National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Response to consultee and commentator comments on the draft remit and draft scope (post-referral)

Section	Consultee/ Commentator	Comments	Action
Background information	Astellas	The draft scope refers to the choice of immunosuppressive therapy being informed by the level of immunological risk, determined by risk factors such as age and antibody reactivity. Astellas would like to suggest adding to this by including that the choice of immunosuppressive therapy is also based on the likelihood of adherence issues and patient choice associated with once daily and twice daily treatment regimens.	Comment noted. The background information has been amended to note that the choice of immunosuppressive therapy is informed by a number of factors.
	Bristol-Myers Squibb	No comments	No action required.
	British Transplantation Society	Accurate and complete	Comment noted. No action required.
	Novartis Pharmaceuticals	No comments	No action required.
	Sandoz	No comments	No action required.
The technology/	Astellas	No comments	No action required.

Section	Consultee/ Commentator	Comments	Action
intervention	Bristol-Myers Squibb	Belatacept is a fusion protein, not a chimeric protein.	Comment noted. The description of belatacept has been revised.
	British Transplantation Society	The list of induction agents to be considered should include: Alemtuzumab Rituximab Eculizumab The list of agents for initial and long-term maintenance therapy should include: Azathioprine Steroid	Comment noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Alemtuzumab, rituximab, eculizumab, azathioprine and steroids are therefore not included as interventions.
	Novartis Pharmaceuticals	The summary table of interventions combines mycophenolate presentations. We would suggest that mofetil and sodium salts are defined as separate interventions. Please see further comments below.	Comment noted. The interventions have been amended to include mycophenolate mofetil

Section	Consultee/ Commentator	Comments	Action
			and mycophenolate sodium separately.
	PenTAG	Should alemtuzumab (Campath) also be considered since it is apparently widely used for induction therapy in the US?	Comment noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Alemtuzumab is therefore not included as an intervention.
	Sandoz	See below	Comments noted; please see responses below.
Population	Astellas	Population appropriately defined. Not aware of any further subgroups in addition to those specified within the scope that should be treated separately. For those subgroups specified within the scope, data may not be readily	Comments noted. The scope notes that subgroups will be considered if evidence allows.

Section	Consultee/ Commentator	Comments	Action
		available to support all of these analyses.	
	Bristol-Myers Squibb	No comments	No action required.
	British Transplantation Society	Inclusion of all adults undergoing transplantation is appropriate. There are some groups with specific immunosuppressive requirements that would be appropriate to consider separately: 1) Patients undergoing removal of blood group or HLA antibodies to allow antibody-incompatible transplantation. 2) Patients at high risk of immunological rejection including re-transplants and patients with pre-formed HLA antibody. 3) Patients at high risk of immunosuppressive complications including New Onset Diabetes After Transplantation (NODAT). 4) Immunosuppression in pregnancy. 5) Immunosuppression for HIV-infected transplant recipients.	Comments noted. The 'Other considerations' section has been revised to specify that if evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered.
	Novartis Pharmaceuticals	Agree	Comment noted. No action required.
	Sandoz	Agree	Comment noted. No action required.
Comparators	Astellas	The draft scope states that everolimus does not currently have a UK marketing authorisation for immunosuppressive treatment in kidney transplantation. If everolimus does not obtain a marketing authorisation will it still be a relevant comparator for Astellas?	Comment noted. The Appraisal Committee can consider as comparators technologies that do not have a marketing

Section	Consultee/ Commentator	Comments	Action
			authorisation for the indication defined in the scope when they are considered to be part of established clinical practice for the NHS. See section 6.2.4 of NICE's Guide to the methods of technology appraisal 2013.
		The draft scope mentions the use of ciclosporin and azathioprine for maintenance therapy which are often used in combination regimens with or without corticosteroids. However, neither ciclosporin or azathioprine have been specifically included as technologies for maintenance therapy alongside tacrolimus, belatacept, mycophenolic acid, sirolimus and everolimus.	Comment noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Ciclosporin and azathioprine are therefore not included as interventions. Because the use of calcineurin inhibitors

Section	Consultee/ Commentator	Comments	Action
			and antiproliferative agents is established clinical practice in the NHS, these drugs are included as comparators. No changes to the scope are required.
		The standard immunosuppressive of choice in the NHS is tacrolimus, which is used by the majority of patients.	Comment noted. No action required.
	Bristol-Myers Squibb	For maintenance therapy, ciclosporin is also a relevant comparator.	Comment noted. Calcineurin inhibitors are included as comparators in the scope.
	British Transplantation Society	These are the standard treatments. The most widely used regimen in the UK at present is induction therapy (usually with Basiliximab) with tacrolimus and mycophenolate ± steroid.	Comment noted. No action required.
	Novartis Pharmaceuticals	Reference should be made to combinations that reflect a reduced calcineurin inhibitor dose with or without corticosteroids. Please see further relevant comments below.	Comment noted. The 'Other considerations' section has been revised to specify that, if evidence allows, the appraisal will consider treatment regimens that aim to reduce or withdraw calcineurin

Section	Consultee/ Commentator	Comments	Action
			inhibitors.
	Sandoz	Immediate release and prolonged release formulations of tacrolimus should be assessed separately as there are differences with respect to dosing and drug levels. Sandoz is planning to launch two novel strengths of immediate release tacrolimus (Adoport) during this appraisal period. The new strengths will have patient benefits in terms of reduction in pill burden and alternative dosing increments for patients who are on small doses. Use of medications outside of their product licence should remain as exceptions within the NICE process. It may however be relevant in this review to reflect current clinical practice and to determine future best clinical practice. • Azathioprine should be included as there is some usage within the UK • Alemtuzumab should be included as there is usage within the UK	Comments noted. The interventions have been revised to specify immediate- and prolonged-release tacrolimus separately. Comment noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Alemtuzumab and azathioprine are therefore not included as interventions. Antiproliferative agents

Section	Consultee/ Commentator	Comments	Action
			are included as comparators.
Outcomes	Astellas	Astellas support that outcomes detailed in the draft scope capture relevant clinical and quality of life measures directly relevant to the NHS. Astellas would like to suggest further outcomes to capture health related benefits including: • Kidney function – specifically glomerular filtration rate • Development of de novo donor specific antibody as a surrogate marker for health outcomes in the long term (Sellares J et al, 2012)	Comment noted. Comment noted. Kidney function and development of donor-specific antibodies are captured by the current outcomes.
	Bristol-Myers Squibb	We would welcome the opportunity to discuss measures of graft function during the scoping workshop.	Comment noted. No action required.
	British Transplantation Society	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No action required.
	Novartis Pharmaceuticals	Consideration should be given to specifying adverse events of key interest, such as new onset diabetes, hypertension and nephrotoxicity	Comment noted. Adverse events such as new onset diabetes, hypertension and nephrotoxicity are captured by the current outcomes. No action required.
	Sandoz	Treatment of acute rejection episodes should be included.	Comment noted.

Section	Consultee/ Commentator	Comments	Action
			Treatment of acute rejection is outside the scope of the current appraisal.
Economic analysis	Astellas	Astellas support the use of the NICE reference case in demonstrating the cost-effectiveness of tacrolimus. A new model will be commissioned to represent the patient flow following successful kidney transplantation through a number of different health states. This Markov model will describe a one year life cycle and will support time horizons of between 5 and 25 years to estimate incremental cost per quality adjusted life years (QALYs) gained. We believe that all important differences in costs and outcomes will be reflected within this time horizon.	Comment noted. No action required.
	Bristol-Myers Squibb	No comments	No action required.
	British Transplantation Society	It is important that the economic analysis considers both short and long-term transplant outcomes. The time horizon needs to be at least 30 years.	Comment noted. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. See section 5.1 of NICE's Guide to the methods of technology appraisal 2013. No action required.

Section	Consultee/ Commentator	Comments	Action
	Novartis Pharmaceuticals	A lifetime horizon would seem appropriate. No further comments	Comment noted. The time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. See section 5.1 of NICE's Guide to the methods of technology appraisal 2013. No action required.
	Sandoz	No comment	No action required.
Equality and Diversity	Astellas	No comments	No action required.
	Bristol-Myers Squibb	No comments	No action required.
	British Transplantation Society	No issues.	No action required.
	Novartis Pharmaceuticals	No comments	No action required.
	Sandoz	No comment	No action required.

Section	Consultee/ Commentator	Comments	Action
Innovation	Astellas	No comments.	No action required.
	Bristol-Myers Squibb	No comments	No action required.
	British Transplantation Society	The key driver to the need for an appraisal is that the current NICE guideline is obsolete	Comment noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website.
	Novartis Pharmaceuticals	Everolimus is an evolution in terms of mTOR inhibition. It is different from sirolimus as it produces a less "blunt therapeutic effect". Sirolimus requires a higher loading dose and has a longer half–life than everolimus leading to prolonged immunosuppression effects. In contrast, as everolimus has a lower loading dose and shorter half-life, its subsequent therapeutic effects are more subdued. The availability of everolimus with its tightly controlled pharmacokinetic profiles provides greater control for physicians and potentially less side effects for patients.	Comment noted. The manufacturer is encouraged to describe the innovative nature of everolimus in its evidence submission. No action required.
	Sandoz	No comment	No action required.
Other considerations	Astellas	Astellas believes the following additional issues should be covered by the proposed appraisal: • The effect of adherence on graft failure rates • The effects of high intra-patient variability in tacrolimus on allograft loss and late acute rejection • The effects of de novo donor specific antibody development and the	Comment noted. The 'Other considerations' section has been revised to specify that, if evidence allows, subgroups based on factors that affect the risks associated with

Section	Consultee/ Commentator	Comments	Action
		associated antibody medicated rejection • Preservation of renal function in the long term (Guirado L , Cantarell C, Franco A et al Efficacy and Safety of Conversion from Twice-daily to Once-daily Tacrolimus in a Large Cohort of Stable Kidney Transplant Recipients American Journal of Transplantation 2011; 11: 1965–1971)	transplant and immunosuppressive treatment will be considered.
	Bristol-Myers Squibb	Other subgroups for potential consideration include; • People at high risk of graft failure, including those with an increased risk of non-compliance/adherence e.g. young adults. • People who have previously had a transplant and nephrotoxicity from their immunosuppressive therapy.	Comment noted. The 'Other considerations' section has been revised to specify that, if evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered.
	British Transplantation Society	The treatment of episodes of acute rejection is outside the scope of this appraisal. This is an important area where there is significant impact on patient outcomes and heterogeneity in practice with some high-cost treatment options. A NICE technology appraisal would be appropriate, either as part of the current appraisal or as a stand-alone appraisal. Appropriate immunosuppression in patients with a diagnosis of chronic rejection could be addressed within the current appraisal.	Comment noted. We note that guidance on the treatment of acute rejection would be valuable, but this is outside the scope of this appraisal.
	Novartis Pharmaceuticals	We recommend caution with regard to some of the identified sub-groups. The clinical definition of level of immunological risk via HLA compatibility / blood group compatibility is difficult and there are not clear thresholds that would allow the higher risk groups to be clearly defined. Similarly, the population at	Comment noted. The 'Other considerations' section has been revised to specify that, if

Section	Consultee/ Commentator	Comments	Action
		high risk of rejection is heterogeneous and may be difficult to define in order to carry out adequate sub-group analyses. Lastly, the definition of previous acute rejection should be clarified by type and severity of previous acute rejection as this may be more relevant in determining patient outcomes with differing immunosuppressive regimes.	evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered. The definitions of immunological risk and acute rejection may be considered by the Committee if appropriate during the appraisal.
	Sandoz	No comment	No action required.
Questions for consultation	Astellas	Would a review of the recommendations in NICE technology appraisal guidance 85 provide value to the NHS? Yes. • If so, should all of the current recommendations be reviewed, or is it only appropriate to review some of the recommendations (that is, undertake a partial review)? Astellas believes all current recommendations should be reviewed since the current NICE guidance is out of date, and does not match current therapy in	Comments noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website. Comment noted. The scope has been developed to allow the Appraisal Committee to review all of the recommendations in NICE technology

Section	Consultee/ Commentator	Comments	Action
		England and Wales. There is currently NICE UK guidance (NICE TA85) and guidance produced by the UK Renal Association (Clinical practice guidelines, 2011) recommending treatment for induction therapy, initial maintenance therapy, and long term maintenance therapy. However although these guidelines exist, centre specific variation occurs within clinical practice and a review of all recommendations will help make it clearer as to which treatments and treatment regimens should be adhered to. • Is it anticipated that the evidence that has emerged since the publication of technology appraisal guidance 85 would lead to a change in the recommendations? Yes. The Symphony study provided evidence for the use of tacrolimus over ciclosporin, and also for use of low doses of tacrolimus (Ekberg et al, 2007 – SYMPHONY study). There is also outcome data (to be published later this year) to show the benefit of Advagraf (once daily tacrolimus) over Prograf (twice daily tacrolimus). Are immunosuppressive treatments frequently used outside of their marketing authorisations in the NHS (for example, in unlicensed combinations or in people with high immunological risk)? Would an appraisal that only considers the use of immunosuppressive treatments within their marketing authorisations reflect current clinical practice and would it be of value to the NHS? No comments	appraisal guidance 85. No action required. Comment noted. The Committee will consider the availability, nature and quality of the clinical evidence during the course of the appraisal. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments	Action
		Should immunosuppressive treatment for episodes of acute rejection also be included in the appraisal? If so, which interventions and comparators should be considered for this? Astellas believes immunosuppressive treatment for episodes of acute rejection should not be included in the appraisal.	Comment noted. No action required..
		• Is azathioprine routinely used in clinical practice as part of immunosuppressive regimens? Yes.	Comment noted. No action required.
		• Should any other induction therapies be considered as comparators for induction therapy? No comments	Comment noted. No action required.
		• Should the different tacrolimus formulations (immediate- and prolonged-release) be considered separately? [redacted] There is further evidence that prolonged-release tacrolimus has advantages over immediate release including: • Reduced intra patient variability • Improved adherence to treatment (Kuypers er al, 2013)	Comment noted. The interventions have been revised to specify immediate- and prolonged-release tacrolimus separately

Section	Consultee/ Commentator	Comments	Action
		• A lower list price for Advagraf in comparison to Prograf	
		• Should the different brands of immediate-release tacrolimus be considered separately? Yes. MHRA indicated in 2012 that tacrolimus products should be prescribed and dispensed by brand name: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON155756	Comment noted. We understand that the MHRA recommends that tacrolimus should be prescribed by brand name, but it is not anticipated that a separate appraisal of each brand would be necessary. No action required.
		• Should the different mycophenolate formulations be considered separately? No comments.	Comment noted. No action required.
		• In clinical practice is an induction therapy always used? Or should the comparator of 'no induction therapy' be considered? No comments.	Comment noted. No action required.
		• Does immunosuppressive treatment differ depending on donor type (cadaveric or living donor)? Should this be considered as a subgroup? No comments.	Comment noted. No action required.
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular	

Section	Consultee/ Commentator	Comments	Action
		protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are and will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. Are there any groups of people who would choose not to take any of the technologies included in this appraisal (for example, those manufactured using human or animal blood products) because of religious or other beliefs? No comments Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits Astellas has clinical studies to present evidence to take account of these benefits.	Comment noted. No action required. Comment noted. The manufacturer is encouraged to describe the innovative nature of its technology in its evidence submission.

Section	Consultee/ Commentator	Comments	Action
			No action required.
	Bristol-Myers Squibb	Is it anticipated that the evidence that has emerged since the publication of TAG85 would lead to a change in the recommendations? New evidence has emerged since the original appraisal and new products are now available. Furthermore, the Symphony study (2009) has impacted clinical practice in the UK. Therefore, TA85 requires updating. Is azathioprine routinely used in clinical practice as part of immunosuppressive regimens? Azathioprine tends to be used in patients with older grafts, but not new patients who tend to receive mycophenolate. Should the different tacrolimus formulations (immediate- and prolonged-release) be considered separately? Yes, as the pharmacokinetics of the treatments change when formulation is changed i.e. picomolar potency. Should the different brands of immediate-release tacrolimus be considered	Comment noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website. Comment noted. The Committee will consider the availability, nature and quality of the clinical evidence during the course of the appraisal No action required. Comment noted. The comparators include calcineurin inhibitors with or without an antiproliferative agent (such as azathioprine). Comment noted. The interventions have been revised to specify immediate- and prolonged-release tacrolimus separately. Comment noted. We

Section	Consultee/ Commentator	Comments	Action
		separately? Yes, as above. In clinical practice is an induction therapy always used? Yes.	understand that the MHRA recommends that tacrolimus should be prescribed by brand name, but it is not anticipated that a separate appraisal of each brand would be necessary. Comment noted. No action required.
	British Transplantation Society	This is highly likely to provide value to the NHS and a full rather than partial review is required. The evidence published since the publication of technology appraisal guidance 85 is highly likely to lead to a change in the recommendations. Many drug regimens in widespread use in transplantation are used outside their marketing authorisations. Therefore, it is essential that consideration of treatments is not restricted to use within their marketing authorisations.	Comment noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website. Comment noted. The Committee will consider the availability, nature and quality of the clinical evidence during the course of the appraisal. No action required Comment noted. Under an exceptional directive from the Department of

Section	Consultee/ Commentator	Comments	Action
		Immunosuppressive treatment for episodes of acute rejection should be included. Interventions that should be considered are: High-dose steroid Antithymocyte globulin For acute antibody-mediated rejection interventions are: Plasma exchange Intravenous immunoglobulin Eculizumab Rituximab	Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. See section 6.1.12 of NICE's Guide to the methods of technology appraisal 2013. Comment noted. We note that guidance on the treatment of acute rejection would be valuable, but this is outside the scope of the current appraisal. No action required.

Section	Consultee/ Commentator	Comments	Action
		Azathioprine is still used in sufficient volume to be included in the appraisal. Additional induction agents that should be considered are: Alemtuzumab Rituximab Eculizumab	Comments noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Alemtuzumab, rituximab, eculizumab and azathioprine are therefore not included as interventions.
		Immediate and prolonged release formulations of tacrolimus should be considered separately. Any potential benefits of use of prolonged release preparations will need to be considered in the context of increased cost as there is no generic option.	Comment noted. The interventions have been revised to specify immediate- and prolonged-release tacrolimus separately.
		There is no need to consider the different brands of immediate release tacrolimus separately.	Comment noted. We understand that the MHRA recommends that tacrolimus should

Section	Consultee/ Commentator	Comments	Action
			be prescribed by brand name, but it is not anticipated that a separate appraisal of each brand would be necessary.
		There is no need to consider the different brands of mycophenolate mofetil separately. There is probably value in commenting on whether there is any reduction in gastrointestinal toxicity with enteric-coated mycophenolate sodium, balanced against the greater cost of this agent.	Comment noted. The interventions have been amended to include mycophenolate mofetil and mycophenolate sodium separately.
		Most transplant patients in the UK now receive induction therapy.	Comment noted. No action required.
		In terms of donor-type, a key question that would be useful to address is whether it is appropriate to alter immunosuppressive therapy in patients at high risk of delayed graft function, eg recipients of transplants from donors who had a circulatory death or extended criteria donors. Minimisation of calcineurin inhibitor therapy with use of a lytic induction agent in this setting is a common practice but with little supporting evidence and is controversial.	Comment noted. The 'Other considerations' section has been revised to specify that, if evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be considered.
		Jehovah's witnesses are sometimes unwilling to be treated with intravenous	Comment noted.

Section	Consultee/ Commentator	Comments	Action
		human immunoglobulin. UK-specific transplant outcome data are available through NHSBT and the UK Renal Registry.	Consideration will be given by the Appraisal Committee to the treatment options available for people who are unwilling to receive human blood products, to ensure that any recommendations do not directly or indirectly discriminate on the basis of religion. Comment noted. No action required.
	Novartis Pharmaceuticals	Our response to the consultation questions are outlined below: **Should TA85 be reviewed?** Given the numerous developments in clinical practise / product availability since the publication of TA85, the majority of recommendations should be reviewed: • Induction: daclizumab is now withdrawn (as noted) and the availability of rabbit AHT immunoglobulin • Tacrolimus generic and extended-release presentations now available • Mycophenolate sodium available • Everolimus potentially being available with evidence that may suggest	Comment noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website. The scope has been developed to allow the Appraisal Committee to review all of the recommendations in NICE technology

Section	Consultee/ Commentator	Comments	Action
		a more favourable tolerability and adverse event profile Significant evidence has been published or will be published after the recommendations made in TA85 including: Campath, Calcineurin Inhibitor Reduction and Chronic Allograft Nephropathy (NCT01120028) Advancing Renal TRANSplant eFficacy and Safety Outcomes With an eveRolimus-based regiMen (TRANSFORM- NCT01950819) Tedesco SH et al Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant* 2010; 10(6):1401-1413. Cibrik D et al. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. Transplantation. 2013 Apr 15;95(7):933-42 Shihab FS et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. Clin Transplant. 2013 Mar-Apr;27(2):217-26. Therefore updating the recommendations made in TA85 should be of value to the NHS. **Use of immunosuppressive regimens outside of marketing authorisations**:	appraisal guidance 85. No action required. Comment noted. The Committee will consider the availability, nature and quality of the clinical evidence during the course of the appraisal No action required. Comment noted. Under an exceptional directive

Section	Consultee/ Commentator	Comments	Action
		The preference should be for treatment regimens to be considered within their license combinations- if clinical practise suggests otherwise then careful consideration should be made before making such recommendations in this review.	from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. See section 6.1.12 of NICE's Guide to the methods of technology appraisal 2013.
		Should immunosuppressive treatment for acute rejection episodes be considered? As treatment of acute rejection depends on the type and severity of the acute rejection which may involve high-dose steroid treatment, changes in immunosuppressive regimen and dose etc.; these complexities may be beyond the scope of this review.	Comment noted. We note that guidance on the treatment of acute rejection would be valuable, but this is outside the scope of this appraisal.
		Have the most appropriate interventions and comparators been considered? Some centres may use alemtuzumab as part of an induction regimen, although it is not licensed for this indication	Comments noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant

Section	Consultee/ Commentator	Comments	Action
		Is azathioprine routinely used in clinical practise? Our understanding of immunosuppressive regimens in centres in England and Wales indicates that azathioprine is rarely used.	marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Alemtuzumab and azathioprine are therefore not included as interventions.
		Prolonged release / brands of tacrolimus No comments	Comment noted. No action required
		Should the different mycophenolate formulations be considered separately? There is evidence to indicate that outcomes and tolerability may differ with mycophenolate presentations. Sollinger H et al. Myfortic vs. CellCept: a large, single-center comparison.2008;8(suppl 2):514. *Am J Transplant.* Cooper M *et al*. Comparing outcomes associated with dose manipulations of enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal	Comment noted. The interventions have been amended to include mycophenolate mofetil and mycophenolate sodium separately.

Section	Consultee/ Commentator	Comments	Action
		transplant recipients. *Transplantation* 2009; 88(4):514-520. Chan L et al Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. *Transplantation* 2006; 81(9):1290-1297. Given this evidence exists, the review of TA85 should treat mycophenolate mofetil and mycophenolate sodium separately in order to assess the potential impact on clinical and health-related quality of life outcomes and therefore the relative cost-effectiveness of the mycophenolic acid interventions. **In clinical practice is an induction therapy always used?** Again, our understanding suggests there is variation between centres with the use of induction therapy. Given that the draft scope defines the various phases of renal transplantation appropriately, the comparator of 'no induction therapy' may logically be included in the potential interventions for induction therapy. **Does immunosuppressive treatment differ depending on donor type?** Donor type alone may not define immunosuppressive treatment and outcomes. Other factors may include oxygen deprivation for the transplant organ regardless of donor type. Therefore assessing sub-groups by donor type may not be feasible.	Comment noted. The comparators for induction therapy include regimens without monoclonal or polyclonal antibodies and the interventions compared with each other. Comment noted. The 'Other considerations' section has been revised to specify that if evidence allows, subgroups based on factors that affect the risks associated with transplant and

Section	Consultee/ Commentator	Comments	Action
			immunosuppressive treatment will be considered.
	PenTAG	The inclusion of azathioprine and treatment for acute rejection would significantly increase the workload for the assessment group, and in particular for the economic analysis.	Comments noted. The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal. Azathioprine is therefore not included as an intervention. We note that guidance on the treatment of acute rejection would be valuable, but this is outside the scope of the current appraisal.

Section	Consultee/ Commentator	Comments	Action
	Sandoz	Sandoz believes a full review is necessary and would be beneficial as it is likely to lead to a change in current recommendations, which will reflect current clinical practice Use of medications outside of their product licence should remain as exceptions within the NICE process. It may however be relevant in this review to reflect current clinical practice and to determine future best clinical practice. Immediate release and prolonged release formulations of tacrolimus should be assessed separately as they are not equivalent 1. Albano L, Banas B, Klempnauer JL et al. OSAKA Trial: A Randomized, Controlled Trial Comparing Tacrolimus QD and BD in Kidney Transplantation. Clin Trans Res 2013; 96(10): 897-903. 2. Backman L and Person CA. An observations study evaluating	Comment noted. The appraisal has been scheduled into the NICE work programme; details can be found on the NICE website. Comment noted. Under an exceptional directive from the Department of Health, the Appraisal Committee may consider making recommendations about the use of drugs outside the terms of their existing marketing authorisation where there is compelling evidence of their safety and effectiveness. See section 6.1.12 of NICE's Guide to the methods of technology appraisal 2013. Comment noted. The interventions have been revised to specify immediate- and prolonged-release

Section	Consultee/ Commentator	Comments	Action
		tacrolimus dose, exposure, and medication adherence after conversion from twice- to once-daily tacrolimus in liver and kidney transplant recipients. Ann Transplant 2014; 19: 138-44. 3. Barraclough KA, Isbel NM, Johnson DW, Campbell SB, Staatz CE. Once- versus twice-daily tacrolimus. Are the formulations truly equivalent? Drugs 2011;71(12):1661-77. 4. Beckebaum S, Iacob S, Sweid D et al. Efficacy, safety and immunosuppressant adherence in stable liver transplant patients converted from a twice-daily tacrolimus-based regimen to once-daily tacrolimus extended-release formulation. Transpl Int 2011; 24(7): 666-75. 5. Crespo M, Mir M, Marin M et al. De novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels. Transplant Proc 2009;41(6):2115-7. 6. de Jonge H, Kuypers DR, Verbeke K, Vanrenterghem Y. Reduced C0 concentrations and increased dose requirements in renal allograft recipients converted to the novel once-daily tacrolimus formulation. Transplantation 2010; 90:523-9 7. Guirado L, Cantarell C, Franco A et al. Efficacy and safety of conversion from twice-daily to once-daily tacrolimus in a large cohort of stable kidney transplant recipients. Am J Transplant 2011;11(9):1965-71. 8. Hougardy J-M, de Jonge H, Kuypers D, Abramowicz D. The once-daily formulation of tacrolimus: a step forward in kidney transplantation? Transplantation 2012;93(3):241-3. 9. Kraemer BK, Charpentier B, Baeckman L et al. Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. Am J Transplant 2010;10:2632-43.	tacrolimus separately.

Section	Consultee/ Commentator	Comments	Action
		10. Krueger B, Banas B, Tomlinson PC, Kraemer BK. Early post-transplant blood levels in de novo renal recipients on tacrolimus prolonged release (TacQD) v tacrolimus immediate release (TacBD) in a phase III double-blind double-dummy study. J Am Soc Nephrol 2010;21(201):3B. 11. Kurnatowska I, Krawczyk J, Oleksik T, Nowicki M. Tacrolimus dose and blood concentration variability in kidney transplant recipients undergoing conversion from twice daily to once daily modified release tacrolimus. Transplant Proc 2011;43:2954-56. 12. Lauzurica R, Morales MM, van Hooff J. Renal function and safety in stable kidney transplant recipients converted from immediate-release to prolonged-release tacrolimus. Transplant Int 2012;25(1):48-55. 13. Sanko-Resmer J, Boillot O, Wolf P, Thorburn D. Renal function, efficacy and safety from postconversion from twice- to once-daily tacrolimus in stable liver recipients: an open-label multicentre study. Transplant Int 2012;25(3):283-93. 14. Silva HT, Yang HC, Abouljoud M et al. One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. Am J Transplant 2007;7:595-608. 15. Srinivas TR, Kaplan B, Meier-Kriesche H-U. The non-inferiority trial: don't do it. Am J Transplant 2010;10(12):2571-3. 16. Trunecka P, Boillot O, Seehofer D et al. Once-daily prolonged-release tacrolimus (ADVAGRAF) versus twice-daily tacrolimus (PROGRAF) in liver transplantation. Am J Transplant 2010;10:2313-23. 17. Wu M-J, Cheng C-Y, Chen C-H et al. Lower variability of tacrolimus trough concentration after conversion from Prograf to Advagraf in stable kidney transplant recipients. Transplantation 2011;92(6):648-652.	

Section	Consultee/ Commentator	Comments	Action
		Tacrolimus should be prescribed by brand as per the recommendations of the MHRA.	Comment noted. We understand that the MHRA recommends that tacrolimus should be prescribed by brand name, but it is not anticipated that a separate appraisal of each brand would be necessary.
		Azathioprine should be included as there is some usage within the UK Alemtuzumab should be included as there is usage within the UK	Comment noted. The comparators include calcineurin inhibitors with or without an antiproliferative agent (such as azathioprine). The technologies to be appraised are those that: were included in technology appraisal guidance 85, have obtained a relevant marketing authorisation in the UK since the publication of technology appraisal guidance 85, or have been referred to NICE by the Department of Health for appraisal.

Section	Consultee/ Commentator	Comments	Action
			Alemtuzumab, and azathioprine are therefore not included as interventions.
		The different mycophenolate formulations produce different clinical outcomes and should therefore be assessed separately.	Comment noted. The interventions have been amended to include mycophenolate mofetil and mycophenolate sodium separately.
		A comparator of no induction therapy should be included	Comment noted. Regimens involving no specific induction therapy will be captured under 'regimens without monoclonal or polyclonal antibodies'.
		Where the evidence allows for comparison, donor influences on outcomes should be assessed	Comment noted. The 'Other considerations' section has been revised to specify that if evidence allows, subgroups based on factors that affect the risks associated with transplant and immunosuppressive treatment will be

Section	Consultee/ Commentator	Comments	Action
			considered.
Additional comments on the draft scope	Astellas	No comments.	No action required.
	British Transplantation Society	No further comments.	No action required.
	Novartis Pharmaceuticals	None	No action required.
	Royal College of Pathologists	In the first paragraph on induction therapy at the bottom of page 2 there is reference to panel reactive antibodies (PRA) indicating that higher PRA confers higher immunological risk. The use of PRA to define sensitisation levels was dropped some years ago as it was realised that this was not an accurate measure of sensitisation. The measure used in the UK is the calculated reaction frequency (CRF). This is the measure used by NHSBT ODT to help in the allocation of organs and to define highly sensitised patients.	Comment noted. The background information has been amended accordingly. It is noted that panel reactive antibody status is a consideration in the marketing authorisation for basiliximab.

The following consultees/commentators indicated that they had no comments on the draft scope:

Department of Health

Pfizer (commented on regulatory issues)

Royal College of Nursing

Teva (commented on regulatory issues)

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add ESPRIT	Astellas		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. ESPRIT has been added to the matrix of consultees and commentators under 'professional groups'.

2.	Remove Commissioning Support Appraisals Service	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Commissioning Support Appraisals Service has been removed from the matrix of consultees and commentators.
3.	Remove Chemidex Pharma	NICE Secretariat		Removed	This organisation's interests are not closely related to the appraisal topic and as per our inclusion criteria. Chemidex Pharma has been removed from the matrix of consultees and commentators.
4.	Remove National Clinical Guidelines Centre for Acute and Chronic Conditions	NICE Secretariat		Removed	This organisation is now part of the National Clinical Guidelines Centre.

5.	Add National Clinical Guideline Centre	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. National Clinical Guideline Centre has been added to the matrix of consultees and commentators under 'associated guideline groups'.
6.	Add Hospital Information Services (Jehovah's Witnesses)	NICE Secretariat		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. Hospital Information Services (Jehovah's Witnesses) has been added to the matrix of consultees and commentators under 'patient groups'.