NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99) [ID346]

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

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

1. Consultee and commentator comments on the Appraisal Consultation Document from:

- Astellas Pharma
- Novartis
- Sanofi
- British Kidney Patient Association
- ESPRIT
- Kidney Research UK
- National Kidney Federation
- Royal College of Physicians

A 'no comments' response was received from the Department of Health and NHS England.

2. Comments on the Appraisal Consultation Document from experts:

- Dr David Milford – Clinical Expert nominated by British Association for Paediatric Nephrology

4 Expert Personal perspective from:

- Professor Nicholas Webb – Clinical Expert nominated by Astellas Pharma

5. Comments on the Appraisal Consultation Document received through the NICE website

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 children and young people (review of technology appraisal guidance 99)

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.

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 UK	Astellas UK welcomes the consultation on the draft recommendations for immunosuppression in children and adolescent kidney transplant patients. The Company recognises that consideration of evidence is difficult in the transplantation therapy area and note that the Committee considered real world evidence in addition to RCTs in order to make recommendations for treatment. The Company has no comment to make on the draft recommendations.	Comment noted.
British Kidney Patient Association	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 used in transplant treatments will not be or 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 children, young people and their families and their clinicians some really important choices to for successful induction and preservation of their transplants. We also do not think that the conclusions take into account the costs in quality of life and side	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 4.29 of the FAD). The Committee recognised that there is a particular need for additional treatment options, such as sirolimus and belatacept, when complications arise

Consultee	Comment [sic]	Response
	effects as well as costs to the system of the patient returning to dialysis if a transplant fails (dialysis is estimated (for adults) 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). For children with kidney failure, who are likely to have very specialised needs, these costs will be much higher. We do of course support the principle that a clinician should use a cost effective approach to the use of NHS resources. 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. According to the UK Renal Registry there are about 890 children a year being treated at 13 specialist centres, of whom about 700 will have a kidney transplant. 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 children, young people and their families and is not explained. It would therefore be possible that funding for these drugs could be withdrawn. 1.4 The statement 'Rabbit anti-human thymocyte immunoglobulin, prolonged-	(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 section 4.77. Comments noted. 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. Comment noted. The Committee recognised the

Consultee	Comment [sic]	Response
	release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in children and young people having a kidney transplant' will mean that patient access to any of these drugs will necessitate Individual Funding Requests and processes that families 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.	urgency of the situation in these rare cases and that individual funding requests might not be sufficiently speedy or suitable for these situations (section 4.77 of the FAD). 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 in children and young people (see FAD sections 4.60, 4.62, 4.65 and 4.66). The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4 and 4.77).
	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 and their families will be expected to stop these medications.	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 parents or carers. No changes required.
	4.22 We note the AG point that for all comparisons, there was a great deal of heterogeneity and the credible intervals were wide, indicating uncertainty in the results. However the AG did make conclusions, including some on products that were shown to be clinically effective but were not recommended.	Comment noted. The Assessment Group is commissioned by the NHS Research and Development Health Technology Assessment (HTA) programme to produce an independent

Consultee	Comment [sic]	Response
		review of the evidence for technologies being appraised within the multiple technology appraisal (MTA) process.
	4.74 and 4.77 We appreciate that the AG have noted the difficulties some children and young people have with swallowing tablets and have therefore agreed that tacrolimus and mycophenolate mofetil can be made available as oral suspensions. We do not feel that the decision to disallow the once a day version of tacrolimus has made any allowance for the well-known issues that adolescents in particular have with adherence to medication. There are many studies attesting to this, such as http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2528818/ "Low adherence to any medical recommendation, …. and for medications to treat severe chronic health conditions such as …. organ transplant, thus possibly resulting in life-threatening consequences." We cannot agree that further evidence in the small population with kidney transplants is needed for the AG to accept this point, and the decision is discriminatory.	Comment noted. The Committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people. See section 4.63 of the FAD.
	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	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).

Consultee	Comment [sic]	Response
	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 which our colleagues at the British Association for Paediatric Nephrology have made. The small numbers do not make it possible to produce meaningful	The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4 and 4.77).

Consultee	Comment [sic]	Response
	evidence on performance of certain treatments on sub-groups and therefore making the decisions described in this appraisal is not supported by the BKPA. 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.	Comments noted. Stakeholders were able to respond to the provisional recommendations during consultation on the appraisal consultation document. Patient and professional kidney charities were invited and attended the second Committee meeting and were given the opportunity to provide further evidence and comments.
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	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

Consultee	Comment [sic]	Response
	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. • Adolescent transplant patients are considered in most units to be at a particularly high risk of non-adherence with immunosuppression regimens, and this can have real clinical implications for the integrity of their transplanted organs. The patients are often 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. We note the Committee had considered adherence but 'agreed that it had not been presented with robust data to show better adherence with prolonged-release tacrolimus (see section 4.63) and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model'. This may well be the case, but real-life experience of transplant experts, particularly those with a special focus on children and adolescents, dictates otherwise. • 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	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. Comment noted. The Committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people. See section 4.63 of the FAD. Comment noted. This multiple technology appraisal only considered the treatments specifically for the prevention of organ rejection in children and young

Consultee	Comment [sic]	Response
	transplants, would just become unavailable, even if they could be used in theory – to the detriment of the patients involved.	people having a kidney transplant.
	• 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.4	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.
	• We welcome the ACD acknowledgement of our previous submissions in relation to switching from proprietary brand to generic immunosuppressants i.e. 'The Committee was aware that there are several brands of oral tacrolimus, and that inadvertent switching between products has been associated with toxicity and graft rejection. It heard from clinical experts that, to minimise the risk of accidental switching, UK clinicians follow advice from the Medicines and Healthcare Products Regulatory Agency to prescribe and dispense oral tacrolimus products by brand name. It heard from clinical experts that, for the same reason, brand names were used when prescribing ciclosporin'. However, it stops there does not go on to make any recommendations about the implications of this. 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	Comment noted. This technology appraisal does not make recommendations on treatment switching as this is beyond the remit granted by the Department of Health. The FAD contains a footnote to recommendation 1.2 referencing MHRA advice on prescribing and dispensing oral tacrolimus by brand name only, to minimise the risk of inadvertent switching between products.

Consultee	Comment [sic]	Response
	transplant patients, as laid out in our original submission. We would urge NICE to reconsider this and include something about generic immunosuppressants in the final guidance, 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.	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.' 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.'
Kidney Research UK	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	Comment noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus,

Consultee	Comment [sic]	Response
	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	everolimus and belatacept are not recommended. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people. See sections 4,60, 4.62, 4.65 and 4.66 of the FAD. Using effectiveness estimates from adults, 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. Principle 6 of NICE’s Social Value Judgements highlights that it should consider and respond to comments it receives about its draft guidance, and make changes where appropriate. But NICE and its advisory bodies must use their judgement to ensure that what it recommends is cost effective and takes account of the need to distribute health resources in the fairest way within society as a whole. Comment noted. The Committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people. See section 4.63 of the FAD.

Consultee	Comment [sic]	Response
	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.	
National Kidney Federation	1. 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. 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.	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. The Committee concluded that there was not enough evidence to establish whether r-ATG, prolonged-release tacrolimus, mycophenolate sodium, everolimus and belatacept were clinically effective in children and young people see sections 4.60, 4.62, 4.65 and 4.66 of the FAD). For sirolimus, the only evidence in children and young people in the AG's review was a non-

Consultee	Comment [sic]	Response
	3. 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.	randomised study that did not find any significant differences between sirolimus and immediate-release tacrolimus (Hymes et al. 2011) the Committee concluded that there was not enough evidence to establish whether sirolimus is clinically effective in children and young people. For prolonged-release tacrolimus, the Committee concluded that it had not been presented with evidence that prolonged-release tacrolimus improved adherence and clinical outcomes in children and young people. 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.' 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

Consultee	Comment [sic]	Response
		value to users of the NHS as a whole.'
	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	

Consultee	Comment [sic]	Response
	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.	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.

Consultee	Comment [sic]	Response
	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.	Comment noted. The Committee had not seen evidence supporting the clinical or cost effectiveness of sirolimus in this situation. Comment noted. The Committee noted that prolonged-release tacrolimus was dominated (that is, it had higher costs and worse outcomes) 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 sections 4.63 and 4.74 of the FAD.

Consultee	Comment [sic]	Response
	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. Any other comments	As part of the evaluation for each intervention, the Assessment Group model included the costs for managing a failed transplant including dialysis (section 4.29 of the FAD). 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.

Consultee	Comment [sic]	Response
	None	
Novartis	We would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to comment on this appraisal. The licensed indications for everolimus and enteric coated mycophenolate sodium do not include the paediatric and adolescent population. However, in the context of the exceptional directive from the Department of Health for NICE and PenTAG to undertake this MTA (ID346) Novartis Pharmaceuticals UK Ltd (Novartis) would like to make a number of observations relating to the Appraisal Consultation Document (ACD). We recognise the challenges faced by the Assessment Group in the assessment of clinical effectiveness of all the products in scope for the review of technology appraisal guidance in the paediatric and adolescent population and welcome their additional literature search which included non-randomised studies with a control group. As acknowledged at the committee meeting on 7th July, the considerations faced by clinicians treating this patient population differ from those faced in management of the adult renal transplant patients and the optimal immunosuppressive therapy regime is not yet fully determined, e.g. with respect to graft longevity, steroid minimization and tolerability of therapies. However in the ACD, NICE has effectively recommended only one treatment combination for maintenance therapy in paediatric and adolescent patients with a renal transplant. As in the ACD for adult renal patients, these recommendations do not account for patients for whom either tacrolimus or mycophenolate mofetil (MMF) are clinically inappropriate, not tolerated or have unacceptable side effects. We are concerned that 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	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. The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4 and 4.77)

Consultee	Comment [sic]	Response
	patients 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. We would, therefore, urge that NICE considers provision of recommendations within the guidance for patients in whom MMF and immediate release tacrolimus are clinically inappropriate, not tolerated or have unacceptable side effects.	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.' 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.'
Royal College of Physicians	I'm writing to confirm that the RCP would like to endorse the British Association of Paediatric Nephrology's response to the above consultation	Comments noted.
Sanofi	Sanofi welcomes the opportunity to provide comments on the Appraisal Consultation Document (ACD) for the above appraisal.	Comments noted. The Committee agreed with the AG that there were insufficient data to permit

Consultee	Comment [sic]	Response
	We accept that the evidence base for Thymoglobuline (rATG) in children and adolescents is limited. However we would like draw the Appraisal Committee's attention to the comments we have submitted in response to consultation on the ACD for adult patients (Review of TA85 [ID456]). These are relevant as the assessment and resulting draft recommendation for rATG in children and adolescents has been made on the basis of extrapolating the effectiveness estimates from the RCT evidence in adults. Principally, as we and others have highlighted, rATG may be particularly beneficial in patients at high risk of acute rejection. The Assessment Group's analysis of rATG combined studies that recruited patients with very different immunological risks, and as different risk groups might be expected to have different outcomes the resulting aggregated effect size is both imprescise and uncessarily uncertain. We believe that an analysis in patients at high risk of acute rejection, would provide a more informative assessment of the relative cost-effectiveness of rATG. We acknowledge that the evidence for this population is limited, as it is for all treatments under consideration in this appraisal, but if the Appraisal Committee are to extrapolate these data to inform decision making in children and adolescents, then we would request that the Appraisal Committee take into consideration our comments on the adult appraisal as also being relevent	analyses of subgroups such as children and young people with different levels of immunological risk. See section 4.56 of the FAD.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
British Association for	Has all of the relevant evidence been taken into account?	Comments noted.

Nominating organisation	Comment [sic]	Response
Paediatric Nephrology (BAPN)	There are few studies of immunosuppression in children undergoing renal transplantation, consequently both the guidance in 2006 and this guidance is hampered by a lack of evidence on which to base recommendations. The use of adult trial data, extrapolated to children, is unsatisfactory but is necessary given the paucity of paediatric trials. The BAPN is pleased that information from the TWIST study has been included in the evidence accepted by The Appraisal Committee. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? There are real concerns that the lack of available evidence makes an assessment of clinical and cost effectiveness almost impossible in a meaningful way. Section 4.4 states that in the 9 years since the last guidance was published there have only been one new RCT of children and young people and 6 new non-randomised studies of children and young people undergoing renal transplantation. Even the inclusion of the TWIST study would not increase the available evidence significantly. Furthermore, there are few studies with long term (more than 5 years) outcome – a crucial issue for children in whom transplantation should facilitate growth, psychosocial development and attainment of employment. Immunosuppression use in children has evolved through dialogue with adult	

Nominating organisation	Comment [sic]	Response
	colleagues and adoption of regimens based on adult practice rather than in response to trial evidence (perhaps with the exception of the use of tacrolimus in both a steroid based and a steroid sparing regimen). The small numbers of children undergoing transplantation in the UK has made sub-group analysis (re-transplants, highly sensitised, etc) impossible although each unit will have a small number of such individuals; there is variation of immunosuppression regimes between units for these patients. Consequently, the trials that have been used to provide clinical and cost effectiveness do not necessarily reflect the complexity of patient mix within the paediatric renal units. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The BAPN accept recommendations 1.1, 1.2 and 1.3. With regard to 1.2, prescribing advice states the need to prescribe tacrolimus by brand because of possible pharmacodynamic differences – this is important for transplanted individuals who are stable on a branded drug. It would be preferable if the recommendation could emphasize the need to avoid brand switching for stable patients until the publication of trials demonstrating the safety of this practice. The BAPN are concerned that recommendation 1.4 could be interpreted as the prescription of rabbit anti-human thymocyte immunoglobulin, prolonged-	Comment noted. This technology appraisal does not make recommendations on treatment switching as this is beyond the remit granted by the Department of Health 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. Comment noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus,

Nominating organisation	Comment [sic]	Response
	release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept is prohibited. While the BAPN accepts there is no published trial data to support the widespread and routine use of these drugs, there are specific instances when these drugs are useful in the management of complex patients alluded to above. Clinicians would like to be reassured this guidance will not prevent the use of these therapies where this is felt to be in the best interest of the patient and that commissioners will continue to fund these therapies. Clinicians accept there may be a need to establish a mechanism by which approval for funding by commissioners is contingent on demonstrating this need through a written application. Neither TA99 nor this revision includes a recommendation concerning the use of ciclosporin, azathioprine or prednisolone, although these have been used as comparitors in the trials reviewed. It is unclear if the omission of these widely used drugs from the list of recommended drugs will prevent their use. It would be helpful if this could be clarified in the final document. Any other comments	everolimus and belatacept are not recommended for routine funding in the NHS to prevent organ rejection in children and young people having a kidney transplant. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people. Using effectiveness estimates from adults, 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. The recommendation does not prevent the use of these technologies if the relevant commissioner supports an individual funding request from the clinician. 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.

Nominating organisation	Comment [sic]	Response
	Summary The BAPN agrees with the points made by the Renal Transplant CRG, which is unable to make recommendations about the use of specific brands or combinations of immunosuppressant, but recommend 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	Comment 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).

Nominating organisation	Comment [sic]	Response
	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.	

Comments received from commentators

None

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS professional		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	Comment noted. Rabbit anti-human thymocyte immunoglobulin (r-ATG), prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people. Using effectiveness estimates from adults, these drugs were either dominated (they had higher costs

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
		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) immunoglobin 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	and worse outcomes) or had an incremental cost-effectiveness ratio (ICER) above £50,000 per QALY gained. 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.' 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.' 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

Role*	Section	Comment [sic]	Response
		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.	rejection in children and young people having a kidney transplant. The Committee concluded that there was not enough evidence to establish whether these drugs are clinically effective in children and young people. Using effectiveness estimates from adults, 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. The Committee considered that there was not enough evidence to support recommendations in specific subgroups (see FAD section 1.4 and 4.77) As part of the evaluation for each intervention, the Assessment Group model included the costs for managing a failed transplant including dialysis (section 4.29 of the FAD).
		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	Comment noted. Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in children and young people having a kidney transplant. Therefore, section 1.5 is

Role*	Section	Comment [sic]	Response
		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	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. It recognised that sirolimus (for nephrotoxicity associated with calcineurin inhibitors) and belatacept (for thrombotic microangiopathy) could potentially be a cost-effective use of NHS resources in these specific situations since the only alternative would be haemodialysis. However, it was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations. The Committee concluded that it was not able to make recommendations for people whose treatment needs to be withdrawn because of complications such as biopsy-proven nephrotoxicity associated with calcineurin inhibitors or thrombotic microangiopathy. See section 4.77 of the FAD As part of the evaluation for each intervention, the Assessment Group model included the costs for managing a failed transplant including dialysis (section 4.29 of the FAD).

Role*	Section	Comment [sic]	Response
		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	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 heard from clinical experts that alemtuzumab is not currently used for children and young people having a kidney transplant in the UK. The Committee agreed that alemtuzumab should not be included as either an intervention or a comparator. 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 a corticosteroid, which were included as comparators only. See section 4.56 of the FAD. Comments noted.

Role*	Section	Comment [sic]	Response
		sometimes only be managed with parenteral immunosuppression (basiliximab, belatacept) to ensure compliance.	

Response to NICE ACD consultation on ID346 : renal immunosuppression in children and adolescents

Astellas UK welcomes the consultation on the draft recommendations for immunosuppression in children and adolescent kidney transplant patients. The Company recognises that consideration of evidence is difficult in the transplantation therapy area and note that the Committee considered real world evidence in addition to RCTs in order to make recommendations for treatment.

The Company has no comment to make on the draft recommendations.

Response to:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

on the Appraisal Consultation Document for Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99)

Prepared by:

Novartis Pharmaceuticals UK Limited

26 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. The licensed indications for everolimus and enteric coated mycophenolate sodium do not include the paediatric and adolescent population. However, in the context of the exceptional directive from the Department of Health for NICE and PenTAG to undertake this MTA (ID346) Novartis Pharmaceuticals UK Ltd (Novartis) would like to make a number of observations relating to the Appraisal Consultation Document (ACD).

We recognise the challenges faced by the Assessment Group in the assessment of clinical effectiveness of all the products in scope for the review of technology appraisal guidance in the paediatric and adolescent population and welcome their additional literature search which included non-randomised studies with a control group. As acknowledged at the committee meeting on 7th July, the considerations faced by clinicians treating this patient population differ from those faced in management of the adult renal transplant patients and the optimal immunosuppressive therapy regime is not yet fully determined, e.g. with respect to graft longevity, steroid minimization and tolerability of therapies.

However in the ACD, NICE has effectively recommended only one treatment combination for maintenance therapy in paediatric and adolescent patients with a renal transplant. As in the ACD for adult renal patients, these recommendations do not account for patients for whom either tacrolimus or mycophenolate mofetil (MMF) are clinically inappropriate, not tolerated or have unacceptable side effects. We are concerned that 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 patients 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.

We would, therefore, urge that NICE considers provision of recommendations within the guidance for patients in whom MMF and immediate release tacrolimus are clinically inappropriate, not tolerated or have unacceptable side effects.

Yours faithfully,

[redacted]

Novartis Pharmaceuticals UK 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: Immunosuppressive therapy for kidney transplantation in children and adolescents (Review of TA99) [ID346]

Dear Meindert,

Sanofi welcomes the opportunity to provide comments on the Appraisal Consultation Document (ACD) for the above appraisal.

We accept that the evidence base for Thymoglobuline (rATG) in children and adolescents is limited. However we would like draw the Appraisal Committee's attention to the comments we have submitted in response to consultation on the ACD for adult patients (Review of TA85 [ID456]). These are relevant as the assessment and resulting draft recommendation for rATG in children and adolescents has been made on the basis of extrapolating the effectiveness estimates from the RCT evidence in adults.

Principally, as we and others have highlighted, rATG may be particularly beneficial in patients at high risk of acute rejection. The Assessment Group's analysis of rATG combined studies that recruited patients with very different immunological risks, and as different risk groups might be expected to have different outcomes the resulting aggregated effect size is both imprescise and uncessarily uncertain. We believe that an analysis in patients at high risk of acute rejection, would provide a more informative assessment of the relative cost-effectiveness of rATG. We acknowledge that the evidence for this population is limited, as it is for all treatments under consideration in this appraisal, but if the Appraisal Committee are to extrapolate these data to inform decision making in children and adolescents, then we would request that the Appraisal Committee take into consideration our comments on the adult appraisal as also being relevent.

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

Yours Sincerely,

[redacted]
Sanofi

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

Response to NICE Appraisal consultation document – immunosuppressive therapy for kidney transplant in children and adolescents (TA 99)

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 used in transplant treatments will not be or 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 children, young people and their families and their clinicians some really important choices to for successful induction and preservation of 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 (for adults) 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). For children with kidney failure, who are likely to have very specialised needs, these costs will be much higher. We do of course support the principle that a clinician should use a cost effective approach to the use of NHS resources.

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. According to the UK Renal Registry there are about 890 children a year being treated at 13 specialist centres, of whom about 700 will have a kidney transplant.

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 children, young people and their families and is not explained. It would therefore be possible that funding for these drugs could be withdrawn.

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 children and young people having a kidney transplant' will mean that patient access to any of these drugs will necessitate Individual Funding Requests and processes that families 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 and their families will be expected to stop these medications.

4.22 We note the AG point that for all comparisons, there was a great deal of heterogeneity and the credible intervals were wide, indicating uncertainty in the results. However the AG did make conclusions, including some on products that were shown to be clinically effective but were not recommended.

4.74 and 4.77 We appreciate that the AG have noted the difficulties some children and young people have with swallowing tablets and have therefore agreed that tacrolimus and mycophenolate mofetil can be made available as oral suspensions. We do not feel that the decision to disallow the once a day version of tacrolimus has made any allowance for the well-known issues that adolescents in particular have with adherence to medication. There are many studies attesting to this, such as http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2528818/
"Low adherence to any medical recommendation, …. and for medications to treat severe chronic health conditions such as …. organ transplant, thus possibly resulting in life-threatening consequences." We cannot agree that further evidence in the small population with kidney transplants is needed for the AG to accept this point, and the decision is discriminatory.

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 which our colleagues at the British Association for Paediatric Nephrology have made. The small numbers do not make it possible to produce meaningful evidence on performance of certain treatments on sub-groups and therefore making the decisions described in this appraisal is not supported by the BKPA.

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

[redacted]

[redacted]
Tel: [redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

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.
- Adolescent transplant patients are considered in most units to be at a particularly high risk of non-adherence with immunosuppression regimens, and this can have real clinical implications for the integrity of their transplanted organs. The patients are often 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. We note the Committee had considered adherence but *'agreed that it had not been presented with robust data to show better adherence with prolonged-release tacrolimus (see section 4.63) and, given the uncertainty in the evidence, it would not be appropriate to include better adherence in the model'*. This may well be the case, but real-life experience of transplant experts, particularly those with a special focus on children and adolescents, dictates otherwise.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

RESPONSE TO ACD

- 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 i.e. '*The Committee was aware that there are several brands of oral tacrolimus, and that inadvertent switching between products has been associated with toxicity and graft rejection. It heard from clinical experts that, to minimise the risk of accidental switching, UK clinicians follow advice from the Medicines and Healthcare Products Regulatory Agency to prescribe and dispense oral tacrolimus products by brand name. It heard from clinical experts that, for the same reason, brand names were used when prescribing ciclosporin'.* However, it stops there does not go on to make any recommendations about the implications of this. 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 in the final guidance, 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.

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 children and adolescents

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

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[redacted]

Meindert Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

tacommd@nice.org.uk

1 September 2015

Dear Meindert,

Re: Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99) [ID346]

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 British Association of Paediatric Nephrology's response to the above consultation.

Yours sincerely

[redacted]

[redacted]

BAPN Response to NICE ACD – Immunosuppressive therapy for kidney transplant in children (review of technology appraisal guidance 99)

Has all of the relevant evidence been taken into account?
There are few studies of immunosuppression in children undergoing renal transplantation, consequently both the guidance in 2006 and this guidance is hampered by a lack of evidence on which to base recommendations. The use of adult trial data, extrapolated to children, is unsatisfactory but is necessary given the paucity of paediatric trials. The BAPN is pleased that information from the TWIST study has been included in the evidence accepted by The Appraisal Committee.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
There are real concerns that the lack of available evidence makes an assessment of clinical and cost effectiveness almost impossible in a meaningful way. Section 4.4 states that in the 9 years since the last guidance was published there have only been one new RCT of children and young people and 6 new non-randomised studies of children and young people undergoing renal transplantation. Even the inclusion of the TWIST study would not increase the available evidence significantly. Furthermore, there are few studies with long term (more than 5 years) outcome – a crucial issue for children in whom transplantation should facilitate growth, psychosocial development and attainment of employment. Immunosuppression use in children has evolved through dialogue with adult colleagues and adoption of regimens based on adult practice rather than in response to trial evidence (perhaps with the exception of the use of tacrolimus in both a steroid based and a steroid sparing regimen). The small numbers of children undergoing transplantation in the UK has made sub-group analysis (re-transplants, highly sensitised, etc) impossible although each unit will have a small number of such individuals; there is variation of immunosuppression regimes between units for these patients. Consequently, the trials that have been used to provide clinical and cost effectiveness do not necessarily reflect the complexity of patient mix within the paediatric renal units.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
The BAPN accept recommendations 1.1, 1.2 and 1.3. With regard to 1.2, prescribing advice states the need to prescribe tacrolimus by brand because of possible pharmacodynamic differences – this is important for transplanted individuals who are stable on a branded drug. It would be preferable if the recommendation could emphasize the need to avoid brand switching for stable patients until the publication of trials demonstrating the safety of this practice. The BAPN are concerned that recommendation 1.4 could be interpreted as the prescription of rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept is prohibited. While the BAPN accepts there is no published trial data to support the widespread and routine use of these

drugs, there are specific instances when these drugs are useful in the management of complex patients alluded to above. Clinicians would like to be reassured this guidance will not prevent the use of these therapies where this is felt to be in the best interest of the patient and that commissioners will continue to fund these therapies. Clinicians accept there may be a need to establish a mechanism by which approval for funding by commissioners is contingent on demonstrating this need through a written application.

Neither TA99 nor this revision includes a recommendation concerning the use of ciclosporin, azathioprine or prednisolone, although these have been used as comparitors in the trials reviewed. It is unclear if the omission of these widely used drugs from the list of recommended drugs will prevent their use. It would be helpful if this could be clarified in the final document.

Any other comments

Summary

The BAPN agrees with the points made by the Renal Transplant CRG, which is unable to make recommendations about the use of specific brands or combinations of immunosuppressant, but recommend 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.

Contact details

Title (e.g. Dr, Mr, Ms, Prof)	**Dr**

Name	David Milford
Job title or role	Consultant Paediatric Nephrologist
Email address	[redacted]

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Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance 99) [ID346]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Nick Webb

Name of your organisation Royal Manchester Children's Hospital, Manchester

Are you (tick all that apply):

- X a specialist in the treatment of people with the condition for which NICE is considering this technology?
- X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

No geographic variation.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Certain renal diseases have a poorer prognosis for the graft following transplantation e.g. steroid resistant nephrotic syndrome without genetic basis and other diseases have a better prognosis e.g. cystinosis. However, most centres will use a reasonably uniform immunosuppression protocol for all patients except those with the most significantly increased risks.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This is generally managed in specialist clinics in tertiary centres – some may share care with local district hospitals where these are geographically remote.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

I am not aware of any such variation.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Appropriate methodology and guidelines used.
It was an omission not to include the TWIST study data. I understand that these were excluded because daclizumab is no longer available. However, this has simply been replaced by basiliximab, which has an identical mode of action and has been shown to have similar clinical outcomes.
Many centres, including my own, currently use the TWIST regimen as their standard protocol.

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Multiple Technology Appraisal (MTA)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

None

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

No stopping rules – in general this therapy is continued for the life of the transplant.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The clinical trials which have been performed have generally recruited lower risk patients i.e. those with good levels of HLA matching and those without significant comorbidities. Patients at higher risk of graft loss, e.g. those with atypical haemolytic uraemic syndrome or those with high levels of preformed anti-HLA antibodies were excluded.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Adverse effects are well known, well recognised and regularly monitored for in routine clinical care.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

The UK South Asian community is over-represented in the paediatric end stage kidney disease population; children of S Asian origin have a 3 fold risk of end stage kidney disease compared with white children. They are less likely to receive a living donor graft and because donation rates are lower in this community, in general they wait somewhat longer to receive deceased donor organs. However, once transplanted they are treated with the same immunosuppressive therapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Registry data e.g. that from the CERTAIN European paediatric renal transplant registry.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

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Multiple Technology Appraisal (MTA)

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)? Care currently being delivered – no change will be required.

Name	[redacted]
Organisation	Institute of Transplantation, Freeman Hospital
Role	NHS Professional
Job title	[redacted]
Location	England
Conflict	
Disclosure	
Comments	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) immunoglobin 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.
Submission date	26/08/2015