to reach the conclusion that the information it contained did not help in making the decisions before it.</p> <p>The Appeal Panel saw it was possible to argue that data from the Liver Transplant Registry could be extrapolated to patients undergoing kidney transplant. However, it recognised that these data related to a different patient population and so any extrapolation was uncertain. It was therefore not unreasonable to disregard the Liver Transplant Registry data.</p> <p>The Appeal Panel also found that the methods of detecting poor adherence proposed by Astellas would help only to find patients after their adherence became poor. There was no simple way to do this in advance, and it was not unreasonable of the Appraisal Committee to conclude that the methods would fail to identify a subgroup prospectively.</p>
51.	The Appeal Panel therefore dismissed the appeal on this point.

### **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 adults having a kidney transplant’ is unreasonable as it has not taken into account the resultant reduction in transplants, which would lead to more dialysis.**

52.	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
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	several treatments were not recommended was made without taking into account the costs of failed transplants and wasted kidneys.
53.	<p>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.</p> <p>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.</p>
54.	<p>Professor McVeigh stated that the Appraisal Committee had considered clinical and cost-effectiveness evidence in what he called '<i>de novo</i>' 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.</p> <p>In the absence of evidence, the Appraisal Committee could generally not make recommendations.</p> <p>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.</p> <p>Where there was evidence regarding treatments that led to worse outcomes and cost more than the reference case treatment, or where</p>

	<p>the incremental cost-effectiveness ratio was extremely high, then the Appraisal Committee stated that those treatments should not be recommended.</p> <p>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.</p> <p>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.</p>
55.	<p>Professor McVeigh was asked by the Panel whether the Final Appraisal Determination referred only to the initial treatment.</p> <p>(The terms 'initial treatment' and 'inception treatment' were used during the Appeal hearing to describe the treatments given to de novo patients.)</p> <p>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.</p>

	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.
56.	<p>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.</p> <p>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.</p>
57.	Dr Snowsill explained that the costs of dialysis were included in the model in two ways: as the cost of providing dialysis, set at £24 000 per year for adults, and as the loss of quality of life, expressed as a decrease in utility of approximately 0.25.
58.	Marcela Haasova, for the Technology Assessment Group, stated that studies in which patients changed treatments after transplantation were excluded. However, if the studies had examined a subgroup at high risk or who had suffered a special toxicity, they would have been included.
59.	<p>The Appeal Panel understood that the Appraisal Committee could only make firm decisions on matters that it had considered. The Panel was uncertain what the Committee had considered.</p> <p>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</p>

	<p>than the two groups identified at paragraph 1.4, in relation to which 'no recommendation' was made.</p> <p>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.</p> <p>The Final Appraisal Determination explains the lack of evidence for recommending treatments for particular subgroups (see e.g. the Final Appraisal Determination at 4.64). 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.</p> <p>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.</p> <p>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 paragraphs 4.75 and 4.76 of the Final Appraisal Determination.</p>
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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

	<p>transplant, that the recommended treatment was not clinically appropriate</p> <p>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.</p> <p>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.</p>
60.	<p>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.</p> <p>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.</p>

	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.
<b>British Kidney Patient Association</b>	
<b>Appeal Point 2.3</b>	
	<b>Recommendation 1.4 does not take into account the quality of life impact resulting from lost transplants for 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.</b>
61.	<p>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.</p> <p>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.)</p>
62.	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.
63.	The Appeal Panel accepted that there were patients in whom the use

	<p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>

### **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.**

64.	Fiona Loud told the Appeal Panel that paragraph 1.4 of the Final
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	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.
65.	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.
66.	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.
67.	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 <u>at the time of transplantation</u> , then the Technology Assessment Group would have included it. (Emphasis supplied.)
68.	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.
69.	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.

70.	<p>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.</p> <p>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.</p> <p>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.</p>

### **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.**

71.	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.
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72.	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.
73.	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.)
74.	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.
75.	<p>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.</p> <p>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.</p>
<b>British Kidney Patient Association</b> <b>Appeal Point 2.8</b>	

**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.**

76.	Dr Hodge had explained very clearly to the Appeal Panel the consequences of intolerance of mycophenolate mofetil.
77.	With regard to the specific issue of whether mycophenolate sodium was better tolerated than mycophenolate mofetil, Professor McVeigh stated that this was a clinical impression. Mycophenolate sodium was developed specifically to try to avoid adverse gastrointestinal effects, but clinical trial data failed to show any significant benefit for mycophenolate sodium over mycophenolate mofetil with regard to gastrointestinal adverse effects. Many patients intolerant of mycophenolate mofetil were also intolerant of mycophenolate sodium and were subsequently switched to sirolimus.
78.	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.
79.	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.

80.	It was not unreasonable for the Committee to prefer to base its conclusion on the evidence from clinical trials.
81.	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 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.**

82.	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.
83.	Mr Nick Palmer, for 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.
84.	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 that this was a particular problem.
85.	Mr Timothy Statham, for the National Kidney Foundation, stated that adherence was an important subject for renal patients, all of whom have a substantial burden of pills to take. It was not, in his view, a problem only for young people.
86.	The Appraisal Committee had examined the evidence from the Kuyper trial and discussed the issue of adherence, as discussed under Astellas Appeal Point 2.2.
87.	<p>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.</p> <p>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.</p> <p>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.</p>
88.	The Appeal Panel therefore dismissed the appeal on this point.
<b>British Kidney Patient Association</b> <b>Appeal Point 2.10</b>	

**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.**

89.	<p>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.</p>
90.	<p>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.</p>
91.	<p>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.</p>
92.	<p>The scope of the appraisal was again important.</p> <p>As discussed above, the Appeal Panel found that the inconsistency between what was set out in the Final Appraisal Determination and</p>

	<p>the position of the Appraisal Committee was unfair and for this reason the appraisal should be remitted to the Appraisal Committee.</p> <p>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.</p>

### **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.**

93.	Mr Boysen made it clear that the Appraisal Committee had not formally considered patients having a second transplant.
94.	The British Kidney Patient Association did not identify any specific group of subjects who were unsuitable for basiliximab as initial therapy.
95.	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) (see section 4.2). 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.'
96.	Professor McVeigh stated that basiliximab was cost-effective, and was the induction treatment most commonly used in the United Kingdom.
97.	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.
98.	The Appeal Panel heard from several appellants that the Appraisal Committee's recommended regimen, which included basiliximab but not ciclosporin, was the standard regimen. (See joint appeal point 2.1, NHS England Appeal Point 2.1 below.) No appellant suggested that the regimen favoured by the Appraisal Committee was unreasonable.
99.	Dr Snowsill explained that the Technology Assessment Group had used data from a 2006 study by Brennan <i>et al</i> to inform the costs in the model and allow for the differences between basiliximab and rabbit anti-human thymocyte globulin. The data therefore came from a prospective, randomized, international study.
100.	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

	<p>recommend the use of drugs outside of the terms of their marketing authorization.</p> <p>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.</p> <p>The Appeal Panel could not see how the actions of the Appraisal Committee could be characterised as unreasonable.</p>
101.	The Appeal Panel therefore dismissed the appeal on this point insofar as it referred to use of basiliximab outside its marketing authorisation.
102.	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.
<b>British Kidney Patient Association</b>	
<b>Appeal Point 2.12</b>	
<p><b>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</b></p>	

<b>been made.</b>	
103.	<p>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.</p> <p>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.</p>
104.	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.
105.	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.
<b>British Transplantation Society, Renal Association, and British Renal Society</b>	

**Appeal ('the Joint Appeal')****Appeal point 2.1**

**Recommendation 1.4 is unreasonable in light of the evidence presented to NICE or lack thereof.**

106.	The points made by the Joint Appeal were unnumbered. The points have been numbered here for clarity.
107.	Dr Nicholas Torpey, for British Transplantation Society, Renal Association, and British Renal Society ('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.
108.	There was also a lack of evidence regarding those patients who are themselves over 65 years old or who receive a kidney from a donor over 65 years old, or both, and who represent about a third of all patients receiving transplants in the United Kingdom.
109.	If the recommendations referred to initial treatment only, then in Dr Torpey's view they were consistent with current practice.
110.	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.

111.	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.
112.	Dr Snowsill stated that, as the scope did not include a population intolerant of the recommended drugs, it referred effectively to initial treatment.
113.	<p>The Appeal Panel noted that this ground of appeal raised similar issues to British Kidney Patient Association Ground 2.12.</p> <p>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.</p>
114.	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.
115.	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.

	<p>The Panel dismissed this appeal point insofar as it related to first-line treatment.</p> <p>However, as discussed above, the Appraisal Committee had not examined second-line treatments.</p>
<b>British Transplantation Society, Renal Association, and British Renal Society</b>	
<b>Appeal Point 2.2</b>	
<p><b>Recommendation 1.4 disadvantages patients who are intolerant of mycophenolate mofetil and experience GI disturbances.</b></p>	
116.	The Appeal Panel noted that this ground of appeal raised similar issues to British Kidney Patient Association Ground 2.8
117.	<p>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.</p> <p>Mycophenolate sodium was developed for that reason, but clinical trial data failed to show any significant benefit of mycophenolate sodium over mycophenolate mofetil. Many patients intolerant of mycophenolate mofetil were also intolerant of mycophenolate sodium and were subsequently switched to sirolimus.</p>
118.	<p>It was not unreasonable for the Committee to prefer to base its conclusion on the evidence from clinical trials.</p>
119.	The Appeal Panel therefore dismissed the appeal on this point.
<b>British Transplantation Society, Renal Association, and British Renal Society</b>	

### **Appeal Point 2.3**

#### **Recommendation 1.4 does not account for drug variability and non-adherence**

120.	Dr Graham Lipkin, for the Joint Appeal, described how at one time a third of patients who had received a kidney transplant as children and then moved to adult care lost the kidney within two years of the move. By introducing a series of measures to improve matters, centres such as the Birmingham Centre had reduced the rate of graft loss to one in ten. One of several interventions that was followed by improvement in graft survival was to prescribe prolonged-release tacrolimus in place of immediate-release tacrolimus. The guidance as published would prevent the use of prolonged-release tacrolimus in this circumstance.
121.	The Appeal Panel had already considered this question of adherence. [Astellas Appeal Point 2.2, British Kidney Patient Association Appeal Point 2.9, 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.
122.	The Appeal Panel therefore dismissed the appeal on this point.

### **British Transplantation Society, Renal Association, and British Renal Society**

#### **Appeal Point 2.4**

#### **Recommendation 1.4 prevents the use of rabbit anti-human thymocyte globulin in ‘high immunological risk’ patients**

123.	Dr Torpey explained that rabbit anti-human thymocyte globulin had been used for over 30 years, and was now widely used in the United States and Europe. It was practice to use rabbit anti-human thymocyte globulin in patients at high risk of rejection, especially those with high titres of antibodies who were considered to be at 'high immunological risk.'
124.	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. They had considered the study by Brennan <i>et al</i> (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.
125.	When the Technology Assessment Group compared basiliximab with rabbit anti-human thymocyte globulin, 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%.
126.	Dr Torpey accepted that there was no evidence from clinical trials to support the use of rabbit anti-human thymocyte globulin, which was based on 'very substantial clinical experience'.
127.	The Appeal Panel saw that the Appraisal Committee was required to make a decision that weighed imperfect clinical trial evidence against unsystematic clinical experience. Insofar as they had been able to

	analyse the data, rabbit anti-human thymocyte globulin was most unlikely to be cost-effective, or to be superior to basiliximab. It was not unreasonable to decide on that basis that it should not be recommended.
128.	The Appeal Panel therefore dismissed the appeal on this point.

**British Transplantation Society, Renal Association, and British Renal Society Appeal**

**Point 2.5**

**Recommendation 1.4 prevents the use of sirolimus as a calcineurin-inhibitor sparing agent or in patients with mycophenolate mofetil intolerance and those with malignancy**

129.	Dr Torpey referred to evidence regarding alternative regimens used second-line in those unable to take first-line treatments. Some of the evidence came from clinical trials, and referred to sirolimus. The evidence suggested that patients fared better on sirolimus.
130.	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.
131.	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.
132.	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.
133.		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.
<b>ESPRIT</b>		
<b>Appeal Point 2.1</b>		
<p><b>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</b></p>		
134.		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.
135.		Professor McVeigh had indicated that the Final Appraisal Determination was intended to refer to initial treatment.
136.		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.
137.		<p>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.</p> <p>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.</p>
<b>ESPRIT</b>		
<b>Appeal Point 2.2</b>		
<p><b>We question how the Assessment Committee arrived at the active ‘not recommended’ statement in section 1.4 of the Final Appraisal Determination</b></p>		
138.		<p>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.</p>
139.		<p>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.</p>

140.	<p>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 neurotoxicity or from thrombotic microangiopathy, circumstances in which there was currently no evidence, and where it would be very difficult to gather evidence.</p>
141.	<p>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).</p> <p>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.</p>
142.	<p>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.</p> <p>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.</p>
143.	<p>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</p>

	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.**

144.	<p>This point had been discussed when the Appeal Panel had considered British Kidney Patient Association appeal point 2.5.</p>
145.	<p>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.</p> <p>However, the Appraisal Committee had not examined second-line treatments, as discussed above.</p>
146.	<p>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.</p> <p>The Panel noted that the scope specifically stated that</p>

	<p>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.</p> <p>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.</p>

## 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.**

147.	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).
148.	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.
149.	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.
150.	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.
151.	<p>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.</p> <p>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.</p>

	<p>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.</p>

**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.**

152.	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.
153.	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 and found no important difference in gastrointestinal effects between the two formulations of mycophenolic acid.
154.	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.**

155.	The Appeal Panel had considered this question above (see appeal points Astellas 2.1, 2.2, British Kidney Patient Association 2.9, Joint Appeal 2.3). It concluded that the Appraisal Committee had not acted unreasonably in stating that prolonged-release tacrolimus was not recommended.
156.	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.**

157.	The Appeal Panel had considered the appraisal of sirolimus above (see British Kidney Patient Association Appeal Point 2.10, Joint Appeal Point 2.5).
158.	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.

		<p>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.</p>
	<b>NHS England</b>	
	<b>Appeal Point 2.5</b>	
		<p><b>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.</b></p>
159.		<p>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 point 2.11).</p>
160.		<p>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.</p>
161.		<p>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 <i>et al</i> 2006 had</p>

	been taken into account, and that included some patients at high immunological risk.
162.	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 basiliximab was not unreasonable.
163.	The Appeal Panel dismissed the appeal on this point as it related to the recommendation for basiliximab for first line treatment.
164.	<p>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.</p> <p>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.</p> <p>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.</p>
<b>NHS England</b>	

## **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.**

165.	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].
166.	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 ‘ <i>de novo</i> ’ transplant patients. [British Kidney Patient Association Appeal Point 2.1].
167.	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.
168.	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.

169.	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.
170.	The Appeal Panel was clear that the approach regarding what Professor McVeigh had termed ' <i>de novo</i> ' patients was reasonable.
171.	<p>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.</p> <p>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.</p>

### NHS England

#### Appeal Point 2.7

##### **The recommendations are based on the wrong comparator used in the economic analysis**

172.	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.
173.	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 <i>et al.</i>
174.	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.
175.	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 2.1, 2.5, ESPRIT 2.3.)
176.	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.
177.	The Appeal Panel therefore dismissed the appeal point insofar as it related to costs used in the economic analysis.
178.	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.
179.	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.

### **National Kidney Foundation**

#### **Appeal Point 2.1**

**It is unreasonable to ignore the weight of joint clinical evidence presented by expert transplant clinicians. There are many holes in the evidence base and these must be filled in by clinical experience to achieve optimum results.**

180.	<p>Mr Statham explained the practical consequences for patients with kidney failure if they had to survive on dialysis and contrasted this with patients who had a functioning transplanted kidney, for whom life was easier. However, immunosuppressant drugs were far from perfect, and the drug regimen post-transplant was complex, which led to difficulties in adherence. The drugs could be toxic. If the patient could not have another medicine as a consequence of the Appraisal Committee's decision that it was not recommended, then the kidney would be lost.</p> <p>In the absence of evidence, decisions that drugs were not recommended should be altered to 'no recommendation can be made.'</p> <p>It was unreasonable to state in the Final Appraisal Determination that some drugs are not recommended, while at the same time stating that there may be clinical indications where they may be of benefit.</p>
181.	The Appeal Panel had established from Professor McVeigh that the

	Appraisal Committee had considered evidence from clinicians, patients and consultees. The Committee had requested relevant evidence, but none was provided. (See British Kidney Patient Association Appeal Point 2.1.)
182.	The Appeal Panel had also considered whether the decision that some drugs were not recommended (as the Committee clarified, for first-line treatment) was reasonable. (For example, Appeal points British Kidney Patient Association 2.1–2.4, 2.10, Joint Appeal 2.1, NHS England 2.1, 2.3, 2.6.)
183.	With regard to the processes of NHS England that determined whether drugs that may sometimes be needed for NHS patients would be funded, that was not directly a concern of the Appraisal Committee.
184.	<p>As before, the Appeal Panel concluded that the Appraisal Committee's decisions regarding drugs used in first-line treatment were reasonable.</p> <p>However, as set out above, it became clear during the Appeal hearing that the Appraisal Committee did not consider 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.</p>
185.	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.
<b>Conclusion and effect of the Appeal Panel's decision</b>	

186.	<p>Given the length of this decision it may assist the Appellants and the Institute if the Appeal Panel summarises its conclusions.</p> <p>The recommendations made by the Appraisal Committee were reasonable insofar as they went. The calculation of prices was carried out fairly.</p> <p>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.</p> <p>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.</p> <p>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</p>
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	use could be the subject of a further appeal.
187.	<p>The following appeal points are <b>dismissed</b>:</p> <ul style="list-style-type: none"> <li>• Astellas 1a.1, 1a.2, 2.1, 2.2</li> <li>• British Kidney Patient Association 2.8, 2.9, 2.10, 2.12</li> <li>• Joint Appeal 2.1, 2.2, 2.3, 2.4, 2.5</li> <li>• ESPRIT 2.2</li> <li>• NHS England 2.2, 2.3, 2.4, 2.6</li> <li>• NKF 2.1</li> </ul>
188.	<p>The following appeal points are <b>allowed</b>:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• ESPRIT 2.1, 2.3 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment)</li> </ul>
189.	<p>The following appeals points are <b>allowed in part</b>:</p> <ul style="list-style-type: none"> <li>• British Kidney Patient Association 2.11 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment)</li> <li>• NHS England 2.1, 2.5, 2.7 (because of the lack of clarity in the Final Appraisal Determination regarding second-line treatment)</li> </ul>
190.	<p>The following appeal points are <b>dismissed in part</b>:</p> <ul style="list-style-type: none"> <li>• British Kidney Patient Association 2.11 (insofar as it relates to use of basiliximab outside the terms of its marketing authorisation)</li> <li>• NHS England 2.1 (insofar as it relates to the unreasonableness of recommendations for first line treatment)</li> <li>• NHS England 2.5 (insofar as it relates to use of basiliximab outside the terms of its marketing authorisation)</li> <li>• NHS England 2.7 (insofar as it relates to dosage and costs)</li> </ul>

191.	<p>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.</p>
192.	<p>The appraisal is remitted to the Appraisal committee who must now take all reasonable steps to address the issues set out in this decision letter.</p>
193.	<p>There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.</p>