

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

**Immunosuppressive therapy for kidney transplantation in adults (review of
technology appraisal guidance 85) [ID456]**

The following documents are made available to the consultees and commentators:

1. ***Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)***
2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
 - [Astellas Pharma](#)
 - [Bristol-Myers Squibb Pharmaceuticals](#)
 - [Novartis Pharmaceuticals](#)
 - [Sandoz](#)
 - [Sanofi](#)
 - [British Kidney Patient Association](#)
 - [Kidney Research UK](#)
 - [National Kidney Federation](#)
 - [British Renal Society](#)
 - [British Transplantation Society](#)
 - [ESPRIT](#)
 - [Renal Association](#)
 - [Royal College of Physicians](#)
 - [NHS England](#)
 - [Health Improvement Scotland](#)
 - [Chiesi](#)

A 'no comments' response was received from the Department of Health and Roche Products

3. **Comments on the Appraisal Consultation Document from experts:**
 - [Mr Colin Wilson](#) – Clinical Expert nominated by Cochrane Renal Group
4. **Comments on the Appraisal Consultation Document received through the NICE website**
5. **New evidence submitted by Astellas:**
 - [Data supporting the effectiveness of prolonged-release tacrolimus](#)
 - [Comments on the Assessment Report](#)
6. **[Assessment Group critique of the additional evidence](#)** from Peninsula Technology Assessment Group (PenTAG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Confidential until publication

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Astellas Pharma Limited	<p>Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We have provided our main responses below under the specific ACD consultations questions with additional comments listed in Table 1. Data demonstrating the benefits of prolonged-release tacrolimus are provided in Appendix One. Specific comments on the Assessment Group Report are provided in Appendix Two.</p> <p>Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>No.</p> <p>We are surprised that the provisional recommendations limit patient and clinician choice when the Committee acknowledges that <i>'immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people'</i> and clearly understood <i>'the value of choice of immunosuppressive therapies'</i> (ACD Section 4.56).</p> <p>We consider that, despite the Committee's acknowledgement that a choice of therapies are required, a number of issues with the data provided within the Assessment Report along with the sole reliance on randomised controlled trial data has resulted in provisional recommendations which actually limit choice and are not a suitable basis for guidance to the NHS. The NHS has invested a significant amount of money (£17,000) in each kidney transplant and the provisional recommendations are not optimising this investment. Limiting treatments potentially consigns more patients to dialysis costing £30,000 per year and returns patients to a waiting list that is already under increasing pressure. Donors and their families also make a significant emotional investment and deserve the full treatment options available to optimise their graft outcomes.</p> <p>Our key concerns relate to:</p> <ul style="list-style-type: none"> The reliance on the non-inferior endpoints from a single clinical study, to infer a clinical benefit in favour of immediate-release tacrolimus over prolonged-release tacrolimus, which is not methodologically appropriate or seen in clinical practice. Specific non-significant outcomes were selected and extrapolated (graft loss, mortality and new onset diabetes after 	<p>Comment noted.</p> <p>Comments noted.</p> <p>Comments noted. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness RCT evidence had been taken</p>

Consultee	Comment [sic]	Response
	<p>transplant [NODAT]) while the costs associated with other significant endpoints e.g. bacterial infection were ignored.</p> <ul style="list-style-type: none"> The inconsistent use of drug acquisition costs based on discounted prices for immediate-release tacrolimus taken from the Commercial Medicines Unit's (CMU) Electronic Market Information Tool (eMit) and the use of a second separate data source (BNF) for the prolonged-release tacrolimus (Advagraf) list price, despite the inclusion of Advagraf on a National Tender, negotiated with the NHS CMU. The lack of consideration of RCT (Kuypers <i>et al.</i>¹) and non-RCT data and the resulting lack of recommendations for potential patient subgroups who may benefit from specific treatment regimens including prolonged-release tacrolimus. <p>These issues are discussed in more detail below.</p> <p>The inclusion of non-significant efficacy and safety endpoints and the exclusion of significant findings Non-significant, short- term efficacy and safety endpoints (including graft loss and mortality, the two most important long term outcome measures) have been used to infer clinically significant differences between immediate and prolonged-release tacrolimus while significant findings that favour prolonged-release tacrolimus have not been fully considered. Taken together, these suggest that the NICE recommendations are based on inappropriate and incomplete evidence. The approach taken within the meta-analysis performed by the Assessment Group is inappropriate and misleading with regard to the inclusion of non-significant findings from a fixed-effects "meta-analysis" of non-inferiority.</p> <p><u><i>Inclusion of non-significant outcomes</i></u> <i>Death and graft loss</i> Within the meta-analysis of death or graft loss only data from Krämer <i>et al.</i> 2010² (Krämer study) inform the analyses. There are a number of issues with how the</p>	<p>into account.</p> <p>Comments noted. The Committee concluded that its preferred analysis used eMIT prices when available and the prices agreed though the Commercial Medicines Unit where this information was made available (Modigraf and Advagraf). See section 4.63 of the FAD</p> <p>Comment noted. The Committee considered the additional evidence received during consultation (see section 4.55 of the FAD). The AG highlighted that the study by Kuypers <i>et al.</i> (2013) had a number of strengths, but also weaknesses, which limited its generalisability. See section 4.65 of the FAD.</p> <p>Comment noted. The Assessment Group highlighted that point estimates and confidence intervals from non-inferiority trials are just as valid as point estimates and confidence intervals from superiority trials – the study objective affects the power calculations but fundamentally the trial design is unchanged. Uncertainty in the relative effectiveness is appropriately propagated through the economic model in the probabilistic sensitivity analyses. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account. See section 4.60 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>data from this study was used:</p> <ul style="list-style-type: none"> The Krämer study was only powered to demonstrate non-inferiority with regard to biopsy-confirmed acute rejection at 24 weeks, yet the Assessment Group analysis uses the intent-to-treat (“overall”) population to model differences in patient and graft survival, instead of the more appropriate per-protocol analysis. Use of this population misses a QALY benefit for the prolonged-release tacrolimus cohort. <p>We would further add that the use of data derived from intent-to-treat populations in meta-analyses of non-inferiority studies is not widely accepted^{3,4}</p> <ul style="list-style-type: none"> The data used in the Assessment Group model includes follow-up from the open-label extension of this study (i.e. data at 12 months post-transplantation after 28 weeks of unblinded follow-up) and the findings of differences in graft loss and patient mortality at 12 months which were not statistically significant (p=0.53 and p=0.61 respectively). This is inappropriate. <p><i>NODAT</i></p> <p>Non-significant NODAT data (from Krämer <i>et al.</i>² and Tsuchiya <i>et al.</i>⁵) was included to infer a clinical difference between immediate-release and prolonged-release tacrolimus.</p> <p>However, we would like to raise a concern that, despite the non-significant difference between tacrolimus formulations, NODAT is the second largest driver of the cost difference between the two formulations in the model second only to the cost of the drug acquisition. Further information on this, which the Committee may wish to consider, is provided in Appendix One and which demonstrates rates of NODAT with prolonged-release tacrolimus (Advagraf) are lower in a UK clinical setting than that reported in the literature for immediate-release tacrolimus.⁶</p> <p>It is unthinkable that the Medicines and Healthcare Products Regulatory Agency (MHRA) would have given a Market Authorisation to prolonged-release tacrolimus (Advagraf), if the incidence of reported adverse events were significantly different to those of immediate-release tacrolimus so as to cause safety concerns.</p> <p><u>Exclusion of significant outcomes</u></p> <p>We would also like to reiterate that the exclusion of significant outcomes from the Krämer <i>et al.</i> study² unfairly biases the analysis in favour of immediate-release</p>	<p>Comment noted. The Assessment Group highlighted that the inclusion of new-onset diabetes after transplant was justified on the basis that there is a significant increase in incidence in diabetes in the first year post-transplantation and as such can be detected in RCTs with limited follow up. The Committee heard from the clinical experts that the lower maintenance doses may be associated with a decrease in the incidence of new-onset diabetes. The Committee accepted that the maintenance therapy dosages and the clinical outcomes associated with them in the AG’s model were based on clinical trials.</p> <p>Comment noted. The Committee understood that the clinical experts were not aware of any additional</p>

Consultee	Comment [sic]	Response
	<p>tacrolimus. The most notable significant outcome overlooked in the Krämer study by the Assessment Group was the incidence of:</p> <ul style="list-style-type: none"> Bacterial infections (22.6% versus 16.0% with immediate-release tacrolimus and prolonged-release tacrolimus respectively; p=0.032) <p>On the basis of the above we recommend a re-analysis of the graft loss and mortality based on the per protocol population in the Krämer study.²</p> <p><u>Inconsistent use of list price</u></p> <p>We would challenge the use of drug acquisition costs taken from the Commercial Medicines Unit's (CMU) Electronic Market Information Tool (eMit) and recommend that, in order to ensure consistency, transparency and time-proof the guidance only list price is used, the approach taken by the All Wales Medicines Strategy Group (AWMSG) in their recent appraisal of Envarsus (extended-release tacrolimus).⁷</p> <p>Drug acquisition costs taken from the CMU eMit are subject to change and the data is updated only every six months. Within the CMU Tender framework agreements, there are potential pricing reviews at the end of an agreed period and relevant termination clauses which make it difficult to confirm which:</p> <ul style="list-style-type: none"> Product will be the most cost effective over time should suppliers amend pricing, and Prices apply over the timeframe of NICE guidance. <p>In addition eMit data used to calculate the average cost paid by the NHS for immediate release tacrolimus capsules is usually only used for generic products and relies upon hospital trusts submitting the data and the relevant data being uploaded. There can be gaps in these hospital data and they do not always include Outsourced Pharmacy and Homecare usage (which can comprise around 60%) depending on whether the data goes through the hospital systems which is a significant route for administration of tacrolimus. In addition since eMit data is only updated every 6 months with the last update being in December 2014 (see https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit) the data used is already out of date. Based on this the assumption of £0.52/mg for immediate-release has a significant risk of being inaccurate.</p> <p>We ask the Committee that in order to:</p> <ul style="list-style-type: none"> Future proof the final guidance and allow for changes in the market dynamics, product availability and tender pricing strategies of the pharmaceutical companies <u>only list prices should be considered</u> 	<p>evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account. See section 4.60 of the FAD.</p> <p>Comment noted. The Committee concluded that its preferred analysis used eMIT prices when available and the prices agreed with the Commercial Medicines Unit where this information was made available (Modigraf and Advagraf). See section 4.63 of the FAD and section 5.5.2 of the NICE Guide to the methods of technology appraisal.</p> <p>The Committee has considered all CMU price agreements where this information was provided by a company. The CMU price for prolonged-release tacrolimus (Advagraf) was used by the Committee in its decision-making. See section 4.63 of the FAD.</p>

Consultee	Comment [sic]	Response
	<ul style="list-style-type: none"> • Ensure appropriate use of NHS resources; guidance states that clinicians should be directed to base their choice of treatment on that which is the most clinically effective for the individual patient with direction given to procuring the most cost effective product(s) available <p>This will enable clinicians to make choices based on individual patient need whilst putting the onus on NHSE and CMU to drive cost effective pricing and encourage increased competition.</p> <p>If, in the event that the Committee prefers to use the prices negotiated nationally by the CMU on the tacrolimus National Tender, this should be applied consistently for all formulations of tacrolimus as prolonged-release tacrolimus (Advagraf) has been awarded at a discounted price on the National Tender, effective from May 2014.</p> <p><u>Prolonged-release tacrolimus in easily identifiable patient subgroups</u></p> <p>We note, as stated above, that the Committee has already acknowledged that some treatments may be particularly beneficial for individual people or groups of people but are concerned that due to the reliance on only RCT data the Committee has not considered the clinical benefits of prolonged-release tacrolimus as a treatment option for a subgroup of patients; specifically those at risk of non-adherence or at risk of high intra-patient variability in tacrolimus trough levels.</p> <p>We disagree with the Committee’s comment that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes and that it would be difficult to identify people who would benefit (ACD, Section 4.64). In addition to the RCT (Kuypers <i>et al.</i>¹) on adherence included in our submission but excluded by the Assessment Group, there is in fact robust non-RCT evidence that supports the use of prolonged-release tacrolimus as a treatment option and which should not be disregarded. These data provide real world evidence on the effectiveness of prolonged-release tacrolimus in clinical practice.</p> <p>Given the evidence available prolonged release tacrolimus should be recommended as a treatment option for patients at increased risk of rejection or graft loss due to non-adherence and/or high variability. Both groups of patients are easily identifiable in clinical practice using current procedures and tools, such as adherence questionnaires and routine blood monitoring and no change to clinical practice would be required. We would also highlight that this subgroup of patients only includes around 30% of patients eligible for treatment with tacrolimus.</p> <p>Effective treatment of these patients is essential in order to ensure that therapeutic levels of tacrolimus are maintained within a narrow therapeutic window. If therapeutic levels are too low, the patient is at risk of organ rejection. Conversely, if</p>	<p>Comment noted. The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas’s approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee considered the additional evidence received during consultation on the appraisal consultation document from Astellas regarding the study by Kuypers et al (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p>

Consultee	Comment [sic]	Response
	<p>levels are too high, over-immunosuppression can result in an increased risk of malignancy, infection and/or nephrotoxicity. In some patients variability occurs where their levels of tacrolimus fluctuate above and below the therapeutic window – this is referred to as intra-patient variability. High levels of intra-patient variability have been shown to be associated with an increased risk of renal graft failure^{8,9,10} with the relative risk of graft failure in these patients 2.38 times higher than in those with low variability⁸. Non-adherence is a significant problem in 20-30% transplant patients¹¹ and is a key cause of intra-patient variability. In patients treated with tacrolimus non-adherence results in variable therapeutic levels and an increased risk of graft failure.¹²</p> <p>Prolonged-release tacrolimus has demonstrated improved adherence and reduced variability in tacrolimus exposure.^{1,13-18} In addition prolonged-release tacrolimus is associated with preserved renal function over time with data available up to 3 years post-transplant.¹⁹ Following agreement with NICE further details of the key studies are provided in Appendix One along with proposals on how the Assessment Group can model adherence.</p> <p>We request that the Committee reviews this evidence and reconsiders recommending prolonged-release tacrolimus in patients identified as non-adherent or at risk of intra-patient variability.</p> <p>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p>No. We consider that the evidence provided in Krämer <i>et al.</i>² and Tsuchiya <i>et al.</i>⁵ have not been interpreted appropriately, as the analysis was extrapolated from endpoints that were not statistically significant, from 24 weeks of blinding out to 50 years. The costs in the model were incorrect, biased in favour of immediate release tacrolimus, all points as documented above.</p> <p>Has all of the relevant evidence been taken into account?</p> <p>No. There are three considerations:</p> <ul style="list-style-type: none"> • Exclusion of significant outcomes from a RCT (Krämer <i>et al.</i>²) • Exclusion of the Kuypers study¹ • The lack of consideration of non-RCT data <p>These points demonstrate that not all relevant and key evidence has been taken into account resulting in provisional recommendations which limit patient and clinician choice and which are not a suitable basis for guidance to the NHS.</p> <p>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual</p>	<p>Comment noted. The Committee concluded that the AG's model was the most informative model for decision-making. It agreed that it was appropriate to use prices from eMIT, if available, because these reflect the prices paid by the NHS (see NICE's guide to the methods of technology appraisal section 5.5.2). See section 4.63 of the FAD.</p> <p>Comment noted. The Committee noted that</p>

Consultee	Comment [sic]	Response
	<p><i>orientation, age, gender reassignment, pregnancy and maternity?</i></p> <p>By limiting patient and clinician choice the provisional recommendations reduce the clinician's ability to tailor treatment to each individual patient and deny patients access to effective treatment.</p> <p>Patients from ethnic minorities, lower socio-economic groups and those with lower literacy levels, learning disabilities or dementia may find it difficult to manage a complex medication regimen and by not recommending medicines which have been shown to improve adherence the Committee are effectively denying these patients access to effective treatments.</p> <p>In light of the information provided, we ask that the Committee:</p> <ul style="list-style-type: none"> • Request the Assessment Group to re-run the economic model using: <ul style="list-style-type: none"> ○ Non-inferior endpoints for mortality, graft loss and risk of NODAT ○ Per-protocol population graft loss and mortality data from Krämer <i>et al.</i>² ○ Using list price for all immunosuppressive therapeutic options. • Request the Assessment Group to update the model and include the effects of non-adherence in line with our recommendations in Appendix One • Considers the RCT and non-RCT data provided for prolonged-release tacrolimus and following this reconsiders recommending prolonged-release tacrolimus in the specific subgroup of patients identified as non-adherent or at risk of high intra-patient variability <p>We look forward to discussions at the next Committee meeting on 4th November 2015. In the intervening period please do not hesitate to contact [REDACTED] if you require any further information.</p> <p>Table 1: Additional comments</p>	<p>improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas's approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee noted additional evidence received during consultation on the appraisal consultation document from Astellas regarding the study by Kuypers <i>et al</i> (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD). Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended for routine funding in the NHS to prevent organ rejection in adults having a kidney transplant. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective. These drugs were either dominated (they had higher costs and worse outcomes) or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained.</p>

Consultee	Comment [sic]		Response
	ACD Section	Comment	
	2.3	In addition to the factors listed immunosuppressive therapy also aims to prevent death from graft failure in addition to the points raised. We would recommend the text is revised as follows: 'Immunosuppressive therapy aims to prevent acute rejection, and optimise the function of the transplanted kidney <u>and prevent death from graft failure</u> , while minimising the adverse effects of immunosuppression	Comment noted. This paragraph is a brief description of the aim of treatment. No change required.
	3.13	In line with our comments above we ask that only list prices are used and cited.	Comment noted. The Committee agreed that it was appropriate to use prices from eMIT, if available, because these reflect the prices paid by the NHS (see NICE's guide to the methods of technology appraisal section 5.5.2). See section 4.63 of the FAD.
	3.16	Further clarification is required on why Envarsus (tacrolimus extended-release tablets, MA granted June 2014) was excluded from the final scope of the appraisal while everolimus (Certican, MA granted November 2014) was included when both had not received Marketing Authorisation prior to the final scope being issued.	Comment noted. NICE was not made aware that the company was intending to submit a marketing authorisation application for Envarsus at the time that the final scope was issued. NICE was only made aware of this mid-way through the appraisal. NICE were made aware of the anticipated marketing authorisation's for both everolimus and belatacept and these were considered through NICE's topic selection function. NICE subsequently received a formal referral from the Department of Health to appraise these drugs.
	4.9	RCT comparisons of immediate and prolonged-release tacrolimus were powered for non-inferiority. The key issue is that the non-inferiority design cannot be used to infer the presence or absence of superiority. We recommend the text is amended as follows: 'Comparison of immediate-release and prolonged-release tacrolimus (plus mycophenolate mofetil) showed no consistent <u>statistically clinically</u> significant differences'	Comment noted. The FAD has been amended to reflect this. See section 4.9 of the FAD.

Consultee	Comment [sic]	Response
	<p>4.24 Living with a kidney transplant is a long-term condition and on this basis it is not appropriate to extrapolate data from the 24 week blinded phase of RCTs to 50 years. We would also repeat our concern on the use of non-significant data to inform the model.</p>	<p>Comment noted. It is often necessary to extrapolate data beyond the duration of the clinical trials and to consider the associated uncertainty (see 5.1.16 of the NICE guide to the methods of technology appraisal). The Committee was aware from the Assessment Group that there is limited long-term evidence from randomised controlled trials and that there was uncertainty.</p>
	<p>4.31 The Assessment Group assumption that corticosteroid use is continuous in a maintenance regimen is flawed. Clinical experts present at the Appraisal Committee meeting indicated that steroid use is intermittent and as short term as possible. Consideration should be given to the impact of intermittent and short-term use on any calculations used to predict steroid side effects in the long term.</p>	<p>Comment noted. The Assessment Group acknowledged that there were limitations and uncertainties in its analysis. It stated that its analysis did not consider changes in graft function over time, the effect of corticosteroid reduction, differences in the severity of acute rejection, stopping or switching treatment (including delayed introduction of sirolimus) or the effect of medication adherence, and did not fully model all adverse events. Committee concluded that the Assessment Group's model was the most informative model for decision-making. See sections 4.54 and 4.64 of the FAD.</p>
	<p>4.37 The current text in the 5th bullet point is misleading. In order to reflect the true situation we ask that the text is amended as follows: "Astellas noted that the model did not consider the effect of adherence. The Assessment Group considered that there was limited <u>RCT evidence to inform decision making</u>, and recommended caution in using this surrogate outcome.</p>	<p>Comment noted. The FAD has amended accordingly. See section 4.37 of the FAD.</p>
	<p>4.40 Omission of ciclosporin did not affect interpretation of the results of the Astellas model, as the publication of the full Astellas model [Muduma et al 2014] was used by the Assessment Group to inform their interpretation. The drug dosages used in the Astellas model reflect current clinical practice.</p>	<p>Comment noted. This paragraph reflects the concerns of the Assessment Group. No change required.</p>
	<p>4.54 We note that the Assessment Group did not model adherence and that there was insufficient evidence to support subgroup</p>	<p>Comment noted. The Committee understood that</p>

Consultee	Comment [sic]	Response
	<p>analysis. We have recommended consideration of non-RCT data on adherence in a specific subgroup of patients eligible for treatment with prolonged-release tacrolimus and modeling considerations which will assist in addressing both these issues.</p>	<p>the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness RCT evidence had been taken into account. See section 4.60 of the FAD.</p>
4.58	<p>The statement about the additional evidence should be amended as follows to reflect the qualification of the consideration of only RCT evidence: ‘The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness <u>RCT</u> evidence had been taken into account’.</p>	<p>Comment noted. The FAD has amended accordingly. See section 4.60 of the FAD.</p>
4.63	<p>The statement ‘calcineurin inhibitors are associated with nephrotoxicity’ is inaccurate and does not acknowledge the fact that tacrolimus is <u>NOT</u> overly nephrotoxic. In patients treated with tacrolimus renal function is maintained and stable over significant periods of time.^{19,20} We would also like to reiterate to the Committee that the doses of calcineurin inhibitors used in the RCTs and used in the AG model are not the doses used in current clinical practice, which are lower, following the publications of the landmark SYMPHONY study.^{21,22} As a point of accuracy the current text should be amended as follows: ‘In particular, calcineurin inhibitors are associated with nephrotoxicity, and, The Committee heard from the clinical specialists that about 5% of people develop nephrotoxicity soon after transplant and more develop it over a longer period.’</p>	<p>Comment noted. The summary of product characteristics for caclineurin inhibitors each refer to the potential for nephrotoxic effects of these agents. No change required.</p>
4.64	<p>We note that the Committee highlighted ‘that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy’. For a slow clearance drug like tacrolimus it would not be the acute effect of missing a single dose that would impact on the consistency of immunosuppression. What would be important is the deviation from total adherence over a period of time. With a once daily formulation, taken in the morning, greater consistency in adherence is seen than with a twice daily formulation and this has been demonstrated to be true in general²³ and also</p>	<p>Comment noted. Considering all the evidence, the Committee concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain. See section 4.65 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>specifically for prolonged-release tacrolimus.¹</p> <p>Full list of references are not included here. These are presented in the Astellas response to consultation, which can be found in the Committee papers.</p>	
<p>Bristol-Myers Squibb</p>	<p>Thank you for your invitation to comment on the Appraisal Consultation Document (ACD).</p> <p>Bristol-Myers Squibb are disappointed that belatacept is not recommended as a treatment option to prevent organ rejection in adults having a kidney transplant despite the fact that it may offer benefits to particular sub-group of patients as noted within the ACD.</p> <p>We acknowledge that in the ACD the estimated incremental cost-effectiveness ratio (ICER) for belatacept in the total population is above the threshold that NICE would consider suitable for recommendation. However, a subgroup analysis was presented by BMS to demonstrate the possibility of appraising the evidence for belatacept for specific groups of patients where belatacept is a clinically- and cost-effective treatment option. The use of belatacept in specific subgroups was supported by clinicians who identified that 5% of patients develop nephrotoxicity to calcineurin inhibitors (CNIs) soon after transplant and more develop it over time. The belatacept regimen is a CNI-free regimen and may therefore be an option for this group of patients.</p> <p>As noted by clinicians, currently individual funding requests (IFRs) are required in order for patients to access belatacept and in some circumstances, access can be delayed. This leads to unequal access across the UK.</p> <p>We acknowledge that there is limited evidence available for specific subgroups. Consideration of belatacept restricted for those patients that lack alternative treatment options would be of benefit to these patients. Therefore we encourage the Committee to reconsider its proposed recommendation and to recommend belatacept for specific subgroups noted in the ACD and identified by clinicians.</p> <p>Finally we confirm that we have not identified any factual inaccuracies in the ACD or</p>	<p>Comment noted. The Committee highlighted that belatacept was associated with ICERs ranging from £241,000 to £424,000 per QALY gained, compared with immediate-release tacrolimus, sirolimus and ciclosporin, and that these ICERs were substantially higher than the range normally considered cost effective. The Committee concluded that belatacept is not a cost-effective use of NHS resources.</p> <p>The Committee understood that sirolimus is routinely commissioned by NHS England for nephrotoxicity. The Committee heard from clinical experts that belatacept could be a treatment option for a small number of people who develop thrombotic microangiopathy during treatment with tacrolimus, ciclosporin, sirolimus or everolimus. The Committee recognised that sirolimus and belatacept could potentially be cost-effective in these circumstances because the only alternative would be haemodialysis. However, the Committee had not seen evidence supporting the clinical or cost effectiveness of belatacept in this situation and recognised that clinical trial evidence would be difficult to obtain. The Committee concluded that it was not able to make recommendations for people whose treatment needs to be withdrawn as a result of thrombotic microangiopathy. See section 4.76 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>the economic model.</p> <p>We would be grateful if you would consider the points that we make in this response prior to the meeting of the Appraisal Committee on Wednesday 4th November 2015.</p>	
<p>Novartis Pharmaceuticals UK Limited</p>	<p>We would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on this appraisal. Having reviewed the Appraisal Consultation Document (ACD), Novartis Pharmaceuticals UK Ltd (Novartis) would like to comment on two specific areas: the relationships between health utilities and renal function and the need for alternative options in certain patient subgroups. Specific issues relating to these areas are outlined below:</p> <p>Link between health utilities and renal function</p> <p>In the ACD, the NICE Appraisal Committee recognised and understood that Novartis used a different approach to modelling utilities to that used by the Assessment Group (AG). It was also acknowledged by the AG, in the assessment report and the ACD, that one of the main strengths of Novartis' model is its account of the effect of renal function on health-related quality of life (QoL) and that this is one of the AG model's limitations (pp 365 ERG report; pp 31 of ACD). The AG's modelling approach excludes any association between utility and renal function and does not reflect the available peer-reviewed evidence, so the appropriateness of this approach could, therefore, be interpreted as perverse in the light of the available methodological evidence.</p> <p>There is also recognition in the ACD that cost-effectiveness in renal transplantation is highly sensitive to the method used to estimate health state utilities. Furthermore, it was acknowledged at the Appraisal Committee meeting on 7 July 2015 that the reference cited for modelling utilities by the AG supported the utility values used; however, this reference did not support the methodology used by the AG.</p> <p>Modelling of health state utility by the AG involved estimating a baseline utility for each patient based on age and gender, with a disutility applied for functioning graft, dialysis or new-onset diabetes after transplantation (NODAT). In contrast, the method used by Novartis linked kidney function (assessed by the estimated glomerular filtration rate) to utility (Neri 2012). The method used by Novartis is more clinically justifiable, as it accounts for a number of disease states, which capture the</p>	<p>Comment noted. The Committee considered that Novartis's analyses implied that the benefits had been underestimated for all treatments, and would be most underestimated for treatments with the largest beneficial effect on eGFR (such as belatacept plus mycophenolate mofetil and tacrolimus plus azathioprine). The Assessment Group acknowledged the company's approach to modelling utility based on graft function, noting that this was a limitation in the AG's model. However, the AG emphasised that there is too much uncertainty in the medium and long-term changes in kidney function to be confident that Novartis's approach is better. The Committee concluded that the AG's model provided a robust analysis of cost effectiveness and was the most informative model for decision-making. See sections 4.48 and 4.63 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>wide variation in QoL associated with a functioning graft, and the long-term nephrotoxicity of calcineurin inhibitors (CNIs), which can affect renal function; thus, it enables the model to be more sensitive to changes in the patient's health. Patients enter the model with a similar utility value in both analyses; however, the approach adopted by Novartis observes a faster decline in utility, reflecting the deteriorating kidney function in transplant patients. Patients in the AG model with a functioning graft follow a pattern of utility changes reflective of the natural decline in QoL in the general population; only a small utility decrement is applied to the QoL of patients with a kidney transplant. The AG's model is structurally insensitive to the differences between the technologies and regimens in terms of their impact on renal function. This insensitivity was noted in discussions at the committee meeting held on 7 July 2015.</p> <p>Moreover, the approach taken by Novartis is based on a tested methodology that clearly found chronic kidney disease (CKD) severity was negatively associated with the EQ-5Dindex in a sample of UK patients (Neri 2012), while a further study found that impaired renal function is associated with worse self-reported outcomes after kidney transplantation (Neri 2011). Neri 2012 was cited by the AG in its report when critiquing the fact that some of the literature identified had not allowed for the impact on health-related QoL (pp 334 of the assessment report), but this was not used by the AG in its model. In addition, in the recently updated NICE guideline for CKD (NCGC 2014), different utility values were assigned to patients at different CKD stages, further supporting the approach that declining kidney function affects the QoL of patients and is the most appropriate method to modelling health utilities for this patient population.</p> <p>The AG correctly noted that there may be some uncertainty associated with the Novartis approach during the later years of model extrapolation. However, all models in renal transplantation are characterised by uncertainty, and non-linearity was also found in the AG model. This uncertainty has been interrogated through the use of probabilistic sensitivity analysis. We request the Committee recommends a re-design to the AG's model, to account for the association of renal function with utilities, incorporating the resultant ICERs in its decision-making. Results of such a re-designed model would offer a fair reflection of the evidence for cost-effectiveness of an initial approach to maintenance therapy.</p> <p>Alternative treatment options for subgroups of patients</p>	<p>Comment noted. The Committee noted that the final</p>

Consultee	Comment [sic]	Response
	<p>In the ACD, NICE has effectively recommended only one treatment combination for maintenance therapy in patients with a renal transplant. This recommendation does not account for patients for whom either tacrolimus or mycophenolate mofetil (MMF) are clinically inappropriate. These subgroups include patients at risk of intolerance to CNIs due to nephrotoxicity (Ponticelli 2011, Pascual 2009), patients with gastrointestinal (GI) disturbances (Ponticelli 2005, Shehata 2009) and patients at high risk of cytomegalovirus (CMV) infection (Vitko 2005, Tedesco Silva 2010 and 2013). In such patients, a regimen of immediate-release tacrolimus, combined with MMF and steroids cannot be considered as a realistic option for a cost-effectiveness comparison, as it is not the most appropriate clinical option for these patients. Published evidence (referenced above) and clinical experience demonstrate that certain subgroups of patients will benefit from alternative therapeutic options.</p> <p>If the ACD recommendations were to be carried forward unchanged to final guidance, the result could be a reduction in five-year graft survival for these groups of patients, as they would be unsuitable for the only reimbursed immunosuppressive regimen. It is well recognised that there is an ethical duty to the transplant recipient, the donor and their families to preserve transplanted organs and we anticipate it is not the intention of NICE to produce final recommendations, which could worsen long-term outcomes in kidney transplantation.</p> <p>Novartis, therefore, requests that NICE reconsiders its recommendations by making available alternative treatment options in subgroups of patients for whom tacrolimus or MMF are clinically inappropriate, with the following arguments in mind:</p> <ol style="list-style-type: none"> 1. NICE noted in the ACD (pp 44) that there are no noticeable differences in clinical effectiveness between enteric-coated mycophenolate sodium (EC-MPS) and MMF; hence, if patient outcome alone is taken into consideration, EC-MPS should be used instead of the currently recommended MMF, as it has a better GI safety profile (Ponticelli 2005, Shehata 2009). 2. In patients for whom MMF is clinically inappropriate due to GI disturbances or intolerance, EC-MPS should be used instead of MMF. 3. In patients at high risk of CMV infection, treatment with everolimus should be considered as an option instead of tacrolimus. <p>Novartis has previously submitted cost-effectiveness analyses and clinical evidence</p>	<p>guidance would apply to the interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone, which were included as comparators only.</p> <p>The Committee recognised that there is a need for other treatment options, such as sirolimus, in the event of nephrotoxicity caused by calcineurin inhibitors. The Committee also noted that a small number of people develop thrombotic microangiopathy during treatment with tacrolimus, ciclosporin, sirolimus or everolimus. In this latter situation clinicians highlighted that belatacept is the only immunosuppressant that might be effective in these circumstances. However, the Committee had not seen evidence supporting the clinical or cost effectiveness in these situations and recognised that obtaining clinical trial evidence would be difficult. It therefore was unable to make recommendations for these technologies in these subgroups See sections 1.4, 4.75 and 4.76 of the FAD.</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that, 'Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.'</p> <p>In addition, 'Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.' The</p>

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	<p>to support the consideration of these subgroups and while we agree with the AG that there is a greater level of uncertainty associated with these analyses, such uncertainty does not lessen the need for additional recommendations appropriate to those subpopulations of patients.</p> <p>We challenge NICE's decision to recommend only one maintenance regimen with no tailoring to the clinical needs of patient subpopulations. Treatment options for renal transplant patients have become well established over time and allow transplant patients to live for an increased number of years with a better QoL, optimising graft survival and use of the precious resource of donated kidneys. We welcome continued dialogue with NICE on this technology appraisal to keep options available for renal transplant patients.</p> <p>Full list of references are not included here. These are presented in the Novartis response to consultation, which can be found in the Committee papers</p>	<p>recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p>
Sandoz Ltd	<p>We would like to take this opportunity to thank the National Institute for Health and Care Excellence (NICE) and the Appraisal Committee for their time and commitment to this submission process.</p> <p>Upon reviewing the Appraisal Consultation Document (ACD), Sandoz Ltd welcomes the Appraisal Committee's preliminary recommendations regarding immediate-release tacrolimus (TAC) products.</p> <p>Sandoz Ltd wishes to comment upon one area of the ACD:</p> <p>1. National tender agreement</p> <p>The ACD reports that Advagraf (a prolonged-release TAC product) is available at a discounted price through a national tender agreement [Page 6 Section 3.16]. Sandoz Ltd notes that Adoport is also available to all UK hospitals at a discounted price through a national tender agreement. It is requested that NICE considers also referencing the availability of this discounted price for Adoport into the ACD.</p>	<p>Comment noted. The FAD has been amended accordingly. See section 3.10 of the FAD.</p>
Sanofi	<p>Sanofi welcomes the opportunity to provide comments on the Appraisal Consultation</p>	<p>Comment noted. The Committee noted comments</p>

Consultee	Comment [sic]	Response
	<p>Document (ACD) for the above appraisal. We have structured our comments in line with the questions for consultation. We are concerned that the Appraisal Committee was unable to support a positive recommendation for rATG, even in the patient group they believe it may offer particular clinical utility; i.e. those at high risk of acute rejection. The Appraisal Committee explains that they take this view because there is insufficient evidence, yet make no specific reference to the good quality RCT examining treatment effectiveness in this group. In combining the effectiveness from all trials of rATG, including patients with various risk levels, the evidence for this higher risk group may have been overlooked in the Appraisal Committee's deliberations. We would therefore request that the Appraisal Committee consider again the available evidence in patients at high risk and review their recommendation for rATG.</p> <p>Response to the ACD: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)</p> <p>Sanofi welcomes the opportunity to respond to the Appraisal Consultation Document (ACD). We have structured our comments in line with the specific questions posed by NICE. In addition a number of minor comments on the ACD are noted at the end of this document.</p> <p>1. Has all the relevant evidence been taken into account?</p> <p>As highlighted by ourselves and other consultees, and in line with the international KDIGO guidelines (KDIGO 2009), rATG may be particularly beneficial in patients with a high risk of acute rejection. Although the ACD acknowledges that rATG may be beneficial in high risk patients it states that there is insufficient evidence on which to base specific recommendations for this population. Sanofi believes that there is indeed robust evidence available to support a recommendation for rATG in patients at high risk of acute rejection. This evidence is summarised below.</p> <p>A relatively large (278 patients), well designed, RCT has compared rATG to basiliximab (Brennan 2006). The trial specifically only included patients at high risk of acute rejection or delayed graft function. The Brennan trial demonstrated that patients who received rATG induction experienced a lower rate of acute rejection when compared to those who received basiliximab induction (Brennan 2006). No differences in terms of mortality or graft loss were identified. The key results from the Brennan trial are provided in the table below. Although studies of daclizumab (another IL-2 receptor antagonist) are not in scope for this appraisal, it should be noted that comparisons of rATG with daclizumab, also in a high risk population, are</p>	<p>received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee considered the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p>

Consultee	Comment [sic]	Response																
	<p>consistent with the Brennan findings (Noël 2009).</p> <p>Table 1: Results from the Brennan 2006 trial (basiliximab vs. rATG)</p> <table border="1" data-bbox="432 344 1155 555"> <thead> <tr> <th></th> <th>OR*</th> <th>Lower 95% CI</th> <th>Upper 95% CI</th> </tr> </thead> <tbody> <tr> <td>Mortality</td> <td>1.03</td> <td>0.32</td> <td>3.28</td> </tr> <tr> <td>Graft loss</td> <td>1.28</td> <td>0.51</td> <td>3.19</td> </tr> <tr> <td>BPAR</td> <td>1.86</td> <td>1.02</td> <td>3.37</td> </tr> </tbody> </table> <p>*An OR greater than 1 favours rATG</p> <p>The Assessment Group's analysis of rATG combined studies that recruited patients with very different risk profiles, and as different risk groups might be expected to have different outcomes the resulting effect size is both imprecise and uncertain. Both of the studies comparing rATG to no induction were conducted in patients with a mixed risk status (Charpentier 2001; Charpentier 2003) and the further two studies comparing rATG to basiliximab were conducted in patients with low/moderate risk status (Lebranchu 2002; Mourad 2004). We believe that the data for high risk patients should be considered in a separate analysis, particularly as it is in this population that rATG is currently used in clinical practice.</p> <p>Sanofi request that the Appraisal Committee reconsider the available evidence for rATG in patients specifically at high risk of acute rejection where the benefits of rATG are likely to be more manifest.</p> <p>2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?</p> <p>Clinical-effectiveness</p> <p>As outlined above Sanofi believes that combining studies that recruited patients with different risk profiles generates unnecessary uncertainty and would suggest that the Appraisal Committee consider the available evidence for patients at high risk of acute rejection. rATG induction has been shown to significantly lower the risk of acute rejection when compared to basiliximab induction, in this patient group (Brennan 2006).</p>		OR*	Lower 95% CI	Upper 95% CI	Mortality	1.03	0.32	3.28	Graft loss	1.28	0.51	3.19	BPAR	1.86	1.02	3.37	<p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee noted the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned</p>
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	<p>Cost-effectiveness</p> <p>Sanofi would like to highlight a number of issues with respect to the assessment of cost-effectiveness which are outlined below.</p> <ol style="list-style-type: none"> Sanofi propose that an analysis of cost-effectiveness based on the results of the Brennan trial could feasibly be conducted and would enable the Appraisal Committee to consider providing a recommendation for rATG in high risk patients. The present cost-effectiveness results are associated with a high degree of uncertainty as they rely on efficacy estimates derived from meta-analyses that incorporate studies that recruited patients with very different risk profiles. An analysis incorporating the results of the Brennan trial (Table 1) would likely demonstrate that rATG is a cost-effective treatment for high risk patients when compared to basiliximab. The Appraisal Committee concluded that basiliximab and rATG have similar efficacy. However, this is at odds with the results of the economic model that indicate that basiliximab is associated with more QALYs than rATG. This appears to be driven largely by an assumed difference in graft function at 12 months between basiliximab and rATG. Importantly this assumption is based on the results of one study (in a low/moderate risk population) that did not find a statistically significant difference in terms of graft function between basiliximab and rATG (Lebranchu 2002). To explore the impact of this assumption, we propose that a sensitivity analysis is conducted that explores the impact of assuming that rATG and basiliximab have equal graft function at 12 months. Changing this single assumption could dramatically reduce the ICERs for rATG versus no induction to levels where rATG would either dominate or be associated with ICERs less than £20,000/QALY (depending on the maintenance regimen used). Furthermore this single modification could mean that rATG was no longer dominated by basiliximab. The Assessment Group's analysis assumes that CMV prophylaxis costs are greater for patients treated with rATG induction. Sanofi believe that this assumption is questionable. As highlighted by a consultee (Page 949 of the committee papers) the prophylaxis and monitoring of CMV is likely to be variable and could differ in centres where rATG is used routinely, and/or at different doses. As seen in the older trials (Charpentier 2001 and 2003) typically higher doses of rATG are used, resulting in approximately 30% CMV infection rates. The more recent Brennan 2006 trial (which used a 	<p>whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p> <p>Comment noted. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. See section 4.67 of the FAD.</p> <p>Comment noted. The Assessment Group highlighted that studies by Lebranchu et al. (2002) and Mourad et al. (2004) reported differences in graft function and time to acute rejection in favour of basiliximab (compared with r-ATG), although the results were not statistically significant. There was no evidence to suggest a statistically significant difference between r-ATG and basiliximab for mortality, graft loss or graft function.</p> <p>Comment noted. The Assessment Group highlighted that this is not a major driver of the model results. The Committee concluded that the Assessment Group's model was the most informative model for decision-making. See sections 4.37 and 4.63 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>lower dose in line with current practice) reported a 7.8% rate of CMV infection, with prophylaxis provided for patients who were seropositive or were receiving a seropositive graft. Of note here, the basiliximab group, who were treated equivalently in terms of prophylaxis, reported a CMV infection rate of 17.5%. It appears contrary to the evidence available that the higher cost for CMV prophylaxis associated with rATG induction versus no induction can be justified, and we propose that CMV prophylaxis costs should be equal to those for no induction and those for basiliximab. The impact of such a modification to the AGs model would likely result in a 15-30% reduction in the incremental costs associated with rATG (depending on the comparison) and in combination with the modifications suggested above would further improve the cost-effectiveness of rATG.</p> <p>The Assessment Group's scenario analyses were limited to those exploring the impact of alternative drug acquisition costs and structural assumptions regarding the surrogate effects of acute rejection, NODAT and graft function on graft survival. Sanofi believe that the additional sensitivity/scenario analyses outlined above would provide important information on the potential for rATG to be a cost-effective treatment option for patients who have a high risk of acute rejection. In particular we believe that a scenario analysis based on the Brennan 2006 data would provide the most informative assessment of the relative cost-effectiveness of rATG.</p> <p>Sanofi would like to emphasise that under plausible conditions it is likely that rATG could be considered cost-effective for the subgroup of kidney transplant patients that are considered high risk.</p> <p>3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>The 2014/15 NHSBT activity report demonstrates that there is a high risk population of patients in the UK. The report shows that there were over 500 transplants from cardiac death donors in patients with level 3 or level 4 HLA mismatch (NHSBT 2015). This is clearly a group of patients who are at high risk who would potentially benefit from having the option of rATG induction. The KDIGO guidelines, which are followed by a group of UK transplant clinicians, recommend the use of ATG induction for these patients (KDIGO 2009). The proposed 'not recommended'</p>	<p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee noted the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p> <p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee noted the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in</p>

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	<p>guidance for rATG would deny patients who are at high risk of experiencing acute rejection access to a clinically and cost-effective treatment option.</p> <p>4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</p> <p>None known.</p> <p>Minor comments</p> <table border="1" data-bbox="432 639 1424 1321"> <thead> <tr> <th data-bbox="432 639 931 671">Section</th> <th data-bbox="931 639 1424 671">Comment</th> </tr> </thead> <tbody> <tr> <td data-bbox="432 671 931 919">Section 4.5 of the ACD highlights the non-significant results of two of the three trials comparing rATG to basiliximab (Lebranchu 2002; Mourad 2004) but fails to highlight the significant result in terms of acute rejection from the third study (Brennan 2006).</td> <td data-bbox="931 671 1424 919">We recommend that in order to present a balanced view of the available data the results of the Brennan 2006 trial should be highlighted here.</td> </tr> <tr> <td data-bbox="432 919 931 1321">In section 4.61 the ACD states that kidney transplants from living donors have become more common in recent years.</td> <td data-bbox="931 919 1424 1321">We would like to highlight that the latest report from the NHSBT states that kidney transplants from living donors accounted for 35% of kidney transplants in the last year (April 2014 - March 2015). The number of transplants from deceased donors has increased from 1526 in 2005/2006 to 2069 in the last year (2014/15) with the number of cardiac death donors increasing from 128 to 510 over the same time frame (NHSBT 2015).</td> </tr> </tbody> </table> <p>References</p> <p>Full list of references are included in the Sanofi response to consultation which can</p>	Section	Comment	Section 4.5 of the ACD highlights the non-significant results of two of the three trials comparing rATG to basiliximab (Lebranchu 2002; Mourad 2004) but fails to highlight the significant result in terms of acute rejection from the third study (Brennan 2006).	We recommend that in order to present a balanced view of the available data the results of the Brennan 2006 trial should be highlighted here.	In section 4.61 the ACD states that kidney transplants from living donors have become more common in recent years.	We would like to highlight that the latest report from the NHSBT states that kidney transplants from living donors accounted for 35% of kidney transplants in the last year (April 2014 - March 2015). The number of transplants from deceased donors has increased from 1526 in 2005/2006 to 2069 in the last year (2014/15) with the number of cardiac death donors increasing from 128 to 510 over the same time frame (NHSBT 2015).	<p>both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p> <p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee noted the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p> <p>Comment noted. No change required.</p>
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Consultee	Comment [sic]	Response
	be found in the Committee papers.	
<p>British Kidney Patient Association</p>	<p>The British Kidney Patient Association (BKPA) is a national charity which works to improve quality of life for kidney patients through advocacy, direct grants, educating and informing patients, counselling and funding patient-centred research, healthcare professionals and projects.</p> <p>The BKPA is very concerned about the conclusions of the Advisory Group, that just 3 drugs (basiliximab, immediate-release tacrolimus and mycophenolate mofetil) are recommended, that 6 other drugs which are currently available will no longer be recommended and that 3 further drugs presently being used have no recommendation attached to them. We believe that this will remove from kidney patients and their clinicians some really important choices to preserve their transplants. We also do not think that the conclusions take into account the costs in quality of life and side effects as well as costs to the system of the patient returning to dialysis if a transplant fails (dialysis is estimated at £30,800 pa not including transport costs, certain drugs, and the cost to carers http://www.england.nhs.uk/wp-content/uploads/2014/04/a07-renal-transpl-ad-0414.pdf and the costs of a failed transplant at £17,000).</p> <p>A kidney transplant is a scarce resource and considered the gold standard treatment for those who are fit enough to be able to receive one. The numbers of transplants fell in the year 2014/15. The strain on resources means a greater reliance on extended criteria kidneys, which need close management to ensure that they are not rejected by the recipient's immune system. The ability of a clinician to be able to use induction and maintenance therapy from the range of treatments is paramount. We do of course support the principle that a clinician should use a cost effective approach to the use of NHS resources but the current practice of swift intervention at the earliest sign of transplant rejection is testament to the increasing levels of experience and success in maintaining those with transplants.</p> <p>We note that 3 existing drugs that have been used for a long time, ciclosporin, prednisolone and azathioprine are not mentioned in the recommendations. This omission does not give clarity for kidney patients and is not explained. It would</p>	<p>Comments noted. The Committee understood the value of having a choice of immunosuppressive therapies. It considered all of the available evidence for each of the interventions included in the scope. As part of the evaluation for each intervention health-related quality of life was taken into account in the Assessment Group's (AG's) model. In addition, the AG model included the costs for managing a failed transplant including dialysis (section 4.30 of the FAD).</p> <p>Comments noted. As described in NICE's Social Value Judgements (Principles for the development of NICE guidance), those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.</p> <p>The Committee recognised that there is a particular need for additional treatment options, such as sirolimus and belatacept, when complications arise (for example, nephrotoxicity or microangiopathy) and could potentially be a cost-effective use of NHS resources in these specific situations since the only alternative would be haemodialysis. However, the Committee considered that there was not enough evidence to support recommendations in specific subgroups. Section 1.4 of the FAD specifically notes that the Committee was unable to make recommendations for important subgroups. Also see FAD sections 4.75 and 4.76.</p> <p>Comments noted. The Committee noted that the final guidance would apply to interventions listed in</p>

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	<p>therefore be possible that funding for these drugs could also be withdrawn.</p> <p>1.3, note 3 We note that the reference to shared decision making in the original NICE TA on immunosuppressant therapies from 2004 is missing from this appraisal. In this example we can find just one reference to ‘informed consent’ and none to sharing decisions with patients.</p> <p>1.4 The statement ‘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’ will mean that patient access to any of these drugs will necessitate Individual Funding Requests and processes that patients will have to go through. However if a clinician needs urgent access to these therapies the current IFR process will not work. The effect of this on transplant outcomes will be significant and unprecedented including loss of transplants, increased mortality, and greater costs elsewhere in the system, not counting the effect on society of a transplant organ being lost due to a completely inappropriate funding mechanism.</p> <p>1.5 We recommend this statement about patients currently on a range of medications ‘continue treatment until they and their NHS clinician consider it appropriate to stop’ should say ‘unless’ rather than ‘until’ as it could imply that</p>	<p>the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone which were included as comparators only. See section 4.59 of the FAD</p> <p>Comment noted.</p> <p>Comment noted. Overall, the Committee concluded that there was not enough evidence to establish whether r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus, belatacept and sirolimus are clinically effective (see FAD sections 4.67, 4.69, 4.70, 4.72-4.74). The Committee explored whether there was any clinical and cost-effectiveness evidence for specific subgroups (see 4.64, 4.75 and 4.76 of the FAD). The Committee recognised the urgency of the situation in these rare cases and that individual funding requests might not be sufficiently speedy or suitable for these situations (section 4.76 of the FAD). The recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p> <p>Comment noted. Section 1.5 states that people should be able to continue treatment and that any decision to stop should be made jointly by the clinician and the child or young person and/or their</p>

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	<p>patients will be expected to stop these medications.</p> <p>4.15 We note the AG point that the wide heterogeneity of evidence meaning that 'limited conclusions' can be made – and yet the AH did make conclusions, including some on products that were shown to be clinically effective but were not recommended.</p> <p>The BKPA notes the helpful comment in the original TA85 appraisal from 2004, that 'the drug which is the least likely to have serious side effects on that particular person should be used'. The principle of adjusting treatment to the patient has been lost from this new TA.</p> <p>The BKPA agrees with the points made by the Renal Transplant Clinical Reference Group, which is unable to make recommendations about the use of specific brands or combinations of immunosuppressant, but recommends the following principles to decide which immunosuppressants are employed in local protocols:</p> <ol style="list-style-type: none"> 1. All clinicians must make cost effective use of NHS resources. Each transplant unit should initiate and maintain immunosuppression with the most clinically cost effective regimen for that patient. 2. Multiple or frequent changes of supplier of critical dose immunosuppressants should be avoided as they can confuse transplant recipients and may lead to adverse outcomes such as acute rejection or nephrotoxicity. 3. There are sub-groups of transplant patients who may benefit from regimens that are more expensive in the short term but which may be more cost-effective in the long term by maximising graft survival. 4. This guidance should not result in only one brand of a critical dose immunosuppressant being prescribed across the country, where more than one 	<p>parents or carers. No changes required.</p> <p>Comment noted. The Assessment group is commissioned by the NHS Research and Development Health Technology Assessment (HTA) programme to produce an independent review of the evidence for technologies being appraised within the multiple technology appraisal (MTA) process.</p> <p>Comment noted. Section 1.1. to 1.3 states that the treatments are recommended as options in addition to the comparators. It is expected that clinicians would consider such factors when deciding which treatment option is most appropriate to start a patient on.</p> <p>Comments noted. The objective of the appraisal was to appraise the clinical and cost effectiveness of the interventions in the final scope. The Committee conducted this in accordance with the Guide to the methods of technology appraisal 2013 and NICE's Social Value Judgements (Principles for the development of NICE guidance).</p>

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	<p>brand is available that fulfils the current European Medicines Agency (EMA) criteria for bioequivalence, and should not be used to facilitate this position. Multiple brands are acceptable; provided cost-effectiveness is the outcome and this does not compromise patient safety.</p> <p>5. Where switching within a transplant or renal unit from one critical dose immunosuppressant to another occurs, it is recognised that support will be needed to facilitate this change. Resultant savings must be shared across the NHS including the unit where the switch is undertaken.</p> <p>6. All prescribing of critical dose immunosuppressants must be by brand name.</p> <p>We support the comments on the limitations in the way the AG has used the evidence that our colleagues at the British Renal Society have submitted.</p> <p>We take these conclusions so seriously that we would like to suggest NICE holds a further evidence session with some of the patient and professional kidney charities. The BKPA would be willing to host this if that would be helpful. As you know, we have already nominated patient experts to attend the closed sessions but we do not feel the joint concerns which patients and professionals share on this draft recommendation have been accounted for.</p>	<p>Comments noted. Patient and professional kidney charities were invited to attend the second Committee meeting and were given the opportunity to provide further evidence and comments.</p>
<p>British Renal Society</p>	<p>I write on behalf of the British Renal Society (BRS), to provide feedback on the Appraisal consultation document on immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85).</p> <p>The BRS is a federation of 16 professional and patient groups involved in kidney care including kidney transplantation. You will receive feedback from BRS member organisations however I write on behalf of our wide constituency.</p> <p>I note there are significant limitations in the literature relating to outcomes following kidney transplantation, particularly beyond the first post-transplant year. This reflects the influence of historical FDA criteria for assessing immunosuppression in the context of kidney transplantation. Understandably the advisory group limited its assessment to 86 randomised control trials of which only 11 adequately matched the population and current practice in the NHS. The limitations of these studies resulted in the development of an economic model that has significant shortcomings arising from assumptions that are described in sections 4.27 and 4.28. These shortcomings are exacerbated by significant heterogeneity in the studies used to</p>	<p>Comment noted. The FAD has been amended to state that 'The Committee concluded that the AG's model provided was the most informative model for decision-making'. There are always likely to be deficiencies in the evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. See section 3.2.2 of the NICE Guide to the methods</p>

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	<p>inform the model. It is therefore not accurate in section 4.61, to describe this model as providing a robust analysis of cost effectiveness. It may or may not be superior to other models presented by the interested parties however it must be limited by shortcomings in the data and inherent in the assumptions used beyond the first year. The model is not robust nor could it be. Indeed the limitations inherent in the assumptions made to generate this model beg the question as to whether other forms of data might provide a more valid estimate of outcome, particularly when considering groups that do not tolerate primary therapy.</p> <p>A more important concern relates to the way in which the literature has been interpreted with respect to broader clinical practice, even within the setting of the studies reported in the literature. As an example I will refer to the Symphony study, the “low dose tacrolimus” arm of which closely resembles the apparent conclusion of the appraisal: “Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as options to prevent organ rejection in adults having a kidney transplant”.</p> <p>In the Symphony study additional therapy was required in 7.5% - 30.3% of patients and the study drug was discontinued in 16.4% - 24.6% of patients. In the “low dose tacrolimus” arm 20.0% withdrew from the study protocol and the rate of discontinuation directly attributed to an adverse event, coexisting illness or treatment failure was 10.4%. The results of this and similar studies can therefore only be interpreted in the context of normal clinical practice involving the ability to change therapy according to conventional clinical indication.</p> <p>This point relates directly to the statement in section 4.61, “there is a particular need for additional treatment options when these complications arise. However (the committee) was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations”. This needs to be placed in context, that there is no such direct evidence because it would be considered unethical not to offer an alternative available medication. This is because there are logical conclusions to be made from interpretation of a series of controlled studies. For example, there is good historical evidence for substantially better outcomes using regime incorporating calcineurin inhibitors than with corticosteroids and anti-metabolites alone. There is now evidence that regime using alternative immunosuppressive agents deliver outcomes that approximate to the use of calcineurin inhibitors. Albeit that in those who can tolerate immediate-release</p>	<p>of technology appraisal.</p> <p>Comments noted. The Committee recognised that obtaining clinical trial evidence would be difficult in these circumstances. Although it understood that sirolimus was used in people who develop nephrotoxicity and belatacept was used in people with thrombotic microangiopathy, it concluded that it was unable to make recommendations for people with biopsy-proven nephrotoxicity associated with the use of calcineurin inhibitors. See sections 4.75 and 4.76 of the FAD.</p>

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	<p>tacrolimus there is a health economic argument in its favour. In those intolerant of immediate-release tacrolimus there is however a reasonable inference that these agents are effective and in all likelihood cost effective, although this has not been approached. I am concerned that the Peninsula Technology Appraisal Group does not seem to have acknowledged these issues. I note their stated position on the size and complexity of the appraisal with consequent delay to the initial meeting of the appraisal committee meeting. The narrow approach used in the analysis presented may be suitable when applied to risk factor management in the general population but its failure to acknowledge the importance of the complete patient pathway, significantly limits the real world applicability of this analysis. I doubt this shortcoming would be considered acceptable by renal transplant recipients or importantly donors and their families.</p> <p>The donor and recipient population in Symphony are somewhat different to current UK practice (for example in the number of donors after cardiac death) in such a way that it is likely that expected rates of conversion from the aforementioned recommended immunosuppression may be even higher than those described above, particularly over the course of long-term follow-up. It is therefore likely that somewhat more than 10.4% of the population will require a significant change to their immunosuppression. The reductive description of this issue as microangiopathy is sufficiently rare to be effectively managed through individual funding requests (Section 4.63), does not coherently represent the problem or solution. This is an important question because Individual Funding Requests™ will lead to significant differences in access to therapy across the jurisdiction and delay timely implementation of any necessary alteration to treatment. It does not seem appropriate that a situation likely to arise in more than 10% of the population is dealt with through IFR™s. The guidance must allow for other immunosuppressive agents to be used under appropriate expert guidance simply to be consistent with the evidence on which the advisory committee™s conclusions are based, let alone any advice from the professional groups involved in kidney care. It is not reasonable for the committee to abrogate responsibility for this matter and yet expect individual commissioners to address these questions. If the committee were so minded it might though be reasonable to mandate the prospective reporting of data on immunosuppression, to identify systematically outlying practice. There are excellent mechanisms in place through UK renal registry and NHSBT by which to do so.</p>	<p>Comment noted. The Committee recognised the need for urgency in this situation and that individual funding requests might not be suitable or approved quickly enough. The Committee recognised that obtaining clinical trial evidence would be difficult in these circumstances. Although it understood that sirolimus was used in people who develop nephrotoxicity and belatacept was used in people with thrombotic microangiopathy, it concluded that it was unable to make recommendations for people with biopsy-proven nephrotoxicity associated with the use of calcineurin inhibitors. See sections 4.75 and 4.76 of the FAD. The Appraisal Committee makes recommendations to NICE regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the Appraisal Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The Committee conducted this in accordance with the Guide to the methods of technology appraisal 2013 and NICE’s Social Value Judgements (Principles for the development of NICE guidance).</p>

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	<p>assessed adequately matched the population and current practice in the NHS. It has discounted the relevance of clinical experience and expertise, particularly with respect to the use of agents that have been in routine use for many years such as Ciclosporin (Neoral), Azathioprine and rATG which are established and effective therapies. Clinicians have gained a breadth of experience with combinations of immunosuppressive drugs outwith RCTs and non-formulary preparations, but which are nevertheless established and effective in clinical practice. The flexibility achieved with the range of preparations currently available has contributed significantly to the improved long term graft and patient survival that is being achieved and may ultimately reduce the need for re-transplantation. This in the light of the organ shortage is an important goal.</p> <ul style="list-style-type: none"> • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? <p>The majority of the RCTs used for the analysis employed a relatively short period of follow-up, and recruited highly selected low-risk transplant patients. This does not truly reflect the real world. Given the limited evidence available, clinical effectiveness of different regimens is underestimated and the cost effectiveness of the recommended regimens is overstated. Cost comparisons do not take into account the improvement in long-term outcomes that have been achieved by access to multiple agents and flexibility in prescribing for individual patients as was reflected in the ‘Symphony study’ and other similar designed studies.</p> <ul style="list-style-type: none"> • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? <p>We believe that the recommendations are highly restrictive and are neither sound nor suitable as guidance to the NHS.</p> <p>There are several clinical situations in which renal transplant experts use a wider range of immunosuppression, tailoring it to the needs of the individual patient: for example: re-introducing Ciclosporin A when appropriate, the ability to withdraw corticosteroids and use alternate regimens for patients with NODAT, Obesity, and T1DM, the use of rATG for steroid resistant rejection and as an induction agent along with Alemtuzumab for those at high risk of rejection such as the highly sensitized patients, or ABOi and HLAi transplants.</p> <p>The decision not to recommend drugs like Advagraf, Envarsus and Alemtuzumab for new patients significantly compromises the ability to tailor immunosuppressant regimens in response to complex individual patient needs. Approximately 5 to 30% of patients find adherence to a twice-daily tacrolimus regimen challenging, which, in turn, compromises the clinical effectiveness of immediate release therapy. This</p>	<p>not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone which were included as comparators only. See section 4.59 of the FAD</p> <p>Comment noted. The Committee were aware that there was limited long-term evidence from randomised controlled trials. The Assessment Group and companies each provided economic models to attempt to take into account long term benefits with the evidence available.</p> <p>The Committee considered that there was not enough evidence to support recommendations in specific subgroups (FAD sections 4.75 and 4.76)</p> <p>Comments noted. The Committee concluded that alemtuzumab should not be included as either an intervention or a comparator. The Committee noted that there were no consistent differences in clinical</p>

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	<p>significant group of patients would achieve a better clinical outcome from a prolonged-release formulation of tacrolimus based on a once-daily dosage. Advagraf is the only oral therapy under appraisal that has been shown to improve adherence and minimise the risk of transplant failure in the non-adherent and high variability cohort. The lack of acknowledgement of the proven link between adherence and graft failure is disappointing.</p> <p>While we realize that clinical trials are rarely powered for specific subgroups analysis, the use of bespoke interventions can never realistically be evaluated by clinical trials. The current recipient population in the UK is now much more heterogeneous and many fall into 'high risk' subgroups. The chronic shortage of donor organs has resulted in the increasing use of extended criteria organs for transplant. These organs require tighter management of the immunosuppressant regimen to ensure long-term graft survival.</p> <p>The statement that 'Treatment should normally be started with the least expensive product' which appears in recommendation 1.2 and 1.3 must not result in only one brand (the cheapest and least effective) being used nationally and compromise patient safety. Recommendations 1.4 and 1.5 are unrealistic and would disadvantage a significant number of patients with a profound effect on long-term outcome. Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept all allow for clinical flexibility with up to 10% of the transplant population requiring their use at some stage to prolong graft outcome.</p> <ul style="list-style-type: none"> • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination? <p>The recommendations will prejudice against women who wish to become pregnant following renal transplantation, as this requires modification of immunosuppression; it will prejudice women who are highly sensitized because of previous pregnancies and require alternative immunosuppression to reduce the risk of rejection; it will prejudice against patients with glucose intolerance.</p> <p>In summary</p> <p>The choice to recommended only Basiliximab, immediate-release tacrolimus and mycophenolate mofetil is appropriate for many patients who are undergoing a renal transplant with low immunological risk, and is in keeping with the practice of many units. However, it is overly restrictive and inappropriate given the evidence base used to support the option appraisal and we feel as a society we cannot support this. The recommendations would preclude prescribing flexibility according to inter-patient variability, immunological risk and other co-morbidities and this will have a</p>	<p>effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. See section 4.69 of the FAD. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p> <p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee considered the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. See section 4.67 of the FAD.</p> <p>Comment noted. The Committee heard that mycophenolate mofetil cannot be taken by women who are pregnant and noted that alternative treatment options are available. See section 4.79 of the FAD</p>

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	<p>direct impact on long-term patient and transplant outcomes.</p> <p>Other comments</p> <ol style="list-style-type: none"> <li data-bbox="427 284 1429 435">1. The clinical experts used by NICE did not include a nephrologist, pharmacist or nurse who are the main prescribers and monitor immunosuppressive therapy – and therefore fails to capture the views of healthcare professionals with the most direct experience of using the therapies being appraised. <li data-bbox="427 954 1429 1074">2. The Society would support the amendment of recommendation 1.4 to 'Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not routinely recommended to prevent organ rejection in adults having a kidney transplant'. <li data-bbox="427 1090 1429 1177">3. As a Society we would support a robust audit of non-recommended immunosuppressant drugs usage and outcomes, which would be beneficial to patients, clinicians and commissioners. 	<p>Comment noted. NICE has to take into account its Social Value Judgements which states that, 'Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.'</p> <p>Comments noted. As described in section 3.6 of the Guide to the processes of technology appraisal, NICE encourages all consultees and commentators to nominate clinical experts and patient experts to take part in the first Appraisal Committee meeting discussion. The Chair of the Appraisal Committee, with input from the NICE project teams selected clinical experts, NHS commissioning experts and patient experts from the nominations received. The Committee heard from these experts at each Committee meeting and also considered written submissions from each representative organisation. See section 9 of the FAD. It also considered all responses received from consultation.</p> <p>Comment noted. The Committee considered that rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept were not cost effective and were therefore not recommended to prevent organ rejection in adults having a kidney transplant. See sections 1.4, 4.67, 4.69 – 4.74 of the FAD. The recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p>

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<p>The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group</p>	<p>As an independent group, the ESPRIT Group (www.esprit.org.uk) does not advocate any particular product and our opinions, recommendations and activities are all our own. As such we could not contribute to NICE's assessment of the comparative efficacy and cost-effectiveness of individual immunosuppressants included in the MTA. However, where the efficacy and safety of treatment of transplant patients is potentially threatened, we feel it of vital importance to highlight our concerns and the principles underlying them.</p> <p>We strongly believe that the current draft guidance should be reassessed, for the following reasons:</p> <ul style="list-style-type: none"> The over-prescriptive and restrictive nature of the guidance would destroy clinicians' ability to provide tailored immunosuppression for individual transplant patients. One of the major advances of the past decades, as experience with immunosuppression has grown, has been the increasing adoption of a flexible approach to immunosuppressant management by transplant professionals. The draft guidance just does not reflect this informed best practice approach, which has undoubtedly led to today's increasing success in managing transplant patients, often over many decades of life. For example, when creatinine rises on an upward curve or a patient cannot tolerate their current regimen, immunosuppression is currently adjusted using the spectrum of immunosuppressants available. It would be a backwards move if a patient who was, for example, seriously GI-intolerant on MMF could not be tried on mycophenolate sodium or, when all other regimens had failed to provide optimum immunosuppression, that sirolimus or belatacept could not be resorted to. Non-adherence with immunosuppression regimens can be an issue in all age groups and can have real clinical implications for the integrity of transplanted organs. However, this is especially so in adolescent transplant patients, who may be classified as 'adults' technically and managed in adult services, but who have very special management needs befitting their actual age. They are sometimes seen in special young persons' clinics to try and avoid loss of organs and are very often put on once-a-day medication regimens, including prolonged-release tacrolimus, to try and maximise the likelihood of adherence. 	<p>Comments noted. As described in NICE's Social Value Judgements (Principles for the development of NICE guidance), those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them. The Committee noted that the final guidance would apply to interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone which were included as comparators only. The Committee acknowledged that there may be some subgroups of people for whom belatacept or sirolimus may provide additional benefits, but considered that there was not enough evidence to support recommendations in specific subgroups. See section 4.59 of the FAD</p> <p>Comments noted. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p>

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	<ul style="list-style-type: none"> • Whilst this ACD relates to renal transplantation, there would be a knock-on impact on other solid organ transplants if the choice of immunosuppressants funded were to be strictly limited. Certain drugs currently used routinely in e.g. liver transplants, would just become unavailable, even if they could be used in theory – to the detriment of the patients involved. • Transplantation immunosuppression is a very specialist area, with just a handful of companies investing in R&D programmes to help advance immunosuppressant practice. The potential impact on innovation generally in solid organ transplantation should not be underestimated in our opinion, at a time when the government is actively promoting wider organ donation. • We welcome the ACD acknowledgement of our previous submissions in relation to switching from proprietary brand to generic immunosuppressants, but would challenge the Committee’s conclusion that it: <ul style="list-style-type: none"> “ did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the product with the lowest acquisition cost”. The rationale for this decision is quoted as being that “clinicians are aware of the risks associated with generic prescribing and switching formulations. The Committee understood that guidance on good practice in prescribing generic immunosuppressive therapies is routinely followed in clinical practice” We would question whether all clinicians really are aware of the full risks involved in uncontrolled switching and the difference between bioequivalence in healthy volunteers and clinical equivalence in transplant patients, as laid out in our original submission. We would urge NICE to reconsider this and include something about generic immunosuppressants, if only for the true critical dose drugs – ciclosporin and tacrolimus. Failure to do this could just result in another case of organ rejection, similar to the one in 2011 when a patient lost their transplanted kidney due to clinical inequivalence between different (licensed) immediate-release tacrolimus products. • Finally, it should be recognised that the cost of immunosuppressant therapy is minimal in comparison with the overall costs of managing a transplant patient – 	<p>Comment noted. This multiple technology appraisal only considered and made recommendations on the treatments specifically for the prevention of organ rejection in adults having a kidney transplant.</p> <p>Comment noted. No evidence was presented in relation to the potential for the treatments not recommended to make a significant and substantial impact on health-related benefits that was not already considered in the QALY calculation.</p> <p>Comment noted. The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comment noted. The FAD has been amended to state that: The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least expensive product <i>when starting treatment</i> See section 4.77 of the FAD.</p> <p>Comment noted. The FAD contains a footnote to recommendation 1.2 referencing MHRA advice on prescribing and dispense oral tacrolimus by brand name only, to minimise the risk of inadvertent switching between products</p> <p>Comment noted. NICE has to take into account its</p>

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	<p>circa 5%. Whilst we totally endorse the need for cost-effective management and fully support the appropriate use of generic immunosuppressants, we urge NICE to allow flexibility for the relatively few patients who really need an immunosuppressant that is not necessarily one with the lowest direct purchase price.</p>	<p>Social Value Judgements which states that, ‘Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their ‘cost effectiveness’) when deciding whether or not to recommend them.’</p> <p>In addition, ‘Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.’</p>
<p>Kidney Research UK</p>	<p>Kidney Research UK was disappointed to learn of the NICE recommendations arising from this review. Our concern is that patient choice will be adversely affected by this decision, namely because prolonged-release technologies are no longer approved.</p> <p>On page 18 of ID456, the report states, “Once-daily (prolonged-release) tacrolimus and the once-monthly regimen for belatacept may help improve adherence.” However, with only immediate-release technologies now to be approved, patients who are more likely to benefit from prolonged-release, will be disadvantaged and may face increased risk of graft failure, especially amongst the younger patients.</p>	<p>Comments noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended</p> <p>The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective (see FAD sections 4.67, 4.69, 4.70, 4.72-4.74). The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas’s approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee considered additional evidence received during consultation on the appraisal consultation document from Astellas regarding the study by Kuypers et al (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However,</p>

Consultee	Comment [sic]	Response
	<p>On page 38, para 4.54 of ID346, it states, “The Committee also heard that it is important to minimise the side effects of immunosuppressive therapies, such as reduced growth and an increased risk of new-onset diabetes. Several submissions from consultees advised that poor adherence (that is, not taking the prescribed medication) is a major cause of graft loss, especially in young people. The Committee heard that different people have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The Committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.”</p> <p>We wonder why this view provided by the consultees is not reflected in the recommendation.</p> <p>The decision also limits the options open to clinicians to offer patients a choice of formulations in order to aid medicines compliance and adherence.</p> <p>NICE itself has produced a guideline on patient choice and adherence concerns: https://www.nice.org.uk/guidance/cg76</p> <p>And we note the emphasis on patient choice on the NHS website: http://www.nhs.uk/choiceintheNHS/Pages/Choicehome.aspx</p> <p>In responding to previous consultations we have been keen to see patient choice reflected in lessening the pill burden e.g in the area of phosphate binders. Amongst dialysis patients, non-adherence is significant; in a survey in 2010, 76% of nephrologists and 63% of dialysis staff thought non-adherence with phosphate binders was the main reason for poor control of phosphate in renal patients. These recommendations on immunosuppression do nothing to reduce the pill burden and would appear to increase it for those currently on prolonged-release treatment.</p>	<p>considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p> <p>Comment noted. Please refer to the technology appraisal for renal immunosuppression in children [ID346].</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that ‘Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.</p>
National Kidney Federation	<p>1.0 Has all of the relevant evidence been taken into account?</p> <p>There appears to be a lack of evidence given that only 11 trials adequately matched the search criteria. Given this fact how valid can the recommendations be when they are serious concerns from stakeholders such as us?</p> <p>2.0 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p>	<p>Comments noted. The Committee noted that the AG’s systematic review was comprehensive and found a large number of randomised controlled trials. It concluded that all the relevant clinical effectiveness evidence had been taken into account. See section 4.60 of the FAD.</p> <p>There are always likely to be deficiencies in the</p>

Consultee	Comment [sic]	Response
	<p>Our concern is around interpretations made from poor quality evidence available, and therefore how valid the summaries of clinical and cost effectiveness can be when the primary evidence is lacking.</p> <p>3.0 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>From our assessment the view of the NKF is that these preliminary recommendations are too restrictive and do not allow flexibility of treatment that will provide the most effective way of preventing rejection in a diverse patient group – we find this deeply concerning. We firmly believe that for such a specialised area of healthcare standardised protocols are not always suitable and the proposed recommendations are potentially damaging for patients requiring unique and tailored protocols.</p> <p>We firmly believe it is essential NICE guidance on the use of immunosuppressive therapy maximises the rate of success for every single kidney transplant and acknowledges the huge difference a successful transplant can make to an individual, their family, wider society and the NHS.</p> <p>As such we firmly believe that our patients should be supported, according to their individual need and tolerability, to enable both the best clinical outcome possible that will enable sustained life and quality of life.</p> <p>Kidney transplantation for those who are suitable is the best possible treatment for end stage kidney failure. The gift of life provided either by deceased or living donation although considered priceless, does have a cost. First year cost estimates</p>	<p>evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. See section 3.2.2 of the NICE Guide to the methods of technology appraisal.</p> <p>Overall, the Committee concluded that there was not enough evidence to establish whether r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus, belatacept and sirolimus were clinically effective (see FAD sections 4.67, 4.69, 4.70, 4.72 - 4.74). The Committee explored whether there was any clinical and cost-effectiveness evidence for specific subgroups (see 4.64 of the FAD). The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4, 4.75 and 4.76).</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that, 'Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.'</p> <p>In addition, 'Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.'</p>

Consultee	Comment [sic]	Response
	<p>are broad ranging dependent on what is included; a cost up to 20k would be conservative with yearly follow-up cost significantly less and dependent on the maintenance protocol usually estimated at 5k/year. While significant, these costs together with the gains in quality of life undercut the yearly 30k cost of dialysis hugely over a five year period.</p> <p>Assessing whether the provisional recommendations are sound and of a suitable basis for guidance to the NHS cost, outcomes and patient choice are essential considerations and influence our response accordingly.</p> <p>We have assessed the appraisal committee's preliminary recommendations. We broadly support recommendations 1.1 1.2 & 1.3.</p> <p>However in its' current form there are a number of concerns which are principally drawn from recommendations contained within 1.4 & 1.5 which appear both unworkable and damaging in terms of choice and individualisation to patient need.</p> <p>We find the report/recommendations perplexing. The committee state that they "understand the value of having a choice of immunosuppressive therapies" (section 4.56), however they provide such a narrow view that there is in effect no choice for our patients or at least presumably no choice that will be funded.</p> <p>For patients who cannot tolerate Tacrolimus and/or MMF and began to see worrying signs of an increasing creatinine there appear to be no options to tailor their drug regimen.</p> <p>For new patients with their first skin malignancy there is now, it would appear, no option of using Sirolimus.</p>	<p>Comment noted. This topic was considered as a multiple technology appraisal through the Technology Appraisal Programme. The Appraisal Committee makes recommendations to NICE regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the Appraisal Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The Committee conducted this in accordance with the Guide to the methods of technology appraisal 2013 and NICE's Social Value Judgements (Principles for the development of NICE guidance). It was not developed as a clinical guideline (which is a different centre within NICE) which make evidence-based recommendations on the overall management of a specific disease area.</p> <p>Comment noted. The Committee had not seen evidence supporting the clinical or cost</p>

Consultee	Comment [sic]	Response
	<p>The NKF strongly believe the inclusion of prolonged release Tacrolimus should be reconsidered. We feel omission would significantly compromise the ability of clinicians to individualise drug regimens to complex individual need.</p> <p>For those in transition and young adults in particular adherence to twice daily tacrolimus has been reported as challenging, especially the evening dose, which compromises treatment and long-term graft survival.</p> <p>Failure to recommend prolonged release Tacrolimus for new kidney patients could potentially result in up to 30% of patients missing out on a drug which makes it easier to take (reducing pill burden) and therefore significantly improves adherence, optimising the likelihood of graft survival.</p> <p>The NKF campaigns for the best treatment and access to services for patients and their carers. Improving access to transplantation and rates of organ donation in the UK is a central strand of our campaigning. There remains a shortage of organs available for transplantation and we believe every single opportunity should count to make a difference to the individual in need and validate the act of organ donation. To that end premature graft failure results in unnecessary suffering and distress as patients return to dialysis and the transplant waiting list. It is our opinion that there are presently (and in the future no doubt) drugs available which reduce the chances of failed grafts which in the long-term are cheaper than cost associated with dialysis. The widely reported total annual cost of dialysis is in the region of £30k.</p> <p>The chronic shortage of donations has resulted in the increasing use of more marginally viable organs for transplant. These organs require increased management of the immunosuppressant regimen to ensure long-term graft survival. We therefore question the validity of recommendations 1.4 & 1.5 and omissions of other drugs that may future proof this guidance.</p> <p>Ciclosporin, Azathioprine and Prednisolone have not been included within the recommendations even though both drugs are in common use. Prednisolone and azathioprine are used in new and maintenance transplant populations. Most centres will have protocols which use tacrolimus however there are instances where patients still need to be switched to Ciclosporin. Similarly a number of centres use azathioprine as the anti-proliferative of choice in low risk patients, which is cheaper than generic MMF. There are also clinical situations where MMF needs to be switched to azathioprine - such as pregnancy or gastrointestinal complications. We</p>	<p>effectiveness of sirolimus in this situation.</p> <p>Comment noted. The Committee noted that prolonged-release tacrolimus was dominated by both immediate-release tacrolimus and ciclosporin in the AG's economic analyses. It considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However considering all the evidence, the Committee concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain. See section 4.65 and 4.69 of the FAD.</p> <p>As part of the evaluation for each intervention, the Assessment Group model included the costs for managing a failed transplant including dialysis (section 4.30 of the FAD).</p> <p>Comment noted. The Committee noted that the final guidance would apply to the interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone, which were included as comparators only. See section 4.59 of the FAD.</p>

Consultee	Comment [sic]	Response
	<p>therefore strongly urge a recommendation that states these drugs can still be used.</p> <p>4.0 Any other comments</p> <p>None</p>	
<p>Renal Association</p>	<p>I write on behalf of the Renal Association in response to the above consultation. The Renal Association is the Professional Body of UK Renal Physicians & Scientists, representing the UK Renal Unit Clinical Directors, the UK Renal Registry & the Renal Research Community. Its members are responsible for the clinical management of patients before and for long term care following kidney transplantation including the critical & complex issue of immunosuppression.</p> <p>We congratulate the AG on extensively reviewing RCTs in this area and developing a financial model to guide the process. However, the Renal Association does not believe that the proposed guidance is fit for purpose for use by the UK Renal Transplant community as it stands & requests significant revision.</p> <p>The guidelines summary recommends the use of 'basilixumab induction, immediate release tacrolimus (least expensive product) & Mycophenolate mofetil (least expensive product). 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'.</p> <p>This guideline proposal represents a restrictive & substantial departure from previous guidance, NICE technology appraisal guidance 85 (2004). The recommendations which are solely based on randomised controlled trials, do not reflect the many clinical complexities of the transplant pathway, nor the requirement for considerable clinical experience of the transplant community to achieve optimum clinical outcomes. Inevitably surrogate measures of long term outcomes are used & a financial model based on acquisition costs for immunosuppressant drugs that are not applicable to many Trusts has led to inevitable conclusions. We believe the guidelines to:</p> <p>1. Be too restrictive in recommended immunosuppressant drug usage so as to inadequately cover the broad range of clinical status of donor kidneys and transplant recipients.</p>	<p>Comments noted.</p> <p>Comment noted. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness RCT evidence had been taken into account. See section 4.60 of the FAD.</p> <p>Comment noted. There are always likely to be deficiencies in the evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. See section 3.2.2 of the NICE Guide to the methods of technology appraisal.</p> <p>Overall, the Committee concluded that there was not enough evidence to establish whether r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus, belatacept and sirolimus are clinically effective (see FAD sections 4.67, 4.69, 4.70, 4.72-4.74). The Committee explored whether there was any clinical and cost-effectiveness evidence for specific subgroups (see 4.64 of the</p>

Consultee	Comment [sic]	Response
	<p>2. To be clinically unworkable particularly where there is a need to change initial post-transplant immunosuppressant therapy (up to 1 in 5); the IFR mechanism is suggested but is not appropriate to deal with up to 20% of the 3121 transplants in 2014.</p> <p>3. Be inconsistent. Immunosuppressive therapy for kidney transplant in children and young people (review of technology appraisal guidance 99) states ‘an alternative product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension’. Young adults, 16-18y may be transplanted in either adult or paediatric units or transfer shortly after to adult care if the latter.</p> <p>Renal transplantation is the optimal treatment for suitable patients with end stage</p>	<p>FAD). The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4, 4.75 and 4.76). The Committee recognised the urgency of the situation in these rare cases and that individual funding requests might not be sufficiently speedy or suitable for these situations (section 4.76 of the FAD). The recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p> <p>Comment noted. The Committee recognised the need for urgency in this situation and that individual funding requests might not be suitable or approved quickly enough. See section 4.76 of the FAD. The Committee recognised that obtaining clinical trial evidence would be difficult in these circumstances. Although it understood that sirolimus was used in people who develop nephrotoxicity and belatacept was used in people with thrombotic microangiopathy, it concluded that it was unable to make recommendations for people with biopsy-proven nephrotoxicity associated with the use of calcineurin inhibitors. See sections 4.75 and 4.76 of the FAD.</p> <p>Comment noted. The recommendations have been updated to state that treatment can be started with an alternative dosage form if the person is not able to swallow capsules as a result of a disability. See section 1 of the FAD.</p> <p>Comment noted. The Committee considered that there are likely to be some subgroups of people for</p>

Consultee	Comment [sic]	Response
	<p>renal failure (ESRF), being associated with improved quality of life & longevity as well as substantially reduced costs compared with dialysis treatment. Transplant kidneys are heterogeneous, originating from deceased donors (brain stem death or cardiac death) of standard or extended criteria or from live kidney donors. The recipients have a wide range of aetiology of ESRF, variable comorbidities & age from young to older adults & immunological rejection profile. Randomised controlled trials have simply not adequately covered the breadth of clinical scenarios commonly encountered in clinical practice. As such highly restrictive prescribing guidance based on these trials could not be expected to cover the whole scope of clinical practice. The guidance states: 'The Committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups'.</p> <p>'The Committee understood that some treatments are associated with complications and so must be avoided or withdrawn for some people. The Committee was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations.' Lack of published subgroup data from RCTs in such a complex clinical area does not equate to no effect. In these situations experienced clinical knowledge must be cautiously exercised rather than deny access to other therapies in a blanket fashion. We note, 'The AG emphasised that there was not enough evidence available for robust sub group analysis.' We believe that more flexibility in use of immunosuppression is required in the final guidance. Tailoring of treatment to the patient based on RCT evidence AND clinical experience, where not covered by RCT evidence is surely a reasonable clinical approach. Commissioning by evaluation, where Trusts are required to report immunosuppression treatment and outcomes in this group through NHSBT/UK Renal Registry returns may be an approach to improve the evidence base.</p> <p>The guidelines do not sufficiently address what happens to patients who do not tolerate or have prior contraindications to the recommended immunosuppression. In routine clinical practice a substantial minority of patients are intolerant of initial therapy & require drug changes. Drug trials in this area report up to 20% of patients unable to tolerate an initial drug regime. Reasons include drug allergy, gastrointestinal intolerance, bone marrow suppression, CNI-induced thrombotic microangiopathy, drug adherence issues, nephrotoxicity to name but a few. In these</p>	<p>whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. Therefore the Committee concluded that it was unable to make recommendations for any of the interventions in specific subgroups. See section 4.64 of the FAD.</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that, 'Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.'</p> <p>This topic was considered as a multiple technology appraisal through the Technology Appraisal Programme. The Appraisal Committee makes recommendations to NICE regarding the clinical and cost effectiveness of treatments for use within the NHS. It is also the role of the Appraisal Committee not to recommend treatments if the</p>

Consultee	Comment [sic]	Response
	<p>settings alternative therapies including mTOR inhibitors, belatacept, and prolonged-release tacrolimus must be available to the clinical team often at short notice. There is good clinical experience of the effectiveness of conversion to these other agents in this setting. Guidance comments only on CNI-induced microangiopathy and that drug change in this situation could be managed by the IFR route. This is wholly inadequate. Most of post-Transplant immunosuppressant drug changes are for other reasons. There were 3,121 renal transplants performed last year. Let us say 15% of incident patients required immunosuppression drug change (over 450 cases) and 3% of prevalent patients (900 cases) per annum, the IFR system is wholly unsuitable to manage. The IFR system is slow & could not possibly cope (nor was designed) with the clinical timescale, often required within 1 day. The resources required of NHEngland and of each transplant Unit merit close thought. We believe that a broader initial guidelines would obviate the need for many IFR requests which is not a suitable route to manage the patient numbers.</p> <p>The age of greatest risk of transplant loss is between 14 and 25 years. This loss relates to challenges in adherence to immunosuppression. The Care Quality Commission & Renal Association documents the need to provide greater focus and support on this high risk group. This includes tailoring immunosuppression in some cases to improve adherence. Recent data confirm improved outcomes for young adults post transplantation by individualised care, part of which includes focus on immunosuppression. The current guidance limits ability to do this. It is highly unlikely that a formal RCT will be sensitive enough to extract the influence of tailored drug therapy from the other aspects of young adult care.</p>	<p>benefits to patients are unproven, or if the treatments are not cost effective. The Committee conducted this in accordance with the Guide to the methods of technology appraisal 2013 and NICE's Social Value Judgements (Principles for the development of NICE guidance). It was not developed as a clinical guideline (which is a different centre within NICE) which make evidence-based recommendations on the overall management of a specific disease area.</p> <p>The Committee recognised that there is a need for other treatment options, such as sirolimus or belatacept, when such complications arise. The Committee recognised the need for urgency in this situation and that individual funding requests might not be suitable or approved quickly enough. However., the Committee had not seen evidence supporting the clinical or cost effectiveness of these treatments in these specific situations and recognised that clinical trial evidence would be difficult to obtain. The Committee concluded that it was not able to make recommendations for people with biopsy-proven nephrotoxicity associated with the use of calcineurin inhibitors or for people whose treatment needs to be withdrawn as a result of thrombotic microangiopathy. See section 4.75 and 4.76 of the FAD for more details.</p> <p>The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas's approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee noted additional evidence received during consultation on the appraisal consultation document from Astellas</p>

Consultee	Comment [sic]	Response
	<p>We are worried by the statement that that treatment should be started with the least expensive product of mycophenolate mofetil and immediate release tacrolimus. There are many formulations of both & complete equivalence have not been shown. It is recognised good practice that patients should not transfer between these formulations of the same drug. Patients become very anxious about preparation exchange of these lifesaving drugs & increased pharmacokinetic monitoring is required. We believe that the statement should be qualified so as to ensure that primary care or pharmacists do not repeatedly change from one formulation to another as costs change.</p> <p>We are rather surprised that ciclosporin is not mentioned as a suitable first line agent. Whilst acute rejection rates are higher than for tacrolimus treated transplants, the risk of post-transplant diabetes is lower and a substantial proportion of prevalent patients receive the micro-emulsion & a smaller number the original Sandimmun formulation. Is exclusion of mentioning azathioprine, a widely used transplant immunosuppressant intentionally omitted?</p> <p>The guideline identifies no significant difference in efficacy or side effect profile of mycophenolate mofetil or mycophenolate sodium. The latter is not recommended on cost grounds. Would an approach whereby guidance suggests the use of either, whichever formulation has the lowest cost be a reasonable approach? By doing so the guidelines will be more future proof should the relative price of either change?</p> <p>In summary, we support the development of updated renal transplant IS guidelines by NICE. The draft guidance is not sufficient to support expert clinical practice. The limitation on recommended baseline IS taken together with the lack of an adequate mechanism (or guidance) for tailoring IS where drug changes are required</p>	<p>regarding the study by Kuypers et al (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p> <p>Comment noted. The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products</p> <p>Comment noted. This guidance considers the use of basiliximab, rabbit anti-human thymocyte immunoglobulin, tacrolimus (immediate-release and prolonged release), mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept after kidney transplant in adults. The final guidance would apply to these interventions and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone, which were included as comparators only. See FAD section 4.59.</p>

Consultee	Comment [sic]	Response
	necessitates significant amendment.	
Royal College of Physicians	<p>The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 31,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.</p> <p>I'm writing to confirm that the RCP would like to endorse the Renal Association's response to the above consultation.</p>	Comments noted.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Cochrane Renal Group	<p>Personal Response Statement</p> <p>Thank you for the opportunity to comment on the preliminary report of the Health Technology Appraisal. As the adult and child appraisals reach broadly the same conclusions I will make general comments applicable to both.</p> <p>On reading the report I am struck by the “competitive” nature of the analyses and consideration. One drug is considered to “outperform” or “dominate” its competitors. However, clinical transplantation is not competitive. The choice of drugs is about finding the best option for individual patients to maximise their longevity, quality of life and graft survival- albeit considering cost as well. In making their deductions I am not sure how keenly the committee have remembered that the option for patients who do not have transplantation is to remain on dialysis- which is a far more costly treatment. Unfortunately, as far as I am aware, none of the randomised controlled trials or studies included in the analysis have “stay on dialysis” as one of the treatment arms. From studies, not considered by this appraisal, we can conclude that transplantation is a highly cost-effective treatment for patients with end stage renal failure and on this basis any immunosuppressant that facilitates this treatment could be considered cost-effective.</p> <p>Comments on individual recommendations</p> <p>1.1 Yes this is a highly accepted treatment with a wide evidence base which has proven to be safe and effective.</p>	<p>Comment noted. ‘Dominance’ is a health economic term. For example, if an intervention is dominated, it has higher costs and worse outcomes than an alternative intervention.</p> <p>It considered all of the available evidence for each of the interventions included in the scope. As part of the evaluation for each intervention health-related quality of life was taken into account in the Assessment Group’s (AG’s) model. In addition, the AG model included the costs for managing a failed transplant including dialysis (section 4.30 of the FAD). Committee considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. Therefore the</p>

Nominating organisation	Comment [sic]	Response
	<p>1.2 This is a well balanced statement which summarises a wealth of literature and forms the baseline for current modern immunosuppressive practice.</p> <p>1.3 As for 1.2</p> <p>1.4 I do not agree with this statement. Rabbit anti-thymocyte (ATG) immunoglobulin is a highly effective immunosuppressant which in your cost-effective analysis is out performed by Basiliximab in some population analyses. For some patients with broad donor reaction profiles and multiple antibodies ATG may be the <i>only</i> option to allow retransplantation to go ahead. “Incompatible” kidney transplantation relies on ATG induction to be available (133 transplants in 2013/14, NHS Blood and Transplant) and without this costly dialysis will remain the only option. Likewise the MTOR inhibitors sirolimus and everolimus may be the only option to allow patients with a history of malignancy to be safely transplanted. In the recently published 3C trial sirolimus was part of the most efficacious treatment group with the best renal function 1 year after randomisation. To discount this treatment as “not recommended” is a distortion and to emphasise population cost rather than individual clinical effectiveness. For example if a single patient with a history of malignancy is successfully transplanted using sirolimus maintenance therapy rather than staying on dialysis then this is cost effective as well for the NHS.</p>	<p>Committee concluded that it was unable to make recommendations for any of the interventions in specific subgroups. See section 4.64 of the FAD.</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that, ‘Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their ‘cost effectiveness’) when deciding whether or not to recommend them.’</p> <p>In addition, ‘Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.’</p> <p>Comment noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended for routine funding in the NHS to prevent organ rejection in adults having a kidney transplant. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective. These drugs were either dominated (they had higher costs and worse outcomes) or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained (see FAD sections 4.67, 4.69, 4.70, 4.72-4.74). The Committee explored whether there was any clinical and cost-effectiveness evidence for specific subgroups (see 4.64 of the FAD). The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4, 4.75 and 4.76). The Committee recognised the urgency of the situation</p>

Nominating organisation	Comment [sic]	Response
	<p>1.5 I am not sure as to the value of this statement unless the vision of this document is to deny certain patient groups access to kidney transplantation (immunological “high risk”, drug induced Haemolytic Uraemic Syndrome, diabetic gastroparesis, patients with learning disabilities, patients with high risk of malignancy, retransplantation).</p> <p>If the Health Technology Appraisal is looking to maintain access for patients to transplantation then a fairer way of phrasing 1.4 would be like this:</p> <p>“Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as <i>first line agents</i> to prevent organ rejection in adults having a kidney transplant. They should only be considered when the alternative for an individual patient is to either remain on dialysis or have suboptimal immunosuppression which could be expected to lead to graft loss”.</p>	<p>in these rare cases and that individual funding requests might not be sufficiently speedy or suitable for these situations (section 4.76 of the FAD). The recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p> <p>Comment noted. Section 1.5 is necessary to clarify that people already on one of these treatments should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. Comment noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended for routine funding in the NHS to prevent organ rejection in adults having a kidney transplant. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective. These drugs were either dominated (they had higher costs and worse outcomes) or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained (see FAD sections 4.67, 4.69, 4.70, 4.72-4.74).</p> <p>The recommendation does not prevent the use of these technologies. In the absence of specific recommendations and evidence from NICE, NHS organisations are expected to use existing arrangements to access the publicly available</p>

Nominating organisation	Comment [sic]	Response
	<p>In response to your specific questions: <i>Has all of the relevant evidence been taken into account?</i> I think the Committee should take additional note of the fact that the alternative to transplantation is a far more costly treatment.</p> <p><i>Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</i> Yes, when comparing one drug regimen with another, but not including some drug regimens (Campath, Rituximab etc) and lack of trial comparisons against dialysis has led to flawed conclusions.</p> <p><i>Are the provisional recommendations a suitable basis for guidance to the NHS?</i> 1.1, 1.2 and 1.3 yes. 1.4 and 1.5 no for the reasons outlined above. No mention of ciclosporin or azathioprine.... Is this an oversight ??</p> <p><i>Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion, sexual orientation, age, gender reassignment,</i></p>	<p>evidence and to determine local policies for the use of a drug in circumstances outside of a NICE appraisal.</p> <p>As part of the evaluation for each intervention, the Assessment Group model included the costs for managing a failed transplant including dialysis (section 4.30 of the FAD).The Committee recognised that there is a particular need for additional treatment options, such as sirolimus and belatacept, when complications arise (for example, nephrotoxicity or microangiopathy) and could potentially be a cost-effective use of NHS resources in these specific situations since the only alternative would be haemodialysis. However, the Committee considered that there was not enough evidence to support recommendations in specific subgroups. Section 1.4 of the FAD specifically notes that the Committee was unable to make recommendations for important subgroups. Also see FAD sections 4.75 and 4.76.</p> <p>The Committee was aware that alemtuzumab does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and is not routinely available for transplant patients (it is available on a 'named patient' basis). It was therefore not included in the scope for this appraisal</p> <p>Comment noted. The Committee noted that the final guidance would apply to the interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone, which were included as comparators</p>

Nominating organisation	Comment [sic]	Response
	<p><i>pregnancy and maternity ?</i></p> <p>Mycophenolate is contraindicated in pregnancy and maternity. Currently we would use azathioprine. Black and minority ethnic transplant populations are more likely to receive a poorly matched graft and require ATG induction. Older patients (> 70) have a different immune response and the recommended regimen of basiliximab, tacrolimus and mycophenolate mofetil in this group may lead to an excess of infections and malignancies. Currently evidence is lacking but this is an evolving field as the recipient age continues to rise.</p> <p>Patients with learning disabilities are a challenging group who can sometimes only be managed with parenteral immunosuppression (basiliximab, belatacept) to ensure compliance.</p>	<p>only.</p> <p>The Committee heard from clinical experts that mycophenolate mofetil cannot be taken by women who are pregnant and noted that alternative effective treatment options are available. The Committee understood that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and noted that a number of effective treatment options are available. The Committee concluded that, when prescribing immediate-release tacrolimus or mycophenolate mofetil, treatment should normally be started with the least expensive product. However it further concluded that treatment could be started with an alternative dosage form if the adult is not able to swallow capsules because of a disability.</p>

Comments received from commentators

Commentator	Comment [sic]	Response
Department of Health	No comment	No action required.
Chiesi Limited	<p>Marketed product: Envarsus[®] (tacrolimus (as monohydrate)) prolonged release tablets</p> <p>Commercial in confidence information is highlighted in blue</p> <p>Academic in confidence information is highlighted in yellow</p> <p>Thank you for the opportunity to comment on this Consultation. Please find our responses to the Consultation questions below. In summary we have four main concerns:</p> <ul style="list-style-type: none"> The analysis did not include data on all prolonged-release (PR) tacrolimus 	<p>Comment noted. The Committee considered</p>

Commentator	Comment [sic]	Response
	<p>and therefore the conclusions cannot apply to all PR-tacrolimus. In particular there is evidence of reduced treatment failures in key subgroups (older patients, black patients) with Envarsus (tacrolimus as monohydrate) compared to immediate-release (IR) tacrolimus as well as a different impact on CNS tolerability with improved quality of life compared to IR-tacrolimus. These factors would contribute to different evaluations in a pharmacoeconomic (PE) model</p> <ul style="list-style-type: none"> • Some of the assumptions within the pharmacoeconomic model are flawed and therefore the recommendations based on the outputs of that model are flawed • The proposed guidance does not accord with other NICE guidance (CG76 Medicines Adherence and CG138 Patient experience in adult NHS services) • The methodology is contradictory with regard to the rationale behind the inclusion/exclusion of different products which is potentially discriminatory <p>Responses to the specific questions in the ACD are as follows:</p> <p>1. Has all of the relevant evidence been taken into account?</p> <p>1.1 The AG decided to use only RCTs in the assessment and in particular, not to use pharmacokinetic (pk) studies. This approach is limited in three ways:</p>	<p>evidence from the Assessment Group and the consultees. The brand name Envarsus was not included in the AG's search for evidence and Chiesi was not asked to submit evidence as part of the appraisal. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account. The Committee considered all consultation responses to the ACD in developing the final appraisal determination. No action required.</p> <p>Comment noted. The Assessment Group acknowledged that there were limitations and uncertainties in its analysis. It stated that its analysis did not consider changes in graft function over time, the effect of corticosteroid reduction, differences in the severity of acute rejection, stopping or switching treatment (including delayed introduction of sirolimus) or the effect of medication adherence, and did not fully model all adverse events. The Committee concluded that the Assessment Group's model was the most informative model for decision-making. See sections 4.54 and 4.64 of the FAD. The Committee noted that the AG's systematic review was comprehensive and found a large number of randomised controlled trials. It concluded that all the relevant clinical effectiveness evidence had been taken into account. See section 4.60 of the FAD</p> <p>Comment noted. The Assessment Group highlighted that point estimates and confidence</p>

Commentator	Comment [sic]	Response
	<p>1.1.2 Firstly, many RCTs have a limited duration (1-2 years) so would not necessarily detect differences that may be seen over the lifetime of a graft (say 10 years).</p> <p>1.1.3 Secondly, RCTs are not always powered to detect differences between treatments. Regulatory studies are typically powered for 'non-inferiority'.</p> <p>1.1.4 Thirdly, looking specifically at calcineurin inhibitors (CNIs), nephrotoxicity is a complex interplay between acute toxic effects, cumulative exposure and the level of immunosuppression. Put plainly, too much drug damages the kidney, not enough drug and the immune system damages the kidney. There is a strong correlation between whole blood levels of tacrolimus and nephrotoxicity [Przepiorka 1999, Bottiger 1999]. Not all tacrolimus formulations are the same. Even where bioequivalence has been demonstrated between different IR tacrolimus products, differences in pk could have an impact on long-term outcomes. For example, for equivalent oral dose and trough levels, Tacni® (Teva) had a significantly higher ($p < 0.01$) Cmax of $30.2 \pm 11.6 \mu\text{g/L}$ compared to $19.6 \pm 6.6 \mu\text{g/L}$ with Prograf® (Astellas) (ratio 1.49. 90% confidence interval 1.35-1.65) [Robertsen 2015]. This difference would not be seen in routine monitoring which measure trough levels, yet in this study, resulted in peak tacrolimus levels substantially over 20ng/ml which could have a deleterious effect on long-term renal function.</p> <p>1.1.5 So in the absence of long-term trials, for products with a narrow therapeutic window, it would be prudent to use a wider scientific evidence base to help guide choices of treatment that could have meaningful long-term impacts on graft and patient survival and on graft function.</p> <p>1.2 Point 3.16 states:</p> <p>'Another brand of prolonged-release tacrolimus, Envarsus (Chiesi), obtained a marketing authorisation after the scope was finalised. The brand name 'Envarsus' was not included in the AG's search for evidence and Chiesi was not asked to submit evidence as part of the appraisal.'</p>	<p>intervals from non-inferiority trials are just as valid as point estimates and confidence intervals from superiority trials – the study objective affects the power calculations but fundamentally the trial design is unchanged. Uncertainty in the relative effectiveness is appropriately propagated through the economic model in the probabilistic sensitivity analyses.</p> <p>Comment noted. The FAD has been amended to state that:</p> <p>“The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least expensive product <i>when starting treatment</i>” See section 4.77 of the FAD.</p> <p>The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>The Committee noted that the AG’s systematic review was comprehensive and found a large number of randomised controlled trials. It concluded that all the relevant clinical effectiveness evidence had been taken into account. See section 4.60 of the FAD.</p>

Commentator	Comment [sic]	Response
	<p>1.2.1 Bibliographic literature searching was conducted on April 14th 2014 and updated 18th November 2014. Envarsus received a Marketing Authorisation (MA) in June 2014, therefore Chiesi Limited feel that the data for Envarsus (also described as LCP-Tacro in clinical studies) should have been included. Particularly since part of the rationale for this Guideline update is to reflect changes in the availability and licensed indications of immunosuppressants (some new, some withdrawn).</p> <p>1.3 Furthermore there appear to be inconsistencies in the approach taken, in that everolimus was included in the appraisal despite Certican® not receiving an MA until November 2014 (also after the scope was finalised), whereas alemtuzumab was not included in the appraisal and part of the rationale for its omission was that it did not have an MA for immunosuppression even though the AG had been granted a dispensation from the Department of Health to consider immunosuppressants outside of their MA. [Point 4.57 of the ACD also explains that part of the rationale not to include alemtuzumab was that it is not routinely available for transplant patients. However, alemtuzumab is routinely used in several transplant centres so its omission does not reflect clinical practice.]</p>	<p>Comment noted. NICE was not made aware that company was intending to submit a marketing authorisation application for Envarsus at the time that the final scope was issued. NICE was only made aware of this mid-way through the appraisal. Therefore, it would not have been included in the AG's protocol and systematic review. NICE were made aware of the anticipated MA's for both everolimus and belatacept and these were considered through NICE's topic selection function. NICE subsequently received a formal referral from the Department of Health to appraise these drugs. The technologies included as interventions in the final scope for appraisal were those that: were included as interventions in technology appraisal guidance 85, 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.</p> <p>Comment noted. The Committee was aware that alemtuzumab does not have a marketing authorisation in the UK for immunosuppression after kidney transplant and is not routinely available for transplant patients (it is available on a 'named patient' basis). It was therefore not included in the scope for this appraisal</p>

Commentator	Comment [sic]	Response
	<p>1.4 Point 4.6 states:</p> <p>'The Committee noted that there were no consistent differences between immediate- and prolonged-release tacrolimus'</p> <p>1.4.1 As Envarsus data was not included in the Appraisal, this statement is inaccurate. It was derived from data only on Advagraf® yet as written applies equally to all prolonged-release tacrolimus preparations including Envarsus.</p> <p>1.5 In Section 4.62, the Committee noted that there were very little subgroup data and had not found enough evidence to inform robust subgroup analyses.</p> <p>1.5.1 Subgroup analysis of Phase III trials with Envarsus shows significantly fewer treatment failures in older kidney transplant recipients (≥65 years) and in black kidney transplant recipients compared to Prograf (Bunnapradist 2013, Budde 2014).</p> <p>1.5.2 Data from two Phase III studies (Bunnapradist 2013, Budde 2014) were pooled to examine efficacy in specific patient subgroups, this has been presented in a poster (Bunnapradist 2014) and review paper (Grinyó 2014). This analysis, which included 861 patients (Envarsus n = 428; Prograf n = 433; 38% of patients were stable [Bunnapradist et al], and 62% were de novo [Budde et al] kidney transplant recipients) found that treatment failure (death, graft failure, centrally read BPAR, or lost to follow-up) at 12-months was significantly lower with Envarsus among black kidney transplant recipients (treatment difference and 95% CI: -13.82% [-27.22%, -0.31%]) and older (≥65) kidney transplant recipients (-13.46% [-25.27%, -0.78%]). Please note there were no significant differences identified in these subgroups in the individual studies.</p>	<p>The Committee considered evidence from the Assessment Group and the consultees. The brand name Envarsus was not included in the AG's search for evidence and Chiesi was not asked to submit evidence as part of the appraisal. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account.</p> <p>The Committee understood that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes, It concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain. The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant randomised controlled trial evidence had been taken into account. See section 4.60 and 4.65 of the FAD.</p>

Commentator	Comment [sic]	Response
	<p>1.5.3 Black kidney transplant recipients (KTR) tend to have poorer outcomes than non-black recipients, require higher oral doses of tacrolimus to achieve the same tacrolimus trough levels and tend to have higher Cmax than non-black KTR (see section 3.3.3)</p> <p>1.5.4 A study in African American kidney transplant recipients (the ASERTAA Study, Trofe-Clarke 2015) identified that:</p> <ul style="list-style-type: none"> • Approximately 80% of African American patients in the study were carriers of the CYP3A5*1 genotype (the variant associated with rapid tacrolimus metabolism) • Regardless of expressor status, these data in African Americans are consistent with the results from previous Envarsus pk studies, showing improved bioavailability, lower peak concentrations, and less peak-to-trough fluctuation compared to immediate-release tacrolimus • Envarsus pk parameters were less impacted by CYP3A5 genotype than IR-tacrolimus • IR- tacrolimus was more affected by expression of the *1 allele, driven primarily by the need to increase the dose to achieve therapeutic trough levels, which also resulted in an incremental increase in tacrolimus intra-day peak levels. <p>1.5.5 Neurotoxicity</p> <p>The exact mechanism by which tacrolimus induces neurological adverse events (AEs) remains unknown; however, it has been observed that many symptoms occur or are most pronounced at peak serum tacrolimus blood concentrations and symptoms generally improve when the tacrolimus dose is reduced or when tacrolimus is withdrawn (Bechstein 2000, Eidelman 1991).</p> <p>1.5.6 Envarsus tremor data</p> <p>A study evaluating the effect of switching patients with tremor from IR-tacrolimus to Envarsus demonstrated an improvement in the tremor score, quality of life and patient and physician global indices.</p> <p>1.5.6.1 Tremor is listed as a very common side-effect (≥10%) for Envarsus (Envarsus SPC). A two-sequence, open-label, multicenter, prospective Phase IIIb</p>	<p>Comment noted. The Committee considered evidence from the Assessment Group and the consultees. The Committee considered all consultation responses to the ACD in developing the final appraisal determination. The Committee considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. See section 4.64 of the FAD.</p> <p>Comment noted.</p> <p>Comment noted. The evaluation of switching treatments is not within the remit of this appraisal. The FAD contains a footnote referencing MHRA</p>

Commentator	Comment [sic]	Response
	<p>study (Langone 2015) was conducted in which stable kidney transplant recipients on Prograf or generic tacrolimus, experiencing tremor, were enrolled. Following 7 days of their pre-enrolment twice-daily tacrolimus, patients were switched to Envarsus at the 1:0.7mg/mg conversion ratio to maintain the same tacrolimus trough levels.</p> <p>1.5.6.2 Tremor pre- and 7-days post-conversion was evaluated by two independent, blinded neurologists using the gold standard Fahn-Tolosa- Marin tremor rating scale and by an accelerometry device that measures frequency and amplitude of tremor (Tremorometer™). Patients completed the Patient Global Impression of Change (PGI) scale and physicians completed the Clinical Global Impression of Improvement (CGI) scale; both are 7-point scales assessing tremor change ranging from very much improved (1) to very much worse (7). Quality of life was assessed by the patient-completed Quality of Life in Essential Tremor (QUEST) scale, a subjective quality of life instrument consisting of 30 items divided into five dimensions (communication, work/finance, hobbies/leisure, physical and psychosocial). Data were available on 38 patients. There was a significant improvement in tremor as indicated by significant decrease (improvement) in the Fahn-Tolosa-Marin score and the Tremorometer score, and significant improvements in the PGI, CGI and quality of life in essential tremor scores.</p> <p>1.5.6.3 This study is believed to be the first trial in kidney transplant recipients that utilises a sophisticated and reproducible measurement of tremor and Envarsus is the first tacrolimus to show that tremor can be reduced in patients without compromising the immunosuppression by lowering the dose (and therefore trough levels) of tacrolimus.</p> <p>1.6 Can we learn anything from liver transplantation?</p> <p>1.6.1 Data has been published showing a beneficial effect of PR-tacrolimus (Advagraf) in liver transplant recipients with regards to renal function and biopsy-confirmed acute rejection (Trunecka 2015).</p> <p>1.6.2 Furthermore, data has also been published in liver transplant recipients that show significantly lower graft failures and mortality rates at 3 years with PR-tacrolimus compared to IR-tacrolimus. [Adam 2015] While these data are in liver transplant recipients, it cannot be discounted that a</p>	<p>advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comment noted. This is outside the remit of the appraisal. No action required.</p>

Commentator	Comment [sic]	Response
	<p>similar mechanism could be seen in kidney transplants with similar results.</p> <p>1.7 Envarsus formulation</p> <p>1.7.1 The Guideline implies that all prolonged-release tacrolimus preparations are the same. Envarsus is the first oral solid-dose formulation that is not mg:mg dose equivalent to existing capsule formulations. The greater bioavailability of tacrolimus in Envarsus, means that Advagraf- or Prograf-treated patients should be converted to Envarsus on a 1:0.7 mg:mg ratio.</p> <p>1.7.2 Envarsus has a lower Cmax and a longer Tmax as well as a lower total daily dose requirement than Prograf or Advagraf.</p> <p>[REDACTED]</p> <p>1.7.4 Furthermore Envarsus is the only tablet formulation of tacrolimus and does not contain gelatin, therefore it would be suitable for those who wish not to ingest gelatin due to religious reasons or reasons of conscience (e.g. Muslims, vegetarians). (See sections 3.3.1 and 3.3.2)</p> <p>1.8 Envarsus (tacrolimus prolonged-release tablets) was not considered in the evidence submitted. Therefore Chiesi Limited would suggest that if recommendation 1.4 is to be implemented, it be amended to specify 'prolonged-release capsules' as Envarsus was not considered in this data and is a tablet prolonged-release formulation of tacrolimus.</p> <p>2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?</p> <p>2.1 The ACD states that PR-tacrolimus is not recommended, however only Advagraf is used in the model, i.e. evidence on the costs and effects of Advagraf. The model does not provide evidence on the cost-effectiveness of any other prolonged-release tacrolimus. We suggest that if the proposed guidance is implemented unchanged, it is made clear in the ACD recommendations that Envarsus was not included in the</p>	<p>Comment noted. The evaluation of switching treatments is not within the remit of this appraisal. The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comment noted. NICE recommendations on interventions associated with animal-derived products do not pose an equality issue. When a topic is referred, the intervention is appraised for the population for which it is intended and the fact that some people may not be able accept the intervention cannot be addressed through any NICE recommendations.</p> <p>Comment noted. The Committee did not consider the different dosage forms of prolonged-release tacrolimus. No action required.</p> <p>Comment noted. The Committee understood that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes. The Committee understood that the clinical experts were not aware of any additional evidence, and</p>

Commentator	Comment [sic]	Response
	<p>cost-effectiveness analyses.</p> <p>2.2 Some relevant comparators were not included in the assessment, BAS+PR-TAC+MMF+ST. The exclusion of this comparator underestimates the potential total QALYs that could be achieved with PR-tacrolimus. It is also likely that this comparator would represent the least costly PR-tacrolimus strategy. Given other suggested changes in the model this combination with PR-tacrolimus may be considered by the committee to be on the cost-effectiveness frontier.</p> <p>2.3 Relative Cost of PR tacrolimus</p> <p>2.3.1 In the reference case there is an inconsistency in the source of the price of drugs. The source of the price of tacrolimus is EMIT while the source of the PR tacrolimus is BNF. There is an expected bias that BNF will be higher than EMIT. This overestimates the cost of PR tacrolimus.</p> <p>2.3.2 The ERG tested a scenario using the 'List price' of immediate-release tacrolimus (IR-tacrolimus). In this analysis the ERG chose the lowest list price of IR-tacrolimus. They have not weighted the price by market share as was done in the reference case. This underestimates the price of IR-tacrolimus. Changing the price of IR tacrolimus to that of Prograf (the most commonly prescribed IR-tacrolimus) results in the discounted total cost of IR-tacrolimus + MMF +ST increasing from £92,226 to £110,544 and PR-tacrolimus being less costly (IR-Tac+MMF+ST = £110,544 compared to PR-Tac+MMF+ST = £109,113)</p> <p>2.3.3 It is important to note that the price of PR-tacrolimus used in the model is the BNF price of Advagraf and does not represent the price of all available PR-tacrolimus agents available. If the price for Envarsus were to be evaluated in the model, the price/mg would need to be adjusted to reflect the greater bioavailability and the subsequent reduced total daily dose of Envarsus compared to other IR- or PR-tacrolimus (Approx 30% less than Prograf or Advagraf (Envarsus SPC, ASTCOFF study)</p> <p>2.4 Relative effectiveness of PR-tacrolimus</p> <p>2.4.1 The ERG state that they 'made no attempt to explicitly model adherence to immunosuppressive medication due to the absence of evidence on this outcome in RCTs included in the systematic review of clinical effectiveness'. Further the ERG state that factoring in greater adherence 'departs from the ITT analysis of the trials',</p>	<p>concluded that all the relevant randomised controlled trial evidence had been taken into account. See section 4.60 and 4.65 of the FAD.</p> <p>Comment noted. This comparator was not included in the scope. The Committee's overall decision on whether a valid comparator is included is guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. See 6.2.3 of the NICE Guide to the methods of technology appraisal.</p> <p>Comment noted. In the Assessment Group's base case, drug acquisition costs were taken from the Commercial Medicines Unit's Electronic Market Information Tool (eMIT) when possible, and from the published list price or company submission otherwise. See section 4.30 of the FAD.</p> <p>Comment noted. In the Assessment Group's base case, drug acquisition costs were taken from the Commercial Medicines Unit's Electronic Market Information Tool (eMIT) when possible, and from the published list price or company submission otherwise. See section 4.30 of the FAD.</p> <p>Comment noted. The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear</p>

Commentator	Comment [sic]	Response
	<p>however the goal of a model is not to replicate trial evidence but to use the trial evidence to reflect clinical practice, i.e. effectiveness. This suggests the need to consider the evidence on adherence and to incorporate observational data. In the ACD the committee suggest the effect of adherence is uncertain, however although the magnitude of effect is uncertain, there should be little debate about the direction of effect, i.e. that better adherence is better for patients clinically. The ERG note that 'there is some evidence that non-adherence is a cause of late acute rejection and graft loss'.</p> <p>2.4.2 The clinical experts commented that patients would benefit from once a day treatment, although the committee stated that these patients could not be identified as a sub-group. The additional quality of life benefit of once a day treatment has not been included in the model. This represents a known benefit that has not been captured and should be considered by the committee. Without this quality of life benefit the current model underestimates the benefits of PR-tacrolimus compared to IR-tacrolimus.</p> <p>2.4.3 The ERG relied on a single head-to-head study between PR-tacrolimus and IR-tacrolimus to estimate the effectiveness of PR-TAC (Kramer 2010). The ERG excluded other trial evidence and observational evidence that is particularly useful when adherence is important. PR-TAC has not been included in the network meta-analysis although the ERG did identify a multicentre study that compared PR-TAC and cyclosporin ME (AG report, page 349).</p> <p>2.4.4 No quality of life related to eGFR states are taken into account, although there is evidence that higher eGFR results in better quality of life. (Gorodetskaya 2005). The exclusion of quality of life benefit associated with eGFR underestimates the benefit of PR-tacrolimus.</p> <p>2.4.5 The overall population used to calculate the head-to-head OR of death of PR-tacrolimus compared to IR-tacrolimus was not the primary endpoint population and included patients with major protocol violations (Kramer 2010). The per-protocol population used to estimate the primary endpoint had 3 deaths in each population of 291 and 280 patients. Using this data decreases the odds of death of PR-TAC+MMF+ST from 1.286 to 1.047. This increases the discounted QALYs of PR-TAC+MMF+ST to 10.8305 compared to 10.8884 for IR-TAC+MMF+ST.</p> <p>2.6 Conclusion</p> <p>2.6.1 The population used to estimate the primary endpoint of Kramer 2010 was not used in the model. Doing so decreases the odds of death of PR-tacrolimus and increases the total QALYs for PR-TAC+MMF+ST.</p> <p>2.6.2 When the BNF price of the most commonly prescribed IR-tacrolimus is used</p>	<p>whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas's approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee noted additional evidence received during consultation on the appraisal consultation document from Astellas regarding the study by Kuypers et al (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p>

Commentator	Comment [sic]	Response
	<p>PR-tacrolimus becomes relatively less costly.</p> <p>2.6.3 When these two scenarios are combined, PR-tacrolimus is less costly and less effective than IR-tacrolimus. The difference in NHB is 0.0038 at a £20,000 threshold and 0.0218 at a £30,000 threshold. However, this does not include the additional benefits of PR-tacrolimus that the model does not incorporate, such as reduced mortality and graft loss of adherence, and improved quality of life from improved eGFR states and once daily dosing.</p> <p>2.6.4 It is also known that dosing in certain subsets of the general population is different. In particular, black (higher tacrolimus dosing) and obese (lower tacrolimus dosing) patients tend to have different requirements. These subsets could have been analysed separately to identify disparities.</p> <p>3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>3.1 The practice across UK transplant centres varies. While the proposed guidance reflects the predominant practice with regard to initiation with tacrolimus (most centres initiate with IR-tacrolimus) it does not recognise that many of those centres also have a policy of initiating or switching to PR-tacrolimus for certain subgroups of patients, usually those at high-risk of non-adherence or a history of non-adherence through a combination of personal circumstances (e.g. shift workers), age (younger adults/adolescents), personality, and lifestyle. Although the AG had difficulty identifying these subgroups in clinical trials, clinicians can identify these patients in practice and many have protocols in place for such groups.</p> <p>3.2 There is a need for heterogeneity in the guidelines to treat the plethora of different clinical scenarios in kidney transplantation (including age, ethnicity, type of graft etc.). The proposed NICE guidance would discriminate against certain subgroups if implemented as proposed (see below).</p> <p>3.3 The guidelines do not reflect the principles set out in Section 1.3 of NICE clinical guideline 138 Patient experience in adult NHS services: improving the experience of care for people using adult NHS services Issued: February 2012. The proposed guidance does not tailor treatment to the individual and furthermore ignores the particular clinical issues facing the management of certain subgroups such as black</p>	<p>Comment noted. The Committee acknowledged that there may be some subgroups of people for whom belatacept or sirolimus may provide additional benefits, but considered that there was not enough evidence to support recommendations in specific subgroups. See section 4.59 of the FAD</p> <p>The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p>

Commentator	Comment [sic]	Response
	<p>or older KTR.</p> <p>3.3.1. We know from the ELITE-Symphony Study, (Ekberg 2007) that a low-dose tacrolimus-based immunosuppression regimen is associate with better renal function, better graft survival and fewer episodes of BPAR than a regimen based on ciclosporin or sirolimus. If patients cannot tolerate immediate-release tacrolimus they should be given the opportunity to have prolonged-release tacrolimus before switching to alternative therapies that may be less effective. The proposed guidance has the potential to reduce quality of care and patient safety</p> <p>3.3.2 There are people who would prefer not to ingest gelatin for reasons of religious belief or conscience (e.g. Muslims or vegetarians). Envarsus is the only solid form oral tacrolimus that does not contain gelatin. As a PR-tacrolimus Envarsus would be caught by the 'not recommended' guidance removing the opportunity to tailor tacrolimus therapy for these particular subgroups</p> <p>3.3.3 Kidney transplant survival rates in African American recipients remain lower than for any other ethnic group. (Fan 2010, Eckhoff 2007). The decline in renal function after kidney transplantation is accelerated in African American patients (Srinivas 2005, Lentine 2010) and long-term graft loss in both adults and children is markedly increased compared with non-African American populations (Press 2005, Meier-Kriesche 2000, Omoloja 2007, Ishitani 2000) This ethnic disparity is observed even in living donor and zero-mismatched patients and after adjustment for patient characteristics (Isaacs 1999, Fan 2010)</p> <p>3.3.3.1 Tacrolimus absorption exhibits ethnicity-specific differences in systemic exposure with 20-50% lower oral bioavailability in African Americans than white patients (Malat 2009) such that the dose needs to be adjusted accordingly.</p>	<p>Comment noted. NICE recommendations on interventions associated with animal-derived products do not pose an equality issue. When a topic is referred, the intervention is appraised for the population for which it is intended and the fact that some people may not be able accept the intervention cannot be addressed through any NICE recommendations. The Committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. See section 4.69 of the FAD</p> <p>Comment noted. The Committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. See section 4.69 of the FAD.</p> <p>Comment noted. The Committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective. See section 4.69 of the FAD.</p>

Commentator	Comment [sic]	Response
	<p>3.3.3.2 Black patients have significantly higher doses of tacrolimus (for similar trough levels) (Narayanan 2013, Gaber 2013,)</p> <p>3.3.3.3 Higher oral doses of IR-tacrolimus are accompanied by higher Cmax. Cmax above 20ng/ml are frequently seen in black patients. (Trofe-Clark 2015)</p> <p>3.3.3.4 Conversion to Envarsus from IR-tacrolimus results in a significant reduction (p<0.0001) in Cmax (ratio of geometric means 71.7 (64.8-79.3)) which may have implications for long-term outcomes.</p> <p>3.3.3.5 In an analysis of two Phase III trials, black patients had fewer treatment failures on Envarsus than on IR-tacrolimus (Prograf). The guidance as proposed would prohibit tailoring treatment to this specific subgroup.</p> <p>3.3.4 The kidney transplant population is growing older. Age at the time of transplantation is clearly correlated with long-term outcome [Legendre 2014]. The mean age of transplant donors and recipients in the UK was 50yrs and 49yrs for kidneys from deceased donors and 47yrs and 43yrs for kidneys from living donors. Thirty one percent of deceased organ donors were aged ≥60 years and 28% of recipients from deceased donors were aged ≥60 years [NHSBT 2015].</p> <p>3.3.4.1 Renal function declines with age so older organs will typically have reduced renal function compared to younger organs. CNIs are nephrotoxic. There is some evidence that the age of a kidney is a major determinant of its susceptibility to CNI nephrotoxicity (Naesens 2009)</p> <p>3.3.4.2 CNI nephrotoxicity is complex but one component is the blood concentration, Cmax. Having a tacrolimus that can deliver effective trough levels but avoid high Cmax provides the opportunity to avoid premature deterioration of transplanted kidneys from older donors. In renal transplant recipients, Envarsus has lower Cmax than IR-tacrolimus (Prograf) [Gaber 2013]</p> <p>3.3.4.3 In a subgroup analysis of two Phase III clinical trials, older patients (≥65 yrs)</p>	<p>Comment noted. The Committee understood that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and noted that a number of effective treatment options are available. See section 4.79 of the FAD.</p> <p>Comment noted.</p>

Commentator	Comment [sic]	Response
	<p>had fewer treatment failures on Envarsus than IR-tacrolimus (Prograf). The guidance as proposed would prohibit tailoring treatment to this specific subgroup.</p> <p>3.4 The proposed Guidance does not accord with the principles set out in NICE CG76. Medicines adherence. Involving patients in decisions about prescribed medicines and supporting adherence. Issued Jan 2009, reviewed March 2015.</p> <p>3.4.1 NICE CG76 establishes that:</p> <ul style="list-style-type: none"> • Non-adherence is common and that most patients are non-adherent sometimes. • Consider assessing non-adherence by asking the patient if they have missed any doses of medicine recently. • Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing. • Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated • with non-adherence if a specific need is identified. Interventions might include: (among others) Simplifying the dosing regimen <p>3.4.2 The practical problems of timing of doses and mealtimes could be an example of where simplifying the dosage regimen could have a positive impact on adherence and outcomes.</p> <p>3.4.3 IR-tacrolimus is widely-referred to as BD dosing. In reality it is dosing every 12 hours. Taking a dose early risks toxicity, taking it late risks under-immunosuppression. If a patient is late taking one dose what do they do the next day? Do they go back to the normal timing and effectively have a small overdose or do they try to rearrange their schedule? Most patients know that if they take too much tacrolimus it will damage their kidney, and also if they take too little it will damage their kidney.</p> <p>3.4.4 Tacrolimus blood levels are strongly impacted by food. The SPCs for Prograf and Advagraf say they need to be taken 1 hour before or 2-3 hours after meals. Not all patients can manage their daily routine so that they can meet the criteria for 12-</p>	<p>Commented noted. The Committee considered all consultation responses to the ACD in developing the final appraisal determination. No action required.</p> <p>Comment noted. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However considering all the evidence, the Committee concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain. See section 4.65 of the FAD.</p> <p>Comment noted. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However considering all the evidence, the Committee concluded that it would be difficult to identify the people who would benefit from prolonged-release tacrolimus, and that the effect on clinical outcomes was uncertain. See section 4.65 of the FAD.</p>

Commentator	Comment [sic]	Response
	<p>hour timing of dosing and timing of mealtimes. Patient groups particularly affected are shift workers, people with chaotic lifestyles (e.g. young adults/ adolescents), people with young families who want to eat with the family etc. Evidence shows that with IR-tacrolimus it is typically the evening dose that is missed [Kuypers 2013]</p> <p>With PR-tacrolimus there is obviously no evening dose to have to consider timing of dose and mealtimes.</p> <p>3.4.5 In Section 1.2.9 of CG 76 it states; Side effects can be a problem for some patients. If this is the case you should: consider adjusting the dosage consider switching to another medicine with a different risk of side effects</p> <p>3.4.6 For tacrolimus therapy, tremor could be an example of a side effect that is problematic for patients. Switching to Envarsus from IR-tacrolimus could reduce tremor and improve quality of life (see Section 1.5.6 of this document)</p> <p>3.4.7 Both Envarsus and Advagraf have a second indication of 'Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.' This proposed guidance would remove two immunosuppressive options for this clinical scenario.</p> <p>3.4.8 In 2012, the Commission on Human Medicines (CHM), updated advice on the prescribing and dispensing of all oral tacrolimus products. This updated advice is that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only. This was a result of the risk to patient safety. The proposed Guidance uses the terms immediate-release tacrolimus and prolonged-release tacrolimus and may imply they are easily interchangeable which contradicts the MHRA guidance.</p> <p>4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?</p>	<p>Comment noted. These other indications were not within the remit of the technology appraisal and therefore the FAD does not make recommendations on allograft rejection that is resistant to treatment.</p> <p>Comment noted. The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comment noted. The FAD has been amended to state that: "The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least expensive product <i>when starting treatment</i>"</p>

Commentator	Comment [sic]	Response
	<p>4.1 Age: Subgroup analysis data for Envarsus demonstrated significantly reduced treatment failure rates in older patients (≥65 yrs) compared to Prograf. This group would be discriminated against by this guideline if implemented as proposed.</p> <p>4.2 Race: Subgroup analysis data for Envarsus demonstrated significantly reduced treatment failure rates black patients compared to Prograf. This group would be discriminated against by this guideline if implemented as proposed.</p> <p>4.3 Religion or belief: Envarsus is a tablet formulation and does not contain gelatin, therefore it would be suitable for those who wish not to ingest gelatin due to religious reasons or reasons of conscience (e.g. Muslims, vegetarians). Envarsus is the only solid form oral tacrolimus that does not contain gelatin. Since immunosuppression based on a tacrolimus regimen has been demonstrated to be more effective than immunosuppression regimens based on ciclosporin or sirolimus (ELITE Symphony study), this guideline would discriminate against these groups if implemented as proposed.</p> <p>4.4 The guideline would also discriminate against those who have difficulties with adherence due to personal, personality or lifestyle factors if implemented as proposed.</p> <p>References: Full list of references were presented in Chiesi's response to consultation documents. This can be found in the Committee papers.</p>	<p>See section 4.77 of the FAD.</p> <p>Comment noted The Committee understood that effective immunosuppression may be particularly beneficial for people from black, Asian and minority ethnic groups, and noted that a number of effective treatment options are available. See section 4.79 of the FAD.</p> <p>Comment noted. NICE recommendations on interventions associated with animal-derived products do not pose an equality issue. When a topic is referred, the intervention is appraised for the population for which it is intended and the fact that some people may not be able accept the intervention cannot be addressed through any NICE recommendations. The Committee noted that there were no consistent differences in clinical effectiveness between immediate- and prolonged-release tacrolimus. It considered that prolonged-release tacrolimus was not cost effective.</p>
<p>Healthcare Improvement Scotland</p>	<p>1. Do you consider that all the relevant evidence has been taken into account? <i>If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?</i></p> <p><i>I think this is a reasonable view. However, it is more a</i></p>	<p>Comments noted. The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least</p>

Commentator	Comment [sic]	Response
	<p><i>pharmacy/economic perspective rather than that of a practising clinician. Transplant outcomes have improved year-on-year across the world in a way that owes more to the application of local guidelines and tailored immunosuppression, particularly the target drug levels. I would have drawn on published and available immunosuppressive protocols (from the Scottish centres) as well as the trial data.</i></p> <p><i>The other data which you might have drawn on are those on bioavailability , and known interactions with food, of the immunosuppressant generics. As someone who sits on an MHRA committee I think your front page advice to use the cheapest drug is dangerous. Unless, it is followed with the recommendation to use the same generic rather than to risk random substitution of generics with varying bioavailability.</i></p> <p>2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? <i>If not, please explain.</i></p> <p><i>I think there is considerable use of once daily Tacrolimus – particularly for younger people with compliance issue. I think that mTOR usage amongst experienced transplant clinicians will probably continue at around 5% of the total population, for the indications of malignancy particularly skin malignancy which is very common, and preventing viral infections. The cost of treating CMV and malignancy was not factored into your analyses, despite evidence that mTOR inhibitors will half the recurrence rate of skin tumours.</i></p> <p>3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? <i>If not, in which areas do you consider that the summaries are not reasonable interpretations?</i></p> <p>I think they are technically OK. However, there is widespread agreement that the current trial end-points of rejection, graft loss and death have limited applicability for the future development of immunosuppression (by the regulatory authorities in Europe and the US) and so reliance on these for your analyses for your economic analyses means they are based on historical datasets that may not</p>	<p><i>expensive product when starting treatment</i> See section 4.77 of the FAD.</p> <p>The FAD contains a footnote referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comments noted. The AG stated that malignancy would only affect the cost-effectiveness conclusions if different agents were associated with different rates of this outcome. See section 4.37 of the FAD. The Committee was aware that subgroup data for people with skin malignancy had not been presented.</p> <p>Comment noted.</p>

Commentator	Comment [sic]	Response
	<p>reflect current outcomes or the population of transplant recipients.</p> <p>4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? <i>If not, why do you consider that the recommendations are not sound?</i></p> <p><i>Basiliximab, Tac and MMF is standard practice for most patients. The rest of the agents are necessary for at least some patients. The recommendation to sue the cheapest drug without highlighting the dangers of variable bioavailability in generics is dangerous.</i></p> <p>5. Are the patient pathways and treatment options described in the assessment applicable to NHS Scotland? <i>If not, how do they differ in Scotland?</i></p> <p><i>I don't think Scotland differs from the UK. However, many patients are managed by clinicians, increasingly, who are not particularly experienced in transplantation, with the growth of transplantation and the geographical delivery of services.</i></p> <p>6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? <i>If so, please describe what these changes would be.</i></p> <p><i>Frankly, I don't think people will pay much (if any) attention to these guidelines and will carry on with their local practices.</i></p> <p>7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? <i>If yes, please explain</i></p>	<p>Comments noted. The Committee concluded that it did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the least expensive product <i>when starting treatment</i>. See section 4.77 of the FAD.</p> <p>The FAD contains a footnoted referencing MHRA advice on prescribing and dispense by brand name only, to minimise the risk of inadvertent switching between products.</p> <p>Comments noted.</p> <p>Comments noted.</p>

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Commentator	Comment [sic]	Response
	<p><i>why this is the case.</i></p> <p>No</p> <p>7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment</p> <p>I would have included local protocols.</p>	<p>Comment noted.</p> <p>Comment noted.</p>

Comments received from members of the public

Summary of comments received from members of the public

Theme	Response
<p>Recommendations too restrictive – they should take into account individual circumstances</p>	<p>The Committee considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups. Therefore the Committee concluded that it was unable to make recommendations for any of the interventions in specific subgroups. See section 4.64 of the FAD.</p>
<p>Role for mTOR inhibitors for patients who have had or are at significant risk of skin malignancy</p>	<p>Comment noted. The Committee had not seen evidence supporting the clinical or cost effectiveness of sirolimus and everolimus in this situation.</p>
<p>Unclear clear where prednisolone, azathioprine and cyclosporine sit within the guidance</p>	<p>Comment noted. The Committee noted that the final guidance would apply to the interventions listed in the scope and would not affect the current use in the NHS of ciclosporin, azathioprine and prednisolone, which were included as comparators only. See section 4.59 of the FAD.</p>

Theme	Response
<p>Paradoxical that the Committee highlights the lack of evidence yet makes absolute/restrictive guidance about usage of the technologies</p>	<p>There are always likely to be deficiencies in the evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. See section 3.2.2 of the NICE Guide to the methods of technology appraisal.</p> <p>Comment noted. NICE has to take into account its Social Value Judgements which states that, 'Those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.'</p> <p>In addition, 'Although NICE accepts that individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole.'</p>
<p>Guidance has only considered "standard risk" patients - rATG must be allowed for high immunological risk recipients</p>	<p>Comment noted. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee considered the Brennan (2006) study in which the mean peak panel-reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk. The Committee concluded that r-ATG is not a cost-effective use of NHS resources, for induction therapy for preventing organ rejection in adults having a kidney transplant. See section 4.67 of the FAD.</p>
<p>People unable to tolerate CNIs due to side effects such as thrombotic microangiopathy, renal impairment, neurotoxicity, diabetes will have limited treatment options if sirolimus and belatacept are not available to them</p>	<p>The Committee recognised that there is a need for other treatment options, such as sirolimus, in the event of nephrotoxicity caused by calcineurin inhibitors. The Committee also noted that a small number of people develop thrombotic microangiopathy during treatment with tacrolimus, ciclosporin, sirolimus or everolimus. In this latter situation clinicians highlighted that belatacept is the only immunosuppressant that might be effective in these circumstances. However, the Committee had not seen evidence supporting the clinical or cost effectiveness in these situations and recognised that obtaining clinical trial evidence would be difficult. See section 4.75 and 4.76 of the FAD. The Committee was therefore unable to make recommendations for specific subgroups.</p>

Theme	Response
<p>Prolonged- release tacrolimus should be made available for certain groups where adherence could be a problem.</p>	<p>Comments noted. The Committee noted that improved adherence associated with prolonged-release tacrolimus had been modelled by Astellas. The Committee highlighted that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy, and that Astellas’s approach assumed the effectiveness of the whole regimen would be increased by improving adherence to tacrolimus. The Committee noted additional evidence received during consultation on the appraisal consultation document from Astellas regarding the study by Kuypers et al (2013). The Committee noted that the study did not report patient-related outcomes such as graft survival. The Committee considered that there may be some people for whom once-daily prolonged-release tacrolimus could improve adherence. However, considering all of the evidence the Committee concluded that it would be difficult to identify the people who would benefit, and that the effect on clinical outcomes was uncertain (see section 4.65 of the FAD).</p>

Astellas Pharma Limited Response –25 August 2015

NICE Appraisal Consultation Document - Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

Thank you for the opportunity to comment on the above Appraisal Consultation Document (ACD). We have provided our main responses below under the specific ACD consultations questions with additional comments listed in Table 1. Data demonstrating the benefits of prolonged-release tacrolimus are provided in Appendix One. Specific comments on the Assessment Group Report are provided in Appendix Two.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No.

We are surprised that the provisional recommendations limit patient and clinician choice when the Committee acknowledges that *'immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people'* and clearly understood *'the value of choice of immunosuppressive therapies'* (ACD Section 4.56).

We consider that, despite the Committee's acknowledgement that a choice of therapies are required, a number of issues with the data provided within the Assessment Report along with the sole reliance on randomised controlled trial data has resulted in provisional recommendations which actually limit choice and are not a suitable basis for guidance to the NHS. The NHS has invested a significant amount of money (£17,000) in each kidney transplant and the provisional recommendations are not optimising this investment. Limiting treatments potentially consigns more patients to dialysis costing £30,000 per year and returns patients to a waiting list that is already under increasing pressure. Donors and their families also make a significant emotional investment and deserve the full treatment options available to optimise their graft outcomes.

Our key concerns relate to:

- The reliance on the non-inferior endpoints from a single clinical study, to infer a clinical benefit in favour of immediate-release tacrolimus over prolonged-release tacrolimus, which is not methodologically appropriate or seen in clinical practice. Specific non-significant outcomes were selected and extrapolated (graft loss, mortality and new onset diabetes after transplant [NODAT]) while the costs associated with other significant endpoints e.g. bacterial infection were ignored.
- The inconsistent use of drug acquisition costs based on discounted prices for immediate-release tacrolimus taken from the Commercial Medicines Unit's (CMU) Electronic Market Information Tool (eMit) and the use of a second separate data source (BNF) for the prolonged-release tacrolimus (Advagraf) list price, despite the inclusion of Advagraf on a National Tender, negotiated with the NHS CMU.

- The lack of consideration of RCT (Kuypers *et al.*¹) and non-RCT data and the resulting lack of recommendations for potential patient subgroups who may benefit from specific treatment regimens including prolonged-release tacrolimus.

These issues are discussed in more detail below.

The inclusion of non-significant efficacy and safety endpoints and the exclusion of significant findings

Non-significant, short-term efficacy and safety endpoints (including graft loss and mortality, the two most important long term outcome measures) have been used to infer clinically significant differences between immediate and prolonged-release tacrolimus while significant findings that favour prolonged-release tacrolimus have not been fully considered. Taken together, these suggest that the NICE recommendations are based on inappropriate and incomplete evidence.

The approach taken within the meta-analysis performed by the Assessment Group is inappropriate and misleading with regard to the inclusion of non-significant findings from a fixed-effects “meta-analysis” of non-inferiority.

Inclusion of non-significant outcomes

Death and graft loss

Within the meta-analysis of death or graft loss only data from Krämer *et al.* 2010² (Krämer study) inform the analyses. There are a number of issues with how the data from this study was used:

- The Krämer study was only powered to demonstrate non-inferiority with regard to biopsy-confirmed acute rejection at 24 weeks, yet the Assessment Group analysis uses the intent-to-treat (“overall”) population to model differences in patient and graft survival, instead of the more appropriate per-protocol analysis. Use of this population misses a QALY benefit for the prolonged-release tacrolimus cohort.

We would further add that the use of data derived from intent-to-treat populations in meta-analyses of non-inferiority studies is not widely accepted^{3,4}

- The data used in the Assessment Group model includes follow-up from the open-label extension of this study (i.e. data at 12 months post-transplantation after 28 weeks of unblinded follow-up) and the findings of differences in graft loss and patient mortality at 12 months which were not statistically significant (p=0.53 and p=0.61 respectively). This is inappropriate.

NODAT

Non-significant NODAT data (from Krämer *et al.*² and Tsuchiya *et al.*⁵) was included to infer a clinical difference between immediate-release and prolonged-release tacrolimus.

However, we would like to raise a concern that, despite the non-significant difference between tacrolimus formulations, NODAT is the second largest driver of the cost difference between the two formulations in the model second only to the cost of the drug acquisition. Further information on this, which the Committee may wish to consider, is provided in Appendix One and which demonstrates rates of NODAT with prolonged-release tacrolimus (Advagraf) are lower in a UK clinical setting than that reported in the literature for immediate-release tacrolimus.⁶

It is unthinkable that the Medicines and Healthcare Products Regulatory Agency (MHRA) would have given a Market Authorisation to prolonged-release tacrolimus (Advagraf), if the incidence of reported adverse events were significantly different to those of immediate-release tacrolimus so as to cause safety concerns.

Exclusion of significant outcomes

We would also like to reiterate that the exclusion of significant outcomes from the Krämer *et al.* study² unfairly biases the analysis in favour of immediate-release tacrolimus. The most notable significant outcome overlooked in the Krämer study by the Assessment Group was the incidence of:

- Bacterial infections (22.6% versus 16.0% with immediate-release tacrolimus and prolonged-release tacrolimus respectively; $p=0.032$)

On the basis of the above we recommend a re-analysis of the graft loss and mortality based on the per protocol population in the Krämer study.²

Inconsistent use of list price

We would challenge the use of drug acquisition costs taken from the Commercial Medicines Unit's (CMU) Electronic Market Information Tool (eMit) and recommend that, in order to ensure consistency, transparency and time-proof the guidance only list price is used, the approach taken by the All Wales Medicines Strategy Group (AWMSG) in their recent appraisal of Envarsus (extended-release tacrolimus).⁷

Drug acquisition costs taken from the CMU eMit are subject to change and the data is updated only every six months. Within the CMU Tender framework agreements, there are potential pricing reviews at the end of an agreed period and relevant termination clauses which make it difficult to confirm which:

- Product will be the most cost effective over time should suppliers amend pricing, and
- Prices apply over the timeframe of NICE guidance.

In addition eMit data used to calculate the average cost paid by the NHS for immediate release tacrolimus capsules is usually only used for generic products and relies upon hospital trusts submitting the data and the relevant data being uploaded. There can be gaps in these hospital data and they do not always include Outsourced Pharmacy and Homecare usage (which can comprise around 60%) depending on whether the data goes through the hospital systems which is a significant route for administration of tacrolimus. In addition since eMit data is only updated every 6 months with the last update being in December 2014 (see <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>) the data used is already out of date. Based on this the assumption of £0.52/mg for immediate-release has a significant risk of being inaccurate.

We ask the Committee that in order to:

- Future proof the final guidance and allow for changes in the market dynamics, product availability and tender pricing strategies of the pharmaceutical companies only list prices should be considered
- Ensure appropriate use of NHS resources; guidance states that clinicians should be directed to base their choice of treatment on that which is the most clinically effective for the individual patient with direction given to procuring the most cost effective product(s) available

This will enable clinicians to make choices based on individual patient need whilst putting the onus on NHSE and CMU to drive cost effective pricing and encourage increased competition.

If, in the event that the Committee prefers to use the prices negotiated nationally by the CMU on the tacrolimus National Tender, this should be applied consistently for all formulations of tacrolimus as prolonged-release tacrolimus (Advagraf) has been awarded at a discounted price on the National Tender, effective from May 2014.

Prolonged-release tacrolimus in easily identifiable patient subgroups

We note, as stated above, that the Committee has already acknowledged that some treatments may be particularly beneficial for individual people or groups of people but are concerned that due to the reliance on only RCT data the Committee has not considered the clinical benefits of prolonged-release tacrolimus as a treatment option for a subgroup of patients; specifically those at risk of non-adherence or at risk of high intra-patient variability in tacrolimus trough levels.

We disagree with the Committee's comment that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes and that it would be difficult to identify people who would benefit (ACD, Section 4.64). In addition to the RCT (Kuypers *et al.*¹) on adherence included in our submission but excluded by the Assessment Group, there is in fact robust non-RCT evidence that supports the use of prolonged-release tacrolimus as a treatment option and which should not be disregarded. These data provide real world evidence on the effectiveness of prolonged-release tacrolimus in clinical practice.

Given the evidence available prolonged release tacrolimus should be recommended as a treatment option for patients at increased risk of rejection or graft loss due to non-adherence and/or high variability. Both groups of patients are easily identifiable in clinical practice using current procedures and tools, such as adherence questionnaires and routine blood monitoring and no change to clinical practice would be required. We would also highlight that this subgroup of patients only includes around 30% of patients eligible for treatment with tacrolimus.

Effective treatment of these patients is essential in order to ensure that therapeutic levels of tacrolimus are maintained within a narrow therapeutic window. If therapeutic levels are too low, the patient is at risk of organ rejection. Conversely, if levels are too high, over-immunosuppression can result in an increased risk of malignancy, infection and/or nephrotoxicity. In some patients variability occurs where their levels of tacrolimus fluctuate above and below the therapeutic window – this is referred to as intra-patient variability. High levels of intra-patient variability have been shown to be associated with an increased risk of renal graft failure^{8,9,10} with the relative risk of graft failure in these patients 2.38 times higher than in those with low variability⁸. Non-adherence is a significant problem in 20-30% transplant patients¹¹ and is a key cause of intra-patient variability. In patients treated with tacrolimus non-adherence results in variable therapeutic levels and an increased risk of graft failure.¹²

Prolonged-release tacrolimus has demonstrated improved adherence and reduced variability in tacrolimus exposure.^{1,13-18} In addition prolonged-release tacrolimus is associated with preserved renal function over time with data available up to 3 years post-transplant.¹⁹ Following agreement with NICE further details of the key studies are provided in Appendix One along with proposals on how the Assessment Group can model adherence.

We request that the Committee reviews this evidence and reconsiders recommending prolonged-release tacrolimus in patients identified as non-adherent or at risk of intra-patient variability.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

No. We consider that the evidence provided in Krämer *et al.*² and Tsuchiya *et al.*⁵ have not been interpreted appropriately, as the analysis was extrapolated from endpoints that were not statistically significant, from 24 weeks of blinding out to 50 years. The costs in the model were incorrect, biased in favour of immediate release tacrolimus, all points as documented above.

Has all of the relevant evidence been taken into account?

No. There are three considerations:

- Exclusion of significant outcomes from a RCT (Krämer *et al.*²)
- Exclusion of the Kuypers study¹
- The lack of consideration of non-RCT data

These points demonstrate that not all relevant and key evidence has been taken into account resulting in provisional recommendations which limit patient and clinician choice and which are not a suitable basis for guidance to the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

By limiting patient and clinician choice the provisional recommendations reduce the clinician's ability to tailor treatment to each individual patient and deny patients access to effective treatment.

Patients from ethnic minorities, lower socio-economic groups and those with lower literacy levels, learning disabilities or dementia may find it difficult to manage a complex medication regimen and by not recommending medicines which have been shown to improve adherence the Committee are effectively denying these patients access to effective treatments.

In light of the information provided, we ask that the Committee:

- Request the Assessment Group to re-run the economic model using:
 - Non-inferior endpoints for mortality, graft loss and risk of NODAT
 - Per-protocol population graft loss and mortality data from Krämer *et al.*²
 - Using list price for all immunosuppressive therapeutic options.
- Request the Assessment Group to update the model and include the effects of non-adherence in line with our recommendations in Appendix One
- Considers the RCT and non-RCT data provided for prolonged-release tacrolimus and following this reconsiders recommending prolonged-release tacrolimus in the specific subgroup of patients identified as non-adherent or at risk of high intra-patient variability

We look forward to discussions at the next Committee meeting on 4th November 2015. In the intervening period please do not hesitate to contact Sachin Patel if you require any further information.

Regards,

■

■■■■■■ ■■■■■■

Table 1: Additional comments

ACD Section	Comment
2.3	<p>In addition to the factors listed immunosuppressive therapy also aims to prevent death from graft failure in addition to the points raised. We would recommend the text is revised as follows:</p> <p>‘Immunosuppressive therapy aims to prevent acute rejection, and optimise the function of the transplanted kidney <u>and prevent death from graft failure</u>, while minimising the adverse effects of immunosuppression</p>
3.13	<p>In line with our comments above we ask that only list prices are used and cited.</p>
3.16	<p>Further clarification is required on why Envarsus (tacrolimus extended-release tablets, MA granted June 2014) was excluded from the final scope of the appraisal while everolimus (Certican, MA granted November 2014) was included when both had not received Marketing Authorisation prior to the final scope being issued.</p>
4.9	<p>RCT comparisons of immediate and prolonged-release tacrolimus were powered for non-inferiority. The key issue is that the non-inferiority design cannot be used to infer the presence or absence of superiority. We recommend the text is amended as follows:</p> <p>‘Comparison of immediate-release and prolonged-release tacrolimus (plus mycophenolate mofetil) showed no consistent statistically <u>clinically</u> significant differences’</p>
4.24	<p>Living with a kidney transplant is a long-term condition and on this basis it is not appropriate to extrapolate data from the 24 week blinded phase of RCTs to 50 years.</p> <p>We would also repeat our concern on the use of non-significant data to inform the model.</p>
4.31	<p>The Assessment Group assumption that corticosteroid use is continuous in a maintenance regimen is flawed. Clinical experts present at the Appraisal Committee meeting indicated that steroid use is intermittent and as short term as possible. Consideration should be given to the impact of intermittent and short-term use on any calculations used to predict steroid side effects in the long term.</p>
4.37	<p>The current text in the 5th bullet point is misleading. In order to reflect the true situation we ask that the text is amended as follows:</p> <p>“Astellas noted that the model did not consider the effect of adherence. The</p>

ACD Section	Comment
	Assessment Group considered that there was limited <u>RCT evidence to inform decision making</u> , and recommended caution in using this surrogate outcome.
4.40	Omission of ciclosporin did not affect interpretation of the results of the Astellas model, as the publication of the full Astellas model [Muduma et al 2014] was used by the Assessment Group to inform their interpretation. The drug dosages used in the Astellas model reflect current clinical practice.
4.54	We note that the Assessment Group did not model adherence and that there was insufficient evidence to support subgroup analysis. We have recommended consideration of non-RCT data on adherence in a specific subgroup of patients eligible for treatment with prolonged-release tacrolimus and modeling considerations which will assist in addressing both these issues.
4.58	<p>The statement about the additional evidence should be amended as follows to reflect the qualification of the consideration of only RCT evidence:</p> <p>‘The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness <u>RCT</u> evidence had been taken into account’.</p>
4.63	<p>The statement ‘calcineurin inhibitors are associated with nephrotoxicity’ is inaccurate and does not acknowledge the fact that tacrolimus is <u>NOT</u> overly nephrotoxic. In patients treated with tacrolimus renal function is maintained and stable over significant periods of time.^{19,20}</p> <p>We would also like to reiterate to the Committee that the doses of calcineurin inhibitors used in the RCTs and used in the AG model are not the doses used in current clinical practice, which are lower, following the publications of the landmark SYMPHONY study.^{21,22}</p> <p>As a point of accuracy the current text should be amended as follows:</p> <p>‘In particular, calcineurin inhibitors are associated with nephrotoxicity, and, Tthe Committee heard from the clinical specialists that about 5% of people develop nephrotoxicity soon after transplant and more develop it over a longer period.’</p>
4.64	We note that the Committee highlighted ‘that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy’. For a slow clearance drug like tacrolimus it would not be the acute effect of missing a single dose that would impact on the consistency of immunosuppression. What would be important is the deviation from total adherence over a period of time. With a once daily formulation,

ACD Section	Comment
	taken in the morning, greater consistency in adherence is seen than with a twice daily formulation and this has been demonstrated to be true in general ²³ and also specifically for prolonged-release tacrolimus. ¹

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26th August 2015

Bristol-Myers Squibb
Sanderson Road
Uxbridge
Middlesex
UB8 1DH



Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence (NICE)
Level 1a, City Tower
Piccadilly Plaza
Manchester
M1 4BT

Re: Kidney transplantation (adults) - immunosuppressive therapy (Review of TA 85) [ID456]

Dear Meindert

Thank you for your invitation to comment on the Appraisal Consultation Document (ACD).

Bristol-Myers Squibb are disappointed that belatacept is not recommended as a treatment option to prevent organ rejection in adults having a kidney transplant despite the fact that it may offer benefits to particular sub-group of patients as noted within the ACD.

We acknowledge that in the ACD the estimated incremental cost-effectiveness ratio (ICER) for belatacept in the total population is above the threshold that NICE would consider suitable for recommendation. However, a subgroup analysis was presented by BMS to demonstrate the possibility of appraising the evidence for belatacept for specific groups of patients where belatacept is a clinically- and cost-effective treatment option. The use of belatacept in specific subgroups was supported by clinicians who identified that 5% of patients develop nephrotoxicity to calcineurin inhibitors (CNIs) soon after transplant and more develop it over time. The belatacept regimen is a CNI-free regimen and may therefore be an option for this group of patients.

As noted by clinicians, currently individual funding requests (IFRs) are required in order for patients to access belatacept and in some circumstances, access can be delayed. This leads to unequal access across the UK.

We acknowledge that there is limited evidence available for specific subgroups. Consideration of belatacept restricted for those patients that lack alternative

treatment options would be of benefit to these patients. Therefore we encourage the Committee to reconsider its proposed recommendation and to recommend belatacept for specific subgroups noted in the ACD and identified by clinicians.

Finally we confirm that we have not identified any factual inaccuracies in the ACD or the economic model.

We would be grateful if you would consider the points that we make in this response prior to the meeting of the Appraisal Committee on Wednesday 4th November 2015.

If you have any questions please do not hesitate to contact me.

Yours sincerely,

A black rectangular redaction box covering the signature of the sender.

Bristol-Myers Squibb Pharmaceuticals Limited

Response to:

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

**on the Appraisal Consultation Document for
Immunosuppressive therapy for kidney transplantation
in adults
(review of technology appraisal guidance 85)**

Prepared by:

Novartis Pharmaceuticals UK Limited

25 August 2015

Dear Sirs,

We would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on this appraisal. Having reviewed the Appraisal Consultation Document (ACD), Novartis Pharmaceuticals UK Ltd (Novartis) would like to comment on two specific areas: the relationships between health utilities and renal function and the need for alternative options in certain patient subgroups. Specific issues relating to these areas are outlined below:

Link between health utilities and renal function

In the ACD, the NICE Appraisal Committee recognised and understood that Novartis used a different approach to modelling utilities to that used by the Assessment Group (AG). It was also acknowledged by the AG, in the assessment report and the ACD, that one of the main strengths of Novartis' model is its account of the effect of renal function on health-related quality of life (QoL) and that this is one of the AG model's limitations (pp 365 ERG report; pp 31 of ACD). The AG's modelling approach excludes any association between utility and renal function and does not reflect the available peer-reviewed evidence, so the appropriateness of this approach could, therefore, be interpreted as perverse in the light of the available methodological evidence.

There is also recognition in the ACD that cost-effectiveness in renal transplantation is highly sensitive to the method used to estimate health state utilities. Furthermore, it was acknowledged at the Appraisal Committee meeting on 7 July 2015 that the reference cited for modelling utilities by the AG supported the utility values used; however, this reference did not support the methodology used by the AG.

Modelling of health state utility by the AG involved estimating a baseline utility for each patient based on age and gender, with a disutility applied for functioning graft, dialysis or new-onset diabetes after transplantation (NODAT). In contrast, the method used by Novartis linked kidney function (assessed by the estimated glomerular filtration rate) to utility (Neri 2012). The method used by Novartis is more clinically justifiable, as it accounts for a number of disease states, which capture the wide variation in QoL associated with a functioning graft, and the long-term nephrotoxicity of calcineurin inhibitors (CNIs), which can affect renal function; thus, it enables the model to be more sensitive to changes in the patient's health. Patients enter the model with a similar utility value in both analyses; however, the approach adopted by Novartis observes a faster decline in utility, reflecting the deteriorating kidney function in transplant patients. Patients in the AG model with a functioning graft follow a pattern of utility changes reflective of the natural decline in QoL in the general population; only a small utility decrement is applied to the QoL of patients with a kidney transplant. The AG's model is structurally insensitive to the differences between the

technologies and regimens in terms of their impact on renal function. This insensitivity was noted in discussions at the committee meeting held on 7 July 2015.

Moreover, the approach taken by Novartis is based on a tested methodology that clearly found chronic kidney disease (CKD) severity was negatively associated with the EQ-5D_{index} in a sample of UK patients (Neri 2012), while a further study found that impaired renal function is associated with worse self-reported outcomes after kidney transplantation (Neri 2011). Neri 2012 was cited by the AG in its report when critiquing the fact that some of the literature identified had not allowed for the impact on health-related QoL (pp 334 of the assessment report), but this was not used by the AG in its model. In addition, in the recently updated NICE guideline for CKD (NCGC 2014), different utility values were assigned to patients at different CKD stages, further supporting the approach that declining kidney function affects the QoL of patients and is the most appropriate method to modelling health utilities for this patient population.

The AG correctly noted that there may be some uncertainty associated with the Novartis approach during the later years of model extrapolation. However, all models in renal transplantation are characterised by uncertainty, and non-linearity was also found in the AG model. This uncertainty has been interrogated through the use of probabilistic sensitivity analysis. We request the Committee recommends a re-design to the AG's model, to account for the association of renal function with utilities, incorporating the resultant ICERs in its decision-making. Results of such a re-designed model would offer a fair reflection of the evidence for cost-effectiveness of an initial approach to maintenance therapy.

Alternative treatment options for subgroups of patients

In the ACD, NICE has effectively recommended only one treatment combination for maintenance therapy in patients with a renal transplant. This recommendation does not account for patients for whom either tacrolimus or mycophenolate mofetil (MMF) are clinically inappropriate. These subgroups include patients at risk of intolerance to CNIs due to nephrotoxicity (Ponticelli 2011, Pascual 2009), patients with gastrointestinal (GI) disturbances (Ponticelli 2005, Shehata 2009) and patients at high risk of cytomegalovirus (CMV) infection (Vitko 2005, Tedesco Silva 2010 and 2013). In such patients, a regimen of immediate-release tacrolimus, combined with MMF and steroids cannot be considered as a realistic option for a cost-effectiveness comparison, as it is not the most appropriate clinical option for these patients. Published evidence (referenced above) and clinical experience demonstrate that certain subgroups of patients will benefit from alternative therapeutic options.

If the ACD recommendations were to be carried forward unchanged to final guidance, the result could be a reduction in five-year graft survival for these groups of patients, as they would be

unsuitable for the only reimbursed immunosuppressive regimen. It is well recognised that there is an ethical duty to the transplant recipient, the donor and their families to preserve transplanted organs and we anticipate it is not the intention of NICE to produce final recommendations, which could worsen long-term outcomes in kidney transplantation.

Novartis, therefore, requests that NICE reconsiders its recommendations by making available alternative treatment options in subgroups of patients for whom tacrolimus or MMF are clinically inappropriate, with the following arguments in mind:

1. NICE noted in the ACD (pp 44) that there are no noticeable differences in clinical effectiveness between enteric-coated mycophenolate sodium (EC-MPS) and MMF; hence, if patient outcome alone is taken into consideration, EC-MPS should be used instead of the currently recommended MMF, as it has a better GI safety profile (Ponticelli 2005, Shehata 2009).
2. In patients for whom MMF is clinically inappropriate due to GI disturbances or intolerance, EC-MPS should be used instead of MMF.
3. In patients at high risk of CMV infection, treatment with everolimus should be considered as an option instead of tacrolimus.

Novartis has previously submitted cost-effectiveness analyses and clinical evidence to support the consideration of these subgroups and while we agree with the AG that there is a greater level of uncertainty associated with these analyses, such uncertainty does not lessen the need for additional recommendations appropriate to those subpopulations of patients.

We challenge NICE's decision to recommend only one maintenance regimen with no tailoring to the clinical needs of patient subpopulations. Treatment options for renal transplant patients have become well established over time and allow transplant patients to live for an increased number of years with a better QoL, optimising graft survival and use of the precious resource of donated kidneys. We welcome continued dialogue with NICE on this technology appraisal to keep options available for renal transplant patients.

Yours faithfully,

[REDACTED]
[REDACTED]

Novartis Pharmaceuticals UK Limited

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Response to:

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

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

Prepared by:

Sandoz Ltd

14 August 2015

Response to the Appraisal Consultation Document: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Commercial in confidence information is highlighted and underlined, e.g. XXXXXX

Any reference to the Assessment Report is referred to in the format: [page X, Section X.X]

Medicinal product:	Tacrolimus monohydrate
Brand name:	Adoport [®]
Manufacturer:	Sandoz Ltd
Date:	14 August 2015

Letter of response

Dear Sirs,

We would like to take this opportunity to thank the National Institute for Health and Care Excellence (NICE) and the Appraisal Committee for their time and commitment to this submission process.

Upon reviewing the Appraisal Consultation Document (ACD), Sandoz Ltd welcomes the Appraisal Committee's preliminary recommendations regarding immediate-release tacrolimus (TAC) products.

Sandoz Ltd wishes to comment upon one area of the ACD:

1. National tender agreement

The ACD reports that Advagraf (a prolonged-release TAC product) is available at a discounted price through a national tender agreement [Page 6 Section 3.16]. Sandoz Ltd notes that Adoport is also available to all UK hospitals at a discounted price through a national tender agreement. It is requested that NICE considers also referencing the availability of this discounted price for Adoport into the ACD.

Yours faithfully,

██████████ ██████████

██████████ ██████████ ██████████, Transplant • Sandoz Limited



Meindert Boysen
Programme Director, Technology Appraisals
Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BD

26th August 2015

Re: Response to the ACD for: Kidney transplantation (adults) - immunosuppressive therapy (Review of TA 85) [ID456]

Dear Meindert,

Sanofi welcomes the opportunity to provide comments on the Appraisal Consultation Document (ACD) for the above appraisal. We have structured our comments in line with the questions for consultation. We are concerned that the Appraisal Committee was unable to support a positive recommendation for rATG, even in the patient group they believe it may offer particular clinical utility; i.e. those at high risk of acute rejection. The Appraisal Committee explains that they take this view because there is insufficient evidence, yet make no specific reference to the good quality RCT examining treatment effectiveness in this group. In combining the effectiveness from all trials of rATG, including patients with various risk levels, the evidence for this higher risk group may have been overlooked in the Appraisal Committee's deliberations. We would therefore request that the Appraisal Committee consider again the available evidence in patients at high risk and review their recommendation for rATG.

Please let me know if you have any questions regarding our comments.

Yours Sincerely,

A black rectangular box redacting the signature of the sender.

Sanofi

Sanofi – 26 August 2015

Response to the ACD: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Sanofi welcomes the opportunity to respond to the Appraisal Consultation Document (ACD). We have structured our comments in line with the specific questions posed by NICE. In addition a number of minor comments on the ACD are noted at the end of this document.

1. Has all the relevant evidence been taken into account?

As highlighted by ourselves and other consultees, and in line with the international KDIGO guidelines (KDIGO 2009), rATG may be particularly beneficial in patients with a high risk of acute rejection. Although the ACD acknowledges that rATG may be beneficial in high risk patients it states that there is insufficient evidence on which to base specific recommendations for this population. Sanofi believes that there is indeed robust evidence available to support a recommendation for rATG in patients at high risk of acute rejection. This evidence is summarised below.

A relatively large (278 patients), well designed, RCT has compared rATG to basiliximab (Brennan 2006). The trial specifically only included patients at high risk of acute rejection or delayed graft function. The Brennan trial demonstrated that patients who received rATG induction experienced a lower rate of acute rejection when compared to those who received basiliximab induction (Brennan 2006). No differences in terms of mortality or graft loss were identified. The key results from the Brennan trial are provided in the table below. Although studies of daclizumab (another IL-2 receptor antagonist) are not in scope for this appraisal, it should be noted that comparisons of rATG with daclizumab, also in a high risk population, are consistent with the Brennan findings (Noël 2009).

Table 1: Results from the Brennan 2006 trial (basiliximab vs. rATG)

	OR*	Lower 95% CI	Upper 95% CI
Mortality	1.03	0.32	3.28
Graft loss	1.28	0.51	3.19
BPAR	1.86	1.02	3.37

*An OR greater than 1 favours rATG

The Assessment Group's analysis of rATG combined studies that recruited patients with very different risk profiles, and as different risk groups might be expected to have different outcomes the resulting effect size is both imprecise and uncertain. Both of the studies comparing rATG to no induction were conducted in patients with a mixed risk status (Charpentier 2001; Charpentier 2003) and the further two studies comparing rATG to basiliximab were conducted in patients with low/moderate risk status (Lebranchu 2002; Mourad 2004). We believe that the data for high risk patients should be considered in a separate analysis, particularly as it is in this population that rATG is currently used in clinical practice.

Sanofi request that the Appraisal Committee reconsider the available evidence for rATG in patients specifically at high risk of acute rejection where the benefits of rATG are likely to be more manifest.

2. Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

Clinical-effectiveness

As outlined above Sanofi believes that combining studies that recruited patients with different risk profiles generates unnecessary uncertainty and would suggest that the Appraisal Committee consider the available evidence for patients at high risk of acute rejection. rATG induction has been shown to significantly lower the risk of acute rejection when compared to basiliximab induction, in this patient group (Brennan 2006).

Cost-effectiveness

Sanofi would like to highlight a number of issues with respect to the assessment of cost-effectiveness which are outlined below.

1. Sanofi propose that an analysis of cost-effectiveness based on the results of the Brennan trial could feasibly be conducted and would enable the Appraisal Committee to consider providing a recommendation for rATG in high risk patients. The present cost-effectiveness results are associated with a high degree of uncertainty as they rely on efficacy estimates derived from meta-analyses that incorporate studies that recruited patients with very different risk profiles. An analysis incorporating the results of the Brennan trial (Table 1) would likely demonstrate that rATG is a cost-effective treatment for high risk patients when compared to basiliximab.
2. The Appraisal Committee concluded that basiliximab and rATG have similar efficacy. However, this is at odds with the results of the economic model that indicate that basiliximab is associated with more QALYs than rATG. This appears to be driven largely by an assumed difference in graft function at 12 months between basiliximab and rATG. Importantly this assumption is based on the results of one study (in a low/moderate risk population) that did not find a statistically significant difference in terms of graft function between basiliximab and rATG (Lebranchu 2002). To explore the impact of this assumption, we propose that a sensitivity analysis is conducted that explores the impact of assuming that rATG and basiliximab have equal graft function at 12 months. Changing this single assumption could dramatically reduce the ICERs for rATG versus no induction to levels where rATG would either dominate or be associated with ICERs less than £20,000/QALY (depending on the maintenance regimen used). Furthermore this single modification could mean that rATG was no longer dominated by basiliximab.
3. The Assessment Group's analysis assumes that CMV prophylaxis costs are greater for patients treated with rATG induction. Sanofi believe that this assumption is questionable. As highlighted by a consultee (Page 949 of the committee papers) the prophylaxis and monitoring of CMV is likely to be variable and could differ in centres where rATG is used routinely, and/or at different doses. As seen in the older trials (Charpentier 2001 and 2003) typically higher doses of rATG are used, resulting in approximately 30% CMV infection rates. The more recent Brennan 2006 trial (which used a lower dose in line with current practice) reported a 7.8% rate of CMV infection, with prophylaxis provided for patients who were seropositive or were receiving a seropositive graft. Of note here, the basiliximab group, who were treated equivalently in terms of prophylaxis, reported a CMV infection rate of 17.5%. It appears contrary to the evidence available that the higher cost for CMV prophylaxis associated with rATG induction versus no induction can be justified, and we propose that CMV prophylaxis costs should be equal to those for no induction and those for basiliximab. The impact of such a modification to the AGs model would likely result in a 15-30% reduction in the incremental costs associated with rATG (depending on the comparison) and in combination with the modifications suggested above would further improve the cost-effectiveness of rATG.

The Assessment Group's scenario analyses were limited to those exploring the impact of alternative drug acquisition costs and structural assumptions regarding the surrogate effects of acute rejection, NODAT and graft function on graft survival. Sanofi believe that the additional sensitivity/scenario analyses outlined above would provide important information on the potential for rATG to be a cost-effective treatment option for patients who have a high risk of acute rejection. In particular we believe that a scenario analysis based on the Brennan 2006 data would provide the most informative assessment of the relative cost-effectiveness of rATG.

Sanofi would like to emphasise that under plausible conditions it is likely that rATG could be considered cost-effective for the subgroup of kidney transplant patients that are considered high risk.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The 2014/15 NHSBT activity report demonstrates that there is a high risk population of patients in the UK. The report shows that there were over 500 transplants from cardiac death donors in patients with level 3 or level 4 HLA mismatch (NHSBT 2015). This is clearly a group of patients who are at high risk who would potentially benefit from having the option of rATG induction. The KDIGO guidelines, which are followed by a group of UK transplant clinicians, recommend the use of ATG induction for these patients (KDIGO 2009). The proposed 'not recommended' guidance for rATG would deny patients who are at high risk of experiencing acute rejection access to a clinically and cost-effective treatment option.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

None known.

Minor comments

Section	Comment
Section 4.5 of the ACD highlights the non-significant results of two of the three trials comparing rATG to basiliximab (Lebranchu 2002; Mourad 2004) but fails to highlight the significant result in terms of acute rejection from the third study (Brennan 2006).	We recommend that in order to present a balanced view of the available data the results of the Brennan 2006 trial should be highlighted here.
In section 4.61 the ACD states that kidney transplants from living donors have become more common in recent years.	We would like to highlight that the latest report from the NHSBT states that kidney transplants from living donors accounted for 35% of kidney transplants in the last year (April 2014 - March 2015). The number of transplants from deceased donors has increased from 1526 in 2005/2006 to 2069 in the last year (2014/15) with the number of cardiac death donors increasing from 128 to 510 over the same time frame (NHSBT 2015).

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British Kidney Patient Association
3 the Windmills,
St Mary's Close, Turk Street
Alton, Hants GU34 1EF
25th August 2015

Response to NICE TA85 review on use of immunosuppressive therapy for adult kidney transplant patients

The British Kidney Patient Association (BKPA) is a national charity which works to improve quality of life for kidney patients through advocacy, direct grants, educating and informing patients, counselling and funding patient-centred research, healthcare professionals and projects.

The BKPA is very concerned about the conclusions of the Advisory Group, that just 3 drugs (basiliximab, immediate-release tacrolimus and mycophenolate mofetil) are recommended, that 6 other drugs which are currently available will no longer be recommended and that 3 further drugs presently being used have no recommendation attached to them. We believe that this will remove from kidney patients and their clinicians some really important choices to preserve their transplants. We also do not think that the conclusions take into account the costs in quality of life and side effects as well as costs to the system of the patient returning to dialysis if a transplant fails (dialysis is estimated at £30,800 pa not including transport costs, certain drugs, and the cost to carers <http://www.england.nhs.uk/wp-content/uploads/2014/04/a07-renal-transpl-ad-0414.pdf> and the costs of a failed transplant at £17,000).

A kidney transplant is a scarce resource and considered the gold standard treatment for those who are fit enough to be able to receive one. The numbers of transplants fell in the year 2014/15. The strain on resources means a greater reliance on extended criteria kidneys, which need close management to ensure that they are not rejected by the recipient's immune system. The ability of a clinician to be able to use induction and maintenance therapy from the range of treatments is paramount. We do of course support the principle that a clinician should use a cost effective approach to the use of NHS resources but the current practice of swift intervention at the earliest sign of transplant rejection is testament to the increasing levels of experience and success in maintaining those with transplants.

We note that 3 existing drugs that have been used for a long time, ciclosporin, prednisolone and azathioprine are not mentioned in the recommendations. This omission does not give clarity for kidney patients and is not explained. It would therefore be possible that funding for these drugs could also be withdrawn.

1.3, note 3 We note that the reference to shared decision making in the original NICE TA on immunosuppressant therapies from 2004 is missing from this appraisal. In this example we can find just one reference to 'informed consent' and none to sharing decisions with patients.

1.4 The statement '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' will mean that patient access to any of these drugs will necessitate Individual Funding Requests and processes that patients will have to go through. However if a clinician needs urgent access to these therapies the current IFR process will not work. The effect of this on transplant outcomes will be significant and unprecedented including loss of transplants, increased mortality, and greater costs elsewhere in the system, not counting the effect on society of a transplant organ being lost due to a completely inappropriate funding

mechanism.

1.5 We recommend this statement about patients currently on a range of medications 'continue treatment until they and their NHS clinician consider it appropriate to stop' should say 'unless' rather than 'until' as it could imply that patients will be expected to stop these medications.

4.15 We note the AG point that the wide heterogeneity of evidence meaning that 'limited conclusions' can be made – and yet the AH did make conclusions, including some on products that were shown to be clinically effective but were not recommended.

The BKPA notes the helpful comment in the original TA85 appraisal from 2004, that 'the drug which is the least likely to have serious side effects on that particular person should be used'. The principle of adjusting treatment to the patient has been lost from this new TA.

The BKPA agrees with the points made by the Renal Transplant Clinical Reference Group, which is unable to make recommendations about the use of specific brands or combinations of immunosuppressant, but recommends the following principles to decide which immunosuppressants are employed in local protocols:

1. All clinicians must make cost effective use of NHS resources. Each transplant unit should initiate and maintain immunosuppression with the most clinically cost effective regimen for that patient.
2. Multiple or frequent changes of supplier of critical dose immunosuppressants should be avoided as they can confuse transplant recipients and may lead to adverse outcomes such as acute rejection or nephrotoxicity.
3. There are sub-groups of transplant patients who may benefit from regimens that are more expensive in the short term but which may be more cost-effective in the long term by maximising graft survival.
4. This guidance should not result in only one brand of a critical dose immunosuppressant being prescribed across the country, where more than one brand is available that fulfils the current European Medicines Agency (EMA) criteria for bioequivalence, and should not be used to facilitate this position. Multiple brands are acceptable; provided cost-effectiveness is the outcome and this does not compromise patient safety.
5. Where switching within a transplant or renal unit from one critical dose immunosuppressant to another occurs, it is recognised that support will be needed to facilitate this change. Resultant savings must be shared across the NHS including the unit where the switch is undertaken.
6. All prescribing of critical dose immunosuppressants must be by brand name.

We support the comments on the limitations in the way the AG has used the evidence that our colleagues at the British Renal Society have submitted.

We take these conclusions so seriously that we would like to suggest NICE holds a further evidence session with some of the patient and professional kidney charities. The BKPA would be willing to host this if that would be helpful. As you know, we have already nominated patient experts to attend the closed sessions but we do not feel the joint concerns which patients and professionals share on this draft recommendation have been accounted for.

Yours sincerely

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Tel: ■■■■■■■■■■

Kidney Research UK response to NICE consultations on ID346 immunosuppression (children & adolescents) and ID456 (adults)

14th August 2015

Kidney Research UK was disappointed to learn of the NICE recommendations arising from this review. Our concern is that patient choice will be adversely affected by this decision, namely because prolonged-release technologies are no longer approved.

On page 18 of ID456, the report states, “Once-daily (prolonged-release) tacrolimus and the once-monthly regimen for belatacept may help improve adherence.” However, with only immediate-release technologies now to be approved, patients who are more likely to benefit from prolonged-release, will be disadvantaged and may face increased risk of graft failure, especially amongst the younger patients.

On page 38, para 4.54 of ID346, it states, “The Committee also heard that it is important to minimise the side effects of immunosuppressive therapies, such as reduced growth and an increased risk of new-onset diabetes. Several submissions from consultees advised that poor adherence (that is, not taking the prescribed medication) is a major cause of graft loss, especially in young people. The Committee heard that different people have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The Committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.”

We wonder why this view provided by the consultees is not reflected in the recommendation.

The decision also limits the options open to clinicians to offer patients a choice of formulations in order to aid medicines compliance and adherence.

NICE itself has produced a guideline on patient choice and adherence concerns:

<https://www.nice.org.uk/guidance/cg76>

And we note the emphasis on patient choice on the NHS website:

<http://www.nhs.uk/choiceintheNHS/Pages/Choicehome.aspx>

In responding to previous consultations we have been keen to see patient choice reflected in lessening the pill burden e.g in the area of phosphate binders. Amongst dialysis patients, non-adherence is significant; in a survey in 2010, 76% of nephrologists and 63% of dialysis staff thought non-adherence with phosphate binders was the main reason for poor control of phosphate in renal patients. These recommendations on immunosuppression do nothing to reduce the pill burden and would appear to increase it for those currently on prolonged-release treatment.

NKF's response to the ACD – Immunosuppressive therapy for kidney transplant in adults

1.0 Has all of the relevant evidence been taken into account?

There appears to be a lack of evidence given that only 11 trials adequately matched the search criteria. Given this fact how valid can the recommendations be when they are serious concerns from stakeholders such as us?

2.0 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Our concern is around interpretations made from poor quality evidence available, and therefore how valid the summaries of clinical and cost effectiveness can be when the primary evidence is lacking.

3.0 Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

From our assessment the view of the NKF is that these preliminary recommendations are too restrictive and do not allow flexibility of treatment that will provide the most effective way of preventing rejection in a diverse patient group – we find this deeply concerning. We firmly believe that for such a specialised area of healthcare standardised protocols are not always suitable and the proposed recommendations are potentially damaging for patients requiring unique and tailored protocols.

We firmly believe it is essential NICE guidance on the use of immunosuppressive therapy maximises the rate of success for every single kidney transplant and acknowledges the huge difference a successful transplant can make to an individual, their family, wider society and the NHS.

As such we firmly believe that our patients should be supported, according to their individual need and tolerability, to enable both the best clinical outcome possible that will enable sustained life and quality of life.

Kidney transplantation for those who are suitable is the best possible treatment for end stage kidney failure. The gift of life provided either by deceased or living donation although considered priceless, does have a cost. First year cost estimates are broad ranging dependent on what is included; a cost up to 20k would be conservative with yearly follow-up cost significantly less and dependent on the maintenance protocol usually estimated at 5k/year. While significant, these costs together with the gains in quality of life undercut the yearly 30k cost of dialysis hugely over a five year period.

Assessing whether the provisional recommendations are sound and of a suitable basis for guidance to the NHS cost, outcomes and patient choice are essential considerations and influence our response accordingly.

We have assessed the appraisal committee's preliminary recommendations. We broadly support recommendations 1.1 1.2 & 1.3.

However in its' current form there are a number of concerns which are principally drawn from recommendations contained within 1.4 & 1.5 which appear both unworkable and damaging in terms of choice and individualisation to patient need.

We find the report/recommendations perplexing. The committee state that they "understand the value of having a choice of immunosuppressive therapies" (section 4.56), however they provide such a narrow view that there is in effect no choice for our patients or at least presumably no choice that will be funded.

For patients who cannot tolerate Tacrolimus and/or MMF and began to see worrying signs of an increasing creatinine there appear to be no options to tailor their drug regimen.

For new patients with their first skin malignancy there is now, it would appear, no option of using Sirolimus.

The NKF strongly believe the inclusion of prolonged release Tacrolimus should be reconsidered. We feel omission would significantly compromise the ability of clinicians to individualise drug regimens to complex individual need.

For those in transition and young adults in particular adherence to twice daily tacrolimus has been reported as challenging, especially the evening dose, which compromises treatment and long-term graft survival.

Failure to recommend prolonged release Tacrolimus for new kidney patients could potentially result in up to 30% of patients missing out on a drug which makes it easier to take (reducing pill burden) and therefore significantly improves adherence, optimising the likelihood of graft survival.

The NKF campaigns for the best treatment and access to services for patients and their carers. Improving access to transplantation and rates of organ donation in the UK is a central strand of our campaigning. There remains a shortage of organs available for transplantation and we believe every single opportunity should count to make a difference to the individual in need and validate the act of organ donation. To that end premature graft failure results in unnecessary suffering and distress as patients return to dialysis and the transplant waiting list. It is our opinion that there are presently (and in the future no doubt) drugs available which reduce the chances of failed grafts which in the long-term are cheaper than cost associated with dialysis. The widely reported total annual cost of dialysis is in the region of £30k.

The chronic shortage of donations has resulted in the increasing use of more marginally viable organs for transplant. These organs require increased management of the immunosuppressant regimen to ensure long-term graft survival. We therefore question the validity of recommendations 1.4 & 1.5 and omissions of other drugs that may future proof this guidance.

Ciclosporin, Azathioprine and Prednisolone have not been included within the recommendations even though both drugs are in common use. Prednisolone and azathioprine are used in new and maintenance transplant populations. Most centres will have protocols which use tacrolimus however there are instances where patients still need to be

switched to Ciclosporin. Similarly a number of centres use azathioprine as the anti-proliferative of choice in low risk patients, which is cheaper than generic MMF. There are also clinical situations where MMF needs to be switched to azathioprine - such as pregnancy or gastrointestinal complications. We therefore strongly urge a recommendation that states these drugs can still be used.

4.0 Any other comments

None

Name	Dr [REDACTED]
Organisation	British Renal Society
Role	NHS professional
Job title	[REDACTED]
Location	England
Conflict	No
Disclosure	I have received support to travel to the World Transplant Congress 2014 and American Transplant Congress 2013 from Astellas
Comments	<p>726</p> <p>I write on behalf of the British Renal Society (BRS), to provide feedback on the Appraisal consultation document on immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85).</p> <p>The BRS is a federation of 16 professional and patient groups involved in kidney care including kidney transplantation. You will receive feedback from BRS member organisations however I write on behalf of our wide constituency.</p> <p>I note there are significant limitations in the literature relating to outcomes following kidney transplantation, particularly beyond the first post-transplant year. This reflects the influence of historical FDA criteria for assessing immunosuppression in the context of kidney transplantation. Understandably the advisory group limited its assessment to 86 randomised control trials of which only 11 adequately matched the population and current practice in the NHS. The limitations of these studies resulted in the development of an economic model that has significant shortcomings arising from assumptions that are described in sections 4.27 and 4.28. These shortcomings are exacerbated by significant heterogeneity in the studies used to inform the model. It is therefore not accurate in section 4.61, to describe this model as providing a robust analysis of cost effectiveness. It may or may not be superior to other models presented by the interested parties however it must be limited by shortcomings in the data and inherent in the assumptions used beyond the first year. The model is not robust nor could it be. Indeed the limitations inherent in the assumptions made to generate this model beg the question as to whether other forms of data might provide a more valid estimate of outcome, particularly when considering groups that do not tolerate primary therapy.</p> <p>A more important concern relates to the way in which the literature has been interpreted with respect to broader clinical practice, even within the setting of the studies reported in the literature. As an example I will refer to the Symphony study, the “low dose tacrolimus” arm of which closely resembles the apparent conclusion of the appraisal: “Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as options to prevent organ rejection in adults having a kidney transplant”.</p>

In the Symphony study additional therapy was required in 7.5% - 30.3% of patients and the study drug was discontinued in 16.4% - 24.6% of patients. In the "low dose tacrolimus"™ arm 20.0% withdrew from the study protocol and the rate of discontinuation directly attributed to an adverse event, coexisting illness or treatment failure was 10.4%. The results of this and similar studies can therefore only be interpreted in the context of normal clinical practice involving the ability to change therapy according to conventional clinical indication.

This point relates directly to the statement in section 4.61, "there is a particular need for additional treatment options when these complications arise. However (the committee) was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations"™. This needs to be placed in context, that there is no such direct evidence because it would be considered unethical not to offer an alternative available medication. This is because there are logical conclusions to be made from interpretation of a series of controlled studies. For example, there is good historical evidence for substantially better outcomes using regime incorporating calcineurin inhibitors than with corticosteroids and anti-metabolites alone. There is now evidence that regime using alternative immunosuppressive agents deliver outcomes that approximate to the use of calcineurin inhibitors. Albeit that in those who can tolerate immediate-release tacrolimus there is a health economic argument in its favour. In those intolerant of immediate-release tacrolimus there is however a reasonable inference that these agents are effective and in all likelihood cost effective, although this has not been approached. I am concerned that the Peninsula Technology Appraisal Group does not seem to have acknowledged these issues. I note their stated position on the size and complexity of the appraisal with consequent delay to the initial meeting of the appraisal committee meeting. The narrow approach used in the analysis presented may be suitable when applied to risk factor management in the general population but its failure to acknowledge the importance of the complete patient pathway, significantly limits the real world applicability of this analysis. I doubt this shortcoming would be considered acceptable by renal transplant recipients or importantly donors and their families.

The donor and recipient population in Symphony are somewhat different to current UK practice (for example in the number of donors after cardiac death) in such a way that it is likely that expected rates of conversion from the aforementioned recommended immunosuppression may be even higher than those described above, particularly over the course of long-term follow-up. It is therefore likely that somewhat more than 10.4% of the population will require a significant change to their immunosuppression. The reductive description of this issue as "microangiopathy" is sufficiently rare to be effectively managed through individual funding requests"™ (Section

	<p>4.63), does not coherently represent the problem or solution. This is an important question because “Individual Funding Requests”™ will lead to significant differences in access to therapy across the jurisdiction and delay timely implementation of any necessary alteration to treatment. It does not seem appropriate that a situation likely to arise in more than 10% of the population is dealt with through IFRs™. The guidance must allow for other immunosuppressive agents to be used under appropriate expert guidance simply to be consistent with the evidence on which it the advisory committee’s™ conclusions are based, let alone any advice from the professional groups involved in kidney care. It is not reasonable for the committee to abrogate responsibility for this matter and yet expect individual commissioners to address these questions. If the committee were so minded it might though be reasonable to mandate the prospective reporting of data on immunosuppression, to identify systematically outlying practice. There are excellent mechanisms in place through UK renal registry and NHSBT by which to do so.</p> <p>In short, whilst the initial conclusion that “Basiliximab, immediate-release tacrolimus and mycophenolate mofetil are recommended as options to prevent organ rejection in adults having a kidney transplant”™ may be a reasonable generalisation in uncomplicated kidney transplantation, the unconditional description of other forms of immunosuppression as not recommended, cannot be supported. Finally, recommendations regarding immunosuppressive therapy must depend upon assured, consistent supply of an actual medicinal product (AMP) to individual patients.</p>
Submission date	26/08/2015



The British Transplantation Society, Chester House, 68 Chestergate, Macclesfield, Cheshire, SK11 6DY
☎ 01625 664547 ✉ secretariat@bts.org.uk

BTS Response to NICE Guidance, ID456 Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85) preliminary recommendations

The BTS has considered the preliminary recommendations from NICE and has significant concerns. In their current format, some of the recommendations are impractical, and do not reflect the real world or established clinical practice. If all these recommendations are adopted, it will have a detrimental effect on patient and transplant outcomes.

Over recent years, there has been an increase in the number of high risk transplants, This has led to the tailoring of immunosuppressive regimens, thereby making successful transplantation possible in all groups. The guidelines as they are currently written are likely to have a major detrimental effect on such patients.

Four specific questions were asked:

- Has all the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination...?

We will respond to these in turn:

- **Has all the relevant evidence been taken into account?**

The recommendations rely upon Randomised Control Trials (RCT) and published evidence, which is, by the report's own admission, limited. Only 11 of the 86 RCTs assessed adequately matched the population and current practice in the NHS. It has discounted the relevance of clinical experience and expertise, particularly with respect to the use of agents that have been in routine use for many years such as Ciclosporin (Neoral), Azathioprine and rATG which are established and effective therapies. Clinicians have gained a breadth of experience with combinations of immunosuppressive drugs outwith RCTs and non-formulary preparations, but which are nevertheless established and effective in clinical practice. The flexibility achieved with the range of preparations currently available has contributed significantly to the improved long term graft and patient survival that is being achieved and may ultimately reduce the need for re-transplantation. This in the light of the organ shortage is an important goal.

- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

The majority of the RCTs used for the analysis employed a relatively short period of follow-up, and recruited highly selected low-risk transplant patients. This does not truly reflect the real world. Given the limited evidence available, clinical effectiveness of different regimens is underestimated and the cost effectiveness of the recommended regimens is overstated. Cost comparisons do not take into account the improvement in long-term outcomes that have been achieved by access to multiple agents and flexibility in prescribing for individual patients as was reflected in the 'Symphony study' and other similar designed studies.

- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

We believe that the recommendations are highly restrictive and are neither sound nor suitable as guidance to the NHS.

There are several clinical situations in which renal transplant experts use a wider range of immunosuppression, tailoring it to the needs of the individual patient: for example: re-introducing Ciclosporin A when appropriate, the ability to withdraw corticosteroids and use alternate regimens for patients with NODAT, Obesity, and T1DM, the use of rATG for steroid resistant rejection and as an induction agent along with Alemtuzumab for those at high risk of rejection such as the highly sensitized patients, or ABOi and HLAi transplants.

The decision not to recommend drugs like Advagraf, Envarsus and Alemtuzumab for new patients significantly compromises the ability to tailor immunosuppressant regimens in response to complex individual patient needs. Approximately 5 to 30% of patients find adherence to a twice-daily tacrolimus regimen challenging, which, in turn, compromises the clinical effectiveness of immediate release therapy. This significant group of patients would achieve a better clinical outcome from a prolonged-release formulation of tacrolimus based on a once-daily dosage. Advagraf is the only oral therapy under appraisal that has been shown to improve adherence and minimise the risk of transplant failure in the non-adherent and high variability cohort. The lack of acknowledgement of the proven link between adherence and graft failure is disappointing.

While we realize that clinical trials are rarely powered for specific subgroups analysis, the use of bespoke interventions can never realistically be evaluated by clinical trials. The current recipient population in the UK is now much more heterogeneous and many fall into 'high risk' subgroups. The chronic shortage of donor organs has resulted in the increasing use of extended criteria organs for transplant. These organs require tighter management of the immunosuppressant regimen to ensure long-term graft survival.

The statement that '*Treatment should normally be started with the least expensive product*' which appears in recommendation 1.2 and 1.3 must not result in only one brand (the cheapest and least effective) being used nationally and compromise patient safety. Recommendations 1.4 and 1.5 are unrealistic and would disadvantage a significant number of patients with a profound effect on long-term outcome. Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept all allow for clinical flexibility with up to 10% of the transplant population requiring their use at some stage to prolong graft outcome.

- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination?**

The recommendations will prejudice against women who wish to become pregnant following renal transplantation, as this requires modification of immunosuppression; it will prejudice women who are highly sensitized because of previous pregnancies and require alternative immunosuppression to reduce the risk of rejection; it will prejudice against patients with glucose intolerance.

In summary

The choice to recommend only *Basiliximab, immediate-release tacrolimus and mycophenolate mofetil* is appropriate for many patients who are undergoing a renal transplant with low immunological risk, and is in keeping with the practice of many units. However, it is overly restrictive and inappropriate given the evidence base used to support the option appraisal and we feel as a society we cannot support this. The recommendations would preclude prescribing flexibility according to inter-patient variability, immunological risk and other co-morbidities and this will have a direct impact on long-term patient and transplant outcomes.

Other comments

1. The clinical experts used by NICE did not include a nephrologist, pharmacist or nurse who are the main prescribers and monitor immunosuppressive therapy – and therefore fails to capture the views of healthcare professionals with the most direct experience of using the therapies being appraised.
2. The Society would support the amendment of recommendation 1.4 to '*Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not **routinely** recommended to prevent organ rejection in adults having a kidney transplant*'.
3. As a Society we would support a robust audit of non-recommended immunosuppressant drugs usage and outcomes, which would be beneficial to patients, clinicians and commissioners.



 , British Transplantation Society
On behalf of the Executive and Council

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 ACD

From: [REDACTED] [REDACTED] on behalf of The Efficacy and Safety of PRescribing In Transplantation (ESPRIT) Group

As an independent group, the ESPRIT Group (www.esprit.org.uk) does not advocate any particular product and our opinions, recommendations and activities are all our own. As such we could not contribute to NICE's assessment of the *comparative* efficacy and cost-effectiveness of individual immunosuppressants included in the MTA. However, where the efficacy and safety of treatment of transplant patients is potentially threatened, we feel it of vital importance to highlight our concerns and the principles underlying them.

We strongly believe that the current draft guidance should be reassessed, for the following reasons:

- The over-prescriptive and restrictive nature of the guidance would destroy clinicians' ability to provide tailored immunosuppression for individual transplant patients. One of the major advances of the past decades, as experience with immunosuppression has grown, has been the increasing adoption of a flexible approach to immunosuppressant management by transplant professionals. The draft guidance just does not reflect this informed best practice approach, which has undoubtedly led to today's increasing success in managing transplant patients, often over many decades of life. For example, when creatinine rises on an upward curve or a patient cannot tolerate their current regimen, immunosuppression is currently adjusted using the spectrum of immunosuppressants available. It would be a backwards move if a patient who was, for example, seriously GI-intolerant on MMF could not be tried on mycophenolate sodium or, when all other regimens had failed to provide optimum immunosuppression, that sirolimus or belatacept could not be resorted to.
- Non-adherence with immunosuppression regimens can be an issue in all age groups and can have real clinical implications for the integrity of transplanted organs. However, this is especially so in adolescent transplant patients, who may be classified as 'adults' technically and managed in adult services, but who have very special management needs befitting their actual age. They are sometimes seen in special young persons' clinics to try and avoid loss of organs and are very often put on once-a-day medication regimens, including prolonged-release tacrolimus, to try and maximise the likelihood of adherence.
- Whilst this ACD relates to renal transplantation, there would be a knock-on impact on other solid organ transplants if the choice of immunosuppressants funded were to be strictly limited. Certain drugs currently used routinely in e.g. liver transplants, would just become

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Multiple Technology Appraisal (MTA)

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RESPONSE TO ACD

unavailable, even if they could be used in theory – to the detriment of the patients involved.

- Transplantation immunosuppression is a very specialist area, with just a handful of companies investing in R&D programmes to help advance immunosuppressant practice. The potential impact on innovation generally in solid organ transplantation should not be underestimated in our opinion, at a time when the government is actively promoting wider organ donation.
- We welcome the ACD acknowledgement of our previous submissions in relation to switching from proprietary brand to generic immunosuppressants, but would challenge the Committee's conclusion that it:

“ did not need to make additional recommendations about the bioequivalence of generic immunosuppressive therapies, and considered that if different preparations are equally suitable, it would be reasonable to recommend using the product with the lowest acquisition cost”. The rationale for this decision is quoted as being that *“clinicians are aware of the risks associated with generic prescribing and switching formulations. The Committee understood that guidance on good practice in prescribing generic immunosuppressive therapies is routinely followed in clinical practice”*

We would question whether *all* clinicians really are aware of the full risks involved in uncontrolled switching and the difference between bioequivalence in healthy volunteers and clinical equivalence in transplant patients, as laid out in our original submission. We would urge NICE to reconsider this and include something about generic immunosuppressants, if only for the true critical dose drugs – ciclosporin and tacrolimus. Failure to do this could just result in another case of organ rejection, similar to the one in 2011 when a patient lost their transplanted kidney due to *clinical inequivalence* between different (licensed) immediate-release tacrolimus products.

- Finally, it should be recognised that the cost of immunosuppressant therapy is minimal in comparison with the overall costs of managing a transplant patient – circa 5%. Whilst we totally endorse the need for cost-effective management and fully support the appropriate use of generic immunosuppressants, we urge NICE to allow flexibility for the relatively few patients who really need an immunosuppressant that is not necessarily one with the lowest direct purchase price.

Dr [REDACTED]

[REDACTED]
Renal Association

[REDACTED]
23rd August 2015

RE: Appraisal consultation document Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

I write on behalf of the Renal Association in response to the above consultation. The Renal Association is the Professional Body of UK Renal Physicians & Scientists, representing the UK Renal Unit Clinical Directors, the UK Renal Registry & the Renal Research Community. Its members are responsible for the clinical management of patients before and for long term care following kidney transplantation including the critical & complex issue of immunosuppression.

We congratulate the AG on extensively reviewing RCTs in this area and developing a financial model to guide the process. However, the Renal Association does not believe that the proposed guidance is fit for purpose for use by the UK Renal Transplant community as it stands & requests significant revision.

The guidelines summary recommends the use of *'basilixumab induction, immediate release tacrolimus (least expensive product) & Mycophenolate mofetil (least expensive product). 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'*.

This guideline proposal represents a restrictive & substantial departure from previous guidance, NICE technology appraisal guidance 85 (2004). The recommendations which are solely based on randomised controlled trials, do not reflect the many clinical complexities of the transplant pathway, nor the requirement for considerable clinical experience of the transplant community to achieve optimum clinical outcomes. Inevitably surrogate measures of long term outcomes are used & a financial model based on acquisition costs for immunosuppressant drugs that are not applicable to many Trusts has led to inevitable conclusions. We believe the guidelines to:

1. Be too restrictive in recommended immunosuppressant drug usage so as to inadequately cover the broad range of clinical status of donor kidneys and transplant recipients.
2. To be clinically unworkable particularly where there is a need to change initial post-transplant immunosuppressant therapy (up to 1 in 5); the IFR mechanism is suggested but is not appropriate to deal with up to 20% of the 3121 transplants in 2014.
3. Be inconsistent. Immunosuppressive therapy for kidney transplant in children and young people (review of technology appraisal guidance 99) states 'an alternative

product could be prescribed if the child or young person is not able to swallow capsules and needs an oral suspension'. Young adults, 16-18y may be transplanted in either adult or paediatric units or transfer shortly after to adult care if the latter.

Renal transplantation is the optimal treatment for suitable patients with end stage renal failure (ESRF), being associated with improved quality of life & longevity as well as substantially reduced costs compared with dialysis treatment. Transplant kidneys are heterogeneous, originating from deceased donors (brain stem death or cardiac death) of standard or extended criteria or from live kidney donors. The recipients have a wide range of aetiology of ESRF, variable comorbidities & age from young to older adults & immunological rejection profile. Randomised controlled trials have simply not adequately covered the breadth of clinical scenarios commonly encountered in clinical practice. As such highly restrictive prescribing guidance based on these trials could not be expected to cover the whole scope of clinical practice. The guidance states: *'The Committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups'*.

'The Committee understood that some treatments are associated with complications and so must be avoided or withdrawn for some people. The Committee was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations.' Lack of published subgroup data from RCTs in such a complex clinical area does not equate to no effect. In these situations experienced clinical knowledge must be cautiously exercised rather than deny access to other therapies in a blanket fashion. We note, *'The AG emphasised that there was not enough evidence available for robust sub group analysis.'* We believe that more flexibility in use of immunosuppression is required in the final guidance. Tailoring of treatment to the patient based on RCT evidence AND clinical experience, where not covered by RCT evidence is surely a reasonable clinical approach. Commissioning by evaluation, where Trusts are required to report immunosuppression treatment and outcomes in this group through NHSBT/UK Renal Registry returns may be an approach to improve the evidence base.

The guidelines do not sufficiently address what happens to patients who do not tolerate or have prior contraindications to the recommended immunosuppression. In routine clinical practice a substantial minority of patients are intolerant of initial therapy & require drug changes. Drug trials in this area report up to 20% of patients unable to tolerate an initial drug regime. Reasons include drug allergy, gastrointestinal intolerance, bone marrow suppression, CNI-induced thrombotic microangiopathy, drug adherence issues, nephrotoxicity to name but a few. In these settings alternative therapies including mTOR inhibitors, belatacept, and prolonged-release tacrolimus must be available to the clinical team often at short notice. There is good clinical experience of the effectiveness of conversion to these other agents in this setting. Guidance comments only on CNI-induced microangiopathy and that drug change in this situation could be managed by the IFR route. This is wholly inadequate. Most of post-Transplant immunosuppressant drug changes are for other reasons. There were 3,121 renal transplants performed last year. Let us say 15% of incident patients required immunosuppression drug change (over 450 cases) and 3% of prevalent patients (900 cases) per annum, the IFR system is wholly unsuitable to manage. The IFR system is slow & could not possibly cope (nor was designed) with the clinical timescale, often required within 1 day. The resources required of NHSEngland and of each

transplant Unit merit close thought. We believe that a broader initial guidelines would obviate the need for many IFR requests which is not a suitable route to manage the patient numbers.

The age of greatest risk of transplant loss is between 14 and 25 years. This loss relates to challenges in adherence to immunosuppression. The Care Quality Commission & Renal Association documents the need to provide greater focus and support on this high risk group. This includes tailoring immunosuppression in some cases to improve adherence. Recent data confirm improved outcomes for young adults post transplantation by individualised care, part of which includes focus on immunosuppression. The current guidance limits ability to do this. It is highly unlikely that a formal RCT will be sensitive enough to extract the influence of tailored drug therapy from the other aspects of young adult care.

We are worried by the statement that that treatment should be started with the least expensive product of mycophenolate mofetil and immediate release tacrolimus. There are many formulations of both & complete equivalence have not been shown. It is recognised good practice that patients should not transfer between these formulations of the same drug. Patients become very anxious about preparation exchange of these lifesaving drugs & increased pharmacokinetic monitoring is required. We believe that the statement should be qualified so as to ensure that primary care or pharmacists do not repeatedly change from one formulation to another as costs change.

We are rather surprised that ciclosporin is not mentioned as a suitable first line agent. Whilst acute rejection rates are higher than for tacrolimus treated transplants, the risk of post-transplant diabetes is lower and a substantial proportion of prevalent patients receive the micro-emulsion & a smaller number the original Sandimmun formulation. Is exclusion of mentioning azathioprine, a widely used transplant immunosuppressant intentionally omitted?

The guideline identifies no significant difference in efficacy or side effect profile of mycophenolate mofetil or mycophenolate sodium. The latter is not recommended on cost grounds. Would an approach whereby guidance suggests the use of either, whichever formulation has the lowest cost be a reasonable approach? By doing so the guidelines will be more future proof should the relative price of either change?

In summary, we support the development of updated renal transplant IS guidelines by NICE. The draft guidance is not sufficient to support expert clinical practice. The limitation on recommended baseline IS taken together with the lack of an adequate mechanism (or guidance) for tailoring IS where drug changes are required necessitates significant amendment.

Dr [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED]

Renal Association



Royal College
of Physicians

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

Danielle Conroy | Committee D Administrator
National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

From [REDACTED]
Dr [REDACTED]

Danielle.Conroy@nice.org.uk

1 September 2015

Dear Danielle,

Re: ACD - Consultees & Commentators: (Kidney transplantation (adults) - immunosuppressive therapy (Review of TA 85)) [ID456]-response request

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 31,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I'm writing to confirm that the RCP would like to endorse the Renal Association's response to the above consultation.

Yours sincerely

[REDACTED]
Dr [REDACTED]

NHS England Response to NICE ACD – Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

Please find NHS England's response to the ACD – Immunosuppressive therapy for kidney transplant in adults which has been reviewed by the Renal Transplant CRG. The Renal Transplant CRG membership includes clinical leaders within the transplant field from all areas of England, representatives of professional organisations and patients.

Has all of the relevant evidence been taken into account?

One of the main concerns and limitations of this work is the paucity of published RCT evidence and it is acknowledged in the ACD that of the 86 randomised controlled trials identified, there were only 11 that adequately matched the population and current practice in the NHS in England. This work has reviewed seven different interventions for maintenance therapy and in addition prednisolone, azathioprine and ciclosporin remain in regular use, and considering the majority of these will be given in dual or triple therapy regimens – then it is clear that there is an incomplete evidence base if there are only 11 adequate studies as this will not cover the permutations of immunosuppressive regimes in current established clinical use. The majority of the relevant RCTs have looked at the effect of one investigational drug compared to the direct comparator, used relatively short outcomes, and recruited selected low-risk transplant patients who are not truly representative of the real world transplant population. Marketing authorisation has been based on the results of these limited RCTs, but the clinical transplant community has gained wide experience in the use of these drugs both within and outwith marketing authorisation. The flexibility with the range of agents and preparations that is currently available is one of the reasons why long term graft and patient survival has improved. However it is recognised that this wealth and breadth of experience has been gained, generally without RCTs and other clinical studies and therefore there is not the published evidence to back up established and effective clinical practice.

There is mention of ciclosporin, azathioprine and prednisolone within the ACD and the MTA document, but they have not been formally assessed as technologies and therefore not included within the recommendations. NHS England therefore assumes that these interventions remain available to the NHS as per NHS England policy.

As a corollary within the ACD, rATG is described as a new technology as it has only received market authorisation since the last NICE guidelines, whereas it has in fact been in routine clinical use within transplantation for both the prevention and treatment of acute rejection for over 25 years.

The AG recognised that there was not enough evidence available for robust subgroup analyses and this is understood. Clinical trials are rarely big enough to power for specific subgroups and the specific use of interventions can never realistically be evaluated by clinical trial because of the logistics involved. We would however argue that there is evidence to recommend rATG in two particular subgroups, and this view was supported by consultees reported in the ACD.

- i) Those who are at higher risk of acute rejection such as those who are of high immunological risk. In section 3.1 of the ACD it is stated that Basiliximab is only licensed in patients with PRA <80%, so the group of high immunological risk patients do potentially benefit from the use of rATG induction. The Brennan (2006) paper (Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation. N Engl J Med 2006; 355:1967-1977) compared the safety and efficacy of Basiliximab and antithymocyte globulin in patients with a high risk of acute rejection or delayed graft function who received a renal allograft from a deceased donor. The antithymocyte globulin group, as compared with the Basiliximab group, had lower incidences of acute rejection (15.6% vs. 25.5%, P=0.02) and of acute rejection that required treatment with antibody (1.4% vs. 8.0%, P=0.005). The outcomes of this study were limited in looking at 1 year graft and patient survival only in addition to biopsy proven rejection, but other evidence would suggest that episodes of severe rejection or any rejection where renal function is not restored to baseline is associated with poorer long term graft survival.
- ii) The subset of patients who would benefit from early steroid withdrawal e.g. the obese and those at high risk of new onset diabetes after transplant (NODAT). There is limited published evidence to confirm this strategy works, but it has been the practical experience of clinical members of the CRG.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

One of our main concerns is how reasonable interpretations can be made of the poor quality of evidence that is available, and how valid the summaries of clinical and cost effectiveness can be when the primary evidence is poor. We have attempted to explain in the previous section some of the reasons why the evidence base is limited and is likely to remain so, and why there needs to be flexibility in the use of existing established agents. We accept that newer and more expensive interventions coming to the market do need to be evaluated in a different way, but have concerns about agents which have been used in routine practice for many years.

The authors of the MTA wrote of the evidence: There are a number of limitations:

- Due to level of reporting detail, we were unable to perform subgroup analysis according to donor or HLA matching.
- Study design and participant characteristics varied widely across studies, leading to substantial heterogeneity
- The 89 included RCTs were of variable quality, but all appear to be flawed. However, due to reporting omissions, for most of the trials it was difficult to make a general assessment regarding quality. The quality appraisal should, therefore, be noted with caution
- Very few trials reported longer term follow up, with the majority reporting data at one year.

Furthermore the authors of the ACD stated, 'The AG acknowledged that there were limitations and uncertainties in its analysis. It stated that its analysis did not consider changes in graft function over time, the effect of steroid reduction, differences in the severity of acute rejection, stopping or switching treatment (including delayed introduction of sirolimus) or the effect of medication adherence, and did not fully model all adverse

events. The AG also noted that there was not enough evidence to support subgroup analyses. The AG highlighted that the calculation of costs did not include transport costs for haemodialysis or continuing immunosuppressive therapy after graft loss.'

As acknowledged many of the interventions are used outside their marketing authorisations, and this is expanded in more detail in the next section and a number of the draft recommendations are made based on use outside marketing interventions. As a result of this there is not the evidence available for sub-group analysis and the summaries of clinical and cost effectiveness seem to have been made assuming a homogenous population with a homogenous use of interventions; whereas clinical practice deals with a heterogeneous population (differing medical and immunological risk factors) with heterogeneous uses of interventions.

Section 3.34 states 'Costs for all of the technologies may vary in different settings because of negotiated procurement discounts.' There then appears to be an inconsistency between how the different maintenance interventions that are currently in use and funded by NHS England have been costed. For immediate release tacrolimus and mycophenolate mofetil the average cost paid by the NHS is used; whereas for prolonged release tacrolimus, mycophenolate sodium, sirolimus the BNF prices are used. Could we clarify that where average cost paid by the NHS is used that this will include discounts applied; whereas this is not the case where BNF prices are used? As immediate release tacrolimus and mycophenolate mofetil are recommended and the other four interventions are not recommended, could it be that the cost effectiveness has been exaggerated where average costs paid by the NHS is used compared with BNF prices?

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

We are content in broad terms with the proposed recommendations 1.1, 1.2 and 1.3, but have significant concern with recommendation 1.4 that we believe would be unworkable in the NHS. Recommendation 1.5 would cover existing patients, but the flexibility of treatment options would be lost for future patients which we believe would be deleterious for patient outcomes.

We are very concerned that the recommendations do not make any allowances for patient variability, patient choice, the need to individualise immunosuppressants to patient need or patient tolerability of immunosuppression, despite the best efforts from patients and clinical experts present to explain to the contrary. In section 4.56 the Committee acknowledged that immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people. The Committee understood the value of having a choice of immunosuppressive therapies and yet this understanding does not translate into recommendation 1.4.

We have already commented in the first section about where the established agents of prednisolone, azathioprine and ciclosporin fit in with the recommendations, and if excluded would also make these guidelines unworkable for the NHS.

We would like to comment on each of the six immunosuppressive agents that are not recommended to prevent organ rejection in adults having a kidney transplant.

Rabbit anti-human thymocyte immunoglobulin

We agree that there is no clinical indication for the use of rATG for the prophylaxis of

rejection as induction therapy for the majority of patients, where Basiliximab is indicated instead. However as we attempted to demonstrate earlier in this response we feel strongly that there is a case for continuing the current clinically effective and selective use of rATG in particular circumstances such as for those patients who are receiving a high immunological risk transplant, or those where early steroid withdrawal is clinically indicated.

We would also wish to confirm that the use of rATG for the treatment of steroid resistant acute rejection is not covered by the scope of this review and will continue

Prolonged-release tacrolimus

The evidence that prolonged-release tacrolimus improves adherence and reduces variability of drug exposure has been discussed thoroughly in both the review and the ACD. Other evidence shows that non-adherence and increased variability do impact upon long term graft survival, but we are not aware of evidence to date in kidney transplantation (although there is some evidence in liver transplantation) that demonstrates long term improved outcomes with prolonged-release tacrolimus. This may reflect a lack of causality or the inability to do subgroup analysis. It is known from studies of adherence that it is the evening dose of drugs that is more frequently missed and that adherence is a particular problem in older teenagers and young adults.

We therefore feel that there is a case to be made for the use of prolonged release tacrolimus in this subgroup of patients where adherence is a problem. A number of units give these patients prolonged-release tacrolimus, azathioprine and prednisolone with good effect meaning that all immunosuppression can be given as a single dose in the morning.

Mycophenolate sodium

We agree that mycophenolate mofetil should be used first line for the prevention of rejection. There is though widespread clinical experience across the UK that mycophenolate sodium benefits some people who have gastrointestinal adverse reactions with MMF. One of the common and significant side effects of MMF is of diarrhoea/abdominal pain and when dose reduction and/or dose splitting does not improve symptoms, switching to mycophenolate sodium does resolve these symptoms in a significant proportion of patients. We feel there is a strong case for mycophenolate sodium being available for those patients with intractable gastrointestinal reactions with MMF.

Sirolimus

In clinical practice Sirolimus is not prescribed as per the marketing authorization in that it is not given in combination with ciclosporin at the time of transplantation due to drug side-effects e.g. wound dehiscence and impeding renal recovery during delayed graft function. Sirolimus is currently used in clinical practice in a number of specific situations which arise 3 months or more after transplantation. These include:

- Substitute for MMF/mycophenolate sodium where these are not tolerated
- As a tacrolimus/ciclosporin sparing agent to preserve renal function.
- When a patient has developed malignancy, particularly for skin cancer, as there is some evidence for an anti-tumour effect
- In difficult to manage cases of ganciclovir CMV resistant disease or persistent CMV viraemia sirolimus has been used as maintenance immunosuppression to reduce CMV viral load, with good effect

On that basis we would agree that it should not be used in the initial post-transplant phase for prevention of rejection, but there are a limited number of post-transplant scenarios where clinical experience has shown a benefit to patients.

Everolimus and Belatacept are both new drugs that are not in routine use although there are potential benefits as demonstrated in clinical trials, but these are not currently funded by NHS England. However rATG, prolonged-release tacrolimus, mycophenolate sodium and sirolimus are all funded by NHS England, and are used in the particular scenarios discussed above.

Any other comments

The Renal Transplant CRG earlier in the year agreed on guidance relating to prescribing of immunosuppressants in renal transplantation, by way of a specialised services circular (see below). This was agreed by clinical leaders representing all areas of England, patients and commissioners. This guidance covers the reasoning behind some of the concerns discussed above. We would ask NICE to consider supporting this guidance.

Summary

Renal Transplant CRG

Guidance on Prescribing of Immunosuppressive Therapy for Kidney Transplant Recipients

The CRG cannot make recommendations about the use of specific brands or combinations of immunosuppressant, but the following principles should be used to decide which immunosuppressants are employed in local protocols:

1. All clinicians must make cost effective use of NHS resources. Each transplant unit should initiate and maintain immunosuppression with the most clinically cost effective regimen for that patient.
2. Multiple or frequent changes of supplier of critical dose immunosuppressants should be avoided as they can confuse transplant recipients and may lead to adverse outcomes such as acute rejection or nephrotoxicity.
3. There are sub-groups of transplant patients who may benefit from regimens that are more expensive in the short term but which may be more cost-effective in the long term by maximising graft survival.
4. This guidance should not result in only one brand of a critical dose immunosuppressant being prescribed across the country, where more than one brand is available that fulfils the current European Medicines Agency (EMA) criteria for bioequivalence, and should not be used to facilitate this position. Multiple brands are acceptable; provided cost-effectiveness is the outcome and this does not compromise patient safety.
5. Where switching within a transplant or renal unit from one critical dose immunosuppressant to another occurs, it is recognised that support will be needed to facilitate this change. Resultant savings must be shared across the NHS including the unit where the switch is undertaken.
6. All prescribing of critical dose immunosuppressants must be by brand name.

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	█
Name	██████ ██████
Job title or role	██████ █████ ██████████ ██████████
Email address	████████████████████

NICE HEALTH TECHNOLOGY APPRAISAL	
COMMENTS ON ACD	
IMMUNOSUPPRESSIVE THERAPY FOR KIDNEY TRANSPLANT IN ADULTS	
TO: NICE	FROM: HEALTHCARE IMPROVEMENT SCOTLAND
26 AUGUST 2015	

Expert comment provided to HIS by:



1. Do you consider that all the relevant evidence has been taken into account? *If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?*

I think this is a reasonable view. However, it is more a pharmacy/economic perspective rather than that of a practising clinician. Transplant outcomes have improved year-on-year across the world in a way that owes more to the application of local guidelines and tailored immunosuppression, particularly the target drug levels. I would have drawn on published and available immunosuppressive protocols (from the Scottish centres) as well as the trial data.

The other data which you might have drawn on are those on bioavailability, and known interactions with food, of the immunosuppressant generics. As someone who sits on an MHRA committee I think your front page advice to use the cheapest drug is dangerous. Unless, it is followed with the recommendation to use the

same generic rather than to risk random substitution of generics with varying bioavailability.

2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? *If not, please explain.*

I think there is considerable use of once daily Tacrolimus – particularly for younger people with compliance issue. I think that mTOR usage amongst experienced transplant clinicians will probably continue at around 5% of the total population, for the indications of malignancy particularly skin malignancy which is very common, and preventing viral infections. The cost of treating CMV and malignancy was not factored into your analyses, despite evidence that mTOR inhibitors will half the recurrence rate of skin tumours.

3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? *If not, in which areas do you consider that the summaries are not reasonable interpretations?*

I think they are technically OK. However, there is widespread agreement that the current trial end-points of rejection, graft loss and death have limited applicability for the future development of immunosuppression (by the regulatory authorities in Europe and the US) and so reliance on these for your analyses for your economic analyses means they are based on historical datasets that may not reflect current outcomes or the population of transplant recipients.

4. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? *If not, why do you consider that the recommendations are not sound?*

Basiliximab, Tac and MMF is standard practice for most patients. The rest of the agents are necessary for at least some patients. The recommendation to sue the cheapest drug without highlighting the dangers of variable bioavailability in generics is dangerous.

5. Are the patient pathways and treatment options described in the assessment applicable to NHS Scotland? *If not, how do they differ in Scotland?*

I don't think Scotland differs from the UK. However, many patients are managed by clinicians, increasingly, who are not particularly experienced in transplantation, with the growth of transplantation and the geographical delivery of services.

6. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? *If so, please describe what these changes would be.*

Frankly, I don't think people will pay much (if any) attention to these guidelines and will carry on with their local practices.

7. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? *If yes, please explain why this is the case.*

No

7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment

I would have included local protocols.

Response to National Institute for Health and Clinical Excellence Appraisal Consultation Document

Immunosuppressive therapy for kidney transplantation in adults (review of TA85)

Comments from Chiesi Limited

August 2015

Marketed product: Envarsus[®] (tacrolimus (as monohydrate)) prolonged release tablets

Commercial in confidence information is highlighted in blue

Academic in confidence information is highlighted in yellow

Thank you for the opportunity to comment on this Consultation. Please find our responses to the Consultation questions below. In summary we have four main concerns:

- The analysis did not include data on all prolonged-release (PR) tacrolimus and therefore the conclusions cannot apply to all PR-tacrolimus. In particular there is evidence of reduced treatment failures in key subgroups (older patients, black patients) with Envarsus (tacrolimus as monohydrate) compared to immediate-release (IR) tacrolimus as well as a different impact on CNS tolerability with improved quality of life compared to IR-tacrolimus. These factors would contribute to different evaluations in a pharmacoeconomic (PE) model
- Some of the assumptions within the pharmacoeconomic model are flawed and therefore the recommendations based on the outputs of that model are flawed
- The proposed guidance does not accord with other NICE guidance (CG76 Medicines Adherence and CG138 Patient experience in adult NHS services)
- The methodology is contradictory with regard to the rationale behind the inclusion/exclusion of different products which is potentially discriminatory

Responses to the specific questions in the ACD are as follows:

1. Has all of the relevant evidence been taken into account?

1.1 The AG decided to use only RCTs in the assessment and in particular, not to use pharmacokinetic (pk) studies. This approach is limited in three ways:

1.1.2 Firstly, many RCTs have a limited duration (1-2 years) so would not necessarily detect differences that may be seen over the lifetime of a graft (say 10 years).

1.1.3 Secondly, RCTs are not always powered to detect differences between treatments. Regulatory studies are typically powered for 'non-inferiority'.

1.1.4 Thirdly, looking specifically at calcineurin inhibitors (CNIs), nephrotoxicity is a complex interplay between acute toxic effects, cumulative exposure and the level of immunosuppression. Put plainly, too much drug damages the kidney, not enough drug and the immune system damages the kidney. There is a strong correlation between whole blood levels of tacrolimus and nephrotoxicity [Przepiorka 1999, Bottiger 1999]. Not all tacrolimus formulations are the same. Even where bioequivalence has been demonstrated between different IR tacrolimus products, differences in pk could have an impact on long-term outcomes. For example, for equivalent oral dose and trough levels, Tacni® (Teva) had a significantly higher ($p < 0.01$) Cmax of $30.2 \pm 11.6 \mu\text{g/L}$ compared to $19.6 \pm 6.6 \mu\text{g/L}$ with Prograf® (Astellas) (ratio 1.49. 90% confidence interval 1.35-1.65) [Robertsen 2015]. This difference would not be seen in routine monitoring which measure trough levels, yet in this study, resulted in peak tacrolimus levels substantially over 20ng/ml which could have a deleterious effect on long-term renal function.

1.1.5 So in the absence of long-term trials, for products with a narrow therapeutic window, it would be prudent to use a wider scientific evidence base to help guide choices of treatment that could have meaningful long-term impacts on graft and patient survival and on graft function.

1.2 Point 3.16 states:

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

1.2.1 Bibliographic literature searching was conducted on April 14th 2014 and updated 18th November 2014. Envarsus received a Marketing Authorisation (MA) in June 2014, therefore Chiesi Limited feel that the data for Envarsus (also described as LCP-Tacro in clinical studies) should have been included. Particularly since part of the rationale for this Guideline update is to reflect changes in the availability and licensed indications of immunosuppressants (some new, some withdrawn).

1.3 Furthermore there appear to be inconsistencies in the approach taken, in that everolimus was included in the appraisal despite Certican® not receiving an MA until November 2014 (also after the scope was finalised), whereas alemtuzumab was not included in the appraisal and part of the rationale for its omission was that it did not have

an MA for immunosuppression even though the AG had been granted a dispensation from the Department of Health to consider immunosuppressants outside of their MA. [Point 4.57 of the ACD also explains that part of the rationale not to include alemtuzumab was that it is not routinely available for transplant patients. However, alemtuzumab is routinely used in several transplant centres so its omission does not reflect clinical practice.]

1.4 Point 4.6 states:

'The Committee noted that there were no consistent differences between immediate- and prolonged-release tacrolimus'

1.4.1 As Envarsus data was not included in the Appraisal, this statement is inaccurate. It was derived from data only on Advagraf® yet as written applies equally to all prolonged-release tacrolimus preparations including Envarsus.

1.5 In Section 4.62, the Committee noted that there were very little subgroup data and had not found enough evidence to inform robust subgroup analyses.

1.5.1 Subgroup analysis of Phase III trials with Envarsus shows significantly fewer treatment failures in older kidney transplant recipients (≥ 65 years) and in black kidney transplant recipients compared to Prograf (Bunnapradist 2013, Budde 2014).

1.5.2 Data from two Phase III studies (Bunnapradist 2013, Budde 2014) were pooled to examine efficacy in specific patient subgroups, this has been presented in a poster (Bunnapradist 2014) and review paper (Grinyó 2014). This analysis, which included 861 patients (Envarsus $n = 428$; Prograf $n = 433$; 38% of patients were stable [Bunnapradist et al], and 62% were *de novo* [Budde et al] kidney transplant recipients) found that treatment failure (death, graft failure, centrally read BPAR, or lost to follow-up) at 12-months was significantly lower with Envarsus among black kidney transplant recipients (treatment difference and 95% CI: -13.82% [-27.22%, -0.31%]) and older (≥ 65) kidney transplant recipients (-13.46% [-25.27%, -0.78%]). Please note there were no significant differences identified in these subgroups in the individual studies.

1.5.3 Black kidney transplant recipients (KTR) tend to have poorer outcomes than non-black recipients, require higher oral doses of tacrolimus to achieve the same tacrolimus trough levels and tend to have higher C_{max} than non-black KTR (see section 3.3.3)

1.5.4 A study in African American kidney transplant recipients (the ASERTAA Study, Trofe-Clarke 2015) identified that:

- Approximately 80% of African American patients in the study were carriers of the CYP3A5*1 genotype (the variant associated with rapid tacrolimus metabolism)
- Regardless of expressor status, these data in African Americans are consistent with the results from previous Envarsus pk studies, showing improved bioavailability, lower peak concentrations, and less peak-to-trough fluctuation compared to immediate-release tacrolimus
- Envarsus pk parameters were less impacted by CYP3A5 genotype than IR-tacrolimus
- IR- tacrolimus was more affected by expression of the *1 allele, driven primarily by the need to increase the dose to achieve therapeutic trough levels, which also resulted in an incremental increase in tacrolimus intra-day peak levels.

1.5.5 Neurotoxicity

The exact mechanism by which tacrolimus induces neurological adverse events (AEs) remains unknown; however, it has been observed that many symptoms occur or are most pronounced at peak serum tacrolimus blood concentrations and symptoms generally improve when the tacrolimus dose is reduced or when tacrolimus is withdrawn (Bechstein 2000, Eidelman 1991).

1.5.6 Envarsus tremor data

A study evaluating the effect of switching patients with tremor from IR-tacrolimus to Envarsus demonstrated an improvement in the tremor score, quality of life and patient and physician global indices.

1.5.6.1 Tremor is listed as a very common side-effect ($\geq 10\%$) for Envarsus (Envarsus SPC). A two-sequence, open-label, multicenter, prospective Phase IIIb study (Langone 2015) was conducted in which stable kidney transplant recipients on Prograf or generic tacrolimus, experiencing tremor, were enrolled. Following 7 days of their pre-enrolment twice-daily tacrolimus, patients were switched to Envarsus at the 1:0.7mg/mg conversion ratio to maintain the same tacrolimus trough levels.

1.5.6.2 Tremor pre- and 7-days post-conversion was evaluated by two independent, blinded neurologists using the gold standard Fahn-Tolosa- Marin tremor rating scale and by an accelerometry device that measures frequency and amplitude of tremor (Tremorometer™). Patients completed the Patient Global Impression of Change (PGI) scale and physicians completed the Clinical Global Impression of Improvement (CGI) scale; both are 7-point scales assessing tremor change ranging from very much improved (1) to very much worse (7). Quality of life was assessed by the patient-completed Quality of Life in Essential Tremor (QUEST) scale, a subjective quality of life instrument consisting of 30 items divided into five dimensions (communication, work/finance, hobbies/leisure, physical and psychosocial). Data were available on 38 patients. There was a significant improvement in tremor as indicated by significant decrease (improvement) in the Fahn-Tolosa-Marin score and the Tremorometer score, and significant improvements in the PGI, CGI and quality of life in essential tremor scores.

1.5.6.3 This study is believed to be the first trial in kidney transplant recipients that utilises a sophisticated and reproducible measurement of tremor and Envarsus is the first tacrolimus to show that tremor can be reduced in patients without compromising the immunosuppression by lowering the dose (and therefore trough levels) of tacrolimus.

1.6 Can we learn anything from liver transplantation?

1.6.1 Data has been published showing a beneficial effect of PR-tacrolimus (Advagraf) in liver transplant recipients with regards to renal function and biopsy-confirmed acute rejection (Trunecka 2015).

1.6.2 Furthermore, data has also been published in liver transplant recipients that show significantly lower graft failures and mortality rates at 3 years with PR-tacrolimus compared to IR-tacrolimus. [Adam 2015]

While these data are in liver transplant recipients, it cannot be discounted that a similar mechanism could be seen in kidney transplants with similar results.

1.7 Envarsus formulation

1.7.1 The Guideline implies that all prolonged-release tacrolimus preparations are the

same. Envarsus is the first oral solid-dose formulation that is not mg:mg dose equivalent to existing capsule formulations. The greater bioavailability of tacrolimus in Envarsus, means that Advagraf- or Prograf-treated patients should be converted to Envarsus on a 1:0.7 mg:mg ratio.

1.7.2 Envarsus has a lower C_{max} and a longer T_{max} as well as a lower total daily dose requirement than Prograf or Advagraf.

1.7.3 The differences in the pharmacokinetics of Advagraf[®], Prograf[®] and Envarsus are further highlighted in the ASTCOFF study to be presented at ESOT 2015. (Tremblay 2015)

1.7.4 Furthermore Envarsus is the only tablet formulation of tacrolimus and does not contain gelatin, therefore it would be suitable for those who wish not to ingest gelatin due to religious reasons or reasons of conscience (e.g. Muslims, vegetarians). (See sections 3.3.1 and 3.3.2)

1.8 Envarsus (tacrolimus prolonged-release tablets) was not considered in the evidence submitted. Therefore Chiesi Limited would suggest that if recommendation 1.4 is to be implemented, it be amended to specify 'prolonged-release capsules' as Envarsus was not considered in this data and is a tablet prolonged-release formulation of tacrolimus.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

2.1 The ACD states that PR-tacrolimus is not recommended, however only Advagraf is used in the model, i.e. evidence on the costs and effects of Advagraf. The model does not provide evidence on the cost-effectiveness of any other prolonged-release tacrolimus. We suggest that if the proposed guidance is implemented unchanged, it is made clear in the ACD recommendations that Envarsus was not included in the cost-effectiveness analyses.

2.2 Some relevant comparators were not included in the assessment, BAS+PR-TAC+MMF+ST. The exclusion of this comparator underestimates the potential total QALYs that could be achieved with PR-tacrolimus. It is also likely that this comparator would represent the least costly PR-tacrolimus strategy. Given other suggested changes in the model this combination with PR-tacrolimus may be considered by the committee to be on the cost-effectiveness frontier.

2.3 Relative Cost of PR tacrolimus

2.3.1 In the reference case there is an inconsistency in the source of the price of drugs. The source of the price of tacrolimus is EMIT while the source of the PR tacrolimus is BNF. There is an expected bias that BNF will be higher than EMIT. This overestimates the cost of PR tacrolimus.

2.3.2 The ERG tested a scenario using the 'List price' of immediate-release tacrolimus (IR-tacrolimus). In this analysis the ERG chose the lowest list price of IR-tacrolimus. They have not weighted the price by market share as was done in the reference case. This underestimates the price of IR-tacrolimus. Changing the price of IR tacrolimus to that of Prograf (the most commonly prescribed IR-tacrolimus) results in the discounted total cost of IR-tacrolimus + MMF +ST increasing from £92,226 to £110,544 and PR-tacrolimus

being less costly (IR-Tac+MMF+ST = £110,544 compared to PR-Tac+MMF+ST = £109,113)

2.3.3 It is important to note that the price of PR-tacrolimus used in the model is the BNF price of Advagraf and does not represent the price of all available PR-tacrolimus agents available. If the price for Envarsus were to be evaluated in the model, the price/mg would need to be adjusted to reflect the greater bioavailability and the subsequent reduced total daily dose of Envarsus compared to other IR- or PR-tacrolimus (Approx 30% less than Prograf or Advagraf (Envarsus SPC, ASTCOFF study))

2.4 Relative effectiveness of PR-tacrolimus

2.4.1 The ERG state that they 'made no attempt to explicitly model adherence to immunosuppressive medication due to the absence of evidence on this outcome in RCTs included in the systematic review of clinical effectiveness'. Further the ERG state that factoring in greater adherence 'departs from the ITT analysis of the trials', however the goal of a model is not to replicate trial evidence but to use the trial evidence to reflect clinical practice, i.e. effectiveness. This suggests the need to consider the evidence on adherence and to incorporate observational data. In the ACD the committee suggest the effect of adherence is uncertain, however although the magnitude of effect is uncertain, there should be little debate about the direction of effect, i.e. that better adherence is better for patients clinically. The ERG note that 'there is some evidence that non-adherence is a cause of late acute rejection and graft loss'.

2.4.2 The clinical experts commented that patients would benefit from once a day treatment, although the committee stated that these patients could not be identified as a sub-group. The additional quality of life benefit of once a day treatment has not been included in the model. This represents a known benefit that has not been captured and should be considered by the committee. Without this quality of life benefit the current model underestimates the benefits of PR-tacrolimus compared to IR-tacrolimus.

2.4.3 The ERG relied on a single head-to-head study between PR-tacrolimus and IR-tacrolimus to estimate the effectiveness of PR-TAC (Kramer 2010). The ERG excluded other trial evidence and observational evidence that is particularly useful when adherence is important. PR-TAC has not been included in the network meta-analysis although the ERG did identify a multicentre study that compared PR-TAC and cyclosporin ME (AG report, page 349).

2.4.4 No quality of life related to eGFR states are taken into account, although there is evidence that higher eGFR results in better quality of life. (Gorodetskaya 2005). The exclusion of quality of life benefit associated with eGFR underestimates the benefit of PR-tacrolimus.

2.4.5 The overall population used to calculate the head-to-head OR of death of PR-tacrolimus compared to IR-tacrolimus was not the primary endpoint population and included patients with major protocol violations (Kramer 2010). The per-protocol population used to estimate the primary endpoint had 3 deaths in each population of 291 and 280 patients. Using this data decreases the odds of death of PR-TAC+MMF+ST from 1.286 to 1.047. This increases the discounted QALYs of PR-TAC+MMF+ST to 10.8305 compared to 10.8884 for IR-TAC+MMF+ST.

2.6 Conclusion

2.6.1 The population used to estimate the primary endpoint of Kramer 2010 was not used in the model. Doing so decreases the odds of death of PR-tacrolimus and increases the

total QALYs for PR-TAC+MMF+ST.

2.6.2 When the BNF price of the most commonly prescribed IR-tacrolimus is used PR-tacrolimus becomes relatively less costly.

2.6.3 When these two scenarios are combined, PR-tacrolimus is less costly and less effective than IR-tacrolimus. The difference in NHB is 0.0038 at a £20,000 threshold and 0.0218 at a £30,000 threshold. However, this does not include the additional benefits of PR-tacrolimus that the model does not incorporate, such as reduced mortality and graft loss of adherence, and improved quality of life from improved eGFR states and once daily dosing.

2.6.4 It is also known that dosing in certain subsets of the general population is different. In particular, black (higher tacrolimus dosing) and obese (lower tacrolimus dosing) patients tend to have different requirements. These subsets could have been analysed separately to identify disparities.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

3.1 The practice across UK transplant centres varies. While the proposed guidance reflects the predominant practice with regard to initiation with tacrolimus (most centres initiate with IR-tacrolimus) it does not recognise that many of those centres also have a policy of initiating or switching to PR-tacrolimus for certain subgroups of patients, usually those at high-risk of non-adherence or a history of non-adherence through a combination of personal circumstances (e.g. shift workers), age (younger adults/adolescents), personality, and lifestyle. Although the AG had difficulty identifying these subgroups in clinical trials, clinicians can identify these patients in practice and many have protocols in place for such groups.

3.2 There is a need for heterogeneity in the guidelines to treat the plethora of different clinical scenarios in kidney transplantation (including age, ethnicity, type of graft etc.). The proposed NICE guidance would discriminate against certain subgroups if implemented as proposed (see below).

3.3 The guidelines do not reflect the principles set out in Section 1.3 of NICE clinical guideline 138 *Patient experience in adult NHS services: improving the experience of care for people using adult NHS services* Issued: February 2012. The proposed guidance does not tailor treatment to the individual and furthermore ignores the particular clinical issues facing the management of certain subgroups such as black or older KTR.

3.3.1. We know from the ELITE-Symphony Study, (Ekberg 2007) that a low-dose tacrolimus-based immunosuppression regimen is associated with better renal function, better graft survival and fewer episodes of BPAR than a regimen based on ciclosporin or sirolimus. If patients cannot tolerate immediate-release tacrolimus they should be given the opportunity to have prolonged-release tacrolimus before switching to alternative therapies that may be less effective. The proposed guidance has the potential to reduce quality of care and patient safety

3.3.2 There are people who would prefer not to ingest gelatin for reasons of religious

belief or conscience (e.g. Muslims or vegetarians). Envarsus is the only solid form oral tacrolimus that does not contain gelatin. As a PR-tacrolimus Envarsus would be caught by the 'not recommended' guidance removing the opportunity to tailor tacrolimus therapy for these particular subgroups

3.3.3 Kidney transplant survival rates in African American recipients remain lower than for any other ethnic group. (Fan 2010, Eckhoff 2007). The decline in renal function after kidney transplantation is accelerated in African American patients (Srinivas 2005, Lentine 2010) and long-term graft loss in both adults and children is markedly increased compared with non-African American populations (Press 2005, Meier-Kriesche 2000, Omolaja 2007, Ishitani 2000) This ethnic disparity is observed even in living donor and zero-mismatched patients and after adjustment for patient characteristics (Isaacs 1999, Fan 2010)

3.3.3.1 Tacrolimus absorption exhibits ethnicity-specific differences in systemic exposure with 20-50% lower oral bioavailability in African Americans than white patients (Malat 2009) such that the dose needs to be adjusted accordingly.

3.3.3.2 Black patients have significantly higher doses of tacrolimus (for similar trough levels) (Narayanan 2013, Gaber 2013,)

3.3.3.3 Higher oral doses of IR-tacrolimus are accompanied by higher C_{max}. C_{max} above 20ng/ml are frequently seen in black patients. (Trofe-Clark 2015)

3.3.3.4 Conversion to Envarsus from IR-tacrolimus results in a significant reduction ($p < 0.0001$) in C_{max} (ratio of geometric means 71.7 (64.8-79.3)) which may have implications for long-term outcomes.

3.3.3.5 In an analysis of two Phase III trials, black patients had fewer treatment failures on Envarsus than on IR-tacrolimus (Prograf). The guidance as proposed would prohibit tailoring treatment to this specific subgroup.

3.3.4 The kidney transplant population is growing older. Age at the time of transplantation is clearly correlated with long-term outcome [Legendre 2014]. The mean age of transplant donors and recipients in the UK was 50yrs and 49yrs for kidneys from deceased donors and 47yrs and 43yrs for kidneys from living donors. Thirty one percent of deceased organ donors were aged ≥ 60 years and 28% of recipients from deceased donors were aged ≥ 60 years [NHSBT 2015].

3.3.4.1 Renal function declines with age so older organs will typically have reduced renal function compared to younger organs. CNIs are nephrotoxic. There is some evidence that the age of a kidney is a major determinant of its susceptibility to CNI nephrotoxicity (Naesens 2009)

3.3.4.2 CNI nephrotoxicity is complex but one component is the blood concentration, C_{max}. Having a tacrolimus that can deliver effective trough levels but avoid high C_{max} provides the opportunity to avoid premature deterioration of transplanted kidneys from older donors. In renal transplant recipients, Envarsus has lower C_{max} than IR-tacrolimus (Prograf) [Gaber 2013]

3.3.4.3 In a subgroup analysis of two Phase III clinical trials, older patients (≥ 65 yrs) had

fewer treatment failures on Envarsus than IR-tacrolimus (Prograf). The guidance as proposed would prohibit tailoring treatment to this specific subgroup.

3.4 The proposed Guidance does not accord with the principles set out in NICE CG76. *Medicines adherence. Involving patients in decisions about prescribed medicines and supporting adherence.* Issued Jan 2009, reviewed March 2015.

3.4.1 NICE CG76 establishes that:

- *Non-adherence is common and that most patients are non-adherent sometimes.*
- *Consider assessing non-adherence by asking the patient if they have missed any doses of medicine recently.*
- *Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing.*
- *Because evidence supporting interventions to increase adherence is inconclusive, only use interventions to overcome practical problems associated*
- *with non-adherence if a specific need is identified. Interventions might include: (among others) Simplifying the dosing regimen*

3.4.2 The practical problems of timing of doses and mealtimes could be an example of where simplifying the dosage regimen could have a positive impact on adherence and outcomes.

3.4.3 IR-tacrolimus is widely-referred to as BD dosing. In reality it is dosing every 12 hours. Taking a dose early risks toxicity, taking it late risks under-immunosuppression. If a patient is late taking one dose what do they do the next day? Do they go back to the normal timing and effectively have a small overdose or do they try to rearrange their schedule? Most patients know that if they take too much tacrolimus it will damage their kidney, and also if they take too little it will damage their kidney.

3.4.4 Tacrolimus blood levels are strongly impacted by food. The SPCs for Prograf and Advagraf say they need to be taken 1 hour before or 2-3 hours after meals. Not all patients can manage their daily routine so that they can meet the criteria for 12-hour timing of dosing and timing of mealtimes. Patient groups particularly affected are shift workers, people with chaotic lifestyles (e.g. young adults/ adolescents), people with young families who want to eat with the family etc. Evidence shows that with IR-tacrolimus it is typically the evening dose that is missed [Kuypers 2013]
With PR-tacrolimus there is obviously no evening dose to have to consider timing of dose and mealtimes.

3.4.5 In Section 1.2.9 of CG 76 it states; *Side effects can be a problem for some patients. If this is the case you should:*

consider adjusting the dosage

consider switching to another medicine with a different risk of side effects

3.4.6 For tacrolimus therapy, tremor could be an example of a side effect that is problematic for patients. Switching to Envarsus from IR-tacrolimus could reduce tremor and improve quality of life (see Section 1.5.6 of this document)

3.4.7 Both Envarsus and Advagraf have a second indication of 'Treatment of allograft

rejection resistant to treatment with other immunosuppressive medicinal products in adult patients.’ This proposed guidance would remove two immunosuppressive options for this clinical scenario.

3.4.8 In 2012, the Commission on Human Medicines (CHM), updated advice on the prescribing and dispensing of all oral tacrolimus products. This updated advice is that all oral tacrolimus medicines in the UK should be prescribed and dispensed by brand name only. This was a result of the risk to patient safety. The proposed Guidance uses the terms immediate-release tacrolimus and prolonged-release tacrolimus and may imply they are easily interchangeable which contradicts the MHRA guidance.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

4.1 Age:

Subgroup analysis data for Envarsus demonstrated significantly reduced treatment failure rates in older patients (≥ 65 yrs) compared to Prograf. This group would be discriminated against by this guideline if implemented as proposed.

4.2 Race:

Subgroup analysis data for Envarsus demonstrated significantly reduced treatment failure rates black patients compared to Prograf. This group would be discriminated against by this guideline if implemented as proposed.

4.3 Religion or belief:

Envarsus is a tablet formulation and does not contain gelatin, therefore it would be suitable for those who wish not to ingest gelatin due to religious reasons or reasons of conscience (e.g. Muslims, vegetarians). Envarsus is the only solid form oral tacrolimus that does not contain gelatin. Since immunosuppression based on a tacrolimus regimen has been demonstrated to be more effective than immunosuppression regimens based on ciclosporin or sirolimus (ELITE Symphony study), this guideline would discriminate against these groups if implemented as proposed.

4.4 The guideline would also discriminate against those who have difficulties with adherence due to personal, personality or lifestyle factors if implemented as proposed.

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Personal Response Statement

Thank you for the opportunity to comment on the preliminary report of the Health Technology Appraisal. As the adult and child appraisals reach broadly the same conclusions I will make general comments applicable to both.

On reading the report I am struck by the “competitive” nature of the analyses and consideration. One drug is considered to “outperform” or “dominate” its competitors. However, clinical transplantation is not competitive. The choice of drugs is about finding the best option for individual patients to maximise their longevity, quality of life and graft survival- albeit considering cost as well. In making their deductions I am not sure how keenly the committee have remembered that the option for patients who do not have transplantation is to remain on dialysis- which is a far more costly treatment. Unfortunately, as far as I am aware, none of the randomised controlled trials or studies included in the analysis have “stay on dialysis” as one of the treatment arms. From studies, not considered by this appraisal, we can conclude that transplantation is a highly cost-effective treatment for patients with end stage renal failure and on this basis any immunosuppressant that facilitates this treatment could be considered cost-effective.

Comments on individual recommendations

- 1.1 Yes this is a highly accepted treatment with a wide evidence base which has proven to be safe and effective.
- 1.2 This is a well balanced statement which summarises a wealth of literature and forms the baseline for current modern immunosuppressive practice.
- 1.3 As for 1.2
- 1.4 I do not agree with this statement. Rabbit anti-thymocyte (ATG) immunoglobulin is a highly effective immunosuppressant which in your cost-effective analysis is out performed by Basiliximab in some population analyses. For some patients with broad donor reaction profiles and multiple antibodies ATG may be the *only* option to allow retransplantation to go ahead. “Incompatible” kidney transplantation relies on ATG induction to be available (133 transplants in 2013/14, NHS Blood and Transplant) and without this costly dialysis will remain the only option. Likewise the MTOR inhibitors sirolimus and everolimus may be the only option to allow patients with a history of malignancy to be safely transplanted. In the recently published 3C trial sirolimus was part of the most efficacious treatment group with the best renal function 1 year after randomisation. To discount this treatment as “not recommended” is a distortion and to emphasise population cost rather than individual clinical effectiveness. For example if a single patient with a history of malignancy is successfully transplanted using sirolimus maintenance therapy rather than staying on dialysis then this is cost effective as well for the NHS.
- 1.5 I am not sure as to the value of this statement unless the vision of this document is to deny certain patient groups access to kidney transplantation (immunological “high risk”, drug induced Haemolytic Uraemic Syndrome, diabetic gastroparesis, patients with learning disabilities, patients with high risk of malignancy, retransplantation).

If the Health Technology Appraisal is looking to maintain access for patients to transplantation then a fairer way of phrasing 1.4 would be like this:

“Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended as *first line agents* to prevent organ rejection in adults having a kidney transplant. They should only be considered when the alternative for an individual patient is to either remain on dialysis or have suboptimal immunosuppression which could be expected to lead to graft loss”.

In response to your specific questions:

Has all of the relevant evidence been taken into account?

I think the Committee should take additional note of the fact that the alternative to transplantation is a far more costly treatment.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Yes, when comparing one drug regimen with another, but not including some drug regimens (Campath, Rituximab etc) and lack of trial comparisons against dialysis has led to flawed conclusions.

Are the provisional recommendations a suitable basis for guidance to the NHS?

1.1, 1.2 and 1.3 yes. 1.4 and 1.5 no for the reasons outlined above. No mention of ciclosporin or azathioprine.... Is this an oversight ??

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion, sexual orientation, age, gender reassignment, pregnancy and maternity ?

Mycophenolate is contraindicated in pregnancy and maternity. Currently we would use azathioprine. Black and minority ethnic transplant populations are more likely to receive a poorly matched graft and require ATG induction. Older patients (> 70) have a different immune response and the recommended regimen of basiliximab, tacrolimus and mycophenolate mofetil in this group may lead to an excess of infections and malignancies. Currently evidence is lacking but this is an evolving field as the recipient age continues to rise.

Patients with learning disabilities are a challenging group who can sometimes only be managed with parenteral immunosuppression (basiliximab, belatacept) to ensure compliance.

Name	██████████
Organisation	
Role	NHS Professional
Job title	Consultant Transplant Surgeon
Location	England
Conflict	No
Disclosure	
Comments	<p>694</p> <p>The appraisal committee does not include any experts in transplantation. The absence of transplantation physicians or surgeons in the appraisal committee is a major shortfall. If details advice was taken from such experts, this should be clearly stated in the document.</p> <p>The recommendations fail to take into account individual patient circumstances, which may necessitate deviation from the recommendations. This specifically applies to the use of prolonged-release tacrolimus, sirolimus, and alemtuzimab. There very clear clinical indications for the use of these therapies in individual patients or patient groups., which will results in better outcomes for those patients. The recommendations should acknowledge the need to take into account such individual circumstances and 'authorise' the use of these agents as clinically indicated.</p>
Submission date	14/08/2015

Name	██████████
Organisation	MRIKPA
Role	Patient
Job title	
Location	England
Conflict	No
Disclosure	
Comments	<p>695</p> <p>As a transplant patient I feel there should be no restrictions on the immunosuppressive available to the new patients</p>
Submission date	17/08/2015

Name	██████████
Organisation	
Role	Patient
Job title	Sales Manager
Location	England
Conflict	No
Disclosure	
Comments	<p>703</p> <p>As a kidney transplant patient, the NHS has invested a significant amount of resource into keeping me alive, giving me a better quality of life & not being a burden to the NHS economically by staying on dialysis.</p> <p>I find it disgusting that the NICE committee can make a decision</p>

on transplant immunosuppression when none of you have any renal or transplant experience. Indeed you did have some excellent & reputable clinical experts but where was the Nephrologist, pharmacist or specialist nurse?

As a patient, I want my kidney to last as long as possible & for this to happen, I want to be on the best immunosuppression available. The impact of Tacrolimus levels on graft survival is well documented in the literature. The variability in these levels can be due to non-adherence, timing of taking medication & also food. I would suggest that in your review, you use trials that reach clinical significance & also look at variability in levels. It's also well known that the evening dose of medication is the most commonly forgotten & this gets worse at weekends, on holidays or a change to the normal patient routine. The recommendation contradicts existing NICE guidance on medicines adherence, which requires clinicians to "Tailor any intervention to increase adherence to the specific difficulties with adherence the patient is experiencing."

During my years as a transplant patient, I have had to be on many different types of immunosuppressant through no fault of my own " Cyclosporine was toxic to my kidney, I had anaphylaxis with Sirolimus, Prograf gave me inconsistent levels of Tacrolimus which were having a detrimental effect on my kidney & the evening dose was a struggle to remember due to my job & lifestyle. So tell me NICE committee, would you like me to die, go back on dialysis or let me as a NHS patient like yourselves have a choice of medication that enables my kidney to last as long as possible so that I am not a burden on the NHS or in a box buried in the ground? Thankfully through expert clinical choice & patient consultation I now take Advagraf. My levels are consistent & there is no evening dose to think about. Yes, you may say I still have to take MMF in the evening but this isn't the cornerstone of the immunosuppressant therapy & doesn't have to be taken 12 hours apart or on an empty stomach or two hours after food. try thinking about that when you are 5 hours behind after a plane journey across the Atlantic.

So by refusing to give clinicians & patients the best choice of immunosuppression, I presume that the committee are quite happy to let more grafts fail, continue to lower the number of transplants as so many people will be waiting for them & let these people cost the NHS £31k a year for dialysis or die.

But most importantly, my kidney was a selfless gift from my father as he wanted to live life to the full. He doesn't have another to give me & by restricting immunosuppression, his gift as well as the generosity of others could be in vain.

Transplantation is a wonderful part of medicine that gives those with failing organs another chance of life. A doctor's oath is to "do no harm". by taking away their choice of immunosuppression, the NICE committee most certainly are

	doing harm.
Submission date	21/08/2015

Name	████████████████████
Organisation	
Role	NHS Professional
Job title	Consultant Nephrologist
Location	England
Conflict	No
Disclosure	
Comments	<p>704</p> <p>Dear Sir/ Madam,</p> <p>I have reviewed this document and would like to comment on the conclusions regarding prolonged-released tacrolimus. Our unit repatriates renal transplant patients at 3 months from the regional transplant centre (Cambridge). Cambridge has used Advagraf (prolonged-release tacrolimus for several years and we have a lot of experience in using this. It is true that there is paucity of data regarding clinical outcome measures with regards to prolonged-release tacrolimus when compared to immediate release tacrolimus. However, there seems to be a preference by some patients to taking tablets once daily as opposed to twice daily. This is especially important since for immediate-release tacrolimus it is advisable to take this on an empty stomach i.e. 1 hour before or 2-3 hours after a meal. This can be a significant inconvenience for the transplant patient who is busy working and socially active. Studies have shown that the evening dose is particularly problematic and there is no doubt that some patients would struggle in adhering to the correct regime with the twice daily regime of immediate release tacrolimus. I would be strongly suggest that the position on prolonged-release tacrolimus is reviewed.</p>
Submission date	23/08/2015

Name	████████████████████
Organisation	
Role	NHS Professional
Job title	Consultant Surgeon
Location	England
Conflict	No
Disclosure	
Comments	<p>706</p> <p>I feel it is dangerous and inappropriate to not include, or indeed recommend the use to long acting formulations of Tacrolimus (Advagraf or Evarus) in certain groups of patients. These drugs are very helpful in transition patients (teenagers) and busy workers and very clearly have a role in this guidance.</p> <p>Excluding the use of Mtor inhibitors (sirolimus and everolimus)</p>

	is very unhelpful, and potentially dangerous. Transplant immunology should be tailored to patients as individuals and these drugs can be very helpful.
Submission date	24/08/2015

Name	██████████
Organisation	
Role	NHS Professional
Job title	
Location	England
Conflict	No
Disclosure	
Comments	<p>707</p> <p>The technology appraisal clearly provides a detailed and evidence-based analysis of the outcomes and cost-effectiveness of all immunosuppressive agents used in clinical renal transplantation. I would like to thank and congratulate all members of the advisory group.</p> <p>With regards to the recommendation of immediate and prolonged-release tacrolimus, there are patients in clinical practice, who are most likely to benefit from administration of once-daily prolonged release tacrolimus; the non-adherent group of patients. They can be easily identified from the very beginning and if, the prolonged -release tacrolimus prescribed, acute rejection rate can be significantly reduced and graft function and graft survival prolonged.</p> <p>I would recommend that the use of prolonged-release tacrolimus should be in the armamentarium for a selected group of patients, although the cost is twice as expensive as the immediate-release preparation.</p>
Submission date	24/08/2015

Name	██████████
Organisation	██████████
Role	NHS professional
Job title	Consultant Transplant Physician
Location	England
Conflict	n/a
Disclosure	<p>I have worked for and have been funded to attend educational meetings by a broad spectrum of pharmaceutical companies.</p> <p>I do not have any particular interest in promoting one product above another.</p>
Comments	<p>709</p> <p>I would like to start by congratulating the committee on providing a thorough review of the evidence for immunosuppression within kidney transplantation and updating the previous advice. Overall, I agree with the main strand of the document that the combination of Simulect induction combined</p>

with generic tacrolimus and mycophenolate do provide the most cost effective long term outcome post transplant. In our own local experience, this strategy has helped save our local health economy over Â£1.5 million per annum whilst also achieving some of the best 5 year kidney transplant survival rates in the UK.

Despite this, I do believe the document is too restrictive in suggesting that this combination is the only way to deliver immunosuppression post kidney transplantation. Given the wide heterogeneity of donor organs and transplant recipients, there has to be flexibility in prescribing for unique clinical situations. Although I agree that the document does acknowledge this fact within section 4.56, there is no compromise for easy access to alternative immunosuppressive strategies and the use of other medication is dismissed due to the lack of randomized controlled trials. Due to the small volume of transplantation, when compared to cardiovascular or malignant disease, large scale randomized controlled trials are not always achievable or fundable to answer individual issues but smaller studies do provide evidence to attribute benefit. In addition, the IFR process for accessing alternative medicines for the treatment of patients is slow and unnecessarily bureaucratic, which may well put patients and transplants at risk.

Whilst I agree that the suggested immunosuppression regimen is an excellent starting point and would suit most kidney recipients, there has to be flexibility for changing to alternative medications in the event of changing clinical circumstances. This could be achieved by specific caveats within the document for use of alternative agents under specific conditions. ATG. Overall, I agree with the guidance that the clinical benefit for this agent over Basiliximab is limited and does not justify the additional cost in standard or extended criteria transplantation. However, ATG has been proven to reduce the risk of rejection and long term development of donor specific antibodies in high immunological risk transplants with superior outcome in this group of patients. Therefore, there should be a specific caveat for the use of this agent as induction therapy for HLA incompatible transplants. Without this caveat, it is likely that the waiting time and therefore mortality of highly sensitized patients is likely to increase, thus discriminating against highly sensitized patients. In addition, the document does not comment on the use of ATG as salvage therapy for rejection and it would be helpful for some guidance on whether this is included within the scope of the document.

mTOR inhibitors do have a place for patients who have had or are at significant risk of skin malignancy. In addition, there is a place for the use of these agents in patients with significant viral infections, such as BK or CMV, where the infections can be life threatening and the alternatives (such as IVIg, Valgancyclovir, Brindcidofovir or Maribivir are significantly more expensive). Without this caveat, the guidance is likely to discriminate against patients with malignancy.

	<p>Lastly, it is not clear where the previously recommended agents (prednisolone, azathioprine and cyclosporine) sit within the guidance. This will require some clarification within the document as to whether these agents are available for kidney transplant immunosuppression or whether their use will require IFR. If not freely available, it is likely to discriminate against black patients who do not always tolerate the use of Tacrolimus and may require conversion to Cyclosporin. In addition, around 15% of patients do not tolerate Mycophenolate due to GI side effects and require conversion to Azathioprine.</p> <p>In summary, I agree with the general recommendations of the guidance but would suggest a greater flexibility with caveats for the use of alternative agents under different clinical conditions and less reliance on the IFR process that is not fit for purpose.</p>
Submission date	25/08/2015

Name	[REDACTED]
Organisation	[REDACTED]
Role	NHS Professional
Job title	[REDACTED], St. James's University Hospital, Leeds
Location	England
Conflict	No
Disclosure	During the last five years I have received honoraria from Sandoz, Novartis, Chiesi and Astellas for attending clinical advisory group meetings.
Comments	<p>710</p> <p>In my opinion this is a heroic attempt to grapple with a difficult subject but ultimately it is severely flawed. It was a curious decision to engage a committee with no expertise in renal transplantation and the evaluation betrays this lack of specialist knowledge.</p> <p>As the lead author of the joint renal association and British Transplant Society guidelines (Baker R, Jardine A, Andrews P. Renal Association Clinical Practice Guideline on post-operative care of the kidney transplant recipient. Nephron Clin Pract 2011;118 Suppl 1(1):c311-347), I have spent a lot of time reviewing the evidence in this area and your evaluation makes a fundamental error in the assumption that there is one uniform 'transplant recipient'. Recipients are a highly heterogeneous group of individuals with different risk factors in different domains as shown by the table below from our guidelines:</p> <p>Risk Type</p> <p>Low Medium High Possible strategy</p>

	<p>Immunological 0-DR mismatch</p> <p>First graft</p> <p>Unsensitised</p> <p>Recipient > 60 1-DR mismatch</p> <p>Afro-Caribbean recipient</p> <p>Historical DSAs</p> <p>ABO incompatible</p> <p>DGF</p> <p>Older donor 2-DR mismatch</p> <p>Previous early immunological graft loss</p> <p>DSAs</p> <p>Sensitised Increase total immunosuppressive load</p> <p>Metabolic Low BMI</p> <p>Age <40</p> <p>Normal Pre-Tx GTT Positive family history Impaired GT</p> <p>BMI>35</p> <p>HCV positive</p> <p>Age > 60</p> <p>Previous CVD</p> <p>Race Avoid/minimise</p> <p>Steroids and tacrolimus</p> <p>Neoplastic Age < 40 Pre-malignant lesion Previous cancer</p> <p>Hereditary syndrome e.g. VHL Consider low total load or sirolimus</p> <p>Ischaemia-reperfusion injury Living donor CIT > 12 hours</p> <p>Donor aged 50 -60 NHBD</p> <p>CIT > 24hours</p> <p>Extended Criteria Donor Reduce CNI exposure</p>
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Non-adherence Poor RRT compliance

Age <20

Transition from paediatric to adult Education

Simple drug regime

Alemtuzumab or Belatacept

In making the decision about immunosuppression for an individual patient it may be necessary to tailor the regime (e.g. avoid steroids when there is a strong family history and high BMI). Your analysis fails to take any consideration of this important issue, but then again there was no one on the AG who actually looks after renal transplant patients.

It should also be born in mind that even the best clinical trials tend to recruit a fairly narrow band of low risk recipients and yet the trial findings are often extrapolated across the wider population.

The result of this evaluation is the recommendation 1.4. "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." This removes the flexibility for clinicians that is essential for managing different patient groups. In the very least I would ask that the wording is revised to, "are not routinely recommended".

It seems paradoxical that in 4.20 you state that, "The AG emphasised that there was not enough evidence available for robust subgroup analyses" and yet you make absolute guidelines about usage. Similarly you state, "The AG stated that because of wide confidence intervals, there was a great deal of uncertainty associated with the results and limited conclusions could be drawn", and yet you draw absolute conclusions.

There are numerous examples in practice where these products may have a useful role in a minority of patients. E.g. Long acting tacrolimus may help increase adherence and reduce tremor in the small number of patients where this is a problem. (Langone A, Steinberg SM, Gedaly R, Chan LK, Shah T, Sethi KD, Nigro V, Morgan JC: Switching Study of Kidney Transplant Patients with Tremor to LCP-TacR (STRATO): an open-label, multicenter, prospective phase 3b study. Clin Transplant 2015;12581; Kuypers DR, Peeters PC, Sennesael JJ, Kianda MN, Vrijens B, Kristanto P, Dobbels F, Vanrenterghem Y, Kanaan N: Improved adherence to tacrolimus once-daily formulation in renal recipients: a randomized controlled trial using electronic monitoring.

	<p>Transplantation 2013, 95:333-40)</p> <p>In summery I fear this is a case of "cutting off your nose to spite your face" . It is essential that some room to manoeuvre is left to clinicians to enable them to address complex issues of a significant minority of renal transplant recipients.</p> <p>I would strongly urge to AG to seek advice from the wider circle of professionals who look after the UK's renal transplant programmes and to work together for a more practical set of guidelines.</p>
Submission date	25/08/2015

Name	[REDACTED]
Organisation	
Role	NHS Professional
Job title	Consultant Transplant Surgeon
Location	England
Conflict	Yes
Disclosure	I received grants and Honoraria from Sanofi, Astella, Novartis/Sandoz
Comments	<p>711</p> <p>Dear</p> <p>The effort on producing this document is highly commendable.</p> <p>In modern Renal transplantation Induction Immunosuppression is considered as standard.</p> <p>In recent year most units have changed their protocol using Lymphocyte Depleting Immunosuppression instead of or in association with IL2 Mab.</p> <p>The widespread use of this practice supported by the 3C trial cannot be excluded from practice.</p> <p>Regarding the document I wish to respond to the AC following their indication:</p> <p>1. Evidence</p> <p>I share the comment made by one of the expert where the search seems incomplete and not having included a very relevant number of studies.</p> <p>For this methodology inaccuracy I believe the recommendations are invalid and the document should be redone in the light of the expert opinion comment.</p> <p>2. Cost effectiveness.</p>

	<p>Considering only the acquisition costs and QALY is NOT correct.</p> <p>For r-ATG the costs presented are incorrect. The standard modern use of this drug is less than 4mg/kg. Costs should be calculated considering this dose as maximum cost. Also its use contributes to reducing doses of CNI. This is not taken into account.</p> <p>Important parameters driving the costs post transplants as re-admissions, dialysis sessions, clinic visits are not taken into account. These are crucial information in the evaluation of cost-effectiveness. Those parameters do not necessarily influence QALY</p> <p>3. Suitable basis for guidance to NHS.</p> <p>I am afraid that this document fails to guide transplant units in the NHS as it does not take into account important evidence and practice. Specifically the use of Lymphocyte depleting Induction Immunosuppression as opposed IL2Mab.</p> <p>Rather than recommending or discouraging the use of drug it would much more valued commenting on a consolidated practice. The document unfortunately is not particularly helpful to the NHS as whole.</p> <p>Very importantly we do transplant >15-20% of immunological high risk recipients per year. The recommendations should take also this into account.</p> <p>Data from NHSBT should be the core of the analysis.</p> <p>I also have noticed in an expert comment presentation of alleged side effect from r-ATG; it is not clear what dose or administration they might have occurred and reflects more an anecdotal experience rather than actual evidence.</p> <p>I hope it is helpful and my final comment is on the lay-out of the comment page of NICE website that unfortunately is rather difficult to write on.</p> <p>Kind Regards</p>
Submission date	25/08/2015

Name	[REDACTED]
Organisation	UK Renal Pharmacy Group
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	No

Disclosure	n/a
Comments	<p data-bbox="472 235 523 264">712</p> <p data-bbox="472 273 1315 1070">The overriding concern from UK RPG members is the excessively restrictive nature of these guidelines and the impact on patient care. There is an assumption that all transplant patients can be treated the same given the paucity of published RCTs to the contrary. The reality is that the majority of patients can be considered “standard risk” and receive the recommended regimen of basiliximab induction with tacrolimus immediate release and mycophenolate mofetil as maintenance immunosuppressive therapy. With developments in immunology and transplantation and NHSBT initiatives to increase both donation rates and transplant numbers more high risk patients are being transplanted. In these situations e.g. HLA incompatible, highly sensitised, ABO incompatible, extended criteria donor transplants the immunosuppressive regimes require tailoring to the patients medical and immunological need. Transplantation is considered the most efficient renal replacement therapy with additional health benefits to patients so we must continue to optimise medical and pharmacological management and maximise graft function to sustain and further improve patient and graft outcomes. By virtue of the heterogeneous transplant population different drug regimes are needed to account not least for individual patient variability and whilst the committee recognised this in section 4.56 it then decided against it.</p> <p data-bbox="472 1106 1315 1711">rATG/alemtuzumab are widely used in clinical practice as induction for high risk transplants and should remain so in this select cohort. Alemtuzumab was excluded from the TA as it does not have a UK marketing authorisation (section 4.57). rATG is licensed for this indication and has been used in transplantation unlicensed for many years and as such was not included in the 2004 NICE TA. In contrast basiliximab is not licensed in highly sensitised patients (PRA>80%). We agree therefore that basiliximab should be the induction antibody of choice for standard risk recipients (as per recommendation 1.1) but that rATG must be allowed for high immunological risk recipients. rATG induction is also used for patients where there is a need for steroid avoidance/minimisation or tacrolimus maintenance monotherapy. In addition rATG is the first line treatment for steroid resistant organ rejection and therefore must be permitted to continue. The guidance requires clarification on this latter point which has not been included in this appraisal.</p> <p data-bbox="472 1747 1315 2029">Ciclosporin, azathioprine and prednisolone have not been formally assessed as part of this technology appraisal. Does this mean they will not be NICE approved? If so this will be unmanageable in clinical practice. We would urge that these drugs remain available for use in transplantation. Some centres use tacrolimus & azathioprine as maintenance regimen. Additionally some patients require a conversion to azathioprine e.g. intolerance of MMF or pregnancy. Ciclosporin needs to remain a choice for patients who require a switch from</p>

tacrolimus due to side effects/ intolerance e.g. tremor, depression or patients at high risk of developing NODAT.

Immediate release tacrolimus. We support recommendation 1.2 but would like to see the recommendation expanded to include - Patients should be started and maintained on the most cost-effective brand. All tacrolimus prescribing must be brand name as it is a critical dose immunosuppressant.

Prolonged release tacrolimus. We agree this should not be widely used but recommend that it should be available for use in small selected cohorts of patients where there is patient and graft outcome benefit from simplification of the drug regimen to once daily e.g. patients with learning difficulties struggling to manage twice a day, patients identified at risk of non-adherence to permit once daily dosing (sometimes supervised) of all their medications. In addition there is some emerging evidence from other transplant groups (liver) that prolonged release tacrolimus can improve long term graft survival by reducing drug level/exposure variability.

Sirolimus. This drug is not used in accordance with its product license immediately post-transplant due to adverse effects on patient and graft (wound dehiscence and prolonging delayed graft function). However it does provide benefit to certain patient cohorts later post-transplant allowing a change in maintenance immunosuppression e.g. substitution of calcineurin inhibitor (CNI) in biopsy proven CNI induced nephrotoxicity, in patients unable to tolerate azathioprine/mycophenolate, in patients with malignancy particularly skin cancer and in patients with difficult to control ganciclovir resistant CMV disease. We therefore would suggest that sirolimus, whilst not used as a routine, should be permitted for use as an alternative maintenance immunosuppressant when difficulties arise later in the transplant course, as illustrated above.

Belatacept. Due to the difference in procurement cost between tacrolimus and mycophenolate based maintenance regimens it is accepted within the transplant community that this drug should not be widely used and currently IFRs are submitted on a case by case basis. If belatacept does not have NICE approval then it will not be funded under any circumstance by NHSE so these limited number of patients will be denied access to this last resort treatment which could then result in graft loss. Examples of specific cases where belatacept has been successfully used: patients with multiple drug intolerances identified post-transplant, post-transplant microangiopathy. Other possible indications -patients with proven CNI nephrotoxicity, non-adherent patients who could be supervised receiving this intermittent intravenous infusion. We would advise belatacept should be permitted but caveated to use when all other therapies have failed (genuinely exceptional cases).

	<p>Mycophenolate mofetil (MMF). We support recommendation 1.3 that mycophenolate mofetil should be prescribed as the least expensive product. However there is some clinical experience to support a switch to Myfortic in patients with marked and debilitating gastrointestinal adverse reactions from MMF where dose reduction and dose splitting have not resolved these symptoms. We would suggest that there is a case for restricted use of Myfortic in such instances.</p> <p>In summary not to allow medication choice to achieve individualisation of immunosuppressive therapy based on clinical need and tolerability, where necessary, will put patients and their grafts at risk. Immunosuppressive agents are potent and at times toxic medications with extensive side effect profiles. A transplant is a precious gift and it is our duty as clinicians and prescribers to protect the patient and the graft and maximise its longevity using all reasonable options available to us in order to avoid an early return to dialysis with its inherent increased cost and associated morbidity and mortality. The committee (section 4.63) stated that it was not able to make recommendations for people whose treatment needs to be withdrawn because of complications. However this is what happens in clinical practice at the patient interface so by not permitting access to the full range of immunosuppressive agents available in order to individualise therapy, it will adversely affect patient and transplant graft outcomes.</p>
Submission date	25/082015

Name	████████████████████
Organisation	
Role	NHS Professional
Job title	Consultant Surgeon
Location	Wales
Conflict	Yes
Disclosure	The transplant Unit has received along the years educational and reserch grants from Novartis, Astellas, Sanofi and Sandoz
Comments	<p>714</p> <p>I read with interest the appraisal of immunosuppressive therapy in kidney transplantation. I find it useful but I note that in its terms tries to take into account current UK practice. There is a number of units using Thymoglobulin as induction treatment for the majority or a subset of their patients successfully. I am not aware that any input has been specifically requested from any of those units. Whilst I appreciate that you will not chase experts, relying only to the relevant companies to provide evidence might be too restrictive.</p> <p>I found the analysis on the use of ATG very restrictive omitting a number of papers that shows its clear superiority compared to IL2 receptors as far as rejection is concerned although not always in survival. I am also aware of published meta-analysis from USA on the subject . Although survival is the ultimate</p>

	<p>outcome in transplantation I have not failed to notice that the rest of your analysis for maintenance immunosuppression is not mainly based on long term survival analysis but rather on short term outcomes (inevitably so). It seems logical that the same should happen on induction. Paper from Cardiff in Transplantation show a rejection rate of 9% in DCD patients with thymoglobulin compared to 22% on IL-2R antibody,($p < 0.001$) in a 6 year cohort of patients (using the ATG produced by Sanofi and the IL-2 antibody produced by Novartis that you use in your appraisal).</p> <p>To go a bit further single centre studies should not be taken in isolation that these results in fact reproduce the national results of the 3C study (LD, DCD, DBD) that have shown that allocation to alemtuzumab produced a 58% proportional reduction in biopsy-proven acute rejection (31 [7.3%] alemtuzumab vs 68 [16.0%] basiliximab; HR 0.42, 95% CI 0.28-0.64; log-rank $p < 0.0001$)</p> <p>Although Campath and ATG have different mechanisms of action it should not have escaped you that the proportional reduction of biopsy proven acute rejection is identical and very unlikely to be caused by chance. Given the problems with provision of Campath at the moment I would consider ATG as the only logical option for patients at least within the groups that has been used extensively namely DCD graft recipients. We would find very difficult locally to recommend anything else to this group of patients given that the alternative (basiliximab) is associated with two and half times higher rejection rate. I understand that Royal London has a very similar experience and you could also easily obtain that. It is also worth noting that in Cardiff the deceased 1 year graft survival rate for 2012-13 has been the highest in the country (been the second highest the year before) using on average higher risk grafts. Although this is not exclusively due to induction it will be difficult to ignore its relevance for a 1 year outcome.</p> <p>I would urge you to reconsider the advice in this section</p>
Submission date	25/08/2015

Name	[REDACTED]
Organisation	Liver4Life
Role	Charity supporting people affected by Liver disease (including Transplantees and their carers)
Job title	[REDACTED]
Location	England
Conflict	Yes
Disclosure	
Comments	<p>715</p> <p>We at Liver4life would like to comment on NICE's decision to provisionally recommended that Advagraf should not be made routinely available on the NHS as an immunosuppressive</p>

	<p>therapy for kidney transplant in adults.</p> <p>We have seen many Liver Transplant patients benefit from the benefit of Advagraf as a once daily dosing regimen. In our opinion this increases adherence, and also allows patients the freedom to manage their lives better.</p> <p>As an example, we had a transplantee who was on a twice daily dosing regimen which restricted his ability to socialize with other as the dose had to be taken with food. His second dose was always taken at 6pm in the evening, which meant that he would often decline the offer of meals with friends as he had already eaten. He is now on Advagraf and feels much more able to manage his immunosuppression around his life, rather than the other way around.</p> <p>The other big advantage of once daily dosing is that it is much easier to remember. We again have heard reports that it is much easier to manage for carers making sure the recipient has taken their medicine once in the morning, rather than twice a day. This particularly applies to young adults for whom adherence is a common issue.</p> <p>We appreciate that we are not Kidney transplant experts, but hope that the committee will see commonality in the issues faced by all transplant recipients, and would ask that NICE reconsider their provisional decision, and make the experience of immunosuppression as simple as possible for patients, and carers.</p>
Submission date	25/08/2015

Name	[REDACTED]
Organisation	
Role	NHS Professional
Job title	Consultant Transplant Surgeon
Location	England
Conflict	No
Disclosure	
Comments	<p>716</p> <p>Although the "one size fits all" approach of tacrolimus/mycophenolate with simulect induction is the most cost-efficient regimen, it is not appropriate in many patients, for example:</p> <p>1 highly sensitised patients who require r-ATG induction or r-ATG treatment for post-transplant rejection</p> <p>2- patients with post-transplant infection with CMV or BK virus who require switching from mycophenolate to sirolimus</p> <p>The current IFR scheme is too onerous for the numbers that would be involved, and there needs to be more flexibility in the</p>

	guidelines to account for the complex nature of post-transplant complications
Submission date	25/08/2015

Name	██████████
Organisation	
Role	NHS Professional
Job title	Consultant Nephrologist
Location	England
Conflict	No
Disclosure	
Comments	<p>719</p> <p>I applaud the recommendations and your efforts (our protocol for >10 years) and it is good to hear that some other therapies are clearly not cost effective for routine protocol IS. However I seriously worry that your wording will result in units being penalized for using agents like mTORi, slow release once a day therapies and induction agents for individual cases. Intolerance, chronic viral infections, poor compliance, malignancy and highly sensitized patients with or without rejection are not adequately studied in the literature but there is no doubt that in some circumstances for some individuals access to this agents is a very important part of the options.</p>
Submission date	26/08/2015

Name	██████████
Organisation	
Role	NHS Professional
Job title	██████████, St George's University of London
Location	England
Conflict	Yes
Disclosure	<p>Research funding from Astellas</p> <p>Speaker honoraria Chiesi</p> <p>Consultancy Novartis</p>
Comments	<p>721</p> <p>There is a risk of this being misinterpreted and applied as a guideline by healthcare funders and a clear statement that this document is not intended to be a guideline for immunosuppression for renal transplantation would be welcome. Importantly, the full spectrum of drugs in current use in the UK for transplant immunosuppression was not considered, as not all were entered into the technology appraisal. Indeed, a NICE guideline in this area would be useful. While this does represent an appropriate assessment of the optimal immunosuppressive regimen for the majority of UK renal transplant recipients as an initial immunosuppressive regimen, it does not allow scope for individualisation to deal</p>

	<p>with specific clinical problems or changes in risk of rejection and complications over time.</p> <p>Generic tacrolimus</p> <p>The advice on the use of the generic tacrolimus brand with the lowest acquisition cost ought to be qualified. The calcineurin inhibitors have a narrow therapeutic index. It is particularly important that generic calcineurin inhibitors meet the more stringent bioequivalence criteria (90-111%) and, ideally have pharmacokinetic data in renal transplant recipients. The European Society for Organ Transplantation has published guidelines on the appropriate use of generic immunosuppressive drugs (1). This guidance includes advocating avoidance of repeated switching between generic preparations that may have different oral bioavailability. This is not made clear in the guidance in the current NICE document.</p> <p>Individualisation of immunosuppressive regimens</p> <p>There are some clinical situations where there is clear benefit from use of an alternative drug regimen, for example the use of sirolimus in patients with skin cancer. Some patients do find compliance with twice daily drug regimens difficult with omission of the evening dose more common than the morning dose. The requirement to take tacrolimus separate from food is generally found to be easier to adhere to reliably in the morning than in the evening. Drug regimens based on once daily preparations including tacrolimus, sirolimus, azathioprine and prednisolone may result in improved compliance in some patients. While the standard regimen is the optimal initial drug combination, there may be benefit to modification of the drug regimen in the longer term. An example of this practised in our unit is a change from the relatively poorly tolerated mycophenolate to azathioprine in low-risk patients after 3 months. The current advice discounts the use of azathioprine. These alternative regimens may be more costly than the standard tacrolimus/mycophenolate regimen advocated here and purchasers may be discouraged from providing appropriate funding based on this guidance.</p> <p>References</p> <p>1. van Gelder T. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. <i>Transpl Int</i> 2011;24: 1135-1141.</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	
Role	NHS Professional
Job title	Consultant Nephrologist
Location	England

Conflict	Yes
Disclosure	<p>I have received research funding from Astellas pharma UK to support the laboratory costs of drug assays in an on-going RCT of Tacrolimus-based maintenance immunosuppression after Alemtuzumab induction in kidney transplantation (Clinical Trials.gov reference NCT00807144).</p> <p>I have also received speaker and advisory board fees, from Astellas pharma UK (as well as Roche UK)</p>
Comments	<p>722 NB: Please see declaration of interest(s)</p> <p>This comment is made from a personal perspective, and I am commenting as an individual who has been involved as a clinician in kidney transplantation for over 20 years, not on behalf of the institution where I work (Imperial College Healthcare NHS Trust).</p> <p>I strongly support NICE's project of ensuring that healthcare interventions in the UK are effective, evidence-based, and good value for money, and their use of good-quality, prospective, randomised controlled trials as the primary evidence from which appraisals and guidelines should be derived.</p> <p>Looking at the development of kidney transplantation in the UK since the widespread adoption of Cyclosporine-based regimens in the 1980s, the advances that have been made in terms of medium and long-term outcomes have been strikingly good, and with NHS-BT national outcome data now showing 3 year graft survival rates approaching 90% and 10-year graft survival better than 70% for DBD kidney recipients, I think we should acknowledge what a very difficult challenge we face as we try to generate an evidence base for any therapies that might improve on such very successful outcomes. I think that there is a risk that by relying on restrictive terms of reference (as this appraisal has done in excluding consideration of regimens using induction with Alemtuzumab) we will cut ourselves off from potential avenues of improvement.</p> <p>Although our outcomes are very good, many grafts are still lost (at great personal cost to kidney transplant recipients) predominantly to chronic antibody mediated rejection, and we lack the diagnostic tools to successfully predict this, and the interventions to forestall or reverse it so there are still very important unmet needs in the field.</p> <p>I have read the current appraisal consultation ID456 without finding any indication that this, the major challenge facing kidney transplant recipients and their doctors for the coming decades has been considered, or even understood, and I am anxious that, because we now have relatively cheap and highly effective immunosuppressive therapies (which is, in itself, surely a very good thing) we may find ourselves trapped by an</p>

	<p>economic model which prevents innovation, and stifles any attempt to undertake the challenging but potentially valuable task of finding better ways of treating our patients for the long term.</p> <p>I think that the recommendations should include some acknowledgment that the regimens suggested are not, in and of themselves, able to address the outstanding issues in long-term graft survival, and that alternative approaches (which should of course be undertaken in such a way that valid data can be derived from their outcomes, and ideally as prospective randomised trials) might require drug combinations that fall outside those that are preferred on a narrow economic basis.</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	Leicester General Hospital
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	No
Disclosure	
Comments	<p>723 Points of concern:</p> <ol style="list-style-type: none"> 1. High risk patient Transplants: Situations e.g. HLA incompatible, highly sensitised, ABO incompatible, extended criteria donor transplants need immunosuppressive regimes require to be tailored to the patients medical and immunological need. 2. Heterogenous transplant population: Transplantation is considered the most efficient renal replacement therapy with additional health benefits to patients so we must continue to optimise medical and pharmacological management and maximise graft function to sustain and further improve patient and graft outcomes. By virtue of the heterogeneous transplant population different drug regimes are needed to account not least for individual patient variability. 3. rATG/alemtuzumab: are widely used in clinical practice as induction for high risk transplants and should remain so in this select cohort. Basiliximab is not licensed in highly sensitised patients (PRA>80%). Basiliximab should be the induction antibody of choice for standard risk recipients (as per recommendation 1.1) though agents like rATG must be allowed for high immunological risk recipients. There are increasing populations with high PRA, sensitisation and previous transplants. The role in cross match negative but high MFI DSA is not clear and the above two play a role. The role of rATG induction should be considered for steroid

avoidance/minimisation or tacrolimus maintenance monotherapy and in the steroid resistant organ rejection is important (1st line) and therefore must be permitted to continue.

4. Prolonged release tacrolimus: It should be recommend that it should be available for use in small selected cohorts of patients where there is patient and graft outcome benefit from simplification of the drug regimen to once daily(learning difficulties, risk of non-adherence). Approximately 5 to 30% of patients 1,2, find adherence to a twice-daily tacrolimus regimen challenging this compromises the clinical effectiveness of immediate release therapy. This group of patients would achieve a better clinical outcome from a prolonged-release formulation of tacrolimus based on a once-daily dosage 3,4 . Loss of 2 grafts due to non-adherence will offset the cost benefits for the whole programme where about 100-120 transplant are done in a year.

In addition there is emerging evidence from other transplant groups(liver) that prolonged release tacrolimus can improve long term graft survival by reducing drug level/exposure variability.

5. Mycophenolate mofetil (MMF): There is clinical experience to support a switch to Myfortic in patients with marked and debilitating gastrointestinal adverse reactions from MMF where dose reduction and dose splitting have not resolved these symptoms. The role of use Myfortic in such instances should be documented in the guidelines.

6. Sirolimus: the option of using sirolimus in patients with recurrent skin cancers (other cancers) and in patients with evidence of CN1 toxicity.

7. Clinical experts used by NICE did not seek opinions from a nephrologist, pharmacist or nurse who predominantly use immunosuppressive medications.

To summarise it is impossible to individualise immunosuppressive therapy regimens in a complex heterogeneous group of patients where factors such as high risk, DSA, non-adherence, learning difficulties not in the patients or clinician control. Day to day clinical practice and patient management to optimise patient out come is the responsibility of the clinician and limitations to do so should be avoided.

██████████ : ██████████

26/08/2015

1. Vlaminc H et al, American Journal of Transplantation, 2004.
2. Denhaerynck K et al, Transplant Review, 2005

	3. Guirado L et al, American Journal of Transplantation, 2011 4. Kuypers D et al, , Transplantation, 2013
Submission date	26/08/2015

Name	[REDACTED]
Organisation	Addenbrookes
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	No
Disclosure	
Comments	<p>725 As [REDACTED] at the [REDACTED], I would like to offer the following comments . The Appraisal Committee states that it is interested in a number of points including: Are the provisional recommendations sound and a suitable basis for guidance to the NHS?</p> <p>I would like to comment that these recommendations, as they stand, are not a suitable basis for guidance to the NHS. The reason for this is twofold: 1. The preliminary recommendations for immunosuppression for kidney transplant in adults does not include all immunosuppressive agents, only those that were included in technology appraisal guidance 85 (TAG85), have obtained a marketing authorisation since TAG85 or have been referred to NICE for appraisal. I understand that the appraisal only focused on new technologies, however for the recommendations to be a suitable basis for guidance all immunosuppression options should be included (ie ciclosporin, azathioprine, steroids, alemtuzumab). A recommendation to the effect that immunosuppressive agents routinely used prior to TAG85 can be used as an option to prevent organ rejection in adults having a kidney transplant would be helpful in making these recommendations a suitable basis for guidance to the NHS. 2. Patient sub groups are not mentioned in the preliminary recommendations, presumably due the paucity of evidence within subgroups. However, for these recommendations to be a suitable guidance for the NHS the recommendations need to also include immunosuppression options for patient subgroups. The preliminary recommendation of "ATG, prolonged release tacrolimus, sirolimus/everolimus and belatacept are not recommended to prevent organ rejection", removes clinician autonomy to tailor immunosuppression therapy to individual patients and certain sub groups of patients will have adverse clinical outcomes because of this.</p> <p>For example:</p> <p>• Patients unable to tolerate CNI's due to side effects</p>

such as thrombotic microangiopathy, renal impairment, neurotoxicity, diabetes will have limited treatment options if sirolimus and belatacept are not available to them

â€¢ Patients unable to tolerate steroids (all kidney pancreas transplant patients requiring transplantation because of diabetes or other kidney transplant patients due to side effects) will have limited treatment options if alemtuzumab is not available to them.

â€¢ Patients requiring removal of blood group or HLA antibody to allow anti-body incompatible transplantation will have limited treatment options if non-standard immunosuppression is not available to them.

â€¢ Patients with known compliance issues who would benefit significantly from a once a day immunosuppression regimen will have reduced treatment options if prolonged release tacrolimus is not available to them.

â€¢ Patients with highly variable tacrolimus levels on an immediate release tacrolimus who would benefit from a prolonged release preparation will have their treatment options reduced.

â€¢ Patients coming to renal transplant with atypical haemolytic syndrome requiring induction with rabbit ATG and eculizumab therapy will have limited treatment options if rATG is not available to them.

A recommendation to the effect that rATG, prolonged release tacrolimus, sirolimus/everolimus and belatacept can be considered as an option to prevent organ rejection in specific subgroups of adults having a kidney transplant would be helpful in making these recommendations a suitable basis for guidance to the NHS.

I would like to comment that these recommendations, as they stand, are not a suitable basis for guidance to the NHS. The reason for this is twofold:

2. Patient sub groups are not mentioned in the preliminary recommendations, presumably due the paucity of evidence within subgroups. However, for these recommendations to be a suitable guidance for the NHS the recommendations need to also include immunosuppression options for patient subgroups. The preliminary recommendation of â€˜rATG, prolonged release tacrolimus, sirolimus/everolimus and belatacept are not recommended to prevent organ rejectionâ€™TM, removes clinician autonomy to tailor immunosuppression therapy to individual patients and certain sub groups of patients will have adverse clinical outcomes because of this.

For example:

	<p>â€¢ Patients unable to tolerate CNIâ€™s due to side effects such as thrombotic microangiopathy, renal impairment, neurotoxicity, diabetes will have limited treatment options if sirolimus and belatacept are not available to them</p> <p>â€¢ Patients unable to tolerate steroids (all kidney pancreas transplant patients requiring transplantation because of diabetes or other kidney transplant patients due to side effects) will have limited treatment options if alemtuzumab is not available to them.</p> <p>â€¢ Patients requiring removal of blood group or HLA antibody to allow anti-body incompatible transplantation will have limited treatment options if non-standard immunosuppression is not available to them.</p> <p>â€¢ Patients with known compliance issues who would benefit significantly from a once a day immunosuppression regimen will have reduced treatment options if prolonged release tacrolimus is not available to them.</p> <p>â€¢ Patients with highly variable tacrolimus levels on an immediate release tacrolimus who would benefit from a prolonged release preparation will have their treatment options reduced.</p> <p>â€¢ Patients coming to renal transplant with atypical haemolytic syndrome requiring induction with rabbit ATG and eculizumab therapy will have limited treatment options if rATG is not available to them.</p> <p>A recommendation to the effect that rATG, prolonged release tacrolimus, sirolimus/everolimus and belatacept can be considered as an option to prevent organ rejection in specific subgroups of adults having a kidney transplant would be helpful in making these recommendations a suitable basis for guidance to the NHS.</p> <p>The use of these new technologies in clinical practice is not just restricted to prevention of rejection following renal transplantation in adults but also extends to other solid organ types, to paediatric patients and to the treatment of rejection. It would be useful if further recommendations could also be made on immunosuppressive therapy for these aspects of solid organ transplantation.</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	Royal Liverpool University Hospital
Role	NHS Professional
Job title	[REDACTED]
Location	England

Conflict	No
Disclosure	
Comments	<p>728</p> <p>The main objective in the post transplant period is the long term survival of the Patient/Graft. It depends upon many donor and recipient factors and also on complications in the post transplant period including rejections and infections especially the viral infections. The infections are directly proportional to immunosuppression load and rejections are inversely. Its very important to keep the Tacrolimus levels in the specified range.</p> <p>We tried to use another brand of Tacrolimus than Prograf and found the levels very erratic in those 10 patients which could effect the long term outcome. I dont think validated data is available for the efficacy of all th ebrands of tacrolimus available in the market As a unit , it was decided in best interest of the patientsnot to use any otherbrand than Prograf which we have been using fo rlong years</p> <p>So I will have my reservations and anxities in using Any cheapest brand of Tacrolimus available in the market which I feel can have impact on long term outcome an dwill defeat the purpose of cost effectiveness</p> <p>Sirolimus is non nephrotoxic and Tacrolimus and Cyclosporine are nephrotoxic. Sirolimus is not used as primary immunosuppression in most of the centres due to its potential complications in the post surgical period and also increased risk of rejection as compared to CNIs in the early transplant period.</p> <p>As sirolimus is non nephrotoxic, it has got its role in managing the marginal kidneys or kidneys with chronic changes in the long term which might be sensitive to CNIs.</p> <p>Regarding the prolong release Tacrolimus, the data is available which shows adherence in the non compliant patients. In our personel experience in the unit, use of prolonged release tacrolimus is also increasing to manage the split doses of tacrolimus, eg, if patient needs 4.5 mg of tacrolimus a day, it cant be divided into 2.25 twice a day as 0.25 tablets are not available instead thispatient can be manged by giving 4.5 mg of prolonged release tacrolimus.</p> <p>These will be my reservation sfo rthese two drugs.</p>
Submission date	26/082015

Name	██
Organisation	Addenbrookes
Role	NHS Professional
Job title	██
Location	England
Conflict	No
Disclosure	

Comments	729 For future appraisals around immunosuppressive therapy in transplantation could the Solid Organ Transplant Pharmacists Association (SOTPA www.sotpa.co.uk) be included to consult?
Submission date	26/08/2015

Name	██████████ ██████████
Organisation	
Role	NHS Professional
Job title	Senior Clinical Pharmacist
Location	England
Conflict	No
Disclosure	I have received disclosed sponsorship from Astellas Pharma for educational meetings.

Comments	<p>731 Dear NICE Team,</p> <p>Re: NICE ACD: Immunosuppressive therapy for kidney transplant in adults (ID456)</p> <p>I would ask NICE to review the evidence outlined in the following paper; Considine, A, Tredger M Heneghan M et al. Liver Transplantation 21:29-37,2015; Performance of modified-release tacrolimus after conversion in liver transplant patients indicates potential favourable outcome in selected cohorts.</p> <p>I disclose I was involved in the completion of the above paper. In my opinion the documented results looking at conversion to Advagraf in the study support the use of this immunosuppressive agent in the renal transplant population.</p> <p>The study was a single centre retrospective triple arm, parallel group of 189 adult and adolescent liver graft recipients. We looked at patients who were converted to Advagraf early (within 1 month of transplantation) and late (> 1 month post-transplant) alongside a parallel reference group of patients maintained on Prograf. A key result we obtained is that over a period of 6 months post liver transplantation increases in median serum creatinine concentrations were smallest following late conversion to Advagraf despite this cohort having the highest median serum creatinine at time of transplantation.</p> <p>We also indirectly assessed adherence by calculating the standard deviation for all dose-equalized tacrolimus concentrations for each patient. The median standard deviation was significantly lower for the early-conversion cohort versus the Prograf cohort. We performed a paired analysis for the late cohort and compared the standard deviations before and after conversion to Advagraf for each patient as a surrogate measure of adherence. This showed a statistically significant reduction of intra-patient variability after conversion.</p>
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	<p>Many thanks for considering the above evidence.</p> <p>Yours Sincerely,</p> <p>[REDACTED]</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	Oxford Transplant Centre
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	
Disclosure	
Comments	<p>Re NICE TA85: ACD on Immunosuppressive therapy for kidney transplant in adults.</p> <p>Comments from: Oxford Transplant Centre, [REDACTED]</p> <p>We are responding as a transplant centre that carries out kidney, pancreas, islet and intestinal transplantation. We believe that the implementation of the ACD would prove excessively restrictive in clinical practice, to the detriment of patient care. In support of this:-</p> <p>The report has only considered “standard risk” patients. As are most transplant units, we transplant high risk patients (e.g. HLA incompatible, immunologically highly sensitised, ABO incompatible, extended criteria donor organs). Even in these settings, there is little doubt but that transplantation is cost efficient to the NHS as well as providing considerable health benefits to the patient over for example dialysis. Such patients are usually excluded from clinical trials and there is, therefore, little published RCT evidence to support what is optimum immunosuppression in these cohorts. However our clinical experience supports the use of rATG or alemtuzumab in these high risk situations. Such patients should not be denied what is widely regarded as best practice therapy due to the paucity of RCT data.</p> <p>There is substantial weight of evidence to support the individualisation of immunosuppressive therapies, giving consideration to genetic predisposition, previous transplant history, other co-morbidities and medication adherence. A one size fits all of immunosuppressive therapies is now regarded as grossly simplistic and, if mandated, would undoubtedly be a retrograde step.</p> <p>The treatment of steroid resistant rejection has not been considered. rATG is clinically accepted as first line agent and is now licensed, having been previously used for over twenty</p>

years in transplantation as an unlicensed medicine. This requires clarification in the final advice.

Effective management of chronic allograft dysfunction is one of the defining challenges in kidney transplantation. Sirolimus is one of the drugs which should always be considered in this situation, due to its lack of nephrotoxicity, and especially if a patient is intolerant of mycophenolate mofetil (GI side effects or lymphopenia). Similarly for extreme GI intolerance with MMF despite dose reduction and increasing dose frequency, Myfortic should be considered in order to seek improved tolerability. The evidence for late post-transplant use of sirolimus is not covered by its licensing approval; however, there is a strong argument for the use of this agent in patients with calcineurin-inhibitor-related graft dysfunction and, also, in patients developing a malignancy post-transplant (because of the known anti-tumour effect of mTOR inhibitors). There is also growing clinical experience and evidence that sirolimus has some anti-viral activity and in difficult-to-manage cases of ganciclovir CMV resistant disease or persistent CMV viraemia; in these situations, sirolimus has been used as maintenance immunosuppression to reduce CMV viral load.

Ciclosporin, azathioprine and prednisolone have not been included in the technology appraisal. These drugs should not be excluded (if this is, indeed, the intention). Ciclosporin is not a first choice agent but would be used in a patient with intolerability of tacrolimus. If a female patient on mycophenolate wished to start a family then therapy should be changed to azathioprine as mycophenolate is a teratogen.

In our centre (as in others) we have introduced a simplified, once a day immunosuppressive protocol for Young Adults (aged <25 years) - a patient population clearly identified as being at very high risk of non-adherence and premature graft loss. This protocol involves the use of prolonged release tacrolimus. We have seen significant reduction in acute rejection episodes and improved patient and graft outcome in this small patient cohort.

There are limited drugs available for use in transplantation (and many patients are treated using agents in unlicensed combinations). It is vital that these drugs should remain available for the benefit of patients that do not conform to the 'average'. This substantial minority of patients should not be denied accepted best practice therapy due to paucity of RCT data. An IFR submission for each of the proposed excluded drugs is not appropriate as these patients constitute small cohorts of transplant patients and to treat them as exceptional individual cases would be unrealistically unwieldy.

	<p>[REDACTED] - [REDACTED]</p> <p>Oxford Transplant Centre</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	North Bristol NHS Trust
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	
Disclosure	
Comments	<p>Response to NICE TA85: ACD on Immunosuppressive therapy for kidney transplant in adults.</p> <p>The [REDACTED] team at North Bristol NHS Trust are concerned that the proposed NICE tag 85 is very restrictive and will have an impact on patient care. Whilst the majority of standard risk kidney transplant recipients can be managed using basiliximab for induction and immediate release tacrolimus and steroids for maintenance immunosuppression plus or minus mycophenolate mofetil there are legitimate occasions where access to modified release tacrolimus, sirolimus, mycophenolic acid, belatacept is required.</p> <p>Tacrolimus - I support the recommendation that immediate release tacrolimus should be used first line and believe that patients should be started and maintained on the most cost effective brand. Tacrolimus should be prescribed by brand to avoid accidental brand switching. There are occasions when modified release tacrolimus can be beneficial. E.g. a patient with learning difficulties struggling to manage a twice daily regimen may benefit from once daily modified release tacrolimus to support both patient and/or carer. Being unable to prescribe modified release tacrolimus could be considered discrimination on the grounds of age/disability. The statement that modified release tacrolimus is not a cost effective use of NHS resources would prevent its use in exceptional cases.</p> <p>Mycophenolic acid (Myfortic) – I support the recommendation that mycophenolate mofetil should be used first line however for patients intolerant to mycophenolate mofetil despite splitting and or reducing the dose Myfortic should be available second line. In practice patients intolerant to mycophenolate mofetil have benefitted from switching to Myfortic and a lack of alternative treatment could result in graft loss.</p> <p>Sirolimus – Sirolimus should not and is not used routinely to prevent rejection in kidney transplant recipients however there is a small group of patients including those with malignancy or difficult to manage CMV disease who benefit from sirolimus. If sirolimus does not have NICE approval then it is unlikely</p>

	<p>sirolimus will be funded in any circumstance.</p> <p>Belatacept - I agree that belatacept should not be prescribed routinely however locally belatacept has been used as a last resort to successfully manage a patient with multiple drug intolerances. If belatacept does not have NICE approval then it will not be funded under any circumstance so this limited number of patients will be denied access to this last resort treatment which could then result in graft loss.</p> <p>Ciclosporin, azathioprine and prednisolone have not been formally assessed as part of this technology appraisal. Does this mean they will not be NICE approved? If so this will be unmanageable in clinical practice. Locally prednisolone is used routinely and azathioprine is sometimes used in patients intolerant of MMF or in pregnancy. Ciclosporin needs to remain a choice for patients who require a switch from tacrolimus due to side effects/ intolerance.</p> <p>This document does not discuss the treatment of rejection rATG needs to remain available for this indication and it would be useful for the TAG to clarify this.</p> <p>In summary I am concerned that the statements that Myfortic, sirolimus and belatacept are not cost effective uses of NHS resources will prevent their use even in exceptional cases. If these agents are not available to manage complex patients then this could result in graft loss and an early return to dialysis. An early return to dialysis would be associated with increased costs as well as associated morbidity and mortality.</p> <p>██████████ – ██████████ ██████████ ██████████ - North Bristol NHS Trust.</p>
Submission date	26/08/2015

Name	██████████
Organisation	Addenbrookes Hospital
Role	NHS Professional
Job title	██████████
Location	England
Conflict	
Disclosure	
Comments	<p>Dear NICE</p> <p>Please find attached a Word document commenting on the Appraisal Consultation Document 'Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)</p> <p>I do not believe the provisional recommendations are a sound and suitable basis for guidance to the NHS. Only one immunosuppressive regimen is recommended, with little regard for the many patients in whom this regimen is not tolerate or is</p>

clinically inappropriate. The ACD chooses not to include several drugs widely used in the UK, despite substantial trial evidence (for example alemtuzumab, used in the very large and well conducted 3C study and the INTAC study).

I think one very obvious feature of the ACD is that it has been written by a group without any clinical experience of either Nephrology or Transplantation. Indeed, where advice from experts has been sought, it has been disregarded in every instance.

I hope the attached comments prove helpful

With best wishes

[REDACTED]

Addenbrookes Hospital

[REDACTED]

Immunosuppressive Therapy For Kidney Transplant in Adults – Response

Preliminary Recommendations

1. The only treatments recommended (points 1.1 – 1.3) are basiliximab, immediate release tacrolimus and mycophenolate mofetil. However each is described as an ‘option’. This is misleading. No other options are recommended. I would suggest removing the word ‘option’ and including a phrase such as ‘recommended as first line immunosuppressive therapy for’
2. The evidence presented in subsequent sections, and the economic evaluation, exclusively refer to combination immunosuppressive therapy. I presume the recommendation is to use as first line therapy basiliximab induction followed by immediate release tacrolimus / MMF / +/- steroid. This should be made clear.
3. Point 1.4 states that rabbit anti-human thymocyte immunoglobulin (rATG) is not recommended to prevent organ rejection’ I would suggest that it is made very clear that this document does **not** include any assessment of, or recommendation for, treatment of acute rejection. rATG is the only available treatment for steroid-resistant rejection. I would suggest that for rATG the recommendation is very specific – ‘is not

recommended for **induction immunosuppression to prevent**'

4. A further point regarding rATG is that, unlike basiliximab, there is no restriction in marketing authorization for immunologically high risk patients (see point 12 below). The committee acknowledges the efficacy of rATG (section 4.5 of draft report), and I would suggest that rATG is allowed as an option when there is proven immunologic risk in sensitized patients (PRA, or more accurately in the UK cRF – calculated reaction frequency - >80%. This issue is poorly addressed in section 4.66.
5. Point 1.4 also precludes the use of alternative agents to calcineurin inhibitors (tacrolimus or ciclosporin – although ciclosporin is not included in any recommendation), in particular sirolimus and belatacept. I believe such an absolute statement is misplaced:
 - a. At least 10% of patients are unable to tolerate a CNI-based regimen – see for example 3 year follow up of the SYMPHONY study (Ekberg et al (2009). Am J Transplant 9, 1876-1885) – 162 of 181 patients with complete data were not on their tacrolimus based regimen at 3 years, with ciclosporin withdrawn from a much higher proportion. This is one of the better studies, and the true figure likely higher – in our own follow-up population 15% are not on a CNI.
 - b. Reasons for tacrolimus intolerance include:
 - i. Nephrotoxicity
 - ii. Neurologic side effects (tremor, neuropathy, PRES)
 - iii. Thrombotic microangiopathy (TMA)
 - c. The suggestion that adverse effects to tacrolimus requiring an alternate treatment are 'sufficiently rare to manage through IFR' (section 4.63, page 39) is simply untrue. 10% of adult transplant recipients equates to nearly 300 / year, which far exceeds NHSE definition of exceptionality (required for an IFR)
 - d. Accordingly I believe NICE should allow for alternatives to tacrolimus (sirolimus or belatacept) where tacrolimus as first line therapy has failed.
 - e. The comment (bottom of page 39) that 'the Committee concluded that it was not able to make recommendations for people whose treatment needs to be withdrawn because of

complications' is at odds with much of the evidence presented. There is ample evidence that licensed and effective medications are available as an alternative to CNI (sirolimus and belatacept), and indeed the evidence for both has been considered in the draft guidelines (see for example section 4.60).

- f. Ant economic evaluation must include the cost of return to dialysis should the graft fail. One year of dialysis costs about £30,000, substantially more than even the most expensive alternative to tacrolimus (belatacept)

Prolonged Release Tacrolimus

6. Evidence regarding the benefits of prolonged release tacrolimus (Advagraf) has been provided by the manufacturer, and opinion provided by patient and clinical experts (section 4.64). However the committee has not taken into account **existing NICE guidance (CG76 – Medicines Adherence)** produced with the NCCPC (National Collaborative Centre for Primary Care). This guideline emphasises the need for patient choice, and for simplified dosing regimens (for example once-daily as opposed to multiple daily dosing). It is very disappointing that this current draft guideline disregards NICE's own advice. Indeed CG76 is not included in the bibliography (section 6, page 60)
7. I would suggest that the proposal 'prolonged release tacrolimus is not recommended' is revised. Could some form of words be found to allow such treatment where clinicians are confident there would be clinical benefit.

Marketing Authorization

8. The use of basiliximab induction followed by immediate release tacrolimus + mycophenolate mofetil +/- steroid falls outside of the marketing authorization for both basiliximab and mycophenolate mofetil. However, the committee has presented extensive contemporary evidence indicating the efficacy of this immunosuppressive regimen.
9. I suggest that the final document specifically addresses this point, with some acknowledgement that NICE considers this regimen the appropriate first line treatment for most patients receiving a kidney transplant.

	<p>10. As it stands this issue is dealt with in footnotes to the preliminary recommendations in a manner that is almost perverse, and in my view demeaning to clinicians. Having recommended only one immunosuppressive combination, the footnote then asks clinicians to ‘take full professional responsibility ...’. Clearly every prescribing clinician takes responsibility for the medications they prescribe. However, in this case NICE is proposing no other option.</p> <p>11. Accordingly I believe there should be a clear statement regarding the outdated nature of the marketing authorizations, the relevance of contemporary studies, and a clear acknowledgement that NICE is recommending treatment outside of marketing authorization. A footnote is not adequate.</p> <p>12. A subsidiary point is that the marketing authorizations and / or associated clinical studies specifically exclude some groups of patients. For example basiliximab is licensed for patients with a PRA <80% (a marker of HLA antibody sensitization). However, more than 20% of the waitlisted UK population have a PRA >80% (UK Renal Registry Annual Report 2013 – see also point 4 above). Similarly most trials exclude kidneys donated by older donors (variously aged >60, 65 or 70), yet such donors make up an increasing number of transplants in the UK with 33% of deceased donors aged over 60 (NHSBT / ODT Annual Report 2015)</p>
Submission date	26/08/2015

Name	[REDACTED]
Organisation	Oxford University Hospitals NHS Trust
Role	NHS Professional
Job title	[REDACTED]
Location	England
Conflict	No
Disclosure	
Comments	<p>732</p> <p>We are responding as a transplant centre that carries out kidney, pancreas, islet and intestinal transplantation. We believe that the implementation of the ACD would prove excessively restrictive in clinical practice, to the detriment of patient care. In support of this:-</p> <p>The report has only considered ‘standard risk’ patients. As are most transplant units, we transplant high risk patients</p>

(e.g. HLA incompatible, immunologically highly sensitised, ABO incompatible, extended criteria donor organs). Even in these settings, there is little doubt but that transplantation is cost efficient to the NHS as well as providing considerable health benefits to the patient over for example dialysis. Such patients are usually excluded from clinical trials and there is, therefore, little published RCT evidence to support what is optimum immunosuppression in these cohorts. However our clinical experience supports the use of rATG or alemtuzumab in these high risk situations. Such patients should not be denied what is widely regarded as best practice therapy due to the paucity of RCT data.

There is substantial weight of evidence to support the individualisation of immunosuppressive therapies, giving consideration to genetic predisposition, previous transplant history, other co-morbidities and medication adherence. A one size fits all of immunosuppressive therapies is now regarded as grossly simplistic and, if mandated, would undoubtedly be a retrograde step.

The treatment of steroid resistant rejection has not been considered. rATG is clinically accepted as first line agent and is now licensed, having been previously used for over twenty years in transplantation as an unlicensed medicine. This requires clarification in the final advice.

Effective management of chronic allograft dysfunction is one of the defining challenges in kidney transplantation. Sirolimus is one of the drugs which should always be considered in this situation, due to its lack of nephrotoxicity, and especially if a patient is intolerant of mycophenolate mofetil (GI side effects or lymphopenia). Similarly for extreme GI intolerance with MMF despite dose reduction and increasing dose frequency, Myfortic should be considered in order to seek improved tolerability. The evidence for late post-transplant use of sirolimus is not covered by its licensing approval; however, there is a strong argument for the use of this agent in patients with calcineurin-inhibitor-related graft dysfunction and, also, in patients developing a malignancy post-transplant (because of the known anti-tumour effect of mTOR inhibitors). There is also growing clinical experience and evidence that sirolimus has some anti-viral activity and in difficult-to-manage cases of ganciclovir CMV resistant disease or persistent CMV viraemia; in these situations, sirolimus has been used as maintenance immunosuppression to reduce CMV viral load.

Ciclosporin, azathioprine and prednisolone have not been included in the technology appraisal. These drugs should not be excluded (if this is, indeed, the intention). Ciclosporin is not a first choice agent but would be used in a patient with intolerability of tacrolimus. If a female patient on mycophenolate wished to start a family then therapy should be changed to azathioprine as mycophenolate is a teratogen.

	<p>In our centre (as in others) we have introduced a simplified, once a day immunosuppressive protocol for Young Adults (aged<25 years) - a patient population clearly identified as being at very high risk of non-adherence and premature graft loss. This protocol involves the use of prolonged release tacrolimus. We have seen significant reduction in acute rejection episodes and improved patient and graft outcome in this small patient cohort.</p> <p>In our centre (as in others) we have introduced a simplified, once a day immunosuppressive protocol for Young Adults (aged<25 years) - a patient population clearly identified as being at very high risk of non-adherence and premature graft loss. This protocol involves the use of prolonged release tacrolimus. We have seen significant reduction in acute rejection episodes and improved patient and graft outcome in this small patient cohort.</p>
Submission date	26/08/2015

Appendix One – Data supporting the effectiveness of prolonged-release tacrolimus

Thank you for the opportunity to provide further data for consideration by the Appraisal Committee.

In response to the Appraisal Committee's comment that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes and that it would be difficult to identify people who would benefit (ACD, Section 4.64) we have provided details of evidence (generally non-RCT data) supporting the effectiveness of prolonged release tacrolimus in improving adherence, reducing intra-patient variability and maintaining renal function.

In summary:

- High intra-patient tacrolimus variability predicts worse long-term outcomes after renal transplantation^{1,2,3}
- Prolonged-release tacrolimus has been shown to reduce intra-patient trough level variability relative to that of immediate-release tacrolimus^{4,5}
- RCT data show that adherence is improved with prolonged-release tacrolimus (once-daily) versus immediate-release (twice-daily) dosing.⁶ NOTE: This was included in the initial Astellas submission document
- Improved adherence with prolonged-tacrolimus leads to improved graft survival in renal transplant recipients in routine clinical practice⁷⁻¹⁰
- Prolonged-release tacrolimus has been shown in a UK clinical setting, to result in lower rates of NODAT than are reported in the literature for immediate release and prolonged release tacrolimus¹¹
- Renal function is maintained with prolonged-release tacrolimus with data available for 3 years post transplant^{12,13}
- Patients demonstrate a preference for the once-daily dosing vs. twice-daily dosing¹²

Economic modelling

In order to ensure robust consideration is given to adherence we recommend the model is updated to capture patient adherence to the prescribed immunosuppressive regimen and would highlight methodological guidance from the ISPOR Economics of Medication Compliance Working Group states that "*consideration of the effects of noncompliance and nonpersistence should be an integral part of pharmacoeconomic evaluations and in the health-care decision-making these evaluations inform*" (Hughes).¹⁴

The most methodologically robust study into adherence in renal transplant recipients we have identified previously to the Committee and the Assessment Group was published by Kuypers *et al.* in 2013.⁶ This study is a RCT, i.e. tightly controlled conditions, comparing medication adherence between tacrolimus once-daily and twice-daily regimens using electronic monitoring.

We would propose using these data to model the proportion of patients adherent to their tacrolimus regimen. Data on adherence to once- and twice-daily tacrolimus from Kuypers *et al.* could reasonably be used as a proxy for other once- and twice-daily oral medications, while adherence to belatacept could be taken from comparable intravenous regimens.¹⁵

A graft failure hazard ratio could then be assigned to the proportion of non-adherent patients based on one of numerous available studies and combined with the existing graft loss hazard ratios based on estimated glomerular filtration rate (eGFR), new onset diabetes after transplantation (NODAT) and biopsy-proven acute rejection (BPAR).⁷⁻⁹

We propose that the Committee requests the Assessment Group to update the model in line with the above recommendations.

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1. Whalen H, Glen J, Stevens J et al. High-inpatient tacrolimus variability in low-dose tacrolimus regimen predicts worse long-term outcomes after renal transplant. Abstract 2923 WTC San Francisco July 2014.
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Appendix Two –Comments on the Assessment Report

Thank you for the opportunity to comment on the Assessment Group assessment report.

While a key error in the initial economic model pertaining to prolonged-release tacrolimus was highlighted in the Novartis response to the Assessment Report (“19 AR response to Novartis Pro-forma executable model”; Issue 1 p3) and has been addressed in the updated model a number of fundamental concerns with the analysis remain. These include:

1. The use of drug acquisition costs based on discounted prices for immediate-release tacrolimus taken from the Commercial Medicines Unit’s (CMU) Electronic Market Information Tool (eMit) and the use of a second separate data source (BNF) for the Advagraf (prolonged-release tacrolimus) list price
2. The inclusion of non-significant efficacy and safety endpoints (including graft loss and mortality, the two most important long term outcome measures) to infer clinically significant differences between immediate and prolonged release tacrolimus combined with the exclusion of significant findings that favour prolonged-release tacrolimus

Each concern is addressed in more detail in the following sections with both points also addressed in our response to the Appraisal Consultation Document.

Inconsistent use of list prices

Drug acquisition costs as reported in the base case analysis are based on heterogeneous data sources that unfairly inflate the cost of prolonged-release tacrolimus relative to immediate-release tacrolimus:

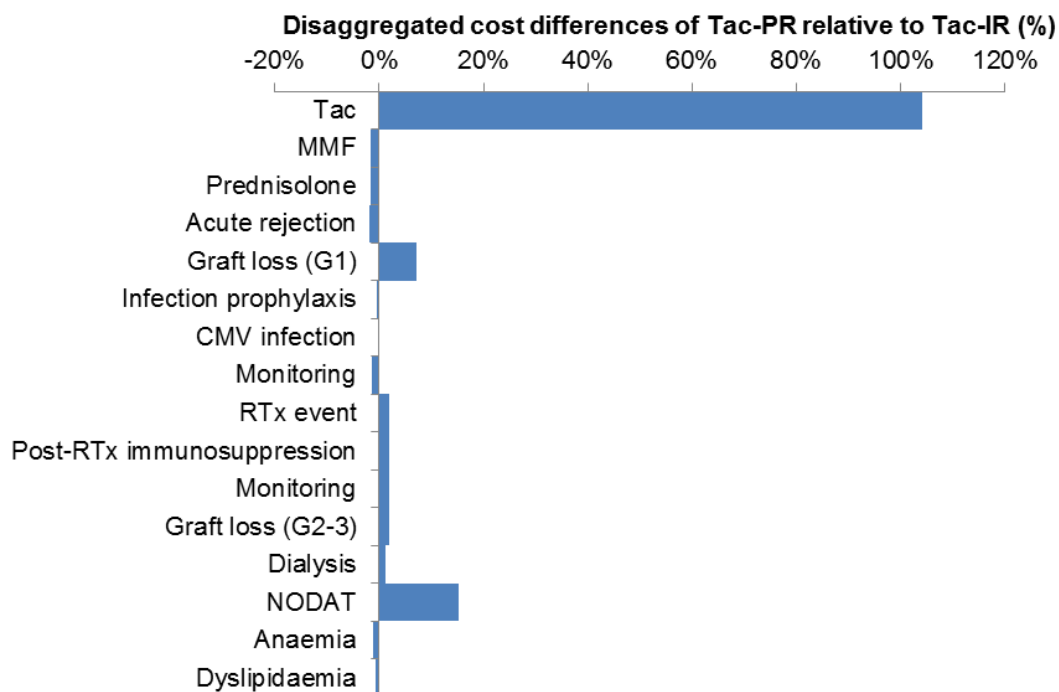
- Prolonged-release tacrolimus costs are taken directly from the BNF 68 list price for tac-PR 5 mg capsules (£1.07/mg), which does not accurately reflect the true cost borne by the NHS
- Immediate- release tacrolimus costs have been based on data from CMU eMit (£0.52/mg), thereby reflecting a manufacturer discount in the immediate-release tacrolimus arm but not the prolonged-release tacrolimus arm
 - These eMit data are incomplete, as stated in our response to the ACD

We acknowledge that the following Section 7.3.6.3 in the Assessment Report explains the use of the 5 mg capsule cost, but note that no rationale is provided for the use of the BNF list prices over CMU eMit for prolonged-release tacrolimus, especially given that the Assessment Report states “The eMit national database was the preferred source as it represents the average cost actually paid by NHS hospitals, including any negotiated discounts.”

Using the prolonged-release tacrolimus list price against the discounted prices for immediate-release tacrolimus results in a significant misrepresentation of the cost ultimately borne by the

NHS as the cost of tacrolimus is by far the largest driver of the cost difference between prolonged-release tacrolimus and immediate-release tacrolimus (Figure 1).

Figure 1 Disaggregated percentage cost differences between prolonged-release tacrolimus and immediate release tacrolimus



We note that in establishing which costs to use in the analysis the Assessment Group has specified:

“Where there was a clear indication that NHS hospitals can obtain drugs at a consistent discounted price (i.e., as shown in eMit), this was included in the analysis (following the NICE reference case).”

In the Astellas response to Assessment Group clarification questions we highlighted that;

“There is no volume commitment on the agreement so all trusts nationally are entitled to the discount price.”

We would ask the Committee to request the Assessment Group re-run the model using only the list price for all medicines.

If, in the event that the Committee prefers to use the prices negotiated nationally by the CMU on the tacrolimus National Tender, this should be applied consistently for all formulations of

tacrolimus as prolonged-release tacrolimus (Advagraf) has been awarded at a discounted price on the National Tender, effective from May 2014.

Use of non-significant findings and the exclusion of significant findings within the meta-analysis

The approach taken within the meta-analysis performed by the Assessment Group is inappropriate and misleading with regard to the inclusion of non-significant findings from a fixed-effects “meta-analysis” of non-inferiority.

Inclusion of non-significant findings

Death and graft loss

Within the meta-analysis of death or graft loss only data from Krämer *et al.* 2010¹ inform the analyses. There are a number of issues with how this study was used:

- The per-protocol analysis in the Krämer study was only powered to demonstrate non-inferiority with regard to biopsy-confirmed acute rejection at 24 weeks, yet the analysis uses the intent-to-treat (“overall”) population to model differences in patient and graft survival. Use of this population misses a QALY benefit for the prolonged-release tacrolimus cohort.

We would further add that the use of intent-to-treat populations in meta-analyses of non-inferiority studies is not widely accepted^{2,3}

- The data used in the model includes follow-up from the open-label extension of this study (i.e. data at 12 months post-transplantation after 28 weeks of unblinded follow-up) and the findings of differences in graft loss and patient mortality at 12 months which were not statistically significant ($p=0.53$ and $p=0.61$ respectively). This is totally inappropriate.

On the basis of the above we would recommend a re-analysis using firstly the per-protocol population graft loss and mortality data from Krämer *et al.*¹ and secondly the test of non-inferiority as it cannot be used to infer the presence or absence of superiority.

NODAT

Non-significant NODAT data (from Krämer *et al.*¹ and Tsuchiya *et al.*⁴) was also included to infer a clinical difference between immediate-release and prolonged-release tacrolimus.

With regard to new onset diabetes after transplantation (NODAT), the revised (and original) Assessment Group report appendix states that “no difference in NODATs [*sic*] and CMV infection were found between TAC and TAC-PR regimens at 1-year follow-up”. However, we

would like to raise a concern that, despite the non-significant difference between tacrolimus formulations, NODAT is the second largest driver of the cost difference between the two formulations in the model (Figure 1), second only to the cost of the drug acquisition.

In addition NODAT rates in the literature are out of date. In a recent publication from a UK centre, the rate of NODAT for prolonged-release tacrolimus over 2 years was 9.66% but only 4.86% required treatment with insulin or oral agents at one year i.e. lower than rates reported previously in the literature.⁵

On the basis of the above we recommend a re-analysis assuming non-inferior or improved NODAT data for prolonged release tacrolimus.

Exclusion of significant outcomes

We would also like to reiterate that the exclusion of significant outcomes from the Krämer study unfairly biases the analysis in favour of immediate-release tacrolimus. -The most notable significant outcomes overlooked in this study by the Assessment Group were the incidence of:

- Bacterial infections (22.6% versus 16.0% with immediate-release tacrolimus and prolonged-release tacrolimus respectively; $p=0.032$)

On the basis of the above we recommend a re-analysis of the non-inferior endpoints of graft loss and mortality based on the per protocol population in the Krämer study.¹

Other comments

Consideration of treatment regimens

We note in section 7.1.1.1. (Interventions and comparators) of the Assessment Report that lists regimens that were included within the analyses that, while Basiliximab (BAS) + Immediate-release tacrolimus (TAC) + Mycophenolate mofetil (MMF) is listed, the combination of BAS + prolonged-release tacrolimus (TAC-PR) + MMF is not.

Within the Assessment Groups economic analysis two options for the combination including immediate-release tacrolimus are presented: with and without induction (BAS). The option with induction (BAS + TAC + MMF) is more cost-effective than without induction.

In the case of prolonged-release tacrolimus, no induction option is considered. There is no clinical reason why a clinician would initiate immediate-release with induction and prolonged-release without induction.

From the above it would seem logical that a BAS + TAC-PR + MMF (with induction) would be more cost-effective than the currently described option of TAC-PR + MMF (without BAS induction) and would also reduce the cost difference with TAC even further.

Mortality approach

The model currently uses a Weibull model to project graft survival factoring in hazard ratios based on from eGFR, NODAT and BPAR. We acknowledge that the Weibull model is commonly

used in survival analysis, but would like to reiterate the concerns raised by the Department of Statistics and Clinical Studies at NHS Blood and Transplant, in their response to the Assessment Report who note that, from their experience, the Weibull model “could lead to higher predicted survival rates and higher medians”. We appreciate the Assessment Group’s response to their concerns, but would strongly recommend that in the interests of transparency and as per the requirements placed on manufacturers the other survival modeling methods are explored by the Assessment Group and are fully documented and the results reported as sensitivity analyses.

Technical report erratum

Finally, we note that some of the relative efficacy data in the model are different from those in the updated Assessment Group report. It appears that the BPAR log odds ratios have been repeated under the heading for graft function in Appendix 10 (Summary of parameter in PenTAG economic model) of the report.

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Peninsula Technology Assessment Group (PenTAG)

South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU
UK

Kate Moore

Technology Appraisals Project Manager – Committee D
National Institute for Health and Care Excellence

Dear Kate,

Please accept our review of the additional evidence submitted by Astellas Pharma Limited (henceforth, Astellas) in their ACD response and submitted appendices. Block quotes from Astellas' ACD response have been used with updated reference numbers for consistency.

Kind regards,

PenTAG

Summary

- Astellas asserted that it was inappropriate to incorporate data on mortality and graft loss from the RCT by Krämer et al.¹ into the model, since no statistically significant results were obtained, and the study was a non-inferiority study, and also that patients were only blinded to 24 weeks, and that per-protocol analyses were more appropriate.
- PenTAG considered it was not inappropriate to incorporate data from this RCT, since the non-inferiority design affected only the power calculations and planned analyses – it did not invalidate the estimated treatment effects. In particular, the purpose of the model was to estimate the magnitude of effects on costs, effectiveness and cost-effectiveness, as opposed to simply test whether differences in outcomes were statistically significant. Further, PenTAG also considered that per-protocol analyses were generally at higher risk of bias than intention-to-treat (ITT) analyses, and there were significant numbers of exclusions without reasons from the per-protocol analyses.
- Astellas asserted that it was inappropriate to incorporate data on new-onset diabetes after transplantation (NODAT) from the RCT by Krämer et al.¹ into the model, for the same reasons as above. Astellas further presented evidence that NODAT is lower for prolonged-release tacrolimus than in the literature for immediate-release tacrolimus, and remarked it would be unthinkable that marketing authorisation would be granted for prolonged-release tacrolimus if it had a significantly worse side-effect profile to immediate-release tacrolimus. Astellas asserted that NODAT was one of the main contributors to cost difference between immediate- and prolonged-release tacrolimus in the PenTAG model and recommended re-analysis assuming non-inferiority with respect to NODAT.
- PenTAG considered, as above, that it was appropriate to incorporate these data. The additional evidence presented by Astellas was retrospective, non-comparative, and did not support lower NODAT rates than those included in the PenTAG model. PenTAG noted that the cost differences due to NODAT were small compared to the cost differences due to drug acquisition costs. PenTAG performed an exploratory analysis in which the rate of NODAT was set equal for immediate- and prolonged-release tacrolimus, and in this exploratory analysis prolonged-release tacrolimus continued to be predicted to be less effective and more costly than immediate-release tacrolimus.
- Astellas suggested that statistically significant differences reported in Krämer et al.¹ had been ignored, citing particularly the adverse event of bacterial infections.
- PenTAG noted that bacterial infections were not identified during its consultation with clinicians while developing the model, and nor were they included in the Astellas model (nor the Novartis or Bristol Myers Squibb models). PenTAG noted that there were other adverse events for which prolonged-release tacrolimus appeared to have significantly higher event rates (that were not included in the model). PenTAG concluded, in agreement with Krämer et al. that caution should

be exercised, given the low event rates, and also that no account was taken of multiple testing.

- Astellas asserted that many of the prices used in the Assessment Report (from the Commercial Medicines Unit Electronic Market Information Tool; CMU eMit) were subject to change and could be out of date already. Astellas recommended that list prices should be used throughout as these are less subject to change, or that if CMU eMit prices were used, then the discounted price for Advagraf from the National Tender should also be used.
- PenTAG considered that the prices used were in line with the NICE guide to methods of technology appraisal reference case. PenTAG highlighted that a scenario analysis in which list prices were used throughout had already been conducted, and that prolonged-release tacrolimus remained more costly and less effective than immediate-release tacrolimus in this scenario.
- Astellas asserted that RCT evidence on adherence with prolonged-release tacrolimus, Kuypers et al.,² had been excluded. Astellas also claimed that there was robust non-RCT evidence that prolonged-release tacrolimus improved adherence and reduced within-patient variability of tacrolimus trough concentrations, and that these outcomes were associated with graft survival. Astellas claimed that prolonged-release tacrolimus should be recommended as a treatment option for patients at increased risk of rejection or graft loss due to nonadherence and/or high variability, and that such patients can be easily identified and constitutes only 30% of patients eligible for treatment with tacrolimus. Astellas suggested changes to the PenTAG economic model to incorporate adherence as an additional predictor of graft survival.
- PenTAG considered that the study by Kuypers et al.² has a number of strengths, but also weaknesses, which place it at risk of bias, and also which limit its generalisability. The study considered stable kidney transplant patients, who were neither representative of patients undergoing transplantation nor of patients at increased risk due to non-adherence and/or high variability. The study also does not report patient-related outcomes such as graft survival. The study shows that on average, implementation (the proportion of patient-days which are correctly implemented) is increased by around 10% by conversion to prolonged-release tacrolimus.
- PenTAG considered that the non-RCT evidence presented gave some evidence that prolonged-release tacrolimus resulted in lower within-patient variability, and also evidence that nonadherence and high within-patient variability are associated with worse outcomes (generally graft loss). PenTAG noted that none of these non-RCTs studied patients at increased risk due to nonadherence and/or high variability, so they may not generalise to this group. PenTAG also noted that no control groups were studied when patients were converted from immediate-release tacrolimus to prolonged-release tacrolimus, so it was not possible to estimate treatment effects.
- PenTAG did not believe that Astellas had demonstrated that the subgroup of patients at increased risk due to nonadherence and/or high variability is easily identifiable. In addition, one non-RCT found that although within-patient variability was associated with graft failure, it had low predictive power for this outcome.

- PenTAG considered the suggested changes to economic modelling and concluded they were not appropriate, due to issues in the heterogeneity of definitions in the studies, and limitations of generalisability. Furthermore these changes could not be made for other immunosuppressive agents.
- Astellas suggested that prolonged-release tacrolimus should have been modelled with induction therapy, as this would have resulted in improved cost-effectiveness results.
 - PenTAG noted that adding induction therapy to intervention and comparator seemed to only have a small effect on cost-effectiveness results and concluded that such a change would be very unlikely to affect the cost-effectiveness of prolonged-release tacrolimus.
- Astellas suggested that PenTAG should explore alternative survival modelling methods to the Weibull distribution.
 - PenTAG explored alternative survival modelling methods and found that the Weibull method was amongst the best to fit the data. PenTAG conducted an exploratory analysis based on the Gompertz method (which had marginally worse fitting performance and predicted lower long-term graft survival) and found that there was little impact on cost-effectiveness, and that prolonged-release tacrolimus remained less effective and more costly than immediate-release tacrolimus.

1 Inclusion of non-significant efficacy and safety endpoints

1.1 Death and graft loss

1.1.1 Astellas' response to ACD

From page 2 of "Astellas Pharma Limited Response – 25 August 2015":

Within the meta-analysis of death or graft loss only data from Krämer et al. 2010¹ (Krämer study) inform the analyses. There are a number of issues with how the data from this study was used:

- The Krämer study was only powered to demonstrate non-inferiority with regard to biopsy-confirmed acute rejection at 24 weeks, yet the Assessment Group analysis uses the intent-to-treat ("overall") population to model differences in patient and graft survival, instead of the more appropriate per-protocol analysis. Use of this population misses a QALY benefit for the prolonged-release tacrolimus cohort.
We would further add that the use of data derived from intent-to-treat populations in meta-analyses of non-inferiority studies is not widely accepted^{3, 4}*
- The data used in the Assessment Group model includes follow-up from the open-label extension of this study (i.e. data at 12 months post-transplantation after 28 weeks of unblinded follow-up) and the findings of differences in graft loss and patient mortality at 12 months which were not statistically significant ($p=0.53$ and $p=0.61$ respectively). This is inappropriate.*

1.1.2 PenTAG review

We agree that the Krämer study¹ did choose biopsy-proven acute rejection (BPAR) at 24 months in a per-protocol analysis as their primary endpoint and that this was used to calculate the study size on the basis of non-inferiority in a per-protocol analysis. We note that ITT analyses were pre-specified alongside per-protocol analyses and that ITT analyses were presented throughout the results section and abstract. We see no reason why the study authors' choice of a per-protocol analysis for one outcome at one time point as primary endpoint should affect our choice of results to include in our meta-analyses. Treatment group crossover was not permitted in the study (page 2633), so the risk of bias from using an ITT analysis would appear to be low in this regard. We note that "major protocol violations" occurred for 17.6% of patients transplanted and treated with immediate-release tacrolimus (TAC) and 19.1% of patients transplanted and treated with prolonged-release tacrolimus (TAC-PR), leading to their exclusion from the per-protocol set. This dropout rate is higher than the 16% anticipated in the study design, and we do not believe the nature of these major protocol violations was described. We believe this results in some risk of bias for the per-protocol analysis, as it is not possible to ascertain whether these are reasonable exclusions.

We note from the Cochrane handbook⁵ that per-protocol analyses are generally considered to be at high risk of bias and therefore consider that our choice of ITT analysis results is appropriate. Furthermore, we do not note anything in the two articles cited^{3, 4} to suggest that the use of data derived from ITT populations in meta-analyses is not widely accepted;

indeed, our reading of these articles is that ITT populations are to be preferred over per-protocol analyses in all designs when trials are conducted well and that non-inferiority studies can themselves still have significant flaws.

Fundamentally, the Krämer study is a randomised-controlled trial, whatever its purpose and pre-specified analyses – patients were randomised to TAC or TAC-PR, and some of them subsequently experienced events of graft loss and/or death. Without any specific evidence of systematic bias, to exclude this study from our meta-analyses on the basis that it followed a non-inferiority design would be unjustified.

Finally, we at no point suggested that there was statistically significant evidence that TAC was superior to TAC-PR on the outcomes considered, which is consistent with the high p -values resulting from the study. The central estimate and imprecision of the effect size for these outcomes were estimated appropriately and carried through to the economic modelling (rather than being excluded structurally due to lack of statistically significant findings), as is considered best practice (i.e., include all applicable evidence).⁶ This is because the objective of cost-effectiveness analysis is to estimate the relative magnitudes of additional costs and QALY benefits rather than statistically testing for significant differences.

1.2 NODAT

1.2.1 Astellas' response to ACD

From page 3 of “Astellas Pharma Limited Response – 25 August 2015”:

Non-significant NODAT data (from Krämer et al.¹ and Tsuchiya et al.⁷) was included to infer a clinical difference between immediate-release and prolonged-release tacrolimus.

However, we would like to raise a concern that, despite the non-significant difference between tacrolimus formulations, NODAT is the second largest driver of the cost difference between the two formulations in the model second only to the cost of the drug acquisition. Further information on this, which the Committee may wish to consider, is provided in Appendix One and which demonstrates rates of NODAT with prolonged-release tacrolimus (Advagraf) are lower in a UK clinical setting than that reported in the literature for immediate-release tacrolimus.⁸

It is unthinkable that the Medicines and Healthcare Products Regulatory Agency (MHRA) would have given a Market Authorisation to prolonged-release tacrolimus (Advagraf), if the incidence of reported adverse events were significantly different to those of immediate-release tacrolimus so as to cause safety concerns.

From page 1 of “Appendix One – Data supporting the effectiveness of prolonged-release tacrolimus”:

Prolonged-release tacrolimus has been shown in a UK clinical setting, to result in lower rates of NODAT than are reported in the literature for immediate release and prolonged release tacrolimus⁸

From page 4 of “Appendix Two – Comments on the Assessment Report”:

In addition NODAT rates in the literature are out of date. In a recent publication from a UK centre, the rate of NODAT for prolonged-release tacrolimus over 2 years was 9.66% but only 4.86% required treatment with insulin or oral agents at one year i.e. lower than rates reported previously in the literature.⁸

On the basis of the above we recommend a re-analysis assuming non-inferior or improved NODAT data for prolonged release tacrolimus.

1.2.2 PenTAG review

We do not accept that a clinical difference was inferred between immediate-release and prolonged-release tacrolimus in the Assessment Report. A mixed treatment comparison (in which only the Krämer¹ and Tsuchiya⁷ studies would inform the treatment effect for TAC-PR) conducted to support the economic modelling gave a 95% CrI for the log odds ratio which crossed zero (-0.45, 0.80). The posterior joint distribution for treatment effects from the mixed treatment comparison was incorporated into the probabilistic sensitivity analysis, giving full attention to the uncertainty due to lack of precision.

The two greatest cost differences between the two formulations (i.e., cost differences between TAC+MMF and TAC-PR+MMF) in the deterministic analysis are those of drug acquisition (TAC-PR £12,953 more costly) and dialysis (TAC-PR £830 more costly). The third greatest cost difference is NODAT (TAC-PR £479 more costly). Clearly at least on this level the cost difference due to NODAT is only a very small component of total cost differences.

In the interest of transparency, we conducted a scenario analysis for this review in which the rate of NODAT for TAC-PR was set equal to that of TAC, though we stress that we do not believe this is best practice (as it ignores evidence from RCTs identified through systematic review) and continue to prefer our base case. As shown in Table 1 this has very little impact on the cost-effectiveness of TAC-PR versus TAC, with TAC-PR continuing to be dominated in the scenario analysis.

Table 1: Impact of equalising NODAT rates for TAC and TAC-PR

Maintenance agent (with MMF)	Base case			Scenario analysis: NODAT rate for TAC-PR set equal to rate for TAC		
	Costs	QALYs	ICER	Costs	QALYs	ICER
TAC	£92,226	10.8884	—	£92,226	10.8884	—
TAC-PR	£106,529	10.7920	Dominated	£106,092	10.8210	Dominated

Considering the new submitted evidence by Digpal et al.⁸ we note that this was a retrospective, non-comparative study. In this study 14/144 patients (9.66%) developed NODAT, which is not significantly different from the 12.3% assumed in the economic model for TAC-PR ($p = 0.12$). This study does not appear to us to be good quality evidence that TAC-PR will result in a reduced rate of NODAT compared to TAC. Our economic modelling did not differentiate between NODAT requiring or not requiring insulin or antidiabetic medication.

Finally, we do not comment on decisions made by the MHRA or other regulators, but we reiterate that we have not suggested there is significant evidence of difference in adverse events or safety profiles between TAC-PR and TAC.

2 Exclusion of significant outcomes

2.1 Astellas' response to ACD

From page 3 of "Astellas Pharma Limited Response – 25 August 2015":

We would also like to reiterate that the exclusion of significant outcomes from the Krämer et al. study¹ unfairly biases the analysis in favour of immediate-release tacrolimus. The most notable significant outcome overlooked in the Krämer study by the Assessment Group was the incidence of:

- *Bacterial infections (22.6% versus 16.0% with immediate-release tacrolimus and prolonged-release tacrolimus respectively; $p=0.032$)*

2.2 PentAG review

Economic modelling is an exercise in identifying which factors and pathways are most likely to result in significant differences in costs and benefits (QALYs in a cost-utility study). Bacterial infections were not identified as likely to result in significant differences in costs and benefits when we conceptualised our economic model in consultation with a consultant nephrologist, and as an outcome it was not reported often enough to obtain sensible estimates of treatment effects for all treatments.

We note that bacterial infections were not identified at any stage in Astellas' submission of clinical effectiveness and cost-effectiveness evidence. Nor indeed did bacterial infections feature in submissions from other companies.

We accept that Krämer et al.¹ report that bacterial infections were more frequent with TAC than TAC-PR, however they also report greater event rates for TAC-PR than TAC for other AEs (some also reported to be statistically significant). In any case, the authors of the study highlight that due to low event rates comparisons should be made with caution, and we would further point out that there are a significant number of outcomes in the study on which TAC-PR and TAC are compared, without any accounting for multiple testing.

3 Inconsistent use of list price

3.1 Astellas' response to ACD

From pages 3–4 of “Astellas Pharma Limited Response – 25 August 2015”:

We would challenge the use of drug acquisition costs taken from the Commercial Medicines Unit's (CMU) Electronic Market Information Tool (eMit) and recommend that, in order to ensure consistency, transparency and time-proof the guidance only list price is used, the approach taken by the All Wales Medicines Strategy Group (AWMSG) in their recent appraisal of Envarsus (extended-release tacrolimus).⁹

Drug acquisition costs taken from the CMU eMit are subject to change and the data is updated only every six months. Within the CMU Tender framework agreements, there are potential pricing reviews at the end of an agreed period and relevant termination clauses which make it difficult to confirm which:

- Product will be the most cost effective over time should suppliers amend pricing, and*
- Prices apply over the timeframe of NICE guidance.*

In addition eMit data used to calculate the average cost paid by the NHS for immediate release tacrolimus capsules is usually only used for generic products and relies upon hospital trusts submitting the data and the relevant data being uploaded. There can be gaps in these hospital data and they do not always include Outsourced Pharmacy and Homecare usage (which can comprise around 60%) depending on whether the data goes through the hospital systems which is a significant route for administration of tacrolimus. In addition since eMit data is only updated every 6 months with the last update being in December 2014 (see <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>) the data used is already out of date. Based on this the assumption of £0.52/mg for immediate-release has a significant risk of being inaccurate.

We ask the Committee that in order to:

- Future proof the final guidance and allow for changes in the market dynamics, product availability and tender pricing strategies of the pharmaceutical companies only list prices should be considered*
- Ensure appropriate use of NHS resources; guidance states that clinicians should be directed to base their choice of treatment on that which is the most clinically effective for the individual patient with direction given to procuring the most cost effective product(s) available*

This will enable clinicians to make choices based on individual patient need whilst putting the onus on NHSE and CMU to drive cost effective pricing and encourage increased competition.

If, in the event that the Committee prefers to use the prices negotiated nationally by the CMU on the tacrolimus National Tender, this should be applied consistently for all

formulations of tacrolimus as prolonged-release tacrolimus (Advagraf) has been awarded at a discounted price on the National Tender, effective from May 2014.

3.2 PenTAG review

We consider that the prices used in the Assessment Report were consistent with the NICE Guide to the methods of technology appraisal¹⁰ and in particular the reference case.

In our Assessment Report we included a scenario analysis in which list prices were used for drug acquisition costs. The results of this scenario analysis are shown for convenience in Table 2. As can be seen, TAC-PR continues to be predicted to be more costly and less effective than TAC.

Table 2: Impact of using list prices for drug acquisition

Maintenance agent (with MMF)	Base case			Scenario analysis: List prices used for drug acquisition costs		
	Costs	QALYs	ICER	Costs	QALYs	ICER
TAC	£92,226	10.8884	—	£104,443	10.8884	—
TAC-PR	£106,529	10.7920	Dominated	£111,581	10.7920	Dominated

4 Prolonged-release tacrolimus in easily identifiable patient subgroups

4.1 Astellas' response to ACD

From page 1 of "Astellas Pharma Limited Response – 25 August 2015":

We are surprised that the provisional recommendations limit patient and clinician choice when the Committee acknowledges that 'immunosuppressive therapies are chosen based on a number of factors, and that some treatments may be particularly beneficial for individual people or groups of people' and clearly understood 'the value of choice of immunosuppressive therapies' (ACD Section 4.56).

We consider that, despite the Committee's acknowledgement that a choice of therapies are required, a number of issues with the data provided within the Assessment Report along with the sole reliance on randomised controlled trial data has resulted in provisional recommendations which actually limit choice and are not a suitable basis for guidance to the NHS. The NHS has invested a significant amount of money (£17,000) in each kidney transplant and the provisional recommendations are not optimising this investment. Limiting treatments potentially consigns more patients to dialysis costing £30,000 per year and returns patients to a waiting list that is already under increasing pressure. Donors and their families also make a significant emotional investment and deserve the full treatment options available to optimise their graft outcomes.

From pages 4–5 of "Astellas Pharma Limited Response – 25 August 2015":

We note, as stated above, that the Committee has already acknowledged that some treatments may be particularly beneficial for individual people or groups of people but are concerned that due to the reliance on only RCT data the Committee has not considered the clinical benefits of prolonged-release tacrolimus as a treatment option for a subgroup of patients; specifically those at risk of non-adherence or at risk of high intra-patient variability in tacrolimus trough levels.

We disagree with the Committee's comment that there is limited evidence on the effect of once-daily dosing on adherence or clinical outcomes and that it would be difficult to identify people who would benefit (ACD, Section 4.64). In addition to the RCT (Kuyppers et al.²) on adherence included in our submission but excluded by the Assessment Group, there is in fact robust non-RCT evidence that supports the use of prolonged-release tacrolimus as a treatment option and which should not be disregarded. These data provide real world evidence on the effectiveness of prolonged-release tacrolimus in clinical practice.

Given the evidence available prolonged release tacrolimus should be recommended as a treatment option for patients at increased risk of rejection or graft loss due to non-adherence and/or high variability. Both groups of patients are easily identifiable in clinical practice using current procedures and tools, such as adherence questionnaires and routine blood monitoring and no change to clinical practice would

be required. We would also highlight that this subgroup of patients only includes around 30% of patients eligible for treatment with tacrolimus.

Effective treatment of these patients is essential in order to ensure that therapeutic levels of tacrolimus are maintained within a narrow therapeutic window. If therapeutic levels are too low, the patient is at risk of organ rejection. Conversely, if levels are too high, over-immunosuppression can result in an increased risk of malignancy, infection and/or nephrotoxicity. In some patients variability occurs where their levels of tacrolimus fluctuate above and below the therapeutic window – this is referred to as intra-patient variability. High levels of intra-patient variability have been shown to be associated with an increased risk of renal graft failure¹¹⁻¹³ with the relative risk of graft failure in these patients 2.38 times higher than in those with low variability¹¹. Non-adherence is a significant problem in 20-30% transplant patients¹⁴ and is a key cause of intra-patient variability. In patients treated with tacrolimus non-adherence results in variable therapeutic levels and an increased risk of graft failure.¹⁵

Prolonged-release tacrolimus has demonstrated improved adherence and reduced variability in tacrolimus exposure.^{2, 16-21} In addition prolonged-release tacrolimus is associated with preserved renal function over time with data available up to 3 years post-transplant.²² Following agreement with NICE further details of the key studies are provided in Appendix One along with proposals on how the Assessment Group can model adherence.

We request that the Committee reviews this evidence and reconsiders recommending prolonged-release tacrolimus in patients identified as non-adherent or at risk of intra-patient variability.

From page 1 of “Appendix One – Data supporting the effectiveness of prolonged-release tacrolimus”:

- *High intra-patient tacrolimus variability predicts worse long-term outcomes after renal transplantation^{11, 23, 24}*
- *Prolonged-release tacrolimus has been shown to reduce intra-patient trough level variability relative to that of immediate-release tacrolimus^{19, 21}*
- *RCT data show that adherence is improved with prolonged-release tacrolimus (once-daily) versus immediate-release (twice-daily) dosing.² NOTE: This was included in the initial Astellas submission document*
- *Improved adherence with prolonged-tacrolimus leads to improved graft survival in renal transplant recipients in routine clinical practice^{15, 16, 18, 20}*
- *Prolonged-release tacrolimus has been shown in a UK clinical setting, to result in lower rates of NODAT than are reported in the literature for immediate release and prolonged release tacrolimus⁸*
- *Renal function is maintained with prolonged-release tacrolimus with data available for 3 years post transplant^{17, 22}*

- *Patients demonstrate a preference for the once-daily dosing vs. twice-daily dosing*¹⁷

From pages 1–2 of “Appendix One – Data supporting the effectiveness of prolonged-release tacrolimus”:

*In order to ensure robust consideration is given to adherence we recommend the model is updated to capture patient adherence to the prescribed immunosuppressive regimen and would highlight methodological guidance from the ISPOR Economics of Medication Compliance Working Group states that “consideration of the effects of noncompliance and nonpersistence should be an integral part of pharmacoeconomic evaluations and in the health-care decision-making these evaluations inform” (Hughes).*²⁵

*The most methodologically robust study into adherence in renal transplant recipients we have identified previously to the Committee and the Assessment Group was published by Kuypers et al. in 2013.² This study is a RCT, i.e. tightly controlled conditions, comparing medication adherence between tacrolimus once-daily and twice-daily regimens using electronic monitoring. We would propose using these data to model the proportion of patients adherent to their tacrolimus regimen. Data on adherence to once- and twice-daily tacrolimus from Kuypers et al. could reasonably be used as a proxy for other once- and twice-daily oral medications, while adherence to belatacept could be taken from comparable intravenous regimens.*²⁶

A graft failure hazard ratio could then be assigned to the proportion of non-adherent patients based on one of numerous available studies and combined with the existing graft loss hazard ratios based on estimated glomerular filtration rate (eGFR), new onset diabetes after transplantation (NODAT) and biopsy-proven acute rejection (BPAR).^{15, 16, 20}

We propose that the Committee requests the Assessment Group to update the model in line with the above recommendations.

4.2 PenTAG review

Astellas have directed attention to the two following subgroups:

- Patients at risk of non-adherence;
- Patients at risk of high intra-patient variability in tacrolimus trough levels.

They also state that non-adherence is a key cause of intra-patient variability, such that these subgroups are related. Neither of these subgroups was listed in the Final Scope from NICE.

Astellas do not appear to have conducted a systematic review to investigate adherence and intra-patient variability in kidney transplantation, so there is a risk of selection bias in studies.

4.2.1 RCT evidence: Kuypers et al. 2013

We first consider the RCT evidence to support the use of TAC-PR in a once-daily dosage regimen, which is the study by Kuypers et al.² This study enrolled patients meeting the following criteria:

- Treated with TAC for at least three months;
- Six months to six years since last transplantation (first or second) – the average time since last transplantation was around three years for both groups;
- Stable health.

All enrolled patients then continued with TAC for a further three months, but with electronic monitoring. After three months, patients not dropping out or otherwise excluded in the first three months were randomised 2:1 to TAC-PR or TAC. Of the 252 enrolled patients, 33 were excluded (31 of these dropped out, two had broken devices) and 219 were randomised: 145 to TAC-PR, 74 to TAC. From this point all analyses were ITT (on all randomised patients).

It is not stated in the report whether concurrent medications were given (e.g., azathioprine, mycophenolate mofetil, corticosteroids), and it is not stated whether these were subject to change at any point in the study.

Two key outcomes were considered: persistence and implementation. Persistence described how long patients “stayed with the treatment” and was defined as the time from the first to the last taken dose. Implementation described how well patients implemented the regimen assuming they were still engaging to the treatment, and was defined as the day-to-day percentage of patients who dosed at a level at least as prescribed. A statistical model (generalised estimating equation, GEE) was fitted to the data to test the difference in implementation between the two arms.

Persistence was marginally higher for TAC-PR than TAC, although not reaching significance at the 0.05 level ($p = 0.08$). The authors hypothesise this may be due to performance bias, in that TAC-PR patients had more clinic visits and attention paid to their ongoing implementation, particularly early after randomisation.

Implementation, based on the GEE model, was significantly better for TAC-PR patients, with an increase of 9.8% ($p < 0.001$). This is an average across patients.

Other outcomes were also assessed, such as time of day of dosing, percentage of missed doses according to the day of the week. No statistically significant within-patient variability of tacrolimus concentrations was observed, but these concentrations were not regularly monitored, so the study may have been underpowered to detect differences.

The key strengths of this study are:

- Patients were randomised using a computer generated sequence, stratified by clinical sites.
- Electronic monitoring was used systematically, which avoids recall bias (when patients are asked to recall their own adherence) and detection bias (when investigators seek out adherence in response to clinical events such as acute rejection).
- The statistical analyses seem to be well conducted.

The key limitations of this study which could lead to bias are:

- Neither participants nor investigators were blinded to the allocation. This was inevitable given the intention was to study two drugs with different dosing schedules, but it increases the risk of bias. Patients receiving TAC-PR may have been encouraged by knowing they were being placed on a drug being investigated for its effect on adherence, while patients receiving TAC may have been disappointed they were not randomised to the study drug.
- Patients receiving TAC-PR required more clinic visits to achieve correct dosing, and this may have led to improved persistence and implementation.

The key limitations of this study which limit its generalisability are:

- The population is not representative of kidney transplant recipients. In particular, it is neither representative of new kidney transplant recipients (the population considered in the appraisal – hence why this RCT was excluded in the systematic review in our Assessment Report), nor of kidney transplant recipients with adherence problems, nor of kidney transplant recipients at risk of adherence problems or high intra-patient variability.
- The main outcomes considered are solely adherence-related, and are not meaningful outcomes for patients (e.g., acute rejection, graft loss, death). It is not clear how these adherence-related outcomes will affect more meaningful outcomes, e.g., is it worse to miss one dose of a twice-daily medication or one dose of a once-daily medication?
- It is not clear what concomitant medications were used.

To conclude, we believe that the study by Kuypers et al. provides good quality evidence that kidney transplant patients who have stable health (i.e., are apparently doing well with TAC) can have their implementation of immunosuppression (i.e., rate of taking the prescribed amount) improved by switching to TAC-PR, although this will likely require additional clinic visits for dose adjustments.

We do not believe it provides compelling evidence that: switching to TAC-PR improves more meaningful outcomes; or that giving TAC-PR to patients from time of transplantation improves outcomes; or that giving TAC-PR to patients suffering from or at risk of non-adherence or high intra-patient variability improves outcomes.

4.2.2 Non-RCT evidence

Borra et al. 2010

Borra et al. 2010¹¹ intended to study the effect of within-patient variability in clearance of tacrolimus and mycophenolate mofetil (MMF) on graft loss. They retrospectively analysed the outcomes for 297 consecutively recruited patients who were treated with tacrolimus and MMF for the period 6–12 months post-transplant and had a functioning graft in the following 12 months. They defined the primary endpoint as time to “graft failure”, a composite endpoint comprising graft loss, biopsy-proven chronic allograft nephropathy and doubling of plasma creatinine concentration. Patients dying with a functioning graft were censored.

Within-patient variability was assessed using at least three sample concentrations. Patients were assigned as having low or high within-patient variability for tacrolimus and MMF

separately according to a median cut-off for each, i.e., half of patients had low within-patient variability and half had high within-patient variability for tacrolimus by definition and likewise for MMF.

Within-patient variability for tacrolimus and MMF were not found to be well-correlated (i.e., a patient with high within-patient variability for tacrolimus was not much more likely to also have high within-patient variability for MMF and vice versa). Within-patient variability was generally greater for MMF than tacrolimus, but within-patient variability for MMF was not significantly associated with graft failure. Although it was predictive, within-patient variability for tacrolimus had limited discriminative value for graft failure (area under receiver-operating characteristic curve 0.59).

A Cox regression analysis was conducted with within-patient variability for tacrolimus and MMF as independent variables as well as a number of predictors for graft survival, including recipient characteristics (sex, age, pre-emptive transplantation), immunological risk (panel reactive antibodies, number of previous transplants), graft characteristics (living donor, HLA mismatch) and graft performance (delayed graft function, acute rejection in first year and serum creatinine at 12 months).

In a multivariate analysis, within-patient variability in clearance of tacrolimus, acute rejection in first year and age at time of transplant were statistically significant predictors of graft failure. The hazard ratio for high versus low variability on graft failure was 3.125.

High within-patient variability in clearance of tacrolimus was judged unlikely to be due to compliance issues because of the very low correlation in variabilities of tacrolimus and MMF, which would be expected to be higher in the presence of poor compliance.

The study by Borra et al.¹¹ lends limited support to the use of within-patient variability as a surrogate for graft failure.

The authors also found that assessment based on routine clinical measurements between 6 and 12 months does not discriminate well for subsequent graft failure, indicating that identifying patients who could benefit from interventions to reduce within-patient tacrolimus variability may not be simple. The authors indicated that variability was unlikely to be due to compliance issues in their study.

We note that the formula for calculating variability is not a standard formula (e.g., coefficient of variation) and would, if implemented as reported, always give result 0. We believe it is most likely that the formula would have taken absolute differences rather than signed differences as reported.

Stevenson et al. 2011 (abstract)

Stevenson et al.¹² performed a retrospective cohort study of 255 adult kidney transplant patients (likely consecutively recruited from a single centre). Seven cases were excluded due to “early graft loss” which was not further defined. Variability in tacrolimus trough levels was assessed based on routine measurements recorded in electronic patient records, and was calculated from all levels in the first year post-transplant (in contrast to Borra et al. who restricted to the period from 6–12 months¹¹). A median variability threshold was used to divide into high and low variability.

Analyses were conducted on the acute rejection rate, graft survival and NODAT. It was stated that univariate and multivariate analyses were conducted including potential

confounding factors, but these factors are not listed and the statistical methods are not described.

A statistically significant difference in the acute rejection rate was observed between high and low variability patients (19.4% versus 8.2%; $p = 0.02$). A statistically significant difference in graft survival at one year was also observed (91.9% versus 99.2%; $p = 0.01$). No statistically significant difference was observed for NODAT.

A full review of this evidence is not possible due to it being published only in abstract form.

Goodall et al. 2014 (abstract)

Goodall et al.¹³ performed a retrospective cohort study of 754 kidney transplant patients (likely consecutively recruited from a single centre) receiving alemtuzumab induction followed by maintenance tacrolimus monotherapy. Within-patient variability was calculated using the coefficient of variation (the ratio of the standard deviation to the mean) of outpatient tacrolimus trough levels taken between six and twelve months post-transplantation. The median coefficient of variation was used as a threshold to class patients as having high or low tacrolimus variability.

Survival analyses were conducted for graft survival, rejection free survival (also divided into cellular and antibody mediated) and transplant glomerulopathy-free survival. Adjustments for potential confounding factors were not conducted or not reported.

Statistically significant differences were observed for all survival outcomes except transplant glomerulopathy-free survival, although the hypothesis tests were not described. Graft survival (likely at eight years) was 95.2% and 86.3% for low and high tacrolimus variability patients respectively.

A full review of this evidence is not possible due to it being published only in abstract form.

Desmyttere et al. 2005

(Note: This was only cited in support of the claim that non-adherence is a significant problem in 20–30% of transplant patients.)

Desmyttere et al.¹⁴ summarised the literature regarding noncompliance in solid organ transplantation (specifically kidney, liver and heart). This was unlikely to be a systematic review.

Desmyttere et al. do state that “Prevalence of noncompliance with immunosuppressive drugs in solid organ transplantation ranges between 20–25%,” which appears to be based on a number of reports, although the methods for identification, selection and appraisal of these studies were not described.

Sellarés et al. 2012

Sellarés et al.¹⁵ performed a cohort study of 315 kidney transplant recipients undergoing biopsy for clinical indications as part of standard care in three centres. A total of 412 biopsies were conducted. Kidney transplant recipients were followed up for a median 31.4 months, by which time sixty kidneys had progressed to failure. The authors developed an algorithm to attribute causes of failure based on biopsy findings and other relevant data, such as HLA antibody status and clinical evidence. Adherence issues were documented in some cases by attending clinicians on the basis of patient admission or strong clinical suspicion. In most

cases (22/26) this was documented at the time of biopsy. The vast majority of adherence issues (25/26) were documented more than 12 months post-transplantation.

Of the 26 patients with nonadherence documented, 19 experienced kidney failure, 17 due to rejection. These “nonadherent” patients accounted for 47% of the failures due to rejection.

The study by Sellarés et al. provides some evidence that nonadherence is a key route to graft failure attributable to rejection (rejection accounted for 64% of graft failure). The authors conclude that nonadherence allows the development of *de novo* donor-specific antibodies and antibody-mediated rejection which is then often resistant to therapy.

The main weakness of this study is that adherence was assessed subjectively by attending clinicians and was not systematically monitored or assessed, which could lead to detection bias (where clinicians seek out adherence issues in patients with poor prognosis).

No evidence was presented regarding the effect of nonadherence on levels of tacrolimus.

The authors do not report which immunosuppressive regimens were employed.

Butler et al. 2004

Butler et al.¹⁶ conducted a systematic review of nonadherence in kidney transplant patients. A systematic search was conducted and 36 studies were included. Of the studies, 15 were cross-sectional studies (estimating the prevalence of nonadherence in patients with functioning grafts), 10 were cohort studies (following a defined cohort of patients and assessing adherence and graft survival) and 12 were case series (assessing adherence in patients whose grafts had failed). Of these studies, only the cohort studies can give an estimate of the impact of nonadherence on graft survival.

The cohort studies were published between 1988 and 2001. The definition of adherence varied between studies and was not given in many. Electronic monitoring was only used in one cohort study (and the presentation of results in this study precluded its inclusion in meta-analysis). The time since transplantation was poorly described in studies.

Nevertheless, the authors conducted a meta-analysis of the odds ratio for graft loss for nonadherent versus adherent patients and found a statistically significant increase in risk (OR 7.1, 95% CI, 4.4 to 11.7).

No evidence was presented regarding the effect of nonadherence on therapeutic levels of immunosuppressive agents. The immunosuppressive regimens were not reported for any of the cohort studies.

This study provides evidence that nonadherence is associated with graft loss, but the effect size reported (odds ratio of 7) may be subject a number of significant biases and it is not clear exactly how it should be interpreted given the heterogeneity of definitions of adherence in the studies.

Guirado et al. 2011

Guirado et al.¹⁷ performed a prospective, non-comparative tacrolimus regimen conversion study in 1,832 stable kidney transplant patients (those with no acute rejection or serum creatinine increase > 10% in the previous 12 months). Patients “considered to be at immunological risk” were excluded. Before conversion all patients received twice-daily tacrolimus and conversion was done 1 mg : 1 mg total daily dose (except for patients with

baseline tacrolimus levels < 6 ng/ml). Patients were followed up for 12 months. Adherence to treatment regimen was self-reported by patients on request at each visit.

The mean time from transplantation to conversion was 5 years (SD 4 years). During the 12-month follow-up period eight patients (0.4%) had biopsy-proven acute rejection “which could not be attributed to noncompliance or low blood levels of tacrolimus” – it is not clear how many acute rejections occurred overall. There were four graft losses, all due to death with functioning graft.

An increase in mean dose of 1.24% between conversion and end of follow-up was observed, and was attributed to dose adjustments relating to reduced blood levels of tacrolimus.

According to the authors, “Patients expressed a clear preference for once-daily tacrolimus (99.4% of positive feeling after conversion), because of the increased convenience of less frequent administration in 66% of patients and because of improved adherence in the remaining 34%.” Measures of adherence were not reported.

This large study appears to demonstrate that it is safe to convert stable kidney transplant patients from twice-daily to once-daily tacrolimus. There were no reported measures of within-patient tacrolimus variability or adherence before and after conversion, so it is not possible to conclude that these were improved by conversion, other than that 34% of patients reporting that it improved adherence.

Slatinska et al. 2013

Slatinska et al.¹⁸ retrospectively analysed the routine clinical records of 589 adult kidney transplant recipients who took up an offer to convert from twice-daily to once-daily tacrolimus. The patients were required to be stable in order to be offered conversion and the mean time since transplantation was 4.55 years. Follow-up was 12 months through 3-monthly routine follow-up clinics.

In the 12-month follow-up period, 47 patients (8%) discontinued TAC-PR: 16 (2.7%) due to graft failure, 16 converted to sirolimus, three reverted to twice-daily tacrolimus. Six patients died. At the end of the 12-month follow-up period 91% of patients were still alive with a functioning graft and receiving TAC-PR. Twenty-five (4.3%) of patients experienced acute rejection after conversion.

Tacrolimus trough levels fell with conversion by 12% but this was not statistically significant, and the between-patient variability also fell but not statistically significantly. The within-patient variability was not reported.

This study provides some evidence of the safety of converting stable kidney transplant patients from twice-daily to once-daily tacrolimus, but there were no measures of within-patient tacrolimus variability or adherence, and there was no comparator group to indicate whether conversion was beneficial, harmful or neutral.

Stiff et al. 2014

Stiff et al.¹⁹ conducted a pharmacokinetic study of conversion from twice-daily to once-daily tacrolimus in 40 stable adult kidney transplant recipients. Each patient was monitored for six weeks while receiving twice-daily tacrolimus (in the form of a weekly 24-hour profile using a dried blood spot taken by the patient). They were then converted to once-daily tacrolimus and once their dose was stabilised (and after at least two weeks) they were again monitored

for six weeks. The study also investigated the impact of the Cyp3A5 genotype; the Cyp3A5*1 allele is expressed in more than 70% of African Americans and 30% of Chinese ethnicity versus 10% in Caucasian.

The coefficient of variation (CV) was calculated for the AUC and C_{min} . After conversion there was a statistically significant reduction in variation of AUC from 14.1% to 10.9% ($p = 0.012$) and a nonsignificant reduction in variation of C_{min} from 15.3% to 13.7% ($p = 0.21$).

Before conversion (i.e., while patients received twice-daily tacrolimus) there was a statistically significant difference in CV of AUC between *1/*3 and *3/*3 genotyped individuals, but this difference was smaller and not statistically significant after conversion, i.e., conversion to TAC-PR appears to reduce the impact of Cyp3A5 genotype on within-patient tacrolimus variability.

This study provides some evidence that converting stable patients from twice-daily to once-daily tacrolimus reduces within-patient variability of tacrolimus levels, and that this might be particularly beneficial for individuals expressing Cyp3A5*1, although limited study size meant that many outcomes failed to reach statistical significance at the conventional 0.05 level.

Due to the strict nature of the protocol, the authors did not believe that adherence could be a significant contributor to the effects seen.

The generalisability of the study is limited by its strict protocol (which would have likely encouraged better adherence) and the inclusion of only stable kidney transplant patients.

Wiebe et al. 2012

Wiebe et al.²⁰ studied a cohort of 392 consecutive patients transplanted at a single centre between January 1999 and December 2008. The authors do not explicitly state whether the study is prospective or retrospective. Patients were excluded if they had donor specific antibody (DSA) pre-transplantation (30/392), primary non-function (11/392), moved and lost to follow-up (14/392) or died with a functioning graft (22/392). The study population was mixed, with 270 adults and 45 paediatric patients.

Antibody monitoring was conducted based on serum samples taken and stored routinely (at 0, 1, 2, 3, 6, 12, 18 and 24 months, then yearly, or at time of biopsy for graft dysfunction). Additional clinical and pathologic monitoring included serum creatinine, proteinuria, and graft biopsy (protocol at 6 months, then as clinically indicated). Nonadherence was defined as patient admission of medication nonadherence documented by clinical staff and/or drug levels below the detectable limit.

Overall the cohort was a low risk group, with 97% receiving their first transplant and 90% of patients having calculated panel reactive antibody < 10%. Mean follow-up was 6.2 years (SD 2.9 years).

De novo DSA (dnDSA) was developed by 47/315 (15%) of patients, at a mean time since transplantation of 4.6 ± 3.0 years. Graft survival was strongly associated with dnDSA, with 10-year graft survival 59% for dnDSA versus 96% for no dnDSA ($p < 0.0001$). Baseline characteristics significantly associated with dnDSA were recipient age, HLA mismatches (immunological risk) and cold ischaemia time. Nonadherence was significantly more prevalent in patients developing dnDSA (49% versus 8%, $p < 0.001$; OR 8.75), and was significantly associated with graft dysfunction at the time of dnDSA detection. Nonadherence was significantly associated with graft loss after adjustment (OR 4.34, $p = 0.016$), as were

dnDSA (OR 6.34, $p = 0.005$), recipient age, delayed graft function and clinical rejection preceding dnDSA. Interaction effects were not studied (e.g., nonadherence but no dnDSA).

This study provides evidence that nonadherence is associated with the development of dnDSA, and that both nonadherence and dnDSA are associated with graft loss. The patient population is representative of low immunological risk patients receiving transplantation.

Wu et al. 2011

Wu et al.²¹ prospectively monitored 129 stable kidney transplant recipients converting from twice-daily to once-daily tacrolimus. To be eligible the twice-daily tacrolimus dose had to be unchanged for the previous three months (the pre-conversion period).

During the pre-conversion period the tacrolimus trough concentration, C_0 , was measured three times. After conversion the concentration was measured at 1 week and then every 2 to 4 weeks, and at least 5 to 7 days after a dose change. Concentration variability was measured using the coefficient of variation, %CV, using all three measurements before conversion and using all measurements post-conversion after the dose was stabilised. Patients were converted 1 mg : 1 mg daily dosage.

Median time since transplantation at time of conversion was 5.4 years.

After conversion mean C_0 dropped from 5.9 ± 1.7 ng/ml to 4.9 ± 1.5 ng/ml at seven days. It subsequently recovered to 5.4 ng/ml at the end of the first month and 5.5 ng/ml at the end of the second month. The mean daily dose was increased from 4.7 ± 2.0 mg to 4.8 ± 2.0 mg at seven days and 4.9 ± 2.1 mg at 1 month through to 6 months. Pre-conversion %CV was 14.0% (SD 7.5%); post-conversion this was 8.5% (SD 5.0%).

The authors identified that high pre-conversion %CV was moderately predictive of reduced C_0 after conversion (sensitivity 0.683, specificity 0.92).

There were no acute rejection episodes and mean serum creatinine was unchanged during the study.

This study provides evidence that 1:1 conversion from twice-daily to once-daily tacrolimus in stable patients results in reduced exposure which must be corrected by dose increases. After dose adjustments once-daily tacrolimus appears to result in reduced %CV.

Guirado et al. 2015

Guirado et al.²² conducted a 3-year extension of the EVOLUTION study¹⁷ (described above). Of the 1,832 included in the original study, 1,798 were enrolled in the extension study with annual visits. Of these, 302 did not reach three years follow-up: 41 discontinued or suspended TAC-PR; 110 lost their grafts; 90 died; 61 were lost to follow-up.

The baseline mean dose was 4.0 ± 2.4 mg/day; at 12 months the mean dose was 4.1 ± 2.4 , but this then decreased to 4.0 ± 2.2 mg/day at 24 months and 3.8 ± 2.2 mg/day at 36 months.

Pre-conversion, 829/1,496 patients (55.4%) had high tacrolimus variation (defined as trough level CV > 20%). Post-conversion this was reduced to 761/1,496 patients (50.9%). This was statistically significant according to the McNemar test ($p = 0.01$).

The 110 patients lost their grafts through antibody-mediated rejection (36, 32.7%), interstitial fibrosis/tubular atrophy (33, 30.0%), chronic allograft nephropathy (non-histologically

confirmed; 22, 20.0%), CNI nephrotoxicity (5, 4.5%), acute rejection (2, 1.8%) and other (12, 10.9%).

Patient survival at 3 years post-conversion was 95.1%. Ninety patients died from: cardiovascular disease (25, 27.8%), neoplasia (25, 27.8%), infection (13, 14.4%), other reasons (16, 17.8%) and unknown causes (11, 12.2%).

Mean renal function (eGFR) was reduced at 12 months, but recovered in patients retaining a functioning graft at 24 months and was increased versus baseline at 36 months, even when patients returning to dialysis were recorded with zero eGFR.

This study provides some evidence that conversion from twice-daily to once-daily tacrolimus can reduce tacrolimus variability. Its main weaknesses are that it is non-comparative and recruited only stable kidney transplant patients.

Whalen et al. 2014 (abstract)

Whalen et al.²³ report on a cohort of 376 patients undergoing renal transplantation receiving tacrolimus-based triple therapy. It appears that consecutive patients were recruited within a time period but patients were then excluded if they lost their graft or died within the first year post-transplantation, or if they were lost to follow-up, or if they switched immunosuppression. Study endpoints were graft survival, acute rejection and graft function (eGFR at 1, 2, 3 and 4 years post-transplantation).

Within-patient tacrolimus variability was reportedly calculated from trough levels from 6–12 months according to the same formula used by Borra et al.,¹¹ although as previously noted, literal implementation of this formula would always result in 0 variability. Median variability (16%) was used as a threshold, with high variability $\geq 16\%$ and low variability $< 16\%$.

Mean follow-up was 4.1 years (± 1.5 years). Baseline characteristics between high and low variability patients were not significantly different. High variability patients suffered more episodes of acute rejection within the first year (36/159 versus 14/167, $p = 0.002$) and after the first year (21/174 versus 9/172, $p = 0.038$). Graft function and graft survival were worse in the high variability group (only p -values reported).

This study, presented in an abstract, gives some evidence that high variability in tacrolimus levels in the period 6–12 months post-transplantation is associated with worse patient outcomes of acute rejection, graft survival and graft function.

Sapir-Pichhadze et al. 2014

Sapir-Pichhadze et al.²⁴ retrospectively studied a cohort of adult kidney transplant recipients initiated and maintained on tacrolimus-based immunosuppression surviving with a functioning graft to at least one year post-transplantation.

They studied two composite endpoints: the primary composite endpoint comprised late rejection (more than one year post-transplantation), transplant glomerulopathy and graft loss (including death with functioning graft); the secondary composite endpoint was the same but excluding death with functioning graft. The primary composite endpoint was intended to capture the consequences of over- and under-immunosuppression, while the secondary composite endpoint was only intended to capture the consequences of under-immunosuppression.

Of the 517 patients receiving a kidney transplant, 161 were excluded (99 had follow-up < 1 year; 23 lost their graft, died or suffered transplant glomerulopathy within 1 year; 19 had previous transplants; 7 were transplanted in a different institution; 13 had two consecutive undetectable tacrolimus levels – likely indicating nonadherence), leaving 356 patients in the study cohort.

Median follow-up was 3.7 years beyond the first year post-transplantation. A total of 62 events were documented: late acute rejection, 16; transplant glomerulopathy, 6; graft loss 10; death with functioning graft, 20 (these numbers are as reported – there is a discrepancy in that these numbers add to 52).

The authors calculated the time-varying standard deviation of tacrolimus trough concentrations (TacSD). It is not clear how the time-varying nature was incorporated – one possible reading is that fixed length time intervals were chosen and for patients not changing their dose within the interval the standard deviation was calculated based on measurements within that interval. The mean number of measurements per TacSD was 19.5 ± 16.8 (median 15, IQR 6–29, range 2–112).

Extended Kaplan–Meier analyses were performed based on TacSD thresholds. These demonstrated that a TacSD threshold of 2.5 ng/ml resulted in a statistically significant difference in cumulative failure curves between high and low variability, as did a higher threshold of 3 ng/ml.

TacSD was then used as a time-varying covariate in Cox proportional-hazards models. The models included a univariate analysis (with only TacSD; model 1) and a number of multivariate analyses (models 2–6). In another analysis TacSD was not included as a linear term, but instead a fractional polynomial approach was used to model the log hazard ratio. In another analysis thresholds were used instead of continuous TacSD.

These models generally produced consistent results. The hazard ratio for a unit increase of TacSD for the primary composite endpoint ranged from 1.22 to 1.27 (all statistically significant) and for the secondary composite endpoint ranged from 1.22 to 1.35 (all statistically significant except model 2 with HR 1.22; lowest statistically significant HR 1.28).

Subgroup analyses were also conducted, and although these were suggestive of interaction effects (for recipient age, recipient sex, cause of end stage renal disease, history of acute rejection and eGFR at 1 year), none of these was a statistically significant interaction.

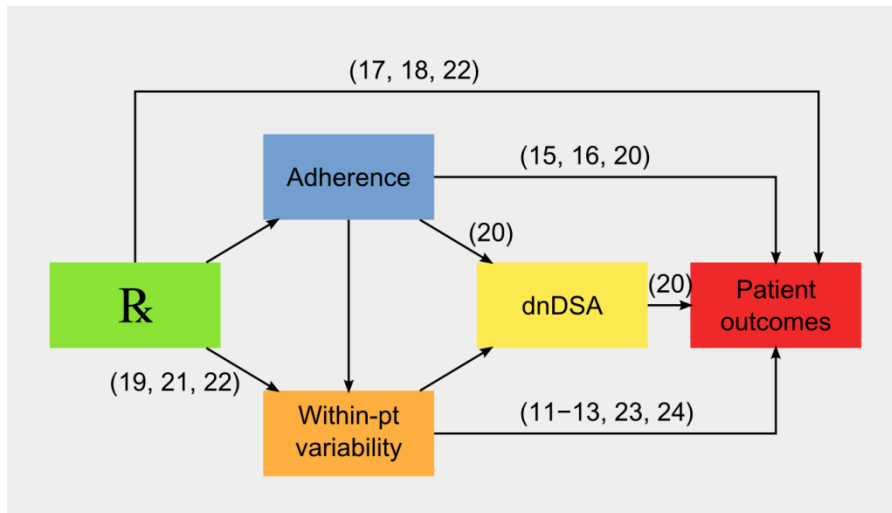
This study provides evidence that tacrolimus variability increases the risk of undesirable outcomes as captured by composite endpoints. The use of composite endpoints makes clinical interpretation somewhat difficult since the component endpoints are not of equal clinical significance – e.g., death with functioning graft is more clinically significant than late acute rejection.

Measures of adherence were not included, so the source of the tacrolimus variability was not identified in the study. The study was also observational and non-comparative. The exclusion criteria may mean the population was of lower risk than general patients receiving a kidney transplant.

Summary of non-RCT evidence

Figure 1 demonstrates where the non-RCT evidence supplied by Astellas corresponds to the pathways from treatment choice to patient outcomes (constructed by considering the claims by Astellas and conclusions from studies).

Figure 1: Influence diagram demonstrating pathways from treatment to patient outcomes



Key: Rx, treatment (i.e., once-daily versus twice-daily tacrolimus); dnDSA, de novo donor specific antibody; pt, patient

Three non-RCTs^{17, 18, 22} (one an extension of another) investigated the patient outcomes for stable kidney transplant recipients converted from twice-daily to once-daily tacrolimus, but crucially these were all non-comparative studies, from which it is not possible to infer the relative effectiveness of once-daily tacrolimus versus other agents. Only one of these studies, Guirado et al. 2015,²² additionally considered the impact of treatment on an intermediate or surrogate outcome, namely within-patient tacrolimus variability; this study did not investigate whether within-patient variability was associated with patient outcomes.

No non-RCTs demonstrated the impact of treatment on adherence (although the RCT by Kuypers et al.² does demonstrate this for stable patients). Also, no non-RCTs demonstrated an association between adherence and within-patient tacrolimus variability. De novo donor specific antibodies were considered by only one non-RCT.²⁰

Three non-RCTs^{19, 21, 22} investigated within-patient variability before and after converting stable patients to once-daily tacrolimus. These all demonstrated a reduction in tacrolimus variability post-conversion, but none of these included a control group, so it is not clear to what extent this reduction can be attributed to conversion.

Five non-RCTs^{11-13, 23, 24} investigated the association between within-patient tacrolimus variability and patient outcomes. These concluded that high variability is associated with worse patient outcomes. These studies all considered patients continuing to receive the same immunosuppressive regimen, and no treatment effects were identified.

Three non-RCTs^{15, 16, 20} investigated the association between adherence and patient outcomes. Butler et al.¹⁶ performed a systematic review and meta-analysis to estimate the odds ratio for graft loss for nonadherent versus adherent patients, but there was substantial

heterogeneity between included studies and poor reporting of key parameters. The other two studies^{15, 20} were cohort studies which demonstrated that nonadherence was a significant cause of antibody mediated rejection and graft loss.

The principal limitation of all of the non-RCTs is that they do not enable calculation of treatment effects. Even the conversion studies cannot be used to estimate treatment effects since there were no control groups.

Moreover, it does not seem possible to derive a surrogate effect from adherence to patient outcomes which can be used to extrapolate from the adherence measures in the RCT by Kuypers et al.²

All the evidence presented amounts to “Level 2” validation of the surrogate outcomes of adherence and within-patient tacrolimus variability.²⁷ Level 2 validation is “Consistent association between surrogate outcome and final patient-related outcome”, evidenced by “Epidemiological (observational) studies demonstrating an association between the surrogate outcome and final patient-related outcome”. The highest level, Level 1 validation, requires “Clinical trial(s) showing that change in surrogate outcome with treatment is associated with a commensurate change in final patient-related outcome”. This has not been demonstrated by any evidence provided.

The evidence provided also suffers from generally short follow-up, not much longer from RCTs which directly demonstrate the impact of treatment on patient-related outcomes.

4.2.3 RCT evidence included by PenTAG

The evidence from these non-RCTs must also be weighed against the evidence from RCTs identified through systematic review by PenTAG, which randomised patients at time of transplantation and considered patient outcomes at six months and one year. A total of 2,027 patients were randomised, transplanted and treated across four RCTs.^{1, 7, 28,29}

Albano et al.²⁸ randomised, transplanted and treated 1,198 patients in a four-arm trial (Arm 1: Tac BID; Arm 2: Tac QD; Arm 3: Tac QD (high); Arm 4: Tac QD plus basiliximab minus corticosteroids), from which Arms 1 and 2 are most relevant. The study was open-label, so treatment effects on adherence and within-patient tacrolimus variability could occur. Follow-up at 24 weeks showed numerically worse graft loss, mortality and graft function results for once-daily tacrolimus ($p > 0.05$) and numerically better BPAR results ($p > 0.05$). The authors concluded their study had demonstrated non-inferiority of once-daily tacrolimus.

Krämer et al.¹ randomised, transplanted and treated 667 patients. Patients were followed-up, blinded, to 24 weeks, after which they were then followed-up open-label to 12 months. During the blinded follow-up period, adherence would not be expected to differ, except where nonadherence was due to different adverse events in each group. Within-patient tacrolimus variability would manifest within that period. In the extension to 12 months there is the possibility of a treatment effect of medication frequency on adherence (as well as a continued potential treatment effect for within-patient variability). Follow-up at 24 weeks showed numerically worse BPAR results for once-daily tacrolimus, but this was not statistically significant ($p > 0.05$). At 12 months graft and patient survival and BPAR were numerically worse for once-daily tacrolimus ($p > 0.05$). Graft function did not differ significantly between the two groups at any point. The declared primary endpoint of the trial was locally assessed BPAR non-inferiority at 24 weeks in the per-protocol group. This endpoint was not reached – the upper limit of the confidence interval was beyond the

predefined non-inferiority margin. The authors drew attention to other results which suggested no statistically significant difference in this and other outcomes and concluded that once-daily tacrolimus was similarly effective to twice-daily tacrolimus.

Oh et al.²⁹ randomised, transplanted and treated 60 patients. Patients were followed-up for 6 months and were not blinded to their treatment. All patients were treated with twice-daily tacrolimus for the first 28 days post-transplantation, after which patients randomised to once-daily tacrolimus were converted 1 mg : 1 mg daily dose. In addition to studying BPAR, graft survival, patient survival and graft function, the authors also used a composite primary endpoint and assessed patient satisfaction with the Immunosuppressant Therapy Barrier Scale (ITBS). The composite primary endpoint was reached by 10.7% of twice-daily tacrolimus patients and no once-daily patients ($p > 0.05$), which demonstrated non-inferiority. Once-daily tacrolimus showed numerically better BPAR and graft loss results ($p > 0.05$) and there were no deaths in either arm. Graft function was similar at all time points. Patient satisfaction was numerically better for once-daily tacrolimus ($p > 0.05$). The authors concluded that once-daily tacrolimus was non-inferior to twice-daily tacrolimus.

Tsuchiya et al.⁷ randomised, transplanted and treated 102 patients. Patients were followed-up for one year and were not blinded to their treatment. At one year, no patients had lost their grafts or died. Graft function was similar for once-daily and twice-daily tacrolimus with no statistically significant difference at any point in the study. BPAR was numerically better for once-daily tacrolimus ($p > 0.05$). Pharmacokinetic results were also reported. The authors concluded that the clinical efficacy, safety and pharmacokinetic profile of once-daily tacrolimus was the same as for twice-daily tacrolimus.

Despite over 2,000 patients being recruited for RCTs comparing once-daily with twice-daily tacrolimus, there were no statistically significant results in individual studies. The larger two studies^{1, 28} showed numerically worse results for graft loss and mortality for once-daily tacrolimus. They gave conflicting results for BPAR and graft function. Neither of these studies monitored adherence or within-patient tacrolimus variability. The smallest study²⁹ considered patient satisfaction and found it was numerically improved with once-daily tacrolimus but the result was not statistically significant.

Non-RCT evidence suggests that adherence issues manifest clinically from 5–6 months post-transplantation onwards,^{20, 30} which means that the two RCTs^{28, 29} following up for only half a year may not have had sufficient follow-up to detect such manifestations. Nevertheless, there would be no reason why, if within-patient tacrolimus variability is an important determinant of patient outcomes, and once-daily tacrolimus is capable of reducing within-patient tacrolimus variability in a clinical setting, none of these studies would show this benefit clearly. It seems that neither adherence nor within-patient variability, if they are affected by treatment with once-daily tacrolimus, had a noticeable impact on patient outcomes within the follow-up time of the RCTs.

4.2.4 Suggested changes to economic modelling

Astellas have suggested that data on adherence from Kuypers et al.² should be used as proxies for once-daily and twice-daily oral medications, and that adherence to belatacept could be taken from comparable intravenous regimens.²⁶ This is immediately problematic because immunosuppressive drugs are very often used in combination regimens. A very commonly used maintenance regimen is immediate-release tacrolimus (twice-daily), MMF (twice-daily), with or without corticosteroids. Replacing immediate-release tacrolimus with

prolonged-release tacrolimus does not in this instance convert from a twice-daily regimen to once-daily. Given that the RCTs identified by PenTAG using prolonged-release tacrolimus all used MMF as concomitant medication it would seem improper to then model prolonged-release tacrolimus in an alternative combination (or as a monotherapy).

Furthermore, adherence is defined in two ways in Kuypers et al.² (and this is broadly consistent with the definitions in Hughes et al. 2007²⁵), being composed of both implementation (on average in what proportion of days is the dose correctly implemented) and persistence (what proportion of patients remain engaged with the treatment). As Kuypers et al. did not identify a statistically significant difference in persistence, we must focus on implementation. Implementation is well-defined in this study, but is reported as mean implementation across patients, rather than identifying the proportion of patients who implement acceptably (which would have been problematic given the absence of any clinically derived threshold). This contrasts with the non-RCTs associating nonadherence with patient outcomes, which classify patients as adherent or nonadherent.

Finally, with regards to the use of data from Kuypers et al.,² to estimate adherence in kidney transplant recipients, it should be noted that patients in the study were stable prior to conversion, i.e., they were likely to be patients at lower immunological risk than new transplant patients and were also less likely to be at risk of adherence issues. The population from this study neither matches the population in the NICE scope (patients undergoing kidney transplantation) or the proposed subpopulations (patients at risk of nonadherence or high within-patient tacrolimus variability).

Astellas also suggest that non-RCTs^{15, 16, 20} could be used to derive a graft failure hazard ratio for nonadherent versus adherent patients. Wiebe et al.²⁰ could potentially be used in this way, but only through an additional intermediate outcome of the development of de novo DSA – this would then further complicate matters since different immunosuppressive agents may have different efficacy against the development of dnDSA independent of adherence. Butler et al.¹⁶ estimate an odds ratio for graft loss according to adherence status, but given the heterogeneity of definitions and poor reporting from the trials identified, and given these trials are now quite outdated, we do not feel this can be used, even if somehow converted to a hazard ratio. Sellarés et al.¹⁵ provide data from which an odds ratio of graft loss may be calculated (but not a hazard ratio), but caution is advised since there is a risk of detection bias in this study, in which nonadherence was subjectively measured and more likely to be sought out and documented for patients with poor graft prognosis.

In conclusion, we believe that the proposed changes to the economic modelling would not be appropriate. Even if adherence could be accounted for with regards to prolonged-release versus immediate-release tacrolimus, this could not be extended to other classes of immunosuppressive agent being considered.

Economic modelling of adherence in this area can only proceed safely when there is consistent RCT evidence across classes of immunosuppressant that adherence is modified by treatment and that this results in a commensurate effect on patient outcomes.

4.2.5 Summary

Astellas identified one RCT by Kuypers et al.² which demonstrated that implementation could be improved in stable patients receiving immediate-release tacrolimus by conversion

to prolonged-release tacrolimus. This RCT did not demonstrate any impact on important patient outcomes such as graft loss, acute rejection, graft function and death.

Astellas further identified a number of non-RCTs which lent some support to the hypothesis that prolonged-release tacrolimus could reduce within-patient tacrolimus variability, and that through this and effects on adherence, prolonged-release tacrolimus could improve patient outcomes. There were substantial limitations to these studies, however, such as the absence of control groups (a problem with all the studies). None of these studies investigated conversion to prolonged-release tacrolimus in patients with pre-existing adherence difficulties or identified as being at risk of nonadherence.

PenTAG identified, through systematic review, four RCTs comparing prolonged-release tacrolimus to immediate-release tacrolimus on key patient outcomes. None of these RCTs demonstrated any statistically significant improvement in outcomes through use of prolonged-release tacrolimus. Follow-up was limited in these RCTs, but the absence of any visible treatment effect is important, given the magnitude of the claims made.

Astellas suggested changes to the PenTAG economic model, but these changes were judged to be inappropriate for a number of reasons, and no such changes have been made.

We note that Astellas have not attempted to demonstrate:

- The identifiability of subgroups who are at risk of nonadherence or high within-patient tacrolimus variability;
- The value of prolonged-release tacrolimus in patients at risk of nonadherence;
- The value of prolonged-release tacrolimus in relation to important patient outcomes.

We recommend that, if benefits to patients are believed to exist from prolonged-release tacrolimus, a high-quality RCT should be conducted. It should be prospectively registered with a detailed protocol and statistical analysis plan. It should have sufficient follow-up time and be powered to detect clinically meaningful differences in key outcomes. If patients are to be recruited at time of transplantation there should be stratification on risk of nonadherence and risk of high within-patient tacrolimus variability. If patients are to be recruited at a later stage (upon demonstrated adherence or variability issues) then there should be a strict trial protocol to ensure there is no performance bias or other biases introduced, and alternative interventions to improve adherence should also be considered. The study should robustly record adherence and within-patient tacrolimus variability. Suitably anonymised study data should be made freely available for independent analysis.

5 Consideration of treatment regimens

5.1 Astellas' response to ACD

From page 4 of "Appendix Two – Comments on the Assessment Report":

We note in section 7.1.1.1. (Interventions and comparators) of the Assessment Report that lists regimens that were included within the analyses that, while Basiliximab (BAS) + Immediate-release tacrolimus (TAC) + Mycophenolate mofetil (MMF) is listed, the combination of BAS + prolonged-release tacrolimus (TAC-PR) + MMF is not.

Within the Assessment Groups economic analysis two options for the combination including immediate-release tacrolimus are presented: with and without induction (BAS). The option with induction (BAS + TAC + MMF) is more cost-effective than without induction.

In the case of prolonged-release tacrolimus, no induction option is considered. There is no clinical reason why a clinician would initiate immediate-release with induction and prolonged-release without induction.

From the above it would seem logical that a BAS + TAC-PR + MMF (with induction) would be more cost-effective than the currently described option of TAC-PR + MMF (without BAS induction) and would also reduce the cost difference with TAC even further.

5.2 PenTAG review

Firstly, given the assumed independence of treatment effects from induction and maintenance therapy, and independence of costs (for the adult model), there is little reason to suspect that altering the induction regimen of TAC-PR and comparing to alternative regimens with the same induction regimen would result in significantly different cost-effectiveness results, since only second-order effects would be in play.

We can consider the case of CSA, which is compared to TAC both with basiliximab induction and with no induction. Without induction CSA is associated with incremental net health loss (versus TAC) of 0.15 QALYs (at willingness-to-pay of £30,000 per QALY). With basiliximab induction, CSA is associated with incremental net health loss of 0.12 QALYs. With rabbit ATG induction, CSA is associated with incremental net health loss of 0.14 QALYs. We can see that changing the induction therapy has a fairly small effect on cost-effectiveness.

Noting that the incremental net health loss for TAC-PR versus TAC without induction is 0.57 QALYs, we do not think it is remotely likely that altering the induction regimen will lead to TAC-PR becoming cost-effective at £20,000 to £30,000 per QALY.

Secondly, we note that of the RCT arms considered, the majority of patients did not receive basiliximab induction; Tsuchiya et al.⁷ (the second smallest study) used basiliximab induction and one arm of Albano et al.²⁸ (ineligible for inclusion in calculations as steroid withdrawal was a concomitant intervention) used basiliximab induction.

If the same critique were applied to every induction and maintenance regimen we would have had to model at least 27 regimens, compared to the already considerable 16.

6 Approach to modelling overall survival

6.1 Astellas' response to ACD

From pages 4–5 of “Appendix Two – Comments on the Assessment Report”:

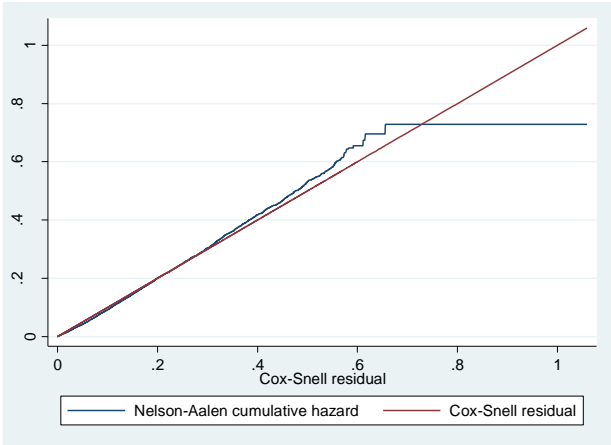
The model currently uses a Weibull model to project graft survival factoring in hazard ratios based on from eGFR, NODAT and BPAR. We acknowledge that the Weibull model is commonly used in survival analysis, but would like to reiterate the concerns raised by the Department of Statistics and Clinical Studies at NHS Blood and Transplant, in their response to the Assessment Report who note that, from their experience, the Weibull model “could lead to higher predicted survival rates and higher medians”. We appreciate the Assessment Group’s response to their concerns, but would strongly recommend that in the interests of transparency and as per the requirements placed on manufacturers the other survival modeling methods are explored by the Assessment Group and are fully documented and the results reported as sensitivity analyses.

6.2 PentAG review

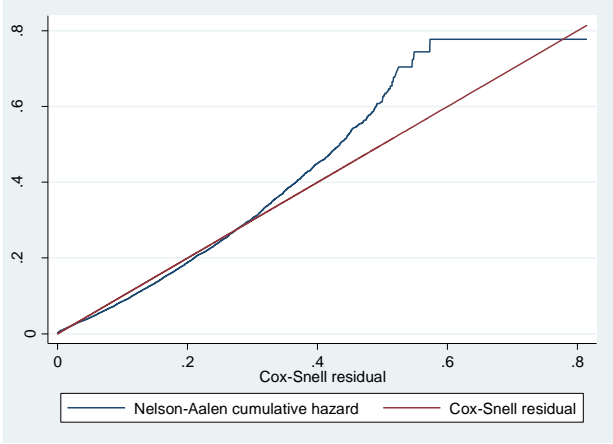
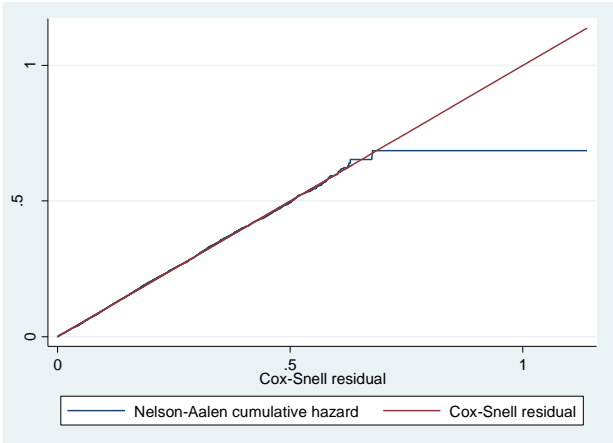
We note that NHS Blood and Transplant have not attempted to fit the Weibull model to conditional survival for patients with a functioning graft at one year, but to fit a Weibull model to survival from time of transplantation. We demonstrated that the Weibull distribution fits survival after one year extremely well.

We have explored a number of possible survival models (Table 3) and confirmed that the Weibull model has almost the lowest AIC, with the Gompertz and generalised gamma models giving fairly similar AICs.

Table 3: Alternative distributions for graft survival

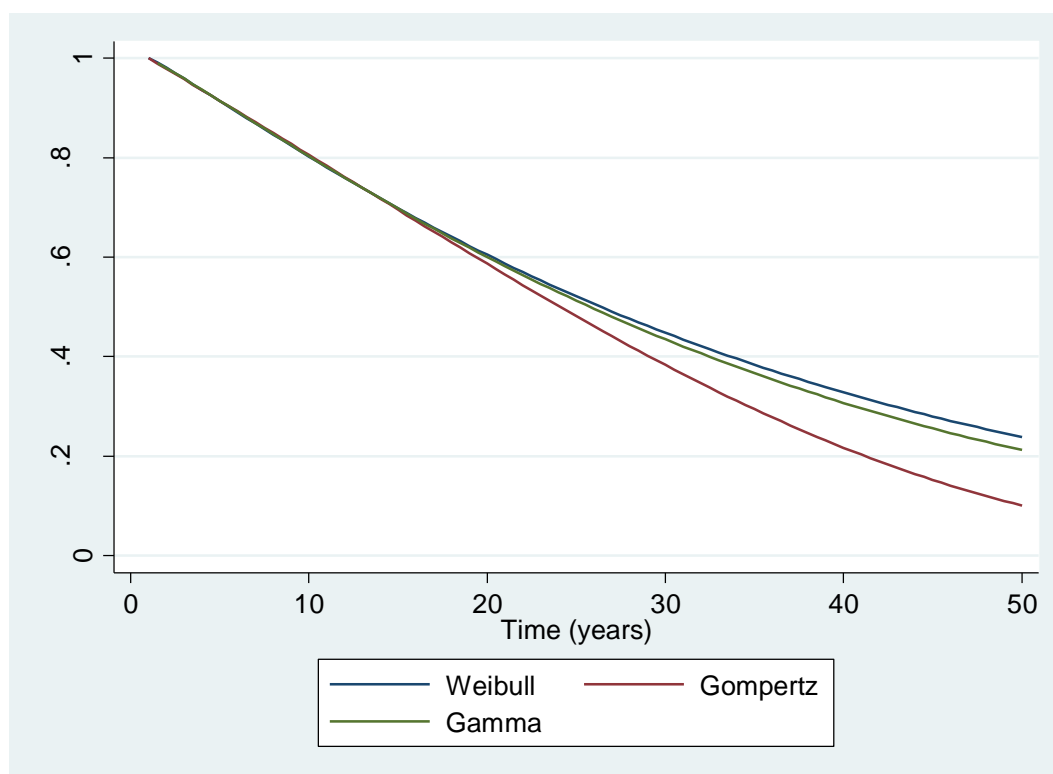
Distribution	AIC	Cox–Snell residuals
Exponential	33412.22	

Distribution	AIC	Cox-Snell residuals
Weibull	33355.85	
Gompertz	33358.66	
Log-normal	33828.08	

Distribution	AIC	Cox-Snell residuals
Log-logistic	33390.83	
Generalised gamma	33355.55	

The survival curves for Weibull, Gompertz and generalised gamma are shown in Figure 2. The Weibull and generalised gamma models have very similar survival up to 50 years, while the Gompertz model predicts reduced survival compared to these from about 20 years onwards.

Figure 2: Comparison of Weibull, Gompertz and generalised gamma survival models



We have conducted an exploratory analysis in which the Gompertz model was used instead of the Weibull model for graft survival. We report the key outputs for the comparison involving prolonged-release tacrolimus in Table 4 and Table 5. As expected, QALYs, graft survival and life expectancy are all reduced when the Gompertz distribution is assumed. Costs also increase, as expected since more patients require dialysis for longer. The impact on cost-effectiveness, however, is not very significant, with incremental net health loss for TAC-PR and CSA (at willingness-to-pay of £30,000 per QALY) changing by approximately 0.01 QALYs.

Table 4: Cost-effectiveness results when Gompertz distribution is used to model graft survival

Maintenance agent (with MMF)	Base case			Scenario analysis: Gompertz distribution used to model graft survival		
	Costs	QALYs	ICER	Costs	QALYs	ICER
TAC	£92,226	10.8884	—	£94,492	10.7990	—
CSA	£97,429	10.9145	£199,118	£99,731	10.8225	£223,174
TAC-PR	£106,529	10.7920	Dominated	£108,500	10.7043	Dominated

Table 5: Graft survival and life expectancy when Gompertz distribution is used to model graft survival

Maintenance agent (with MMF)	Base case		Scenario analysis: Gompertz distribution used to model graft survival	
	1 st graft survival	Life years	1 st graft survival	Life years
TAC	16.589	22.421	15.963	22.123
CSA	15.912	22.397	15.275	22.095
TAC-PR	16.323	22.248	15.709	21.956

We believe this exploration of alternative parametric distributions, plus our previous exploratory analysis (in response to the comments from NHS Blood and Transplant) in which long-term survival with the Weibull method was manually reduced, confirm that our choice of distribution was appropriate, and that cost-effectiveness results are not particularly sensitive to viable alternative distributions.

7 Additional comments

ACD Section	Comment	PenTAG response (where appropriate)
2.3	<p>In addition to the factors listed immunosuppressive therapy also aims to prevent death from graft failure in addition to the points raised. We would recommend the text is revised as follows: ‘Immunosuppressive therapy aims to prevent acute rejection, and optimise the function of the transplanted kidney <u>and prevent death from graft failure</u>, while minimising the adverse effects of immunosuppression</p>	<p>The proposed revision could give the impression that graft failure is often fatal – it is not. Preventing graft loss is a long-term goal of immunosuppression, and dependence on dialysis is associated with higher mortality. This is a more nuanced picture.</p>
3.13	<p>In line with our comments above we ask that only list prices are used and cited.</p>	<p>As indicated, we believe the prices used were the most appropriate prices and that using list prices for certain drugs (such as immediate-release tacrolimus) would not be representative of current and likely future prices.</p>
3.16	<p>Further clarification is required on why Envarsus (tacrolimus extended-release tablets, MA granted June 2014) was excluded from the final scope of the appraisal while everolimus (Certican, MA granted November 2014) was included when both had not received Marketing Authorisation prior to the final scope being issued.</p>	<p>No response.</p>
4.9	<p>RCT comparisons of immediate and prolonged-release tacrolimus were powered for non-inferiority. The key issue is that the non-inferiority design cannot be used to infer the presence or absence of superiority. We recommend the text is amended as follows: ‘Comparison of immediate-release and prolonged-release tacrolimus (plus mycophenolate mofetil) showed no consistent statistically <u>clinically</u> significant differences’</p>	<p>We disagree. An RCT is an RCT. The non-inferiority design relates to its power and planned analyses. The proposed revision is neither necessary nor substantiated.</p>
4.24	<p>Living with a kidney transplant is a long-term condition and on this basis it is not appropriate to extrapolate data from the 24 week blinded phase of RCTs to 50 years. We would also repeat our concern on the use of non-significant data to inform the model.</p>	<p>Short trial follow-up of included trials is an acknowledged limitation of the systematic review and economic evaluation. Three of the four RCTs for prolonged-release tacrolimus were funded by the company. Extrapolation is necessary to capture the likely downstream costs and benefits of treatment. It should also be noted that the RCT evidence was primarily used to estimate outcomes for the first graft (mean survival for TAC-PR+MMF 16.3 years).</p>

4.31	<p>The Assessment Group assumption that corticosteroid use is continuous in a maintenance regimen is flawed. Clinical experts present at the Appraisal Committee meeting indicated that steroid use is intermittent and as short term as possible. Consideration should be given to the impact of intermittent and short-term use on any calculations used to predict steroid side effects in the long term.</p>	<p>The lack of statistical significance was carried through, as appropriate, to the probabilistic sensitivity analysis.</p> <p>The model assumed the use of corticosteroids at a low maintenance dose on average. Effectiveness estimates for regimens included RCTs in which corticosteroids were continued and in which they were discontinued, and in which they were managed as clinically appropriate, however the management was the same across study arms. Incremental effects on side effects should therefore have been from other immunosuppressants.</p> <p>In our experience reading many RCTs we noted that steroid discontinuation was not always possible, particularly when it was not planned to occur very soon after transplantation.</p>
4.37	<p>The current text in the 5th bullet point is misleading. In order to reflect the true situation we ask that the text is amended as follows: “Astellas noted that the model did not consider the effect of adherence. The Assessment Group considered that there was limited <u>RCT evidence to inform decision making</u>, and recommended caution in using this surrogate outcome.</p>	<p>Astellas have not presented any argument as to why the inclusion of low dose maintenance corticosteroids biases cost-effectiveness estimates in any way.</p> <p>Comment noted.</p>
4.40	<p>Omission of ciclosporin did not affect interpretation of the results of the Astellas model, as the publication of the full Astellas model³¹ was used by the Assessment Group to inform their interpretation. The drug dosages used in the Astellas model reflect current clinical practice.</p>	<p>No reason was given as to the omission of ciclosporin from the submitted model which was a clear deviation from the NICE scope and was utterly unjustifiable given Astellas clearly already had a decision model with ciclosporin included. Astellas did not refer to the full publication in their submission.</p> <p>Excluding comparators is a serious matter. In this case led to ambiguous evidence because Astellas used one model to compare PR-Tac (“Advagraf”) with TAC (“Prograf”) and another to compare Prograf with other regimens. The reported costs and QALYs for Advagraf were not comparable with those for regimens other than Prograf since other regimens’ effect on adherence was not modelled. Advagraf was more costly and more effective than Prograf with an ICER around £60,000 per QALY. It may be noted that correct interpretation of the results was absent from the company</p>

		submission and Muduma et al. ³¹
4.54	We note that the Assessment Group did not model adherence and that there was insufficient evidence to support subgroup analysis. We have recommended consideration of non-RCT data on adherence in a specific subgroup of patients eligible for treatment with prolonged-release tacrolimus and modeling considerations which will assist in addressing both these issues.	Addressed above.
4.58	The statement about the additional evidence should be amended as follows to reflect the qualification of the consideration of only RCT evidence: 'The Committee understood that the clinical experts were not aware of any additional evidence, and concluded that all the relevant clinical effectiveness <u>RCT</u> evidence had been taken into account'.	No response.
4.63	The statement 'calcineurin inhibitors are associated with nephrotoxicity' is inaccurate and does not acknowledge the fact that tacrolimus is <u>NOT</u> overly nephrotoxic. In patients treated with tacrolimus renal function is maintained and stable over significant periods of time. ^{22, 32} We would also like to reiterate to the Committee that the doses of calcineurin inhibitors used in the RCTs and used in the AG model are not the doses used in current clinical practice, which are lower, following the publications of the landmark SYMPHONY study. ^{33, 34} As a point of accuracy the current text should be amended as follows: ' In particular, calcineurin inhibitors are associated with nephrotoxicity, and, The Committee heard from the clinical specialists that about 5% of people develop nephrotoxicity soon after transplant and more develop it over a longer period.'	No response.
4.64	We note that the Committee highlighted 'that it was unclear whether the company had captured the different effects of missing a dose of a once-daily or a twice-daily therapy'. For a slow clearance drug like tacrolimus it would not be the acute effect of missing a single dose that would impact on the consistency of immunosuppression. What would be important is the deviation from total adherence over a period of time. With a once daily formulation, taken in the morning, greater consistency in adherence is seen than with a twice daily formulation and this has been demonstrated to be true	We do not believe this point has been addressed adequately by Astellas. Kuypers et al. ² raised this issue and highlighted it as an area requiring further research.

in general³⁵ and also specifically for
prolonged-release tacrolimus.²

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