NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Everolimus (Certican®) for preventing organ rejection in liver transplantation

Specification for manufacturer/sponsor submission of evidence

24th September 2014

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices

should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

List of Abbreviations

Abbreviation	Definition
AE	Adverse Events
AIKP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase Test
ATC	American Transplant Congress
ATG	Anti-lymphocyte globulin
AZA	Azathioprine
bid	Twice Daily
BPAR	Biopsy proven acute rejection
BTS	British Thoracic Society
CCR	Creatinine Clearance Rate
CFB	Complement factor B
CKD	Chronic Kidney Disease
CIC	Ciclosporin
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRD	Centre for Reviews and Dissemination
CREST	Clinical Research Est Northern Ireland
CrI	Credible Intervals
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviation Information Criterion
DoH	Department of Health
DSU	Decision Support Unit
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	Euroqol 5-dimensions
ESLD	End Stage Liver Disease
ETOH	Alcoholic liver disease
EVR	Everolimus

EudraCT	European Union Drug Regulating Authorities Clinical Trials
FSH	Follicle stimulatory hormone
GAIN	Guidelines and Audit Implementation Network
GGT	Gamma-glutamyl Transferase
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HMG	3-hydroxy-3-methyl-glutaryl
HR	Hazard Rate
HRG	Health Resource Group
HRQL	Health Related Quality of Life
HSUV	Health State Utility Values
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ILTS	International Liver Transplantation Society
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect Treatment Comparison
ITT	Intention to Treat
IUD	Intrauterine Device
IVRS	Interactive Voice Response System
KM	Kaplan Meier
LY	Life year
MCMC	Markov Chain Monte Carlo
MDRD4	Four-variable Modification of diet in renal disease
MELD	Model for End-Stage Liver Disease
MHRA	Medicines and Health Products Regulatory Authority
MMF	Mycophenolate Mofetil
MTC	Mixed Treatment Comparison
mTOR	Mammalian target of rapamycin
NA	North America
NASH	Non-Alcoholic Steato-hepatitis
NCGC	NICE Clinical Guideline Centre

ng/ml	Nanogram per millilitre
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network Meta-Analysis
NR	Not Reported
NTLC	Nutritional-toxic liver cirrhosis
PCR	Polymerase Chain Reaction
PICOS	Population Intervention(s)/Comparators(s), Outcome(s) and Study Design
PSSRU	Personal and Social Services Research Unit
QALY	Quality Adjusted Life Year
RAI	Rejection Activity Index
RCT	Randomised Controlled Trial
rTAC	Reduced dose Tacrolimus
SD	Standard Deviation
SE	Standard Error
SEGA	Subependymal giant cell astrocytoma
SIGN	Scottish Intercollegiate Guidelines Network
SKU	Stock keeping unit
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
tBPAR	Treated biopsy proven acute rejection
TAC	Tacrolimus
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal
UNOS	United Network Organ Sharing
VAT	Value added tax
WOCBP	Women of child-bearing potential

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

Introduction

Liver transplantation offers significant benefits for End Stage Liver Disease patients, who have a very poor prognosis without a transplant. Calcineurin inhibitors (CNIs) remain the backbone of immunosuppression following liver transplantation despite their significant association with long-term complications including renal toxicity (Meier-Kriesche *et al.*, 2006[1]). While their use is important due to proven effectiveness in reducing acute rejection, there is an urgent need to reduce CNI-related complications including nephrotoxicity in liver transplantation patients.

Certican® (everolimus) is orally active and works as a cell mammalian target of rapamycin (mTOR) inhibitor. It has a distinctive mechanism of action that provides both immunosuppressive and anti-proliferative effects, differentiating everolimus from other immunosuppressive agents such as calcineurin inhibitors. Everolimus supports reducing CNI use in maintenance liver transplantation and this serves as an important therapy to reduce the costly impact of nephrotoxicity associated with calcineurin inhibitors (Ganschow *et al.*, 2014[2]).

Everolimus was submitted to the MHRA on the [redacted] with UK approval due [redacted]. Everolimus is anticipated to be indicated for the prophylaxis of organ rejection in patients receiving a hepatic transplant and should be used in combination with reduced dose tacrolimus and corticosteroids. Everolimus (Certican® 0.25mg, 0.5mg, 0.75mg aluminium PVC blister packs containing 60 tablets) should be initiated at a daily dose of 2.0 mg (1.0 mg twice daily) 30 days post liver transplant with the dose targeted to remain at a trough level of 3 to 8 ng/mL in combination with reduced tacrolimus at 3 to 5 ng/mL and corticosteroids, which can be tapered if necessary. The acquisition cost of everolimus is £148.50, £297.00 and £445.50 for the 0.25mg, 0.5mg and 0.75mg packs respectively (ex. VAT).

Clinical Evidence

The pivotal study H2304 was a large Phase III RCT that evaluated the efficacy and safety of everolimus in combination with reduced dose tacrolimus compared to both standard dose tacrolimus and tacrolimus elimination in treatment naïve liver transplant recipients over a 36 month follow-up period. The study did not compare directly with the decision problem comparators which include mycophenolate mofetil

(MMF) plus standard dose tacrolimus and azathioprine plus standard dose tacrolimus, but the study did include an active comparator arm which has enabled a network meta-analysis (NMA) to be undertaken. The NMA included 22 studies and synthesised the evidence for the relevant and feasible decision problem outcomes, with a comprehensive set of seven scenario analyses to test the robustness of the results. No relevant non-RCT evidence was identified for everolimus in combination with reduced dose tacrolimus for immunosuppression in liver transplant patients.

Early introduction of everolimus plus reduced-dose tacrolimus provides superior renal function (renal sparing) at 1, 2 and 3 years after liver transplantation compared to a standard dose tacrolimus regimen, with equivalent immunosuppression despite reduced tacrolimus concentrations (Saliba *et al.*, 2014[3]). The results of the NMA are supportive of this finding and indicate that the everolimus plus reduced dose tacrolimus arm compared to a standard dose tacrolimus regimen is more efficacious with respect to preserving renal function at 12 months after liver transplantation:

- The pivotal study H2304 demonstrated that for the primary composite efficacy endpoint of treated biopsy proven acute rejection (tBPAR), graft loss or death, the everolimus plus reduced dose tacrolimus arm was statistically non-inferior to the control standard dose tacrolimus arm at 12 and 24 months after liver transplantation.
- The 12 month data from H2304 demonstrated a significantly superior difference in renal function between the everolimus and reduced dose tacrolimus arm compared to the standard dose tacrolimus arm (eGFR difference between arms 8.5 ml/min/1.73m^2, $p \leq 0.001$). Data from the 24 month time point confirmed the superiority of everolimus and reduced dose tacrolimus with regard to preservation of renal function (eGFR difference between arms 6.7 ml/min/1.73m^2, $p \leq 0.001$).
- Within the subgroup analyses in the pivotal H2304 study, it was found that there were no statistically significant differences in the incidence of HCC/HCV recurrence or HCV-related fibrosis progression between everolimus plus reduced dose tacrolimus and the control standard-dose tacrolimus arm.
- The NMA demonstrated that everolimus plus reduced dose tacrolimus was comparable with the comparator set for hypertension, new onset diabetes, infections, HCV recurrence (with exception of azathioprine plus ciclosporin). A network was not feasible for HCC recurrence and the findings for withdrawals due to adverse events should be treated with caution.

Economic Evidence

A *de novo* cost-effectiveness analysis was undertaken to consider patients who have undergone liver transplantation for any reason. A patient level simulation model was designed to consider a core (hepatic) cost-effectiveness model and renal sub-model, because it was important to consider accurately the impact upon multiple aspects of

a patients' health. The patient level simulation structure allowed individual variation in patient history to be taken into account. There are two pivotal assumptions in the model (i) The immunosuppressive regimen determines the renal function decrease during year 1 and then differences between the regimens is assumed constant, (ii) Mild chronic rejection cannot occur in the first 12 months post-transplant and is not dependent on immunosuppressive regimen.

Table 1 presents the base case cost-effectiveness results. The mean total costs and QALYs for everolimus plus reduced dose tacrolimus of £140,750 and 4.210 respectively, £102,746 and 3.867 MMF plus standard dose tacrolimus, and £105,529 and 4.022 for azathioprine plus standard dose tacrolimus. There is a notable difference in renal costs for everolimus plus reduced dose tacrolimus of £49,299 in comparison to MMF plus standard dose tacrolimus of £56,926 and £57,475 for azathioprine plus standard dose tacrolimus. This can be explained by the prevention of downstream costs (e.g. dialysis) associated with end stage renal dysfunction when using the everolimus combination.

Table 1: Base-case cost-effectiveness results

	EVR + reduced TAC	**MMF + standard TAC**	**AZA + standard TAC**
Technology acquisition cost	£73,039	£28,401	£25,219
Renal costs	£49,299	£56,926	£57,475
Other costs	£18,412	£17,419	£22,835
Total costs	£140,750	£102,746	£105,529
Difference in total costs	N/A	£38,004	£35,222
LYG	10.171	9.691	9.796
LYG difference	N/A	0.480	0.375
QALYs	4.210	3.867	4.022
QALY difference	N/A	0.343	0.188
ICER	N/A	£110,797	£187,842

Table 2 presents the cost-effectiveness result for everolimus plus reduced dose tacrolimus of £110,797 per QALY gained in comparison to MMF plus standard dose tacrolimus. The deterministic incremental cost-effectiveness of everolimus plus reduced dose tacrolimus in comparison to azathioprine plus standard dose tacrolimus is £187,842 per QALY gained.

Table 2: Incremental cost-effectiveness results

Technology	Total costs (£)	Total LYG	Total QALYs	Increment-al costs (£)	Increment --al LYG	Increment -al QALYs	ICER (£) versus baseline (QALYs)	ICER (£) increment -al (EVR vs AZA) (QALYs)
MMF + standard TAC*	102,746	9.691	3.867					
AZA + standard TAC	105,529	9.796	4.022	2,783	0.106	0.156	17,895	-
EVR + reduced TAC	140,750	10.171	4.210	38,004	0.480	0.343	110,797	187,842
*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sub-group analyses

Sub-group analyses on regional sub-populations were undertaken in the trial, but not considered in this cost-effectiveness analysis. Further sub-group analyses on disease progression in HCC and HCV patients were undertaken, though the H2304 trial indicated that there were few differences between these patients and the ITT population. Due to a lack of evidence, subgroup analyses were not feasible in the NMA. Therefore, the economic model did not explicitly investigate subgroups. However, a renal sub-model was included. The cost-effectiveness results indicated that the model was sensitive to the removal of the renal sub-model.

Conclusions

- Everolimus supports reducing CNI use in maintenance liver transplantation and this serves as an important therapy to reduce the costly impact of nephrotoxicity associated with calcineurin inhibitors.
- In the pivotal phase III RCT (H2304), 719 de novo liver transplant recipients were randomised to everolimus plus reduced dose tacrolimus, standard dose tacrolimus, or everolimus with tacrolimus elimination. Tacrolimus exposure was reduced by 39% in the everolimus plus reduced dose tacrolimus group compared with in the standard dose tacrolimus group. Everolimus in combination with reduced dose tacrolimus proved to be non-inferior to standard dose tacrolimus, showing a numerically lower incidence rate of the primary endpoint of efficacy failure, defined as tBPAR, graft loss or death.
- An NMA was conducted to analyse the relative efficacy and safety of comparator treatments. This analysis supported the H2304 trial result that everolimus plus reduced dose tacrolimus arm compared with a standard dose tacrolimus regimen is potentially more efficacious with respect to preserving renal function at 12 months after liver transplantation.

- A *de novo* cost-effectiveness model was built to evaluate the cost-effectiveness of everolimus plus reduced dose tacrolimus compared to the comparator treatments. The analysis found that everolimus plus reduced dose tacrolimus offers the highest QALY gain of the treatment regimens modelled. This result was maintained in all of scenario analyses conducted to examine the structural and parameter sensitivities of the model. In the base case deterministic analysis, the model estimated that everolimus plus reduced dose tacrolimus has an incremental cost-effectiveness ratio of £110,797 versus MMF plus standard dose tacrolimus.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Certican®

Approved name: everolimus.

Therapeutic class: everolimus is a protein kinase inhibitor. More specifically, everolimus is an inhibitor of the mammalian target of rapamycin (mTOR).

ATC code: L04AA18

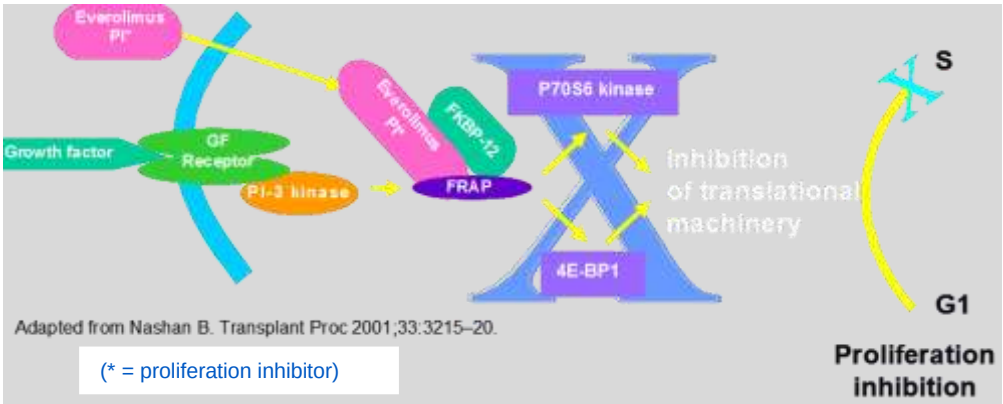
1.2 What is the principal mechanism of action of the technology?

Everolimus has a distinctive cellular mechanism of action that differentiates it from other immunosuppressive agents, in particular calcineurin inhibitors (CNIs). Its mode of action provides both immunosuppressive and anti-proliferative effects. It is orally active, and works as a cell mammalian target of rapamycin (mTOR) inhibitor (Figure A-1) (Nashan, 2001[4], Nashan, 2002[5], Schuler *et al.*, 1997[6]).

At the cellular level, everolimus inhibits the proliferation, and thus clonal expansion, of antigen-activated T cells, which is driven by T cell-specific interleukins. It inhibits an intracellular signaling pathway triggered when these T cell growth factors bind to their respective receptors, which normally leads to cell proliferation. The blockage of this signal by everolimus leads to an arrest of the cells at the G1 stage of the cell cycle. The effect of everolimus is not restricted to T cells as it inhibits growth factor-stimulated proliferation of hemopoietic as well as non-hemopoietic cells, such as vascular smooth muscle cells.

Growth factor-stimulated vascular smooth muscle cell proliferation (triggered by injury to endothelial cells and leading to neointima formation) plays a key role in the pathogenesis of chronic rejection (Nashan, 2001[4]).

Figure 1: Everolimus cellular mechanism of action



At the molecular level, everolimus forms a complex with the cytoplasmic protein FK506 binding protein (FKBP)-12. In the presence of everolimus, the growth factor-stimulated phosphorylation of the p70 S6 kinase is inhibited. Since p70 S6 kinase phosphorylation is under the control of mTOR, this finding suggests that the everolimus-FKBP-12 complex binds to and thus interferes with the function of mTOR. The mTOR protein is a key regulatory protein that governs cell metabolism, growth and proliferation. Everolimus disables mTOR function causing cell cycle arrest (Nashan, 2001[4], Nashan, 2002[5]).

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

[redacted]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

The feedback from the MHRA in their MRP day 50 comments is “The UK agrees with the overall conclusion of the RMS and is therefore prepared to grant a marketing authorisation for Certican.” and “no potential serious risks to public health”

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated UK indications are as follows:

[redacted]

[redacted]

Please note that the molecule everolimus has different indications, posology, and packaging under the Afinitor® and Votubia® brand names as follows:

Afinitor:

Hormone receptor-positive advanced breast cancer:

The treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

Neuroendocrine tumours of pancreatic origin:

Indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Renal cell carcinoma:

Indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Votubia:

Renal angiomyolipoma associated with tuberous sclerosis complex (TSC):

Indicated for the treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex (TSC) who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery.

Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC):

Indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.

For clarification, due to the very different therapeutic use of everolimus, these indications have their own specific brand name and Summary of Product Characteristics, own discrete packaging (with different colours) and own SKU code.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The pivotal registration study H2304/(de Simone *et al.*, 2012[7], Saliba, 2013[8]) is discussed in further detail in the body of the submission. Results of the 36-month data from H2304/(Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]) were presented in April 2014. Study H2307 (NCT01888432) is an ongoing study to demonstrate the efficacy and safety of everolimus in combination with reduced dose

tacrolimus, compared to tacrolimus control, in living donor liver transplant recipients. Outputs are not expected until April 2017.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

[redacted]

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Certican has regulatory approval for the prophylaxis of organ rejection following hepatic transplantation in the following countries:

Argentina, Armenia, Aruba, Australia, Austria, Bahrain, Bangladesh, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Chile, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Israel, Italy, Jamaica, Latvia, Lebanon, Lithuania, Maldives, Malta, The Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Paraguay, Peru, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, Slovak Republic, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Sweden, Switzerland, Syria, Taiwan, Thailand, Trinidad and Tobago, Turkey, United States (trade name Zortress®), Uruguay and Venezuela.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

We expect Certican to be assessed by the SMC, with a submission estimated for [redacted] with guidance estimated to be published in [redacted]

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 3: Unit costs of technology being appraised

Pharmaceutical formulation	Tablet
Acquisition cost (excluding VAT)	0.25mg x 60 £148.50 0.5mg x 60 £297.00 0.75mgx 60 £445.50
Method of administration	Oral
Doses	0.25mg,0.5mg and 0.75mg will be available
Dosing frequency	A starting dose of 1.0 mg twice daily is recommended with the initial dose approximately 4 weeks after transplantation.
Average length of a course of treatment	Treatment would be expected to continue for the life of the graft/patient
Average cost of a course of treatment	To be confirmed
Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	For patients with moderate or severe hepatic impairment (Child-Pugh B or C) the dose should be reduced to one half of the normal dose. Hepatic transplant patients should have the tacrolimus exposure reduced to minimize calcineurin-related renal toxicity. The tacrolimus dose should be reduced starting approximately 3 weeks after initiation of dosing in combination with Certican based on tacrolimus blood trough levels (C_0) targeting 3-5 ng/ml. Certican has not been evaluated with full dose tacrolimus in controlled clinical trials.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests or investigation are needed for selection of patients for this technology.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

As for other immunosuppressants; routine therapeutic drug monitoring is recommended for all patients. The draft summary of product characteristics specifies that monitoring should be performed every 4-5 days following the start of treatment or dose adjustment. Monitoring should continue until 2 consecutive trough levels show stable everolimus concentrations. Based on exposure-efficacy and exposure-safety analysis, patients achieving everolimus whole blood trough levels ≥3ng/ml have been found to have a lower incidence of biopsy-proven acute rejection in renal, cardiac and hepatic transplantation compared with the patients whose trough levels are below 3ng/ml. The upper limit to the therapeutic range is recommended at 8ng/ml.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

As outlined above, for the prophylaxis of organ rejection following liver transplantation, Certican should be used in combination with tacrolimus and corticosteroids. Tacrolimus dosing should be reduced after three weeks of concomitant dosing with Certican.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

End stage liver disease (ESLD) is caused by a group of severe liver diseases; it is progressive and irreversible, ultimately resulting in death. ESLD patients experience life-threatening complications such as variceal hemorrhage or hepatoma, combined with multiple debilitating symptoms; ascites, extreme fatigue, pruritus, and cachexia (d'Amico *et al.*, 2006[9]).

In the last few decades, liver transplantation has become a reliable and life-saving intervention for patients with ESLD. There is no interim therapeutic option for end-stage liver failure (i.e. nothing similar to dialysis exists for these patients); the patient will die if not transplanted. Acute liver failure, chronic liver failure, cirrhosis, and the accompanying metabolic abnormalities can all be corrected by liver transplantation. In Europe the most common underlying causes of ESLD are hepatitis C virus infection (HCV), nutritional-toxic liver cirrhosis (NTLC) and malignancy, predominantly hepatocellular carcinoma (HCC) (European Liver Transplant Registry, 2013[10], Gallegos-Orozco *et al.*, 2009[11], Muhlberger *et al.*, 2009[12]).

Transplantation is reserved for patients with the most critical need (defined according to the MELD score). Prognosis without a transplant is very poor; worldwide mortality reported for adult patients on liver transplant waiting lists is 10-20%.(Muller *et al.*, 2007[13]) In the United Kingdom (UK), approximately 14% of all waiting list patients die or become too ill to undergo the transplant procedure before a donor liver becomes available (van der Meulen *et al.*, 2007[14]).

Although liver transplants are more resistant to rejection than other solid organ transplants, immunosuppressant therapy is still required to prevent graft rejection. In the short-term, poorly controlled immunosuppression can lead to acute rejection of the graft (which may be asymptomatic) and progress to chronic rejection. Long-term post-transplant complications may be related to recurrence of the underlying cause of liver disease (e.g. chronic hepatitis C infection) or to the immunosuppression regimen being used. Complications that may be attributable to immunosuppressive treatment include renal dysfunction, new onset diabetes mellitus and cardio-vascular disease.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

In the period from 1 April 2012 – 31 March 2013 in the UK there were 719 liver transplants (Organ Donation, 2014[15]).

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

A study using the National Transplant Database held by UK Transplant has estimated median survival time of adult liver allograft recipients to be 22.2 years (95% confidence interval 19.3-25.6), with an estimated loss of seven life years compared with age and sex matched population (Barber *et al.*, 2007[16]).

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There is no current NICE guidance that considers immunosuppression following liver transplant. There are no national protocols, with the liver transplant centres following locally developed protocols for the management of immunosuppressive treatment.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

As Certican will be used following successful liver transplantation the relevant clinical pathway relates to post-transplant immunosuppression to prevent graft rejection. Therefore, post-transplant management requires that a liver transplant recipient is maintained on immunosuppressive therapy such that graft rejection (either acute or

chronic) does not occur. If rejection does occur; then it is managed with the goal of the patient returning to a stable post-transplant state. Adjustments to immunosuppressant dosing may need to be made to treatment in response to more long-term post-transplant complications such as renal dysfunction, as discussed previously. Certican will fit in to the existing post-transplant clinical pathway by offering an alternative choice of immunosuppressive therapy. As previously discussed, there is no NICE clinical guideline related to the management of patients post liver transplant.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As noted in section 2.4 there are no national protocols in place with regard to hepatic post-transplant immunosuppression. Variations may exist between centres with regard to choice of immunosuppressive therapy and the long-term management of treatment with regard to dose adjustment to avoid treatment-related complications whilst ensuring survival of the graft.

2.7 Please identify the main comparator(s) and justify their selection.

From historical discussions with NICE in reference to the "draft" scope and the scoping workshop subsequently held on the 24th July 2013, the key comparator is tacrolimus in combination with mycophenolate mofetil with or without corticosteroids. The other comparator of relevance is azathioprine, which replaces mycophenolate in the above combination. The scoping process for this appraisal has indicated that these are the relevant comparators. Current UK clinical practice bases prophylaxis of hepatic graft rejection on tacrolimus-containing regimens.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Incidence of acute rejection is treated with high-dose steroids that may require in-patient hospital stays. Transplant recipients who may be at higher risk of cytomegalovirus (CMV) infection may require anti-viral prophylaxis. Post-transplant infections such as CMV or other viral / bacterial causes are treated with appropriate antibiotics / anti-virals. Patients should be monitored for occurrence of hyperlipidaemia and new-onset diabetes. HMG co-reductase inhibitors may be prescribed for hyperlipidaemia. Renal dysfunction is managed with a combination of pharmaceutical intervention and dialysis / renal transplantation for those patients who progress to end-stage renal disease.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

In addition to drug acquisition cost for immunosuppressive therapy, the resource use to the NHS includes inpatient stays and outpatient visits in order to manage complications such as acute rejection and renal dysfunction. Therapeutic drug monitoring is required to ensure immunosuppressive treatment blood-levels are appropriate and dose adjustments made. As noted in 2.10, Certican does not require any additional resource use above that already in place for existing post-transplant immunosuppressive therapy. Costs to inform resource use are taken from NHS reference costs, PSSRU costs and previous NICE technology appraisals.

2.10 Does the technology require additional infrastructure to be put in place?

Certican will not require any additional infrastructure beyond that already in place for NHS transplant services.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- 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 provide us with any evidence that would enable the Committee to identify and consider such impacts.

No issues identified.

3.1.2 How has the analysis addressed these issues?

No issues identified.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

Liver transplantation provides a significant benefit to patients with ESLD, but although patient survival has improved steadily in the last 10 to 20 years, many deaths still arise from complications attributable to immunosuppressant drugs. There is a need for treatment that maintains the recent advances achieved in short-term graft and patient survival at the same time as delivering improvements in long-term patient outcomes.

Calcineurin inhibitors (CNIs) remain the backbone of immunosuppression following liver transplantation despite their significant association with long-term complications including renal toxicity (Meier-Kriesche *et al.*, 2006[1]). While their use is important due to proven effectiveness in reducing acute rejection, there is an urgent need to reduce CNI-related complications including nephrotoxicity in liver transplantation patients.

Immunosuppressants of the mammalian target of rapamycin (mTOR) inhibitor class act synergistically with CNIs, offering an opportunity to minimise CNI dose (Schuler *et al.*, 1997[6]). Everolimus also has anti-proliferative activity and is licensed for oncology indications and as such has potential anti-tumour capabilities (Gomez-Camarero *et al.*, 2007[17]).

The global everolimus liver registration trial H2304/(Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]) is the largest liver transplantation study to date and was conducted to establish the efficacy and safety of everolimus in *de novo* liver transplant patients. This study demonstrated that everolimus facilitated early tacrolimus reduction showing comparable efficacy and superior renal function compared to standard exposure tacrolimus at 24 months post-liver transplantation.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

As discussed in section 5, due to limitations of available evidence, some aspects of the innovative nature of everolimus may not have been captured in the cost-effectiveness model, particularly the impact of everolimus on the recurrence of

hepatocellular carcinoma. In addition, the feasibility of modelling complex long-term complications such as diabetes mellitus and cardio-vascular disease could mean the QALY calculation does not fully consider these events.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Naïve comparison data for outcomes such as recurrence of hepatocellular carcinoma will be presented in the submission from the pivotal registration trial H2304, for which 36-month data are available compared with more limited data for the relevant comparators.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults undergoing allogeneic liver transplantation.	Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	The expected license for everolimus is as a component of immunosuppressive therapy for the prophylaxis of graft rejection after liver transplantation. Initiation of treatment begins 4 weeks after transplantation; therefore the submission addresses maintenance therapy only. Expected license for everolimus is for prophylaxis of graft rejection after liver transplantation.
Intervention	Everolimus in combination with tacrolimus and a corticosteroid.	Everolimus in combination with reduced dose tacrolimus with or without corticosteroids.	The clinical evidence informing the submission relates to everolimus in combination with reduced dose tacrolimus. In clinical practice corticosteroids are withdrawn or reduced in dose depending on patient response in order to reduce the risks of long-term adverse events associated with corticosteroid use Clinical practice may mean that corticosteroids are

			withdrawn from immunosuppressive regimens.
Comparator(s)	Standard immunosuppressive therapy with a calcineurin inhibitor (such as ciclosporin or tacrolimus) and a corticosteroid, in combination with: • Azathioprine, or • Mycophenolic acid.	Tacrolimus in combination with azathioprine or mycophenolate mofetil with or without corticosteroids.	Clinical practice for post-liver transplant immunosuppression in the UK is based on tacrolimus combination regimens. Mycophenolate mofetil is specified in the submission as mycophenolate sodium (an alternate presentation of mycophenolic acid) does not have a license in liver transplantation.
Outcomes	The outcome measures to be considered include: • patient survival • graft survival • graft function • graft fibrosis • time to acute rejection • time to recurrence of hepatocellular carcinoma • renal function • time to end-stage renal disease • adverse effects of treatment • Health-related quality of life.	The economic analysis includes these outcomes with the exception of two: • Graft function / fibrosis • Time to recurrence of hepatocellular carcinoma	Expert opinion advised that in clinical experience there was limited evidence to differentiate between interventions with regard to these outcomes. Long-term data from the pivotal everolimus trial with regard to these outcomes is presented in the body of the submission.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to	Cost-effectiveness expressed as incremental cost per quality-adjusted life year, with a lifetime horizon, considering costs from an NHS and PSS perspective.	As per reference case.

	reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	People with hepatitis C infection. People with renal dysfunction.	Renal dysfunction is modelled but is not included as a subgroup. Hepatitis C is not included as subgroup in the model.	Patients with Hepatitis C were not included in the model after clinical advisers stated that their expert judgement was that there would be no differences expected between treatment arms following liver transplantation regarding recurrence rates or treatment of HCV.
Special considerations, including issues related to equity or equality	No issues identified.	No issues identified.	As per scope.

Section B – Clinical and cost-effectiveness

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

Section 6 presents four systematic literature reviews that were conducted in order to identify relevant published and unpublished clinical data:

1. *Section 6.2:* Relevant clinical data were identified for the intervention of interest (everolimus in combination with reduced dose tacrolimus with or without corticosteroids).
2. *Section 6.7: S*tudies were identified that are suitable for a network meta-analysis (NMA), both for the intervention of interest and the two relevant comparator regimens (mycophenolate mofetil [MMF] with standard dose tacrolimus with or without corticosteroids, and azathioprine with standard dose tacrolimus with or without corticosteroids).
3. *Section 6.8:* Relevant non-RCT data were identified for the intervention of interest (everolimus in combination with reduced dose tacrolimus with or without corticosteroids).
4. *Section 6.9:* Relevant adverse event data were identified for the intervention of interest (everolimus in combination with reduced dose tacrolimus with or without corticosteroids) from studies that are designed primarily to assess safety outcomes.

Search Strategy

A single clinical search strategy was performed because the same population and disease terms were required for all searches (including the later searches in section 7), and it was expected that some studies would be relevant for more than one of the four sections (for example, an RCT for the intervention of interest may contain data relevant to sections 6.1, 6.7 and 6.9).

The following computerised bibliographic databases advised by the CRD (Centre for Reviews and Dissemination, 2009[18]) were searched:

- MEDLINE
- MEDLINE In-Process
- EMBASE
- Cochrane Library (including Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR]) and The Database of Abstracts of Reviews of Effects (DARE).

Medline and Embase were searched via the OVID search platform, while the Cochrane Library was searched directly, and the CRD portal was used to search DARE. Registries were searched in order to identify potentially relevant studies that are still in development or in current regulatory submission stages, including the following websites:

- European Medicines Agency (EMA)
- The U.S. Food and Drug Administration (FDA)
- US National Library of Medicine ClinicalTrials.gov
- European Union Drug Regulating Authorities Clinical Trials (EudraCT).

Conference proceedings were searched including the following:

- The 2012 and 2013 International Liver Transplantation Society (ILTS) conferences
- The 2012 and 2013 American Transplant Congress (ATC)
- The 2011 and 2012 European International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conferences.

In addition to population and disease terms, the search strings included intervention terms (everolimus plus reduced dose tacrolimus) for the intervention of interest, relevant for all four sections; terms were also included for the two comparator regimens (MMF plus standard dose tacrolimus, and azathioprine plus standard dose tacrolimus), relevant for the NMA in section 6.7. The search was not limited by any outcome terms, terms to restrict study design or by language. A date limit was applied so that only studies from 1990

onwards were included. The date limit decision was informed by advice from clinical experts that due to changes in clinical practice over the last 20 years, studies before 1990 would not be relevant to the decision problem. Full details of the search strategies implemented are given in Section 10.2 Appendix 2.

The initial clinical search was conducted on 8th August 2013, where 7,616 records were retrieved. Following an update of the search on 12th August 2014, the number of retrieved records increased to 8,416. Four study eligibility criteria were applied to select relevant records to inform the four sections (sections 6.2, 6.7, 6.8 and 6.9) as illustrated in the PRISMA study selection flow diagrams (Figure 2, Figure 7, Figure 8). Details of the process of study selection for each of the four respective searches can be found in the relevant sections (section 6.2 for RCTs, section 6.7 for the NMA, section 6.8 for non-RCTs and section 6.9 for safety studies).

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The process for study selection was performed in two stages. The first stage involved two researchers independently screening all records by title and abstract against the pre-determined eligibility criteria. Where exclusion based on the title/abstract was not possible, the full publication was retrieved and evaluated against the eligibility criteria in the second stage screening. Eligibility of full text publications was conducted by two independent reviewers in line with pre-set eligibility criteria for Population, Intervention(s)/Comparator(s), Outcome(s) and Study design (PICOS), presented in Table 4. As the main choice of immunosuppression is now tacrolimus instead of ciclosporin (de Mare-Bredemeijer *et al.*, 2012[19]), only tacrolimus-based combination therapies were chosen as comparators. These criteria were in line with the decision problem (detailed in Section 5). Any judgment based on titles/abstracts or full text selection where consensus was not achieved were reviewed again by both researchers and then by a third independent researcher if agreement could not be reached.

Table 4: Eligibility criteria used in the search for RCTs

Criteria	Inclusion criteria	Exclusion criteria	Justification
Population	Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.	The expected license for everolimus is in combination with reduced dose tacrolimus as immunosuppressive therapy for the prophylaxis of graft rejection after liver transplantation. Initiation of treatment begins 4 weeks after transplantation; therefore the submission addresses maintenance therapy only.
Intervention/ Comparators	Everolimus in combination with reduced dose tacrolimus with or without corticosteroids.	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.	• The clinical evidence informing the submission relates to everolimus in combination with reduced dose tacrolimus. • In clinical practice, corticosteroids are withdrawn or reduced in dose in immunosuppressive regimens depending on patient response in order to reduce the risks of long-term adverse events associated with corticosteroid use. Therefore studies with or without corticosteroids were included to take into account clinical practice.
Outcomes	• Patient survival; • Graft survival; • Time to acute rejection; • Renal function; • Time to end-stage renal disease; • Time to recurrence of hepatocellular carcinoma; • Adverse effects of treatment; • HRQL.	• Studies that do not focus rejection of the liver as an outcome (efficacy) or HRQL. • Studies with only cost and no clinical outcomes.	These include all the outcomes derived from the final scope issued by NICE, except for the following: • Graft function / fibrosis • Time to recurrence of hepatocellular carcinoma. • Expert opinion advised that in clinical experience there was limited

			evidence to differentiate between interventions with regard to the two outcomes above.
Study design	• RCTs of any duration, including cross-over RCTs if data were presented at cross-over. • Studies published as abstracts or conference presentations were eligible for the primary analysis of clinical effectiveness if adequate data are provided.	• Non-RCT study designs or articles reporting results of RCTs published elsewhere, e.g. reviews, meta-analyses/pooled analyses, editorials, notes, comments or letters.	• Only RCTs were considered in line with the objective of this literature search.

Abbreviations: HRQL, Health Related Quality of Life; RCT, Randomised Controlled Trial

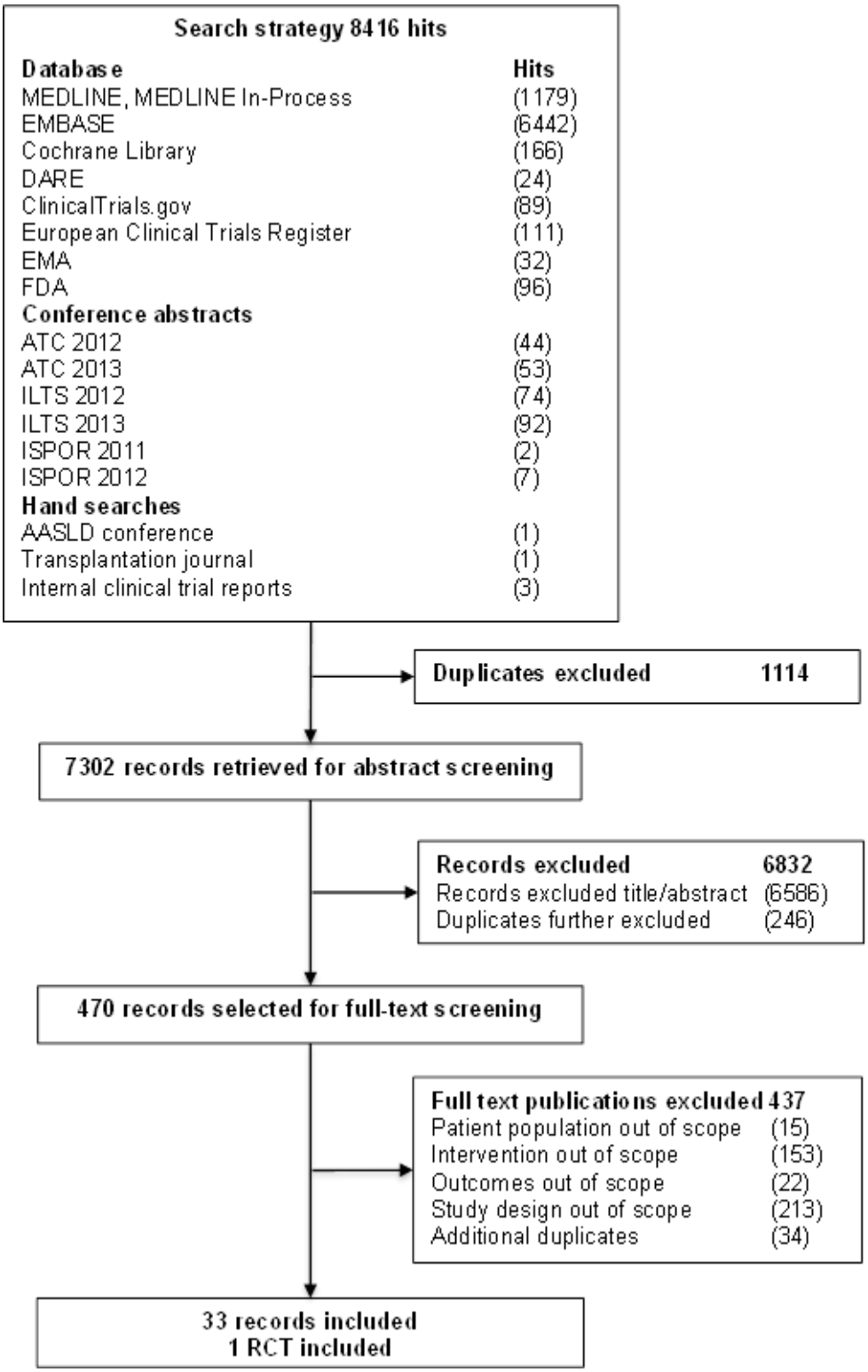
6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The search (Appendix 2) identified 8,416 records from databases and registries (search updated on 12th August 2014). Three unpublished clinical study reports (12-month, 24-month and 36-month reports for the pivotal Phase III H2304 trial), two studies identified through hand searching, and 272 conference abstracts were also identified.

Titles and abstracts were screened against the pre-defined inclusion / exclusion criteria and 470 full text documents were retrieved for evaluation against these criteria. One RCT the H2304/(de Simone *et al.*, 2012[7]) that studied the intervention of interest (everolimus in combination with reduced dose tacrolimus with or without corticosteroids) was identified, although 33 individual records were related to this RCT (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8], Brown *et al.*, 2013[20], Brown *et al.*, 2013[21], Chapman *et al.*, 2013[22], ClinicalTrials.gov, 2008[23], ClinicalTrials.gov, 2010[24], de Simone, 2013[25], de Simone *et al.*, 2013[26], de Simone *et al.*, 2013[27], de Simone *et al.*, 2012[28], Duvoux *et al.*, 2013[29], Fischer *et al.*, 2012[30], Fischer *et al.*, 2012[31], Fischer *et al.*, 2013[32], Fischer *et al.*, 2013[33], Fung *et al.*, 2013[34], Fung, 2013[35], Fung, 2013[36], Fung *et al.*, 2012[37], Grazi *et al.*, 2012[38], Hexham *et al.*, 2011[39], Hmwu, 2013[40], Junge *et al.*, 2013[41], Lopez *et al.*, 2013[42], Nevens *et al.*,

2012[43], Nevens, 2013[44], Rauer *et al.*, 2014[45], Saliba *et al.*, 2011[46], Saliba *et al.*, 2012[47], Saliba, 2013[48], Saliba *et al.*, 2012[49]). Figure 2 illustrates the study selection process.

Figure 2: Flowchart of the article selection process for clinical RCTs – original and updated searches (PRISMA diagram)



6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Study H2304 (*RAD001H2304*; ClinicalTrials.gov Identifier NCT00622869) is a Phase III RCT that investigated concentration-controlled everolimus with early tacrolimus minimisation in *de novo* liver transplant recipients. This was a 3-arm study: (i) everolimus in combination with reduced dose tacrolimus with corticosteroids *(intervention)*; (ii) tacrolimus elimination *(intervention)*; (iii) standard dose tacrolimus *(control)*.

Table 5: Records pertaining to the H2304 Phase III study

Clinical Study Reports (CSRs) for H2304	
(Hexham *et al.*, 2011[39])	Everolimus clinical study report 12 months
(Lopez *et al.*, 2013[42])	Everolimus clinical study report 24 months
(Rauer *et al.*, 2014[45])	Everolimus clinical study report 36 months
Published articles	
(Chapman *et al.*, 2013[22])	Everolimus facilitated reduction of tacrolimus in de novo liver transplant recipients: 12-24 month data from North America
(de Simone *et al.*, 2012[7])	Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: A randomized controlled trial
(de Simone *et al.*, 2013[26])	Superior renal function sustained for 24 months through early everolimus-facilitated reduction of tacrolimus versus standard tacrolimus in de novo liver transplant recipients: Results of a randomized trial
(de Simone, 2013[25])	Efficacy and safety of everolimus-facilitated tacrolimus reduction versus standard tacrolimus
(Duvoux *et al.*, 2013[29])	Randomized, multicenter study of everolimus with early reduction or elimination of tacrolimus in 719 *de novo* liver transplant recipients: Results at 24 months
(Fung, 2013[36])	Everolimus plus reduced tacrolimus in *de novo* liver transplant recipients achieves comparable overall efficacy with fewer biopsy-proven acute rejections versus standard tacrolimus: 24-month results of a randomized trial
(Fung *et al.*, 2013[34])	Early everolimus-facilitated minimization of tacrolimus: Progression or renal function and effect on proteinuria at 24 months
(Fung, 2013[35])	Everolimus-facilitated reduction of tacrolimus in de novo liver transplant recipients achieves comparable overall efficacy with fewer biopsy-proven acute rejections versus standard tacrolimus: 24-month results of a randomized trial
(Hmwu, 2013[40])	Preservation of renal-sparing effect of early everolimus (EVR)-facilitated reduction of tacrolimus (TAC) in *de novo* liver transplant recipients (LTxR) from North America (NA)

(Nevens *et al.*, 2012[43])	Everolimus with early reduction or elimination of tacrolimus: 12 Month results of a randomized, controlled study in 719 de novo liver transplant recipients
(Nevens, 2013[44])	Everolimus-based immunosuppression provides superior renal function and comparable efficacy versus standard tacrolimus in de novo liver transplant recipients: 24-Month results of a randomised controlled trial
(Saliba, 2013[8])	Renal function at two years in liver transplant patients receiving everolimus: Results of a randomized, multicenter study
(Junge *et al.*, 2013[41])	RAD001 (everolimus) in liver transplantation - A rational approach to quantify and predict the mTOR treatment effect
(Brown *et al.*, 2013[20])	Preservation of renal-sparing effect of early everolimus (EVR)-facilitated reduction of tacrolimus (TAC) in *de novo* liver transplant recipients (LTxR) from North America (NA)
Clinical trials records	
NCT00622869 (ClinicalTrials.gov, 2008[23])	Efficacy and Safety of Concentration-controlled Everolimus to Eliminate or to Reduce Tacrolimus Compared to Tacrolimus in de Novo Liver Transplant Recipients (RAD)
NCT01150097 (ClinicalTrials.gov, 2010[24])	Extension Study to Evaluate the Long-term Efficacy and Safety of Everolimus in Liver Transplant Recipients
Conference posters and abstracts	
(Brown *et al.*, 2013[21])	Preservation of renal-sparing effect of early everolimus (EVR)-facilitated reduction of tacrolimus (TAC) in *de novo* liver transplant recipients (LTxR) from North America (NA) International Liver Transplant Society 2013: P-53
(de Simone *et al.*, 2012[28])	Evolution of renal function with early everolimus-facilitated reduction or elimination of tacrolimus in 719 *de novo* liver transplant recipients: 12 month data of the H2304 study American Transplant Congress 2012: 705
(de Simone *et al.*, 2013[27])	Everolimus-facilitated reduction of tacrolimus maintains comparable efficacy and better renal function versus standard tacrolimus in *de novo* liver transplant recipients International Liver Transplant Society 2013: O-135
(Fischer *et al.*, 2012[30])	mTOR inhibitor attributed adverse events: results from the H2304 study comparing everolimus and tacrolimus in *de novo* liver transplant recipients. American Transplant Congress 2012: 332
(Fischer *et al.*, 2012[31])	Wound healing events and arterial complications with everolimus versus tacrolimus based regimens in de novo liver transplant recipients International Liver Transplant Society 2012: O-22
(Fischer *et al.*, 2013[33])	Exposure-response analysis of everolimus and tacrolimus in *de novo* liver transplant recipients: 24-month results from the H2304 study International Liver Transplant Society 2013: P-54
(Fischer *et al.*, 2013[32])	Effects of everolimus and tacrolimus exposure on efficacy and renal function in liver transplant recipients at 24 months in a randomized trial (H2304)

	American Transplant Congress 2012: 282
(Fung *et al.*, 2012[37])	Everolimus with early reduction or elimination of tacrolimus in 719 *de novo* liver transplant recipients – 12 month efficacy and safety results from H2304 study American Transplant Congress 2012: 5
(Grazi *et al.*, 2012[38])	Efficacy and safety of calcineurin-inhibitor-free *de novo* immunosuppression with everolimus after liver transplantation International Liver Transplant Society 2012: P-256
(Saliba *et al.*, 2011[46])	Efficacy and safety of everolimus with early reduction or elimination of tacrolimus in 719 *de novo* liver transplant recipients: 12 month results of a phase III, randomized, controlled study
(Saliba *et al.*, 2012[47])	Everolimus with reduced tacrolimus exposure versus standard tacrolimus in hepatitis C virus positive *de novo* liver transplant recipients
(Saliba *et al.*, 2012[49])	Efficacy and safety of everolimus based immunosuppression in HCV positive *de novo* liver transplant recipients American Transplant Congress 2012: 331
(Saliba, 2013[48])	Everolimus based immunosuppression in hepatitis C virus positive *de novo* liver transplant recipients: 24 month results from a randomized controlled trial
(Saliba *et al.*, 2014[3])	Everolimus-based immunosuppression provides superior renal function and comparable efficacy versus standard tacrolimus in *de novo* liver transplantation: 3-year results from H2304 study extension

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Study H2304 is a Phase III RCT that evaluated the efficacy and safety of everolimus in combination with reduced dose tacrolimus with corticosteroids (concentration-controlled everolimus with early tacrolimus reduction) compared to standard dose tacrolimus in liver transplant recipients initiated on an immunosuppressive regimen containing tacrolimus and corticosteroid (Table 6).

Table 6: Details of the H2304 Study

Trial name	Population	Interventions	Comparator	Primary study reference
H2304	Adult (18-70 years) *de novo* liver transplant recipients, who have received a full size liver transplant from a deceased donor; recipient has been initiated on an immunosuppressive regimen containing tacrolimus and corticosteroid (with or without mycophenalate mofetil).	1) everolimus (2mg daily dose) + reduced dose tacrolimus (3-5 ng/mL) + corticosteroids 2) everolimus (2mg daily dose) + tacrolimus elimination (3-5 ng/mL until complete elimination) + corticosteroids	Standard-dose tacrolimus (8-12 ng/mL reduced to 6-10 ng/mL at month 4 until end of study) + corticosteroids .	(de Simone *et al.*, [7]).

Abbreviations: EVR, everolimus; TAC, tacrolimus; CSR, clinical study report

Other studies examining immunosuppression of adult patients following liver transplantation were identified in the search that contained everolimus in combination with standard dose tacrolimus within a treatment arm; however these studies have been excluded because they are not relevant to the decision problem addressed in line with the licensed indication for everolimus for the final scope (Section A – 5); (Table 7).

Table 7: Excluded studies that contained a regimen of everolimus in combination with tacrolimus

Study	Everolimus arm	Reason for exclusion	Reference
RESCUE	Everolimus with reduced or eliminated calcineurin inhibitor with/without steroids	Both tacrolimus and ciclosporin combined with everolimus and mycophenolic acid (MPA) and azathioprine also added to regimens	(De Simone *et al.*, 2009[50])
PROTECT	Everolimus with calcineurin inhibitor	Everolimus in combination with calcineurin inhibitor withdrawal, not calcineurin inhibitor reduction	(Fischer *et al.*, 2012[51]) (Schlitt *et al.*, 2011[52])
EPOCAL	Everolimus with withdrawn calcineurin inhibitor	Everolimus with tacrolimus discontinuation after 30 days	(Cillo *et al.*, 2013[53])
Study not specified	Everolimus with standard dose tacrolimus	Not reduced dose tacrolimus	(de Ruvo *et al.*, 2012[54])
H2307	Everolimus with reduced dose tacrolimus	Study in progress, no data	(Song *et al.*, 2013[55])
T2304	Everolimus with reduced dose tacrolimus	Data not reported sufficiently; only the efficacy response relationship and contribution of everolimus to efficacy reported.	(Junge *et al.*, 2013[56]) (Junge *et al.*, 2013[57])

A number of RCTs included in the submission to the MHRA have been excluded in the current submission as they are not relevant to the decision problem addressed as derived from the final scope (section A – 5). These include the following:

- RESCUE (De Simone *et al.*, 2009[50]) (Table 7)
- PROTECT (Fischer *et al.*, 2012[51], Schlitt *et al.*, 2011[52]) (Table 7)
- B158 PK study (study of everolimus monotherapy)
- H2301 (study in fibrosis progression in liver transplant patients with hepatitis C)

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

There are none. Study H2304 is the only relevant RCT to the decision problem, and it does not compare against either of the two listed active comparators in the final scope, namely:

- Azathioprine with standard dose tacrolimus and corticosteroids.
- MMF with standard dose tacrolimus and corticosteroids.

In the H2304 study, *de novo* liver transplant patients were randomised at 30 days (±5 days) post-transplantation, to the following treatment arms:

- *Arm 1:* everolimus initiation with tacrolimus elimination (TAC Elimination).
- *Arm 2:* everolimus initiation with reduced dose tacrolimus (EVR + Reduced TAC).
- *Arm 3:* standard dose tacrolimus (TAC Control).

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No identified studies have been excluded from further discussion; however it should be noted that Arm 1 of H2304 was stopped early due to safety reasons and is excluded from further discussion in this submission.

In April 2010, an independent Data Monitoring Committee recommended stopping enrolment into the tacrolimus elimination arm (Arm 1) of H2304, when approximately 690 patients had been randomised and a number of patients were in the screening/run in phase, due to a higher rate of acute rejection and discontinuations in this group. The remaining patients were randomised into the two remaining treatment arms: everolimus in combination with reduced dose tacrolimus with corticosteroids and the standard dose tacrolimus control arm. The patients in the tacrolimus elimination arm who had not reached Day 180 post-randomisation were discontinued from the assigned study treatment and switched to local standard treatment, while patients who stayed beyond Day 180 post-randomisation either continued their treatment or converted to local standard approved treatment.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

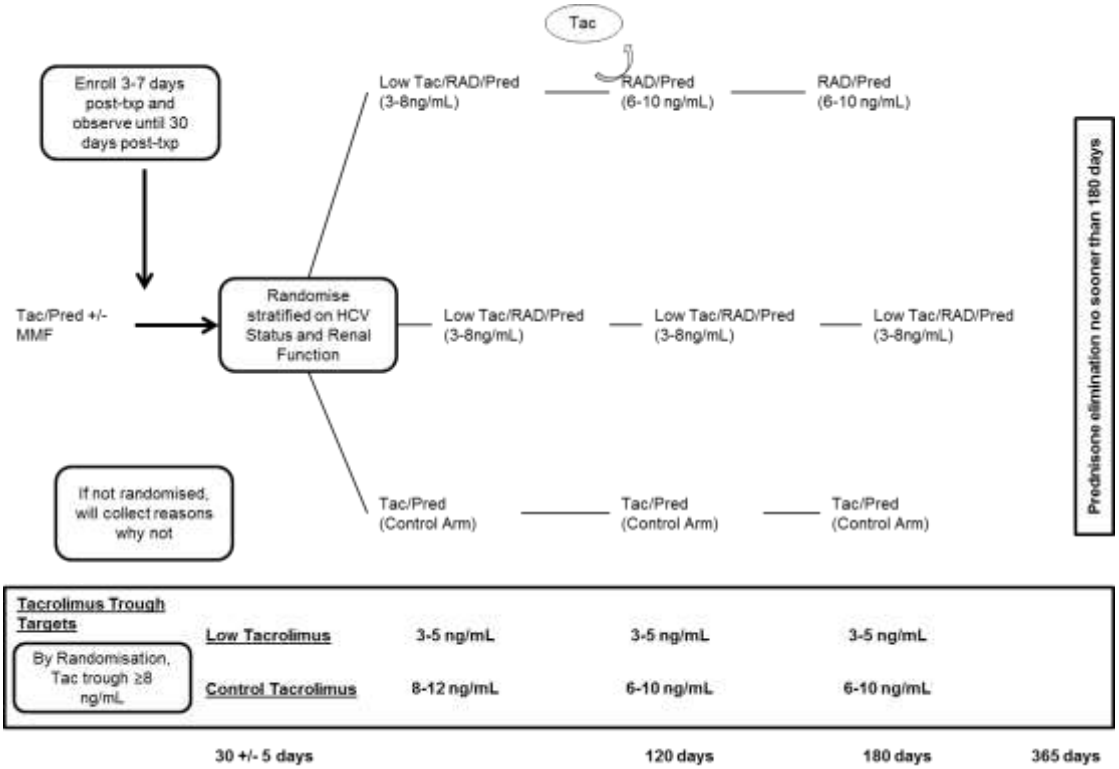
There were no non-RCTs identified that were relevant to the decision problem (see section 6.8).

6.3 *Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Study H2304 was a 24-month, multicentre, open-label, randomised, controlled study that consisted of a screening period, a baseline period (3 to 7 days post-transplantation) followed by a run-in period that ended on the day of randomisation at 30 days (± 5 days) post-transplantation (Figure 3).

Figure 3: Study design



Source: (Lopez *et al.*, 2013[42]) *Note that the TAC elimination arm was stopped early due to safety concerns; RAD = everolimus

Additional detail regarding study design and secondary outcomes are provided in Section 10.6 Appendix 16.

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The methodology of Study H2304 is summarised below (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8], Brown *et al.*, 2013[20], Brown *et al.*, 2013[21], Chapman *et al.*, 2013[22], ClinicalTrials.gov, 2008[23], ClinicalTrials.gov, 2010[24], de Simone, 2013[25], de Simone *et al.*, 2013[26], de Simone *et al.*, 2013[27], de Simone *et al.*, 2012[28], Duvoux *et al.*, 2013[29], Fischer *et al.*, 2012[30], Fischer *et al.*, 2012[31], Fischer *et al.*, 2013[32], Fischer *et al.*, 2013[33], Fung *et al.*, 2013[34], Fung, 2013[35], Fung, 2013[36], Fung *et al.*, 2012[37], Grazi *et al.*, 2012[38], Hexham *et al.*, 2011[39], Hmwu, 2013[40], Junge *et al.*, 2013[41], Lopez *et al.*, 2013[42], Nevens *et al.*, 2012[43], Nevens, 2013[44], Rauer *et al.*, 2014[45], Saliba *et al.*, 2011[46], Saliba *et al.*, 2012[47], Saliba, 2013[48], Saliba *et al.*, 2012[49]):

- *Locations:* Europe, North/South America and Australia.
- *Design:* Multicentre, open-label, randomised, controlled study.
- *Duration of study:* 24 months.
    - *Method of randomisation:* Patients were stratified according to pre-transplant hepatitis C status and quartiles of renal function in order to balance the risk factors for graft and patient survival and then randomised in a 1:1:1 ratio. Patients were linked to a treatment arm through a randomisation number assigned using an interactive voice response system (IVRS). A patient randomisation list was produced by the IVRS provider using a validated system that automated the random assignment of the patient numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers. The randomisation scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group. In the event that a randomised patient did not enter the trial, the assigned treatment could not be re-allocated to another patient.
- *Method of blinding:* No blinding; this was an open label trial.
- *Intervention*: *Everolimus in combination with reduced dose tacrolimus with corticosteroids (up to 6 months):* Everolimus was initiated at a daily dose of 2.0 mg 30 days post-transplant; dose was targeted to be maintained at a trough level of 3 – 8 ng/mL. Tacrolimus was initiated at a dose based on the prescribing information as per approved labels.

After everolimus whole blood trough levels were confirmed to be in the target range (3 – 8 ng/mL), tacrolimus tapering began, achieving a target trough level of 3 – 5 ng/mL by three weeks after randomisation and continuing through the remainder of the study. Corticosteroid (30 days post-transplant) was given at a minimum dose of 5 mg per day until at least 6 months.

Information on *the tacrolimus elimination* arm is not included due to the reasons discussed in Section 6.2.6.

- *Comparator:* Tacrolimus was initiated at a dose based on the prescribing information as per approved labels. Tacrolimus trough levels were targeted to be maintained at 8 – 12 ng/mL until Month 4. At Month 4, tacrolimus was tapered to a target trough level of 6 – 10 ng/mL for the remainder of the study. Corticosteroids (30 days post-transplant) were given at a minimum dose of 5 mg per day for at least 6 months.
- *Previous/existing treatment:* At randomisation, 70% of the everolimus plus reduced dose tacrolimus and 70% of the tacrolimus standard dose groups were receiving MMF, which was discontinued according to protocol. Patients receiving azathioprine and sirolimus therapy were prohibited from entering the study.
- *Primary outcomes:* Composite efficacy failure rate of treated biopsy proven acute rejection (tBPAR), graft loss or death at 12 months post transplantation (excluding events before randomisation).
- *Secondary outcomes*: The key secondary outcome was change in renal function over time from randomisation to 12 months and 24 months post-transplantation. This was assessed by estimated glomerular filtration rate (eGFR) using the four-variable modification of diet in renal disease (MDRD4) formula and confirmed using other methods of assessing renal function (serum creatinine, Cystatin C, other formulae for eGFR calculation [MDRD-6, Nankivell, Cockcroft-Gault and Hoek formulae], and proteinuria as determined by a spot urine protein/creatinine ratio). The full list of secondary outcomes for H2304 are provided in Appendix 16, Section 10.16.
- *Duration of follow-up:* 12, 24 and 36 months.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there are more than one RCT. Highlight any differences between the trials.

In study H2304 (de Simone *et al.*, [7], Hexham *et al.*, 2011[39]), the randomised study population consisted of a group of male and female primary liver transplantation patients, 18 to 70 years of age, who had received an allograft from a deceased donor. Patients who met the following eligibility criteria were offered enrolment in the study.

Inclusion criteria:

- Ability and willingness to provide written informed consent and adhere to study regimen.
- Recipients who were 18 to 70 years of age of a primary liver transplant from a deceased donor.
- Allograft was functioning at an acceptable level by the time of randomisation as defined by the aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin levels ≤ 3 times ULN, and AlkP and gamma-glutamyl transferase (GGT) levels ≤ 5 times ULN. Elevated GGT alone, in combination with AST, ALT, total bilirubin and AlkP within the defined range does not exclude patients from randomisation.
- Recipients who had initiated on an immunosuppressive regimen that contains corticosteroids and tacrolimus, 3–7 days post-transplantation.
- Confirmed recipient HCV status at screening (either by serology or by polymerase chain reaction).
- Abbreviated MDRD eGFR ≥ 30 mL/min/1.73m^2. Local and central serum creatinine results obtained within 5 days prior to randomisation were acceptable, however no sooner than Day 25 post-transplantation.
- Verification of at least one tacrolimus trough level of ≥ 8 ng/mL in the week prior to randomisation. Investigators should make adjustments in tacrolimus dosing to continue to target trough levels above 8 ng/mL prior to randomisation.
- Patients who were able to take oral medication at time of randomisation.

Exclusion criteria:

- Patients who were recipients of multiple solid organ or islet cell tissue transplants, or had previously received an organ or tissue transplant. Patients who had a combined liver-kidney transplant.
- Recipients of a liver from a living donor, or of a split liver.
- History of malignancy of any organ system within the past 5 years whether or not there was evidence of local recurrence or metastases, other than non-metastatic basal or squamous cell carcinoma of the skin or hepatocellular carcinoma (HCC); (see next criteria).
- HCC that did not fulfill Milan criteria (1 nodule ≤ 5 cm, 2–3 nodules all < 3 cm, at the time of transplantation as per explant histology of the recipient liver.
- Any use of antibody induction therapy.
- Patients with a known hypersensitivity to the drugs used on study or their class, or to any of the excipients.
- Patients who were recipients of ABO incompatible transplant grafts.
- Recipients of organs from donors who test positive for Hepatitis B surface antigen or HIV were excluded.
- Patients who had any surgical or medical condition, which in the opinion of the investigator, might significantly alter the absorption, distribution, metabolism and excretion of study drug.
- Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners had been sterilised by vasectomy or other means, unless (1) they met the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhoea or 6 months of spontaneous amenorrhoea with serum follicle stimulating hormone (FSH) levels > 40 mIU/mL, or (2) had past 6 weeks from surgical bilateral oophorectomy with or without hysterectomy or (3) were using one or more of the following acceptable methods of contraception: surgical sterilisation (e.g. bilateral tubal ligation or vasectomy), hormonal contraception (implantable, patch, oral), copper coated intra-uterine device and double-barrier methods (any double combination of male or female condom with spermicidal gel, diaphragm, sponge or cervical cap). Periodic abstinence (e.g. calendar, ovulation, symptothermal or post-ovulation methods) and withdrawal were not acceptable methods of contraception. Reliable contraception

was maintained throughout and for 3 months after study drug discontinuation.

- Patients with any history of coagulopathy or medical condition requiring long-term anticoagulation that would preclude liver biopsy after transplantation (low dose aspirin treatment or interruption of chronic anticoagulant was allowed).

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Patient characteristics at baseline for Study H2304 are summarised in Table 8. These baseline characteristics include age, gender, Body Mass Index (BMI), the proportion of patients with HCV and HCC, and kidney function measured by eGFR. The prevalence of diabetes and hypertension are also presented, as well as donor age and cold ischaemic time of the donor organ.

Table 8: Characteristics of participants in Study H2304 across randomised groups

Baseline characteristic	EVR + reduced dose TAC + corticosteroids (n = 245)	Standard dose TAC + corticosteroids (n = 243)
Age in years, mean (SD)	53.6 (9.2)	54.5 (8.7)
Male (%)	73.5%	73.7%
BMI in kg/m^2, mean (SD)	25.1 (4.2)	24.5 (4.2)
HCV positive (%)	31.8%	14.4%
eGFR (MDRD4) in mL/min/1.73m^2, mean (SD)	80.8 (32.7)	78.9 (27.7)
HCC (%)	17.1%	31.3%
Hypertension (%)	33.7%	33.3%
Diabetes (%)	38.8%	41.6%
Cold ischaemic time in hours, mean (SD)	8.4 (4.4)	8.0 (5.2)
Donor age in years, mean (SD)	48.8 (18.2)	48.7 (17.4)

Source: (de Simone *et al.*, [7]). Abbreviations: EVR, everolimus; TAC, tacrolimus; SD, standard deviation; HCV, hepatitis C virus; HCC, hepatocellular carcinoma

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The therapeutic outcomes investigated in Study H2304 and their relevance with respect to the decision problem are presented below.

Primary outcome:

The primary outcome was the composite efficacy failure rate of treated biopsy proven acute rejection (tBPAR), graft loss or death at 12 months post transplantation (excluding events before randomisation). tBPAR was determined as acute rejection with a locally confirmed rejection activity index (RAI) ≥ 3 according to the Banff 1997 criteria when treated with anti-rejection therapy. Banff schema is a consensus document that was designed to provide an internationally accepted standard for the purpose of grading acute liver allograft rejection. The Banff RAI comprises 3 components scored from 0 to 3: venous endothelial inflammation (E), bile duct damage (B), and portal inflammation (P), the scores are combined to an overall score (the RAI). The primary outcome is a composite of three outcomes relevant with reference to the decision problem as derived from the final scope issued by NICE.

Secondary efficacy outcomes:

Please see Appendix 16, section 10.16 for the full list of secondary efficacy outcomes. The key secondary efficacy outcome was change in renal function from randomisation to Month 12 post transplantation, measured by eGFR. The MDRD4 formula was used for eGFR measurement, which is valid globally in clinical practice. Measurement of renal function is relevant with reference to the decision problem as the purpose of the intervention is to provide renal sparing through reduction in the dose of tacrolimus.

Safety related secondary outcomes:

Safety related secondary outcomes included the incidence of adverse events, defined as the appearance or worsening of any undesirable sign, symptom, or

medical condition occurring after starting the study drug even if the event was not considered to be related to study drug. These included assessment of the following important treatment-related adverse events and other adverse events of interest:

- Hypertension
- New onset diabetes
- Infections

The occurrence of adverse events was sought by non-directive questioning of the patient at each visit during the study. Adverse events were also detected when they were volunteered by the patient during or between visits. They were assessed through physical examination, laboratory tests or other specific measurements as appropriate for the condition.

These safety outcomes are relevant with reference to the decision problem as derived from the final NICE scope. Additionally, HCC/HCV-related adverse events were recorded as safety related secondary outcomes.

Please see Section 10.16, Appendix 16 for details of additional outcomes investigated.

Patient-related outcomes:

There were no patient-related outcomes such as HRQL measured in the trial.

Compliance:

If patients did not comply with the follow-up visit schedule, they were withdrawn from the study. For patients who were lost to follow-up, the investigator showed diligence by documenting in the patient records steps taken to contact the patient, e.g. dates of telephone calls and registered letters.

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Statistical analyses for Study H2304 (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]) are summarised below:

- *Hypothesis objective:* A non-inferiority test was conducted of the null hypothesis that the control was superior to the treatment against the alternative that the treatment was not inferior to the control. The non-inferiority margin of 12% was pre-defined based on a $p<0.001$ value.
- *Statistical analysis:* The primary composite endpoint was Kaplan Meier incidence rate at 12 months (percentage), and the difference was determined at the 97.5% confidence interval. For each of the secondary endpoints, a difference (two tailed test) was applied.
- *Sample size, power calculation:* A sample size of 242 patients per arm was calculated to provide:
    i. At least 80% power at the one-sided 0.0125 level for non-inferiority of the everolimus plus reduced dose tacrolimus group versus the tacrolimus control arm in the proportion of patients with tBPAR, graft loss or death, assuming that both groups each have a true proportion of tBPAR, graft loss or death of 24% and a non-inferiority margin of 12%.
    ii. At least 90% power at the one-sided 0.0125 level for non-inferiority of the everolimus plus reduced dose tacrolimus group versus the tacrolimus control arm for mean change in eGFR from randomisation to month 12, assuming a non-inferiority margin of the difference in eGFR is −6.0 mL/min with a standard deviation (SD) of 20 mL/min and a correlation coefficient with pre-randomisation eGFR of 0.5, using an analysis of covariance (ANCOVA) model.
- *Data management, patient withdrawals:* The endpoints were revised following a protocol amendment to discontinue the tacrolimus elimination arm in accordance with the European Medicines Agency (EMA) guidelines. Patients in the tacrolimus elimination arm who discontinued study medication due to the decision by the Data Monitoring Committee were expected to be converted to local standard treatment and to enter the follow-up phase.
- Where patients refused to return or were unable to do so, efforts were made to ascertain their status through the study site coordinator or other knowledgeable persons to determine information on survival status, graft loss, rejection episodes, malignancies, opportunistic infections and immunosuppressive therapies. Patients with missing efficacy evaluations for the 12 and 24-month analyses were censored at the latest day known to be free of the event.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The following pre-planned subgroup analyses were undertaken:

- Subgroup summaries (by region, age group, gender, race, renal function strata at randomisation, HCV status, recipient MELD score categories and types of end stage disease leading to transplantation), were reported for the primary efficacy endpoint tBPAR/GL/D (Table 11, Table 12).
- The summary of eGFR and change in eGFR from screening, week 2 post-transplantation and randomisation to Month 6 and Month 12 were presented in the following subgroups based on the intention-to-treat (ITT) population: age group, gender, race, renal function strata based on eGFR (MDRD-4) at randomisation (strata were: (a) < 30, 30 - 44, 45 - 59, ≥ 60 mL/min/1.73m^2; (b) below/above 45 mL/min/1.73m^2; and (c) below/above 60 mL/min/1.73m^2), HCV status, MELD score categories (≤ 14, 15 - 19, 20 - 24, 25 - 29, ≥ 30), and diagnosis (end stage disease) leading to transplantation (Table 13).

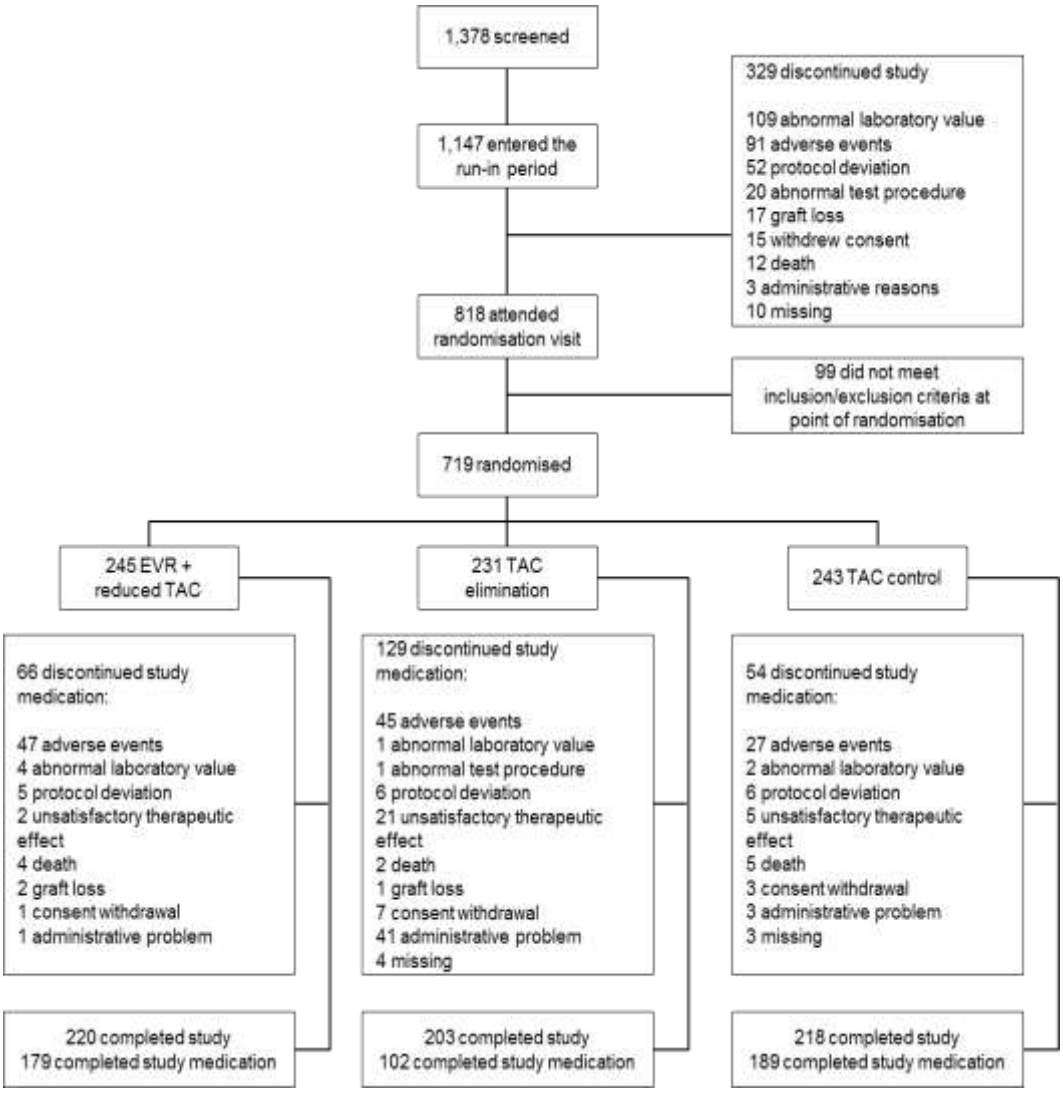
These subgroups were pre-planned as patients in these subgroups may have differential responses to immunosuppressive therapy in terms of efficacy and adverse event incidence.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

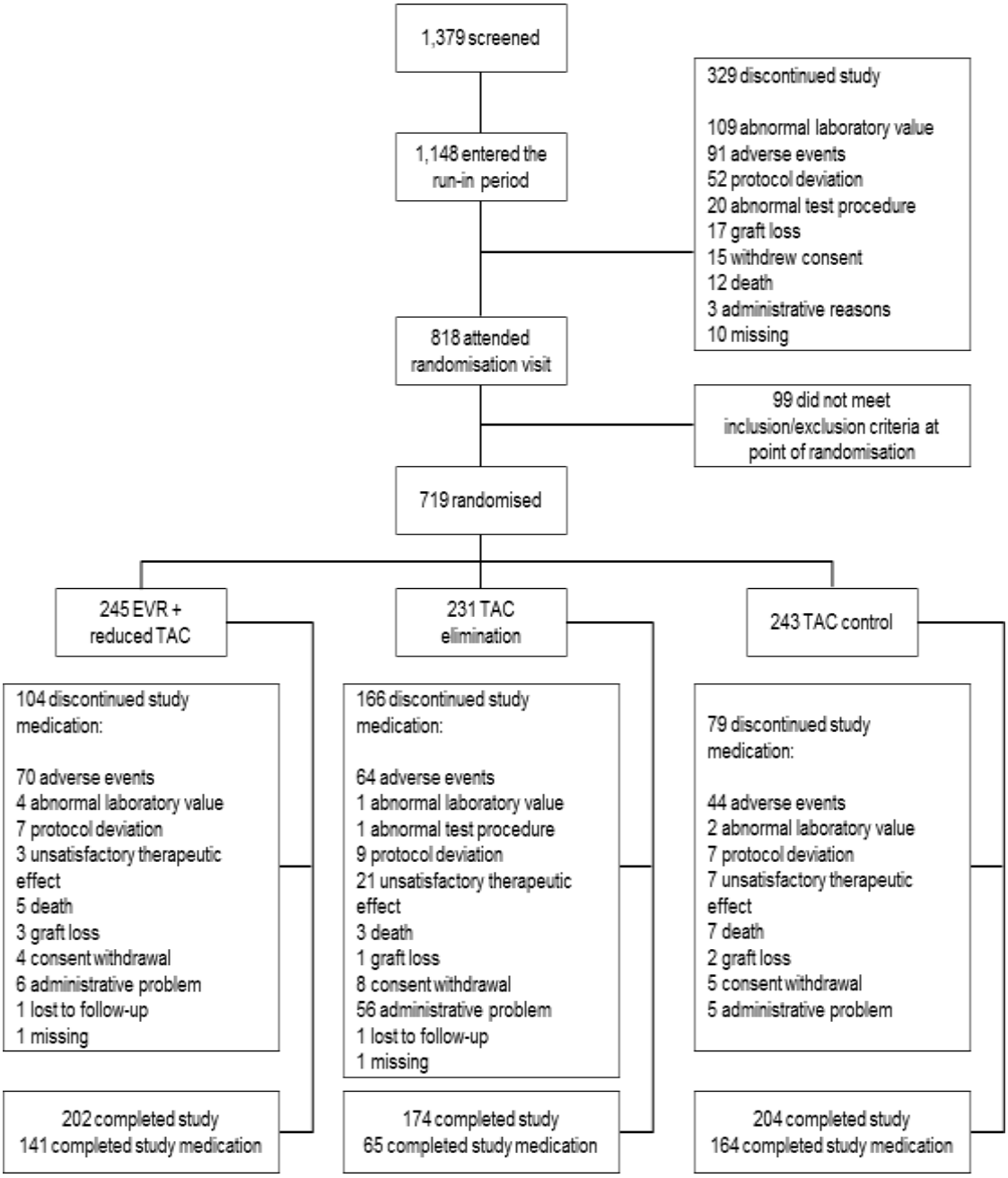
A CONSORT flow chart showing the number of patients who were eligible to enter Study H2304 (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]) and were randomised to each treatment is presented in Figure 4 (for 12 months) and Figure 5 (for 24 months).

Figure 4: Flow chart presenting the patient flow within the H2304 study up to the 12 month study endpoint



*Cut-off point was day 286

Figure 5: Flow chart presenting the patient flow within the H2304 study up to the 24 months study endpoint



*Including patients ≤ 180 days post-randomisation who were converted to standard treatment

6.4 *Critical appraisal of relevant RCTs*

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

For the critical appraisal of relevant RCTs, the NICE checklist for RCTs (adapted from (Centre for Reviews and Dissemination, 2009[18])) was used as it has been tested for internal consistency, reliability, and validity and is relatively easy to use.

See Section 10.3 Appendix 3 for full details of the critical appraisal. The responses applied to each of the critical appraisal criteria are as follows:

- Was the method used to generate random allocations adequate?

  Yes. Randomisation was carried out using an interactive voice response system (IVRS). The randomisation scheme for patients was reviewed and approved by a member of the Biostatistics Quality Assurance Group.

- Was the allocation adequately concealed?

  Yes. The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff. A patient randomisation list was produced by the IVRS provider using a validated system that automated the random assignment of the patient numbers to randomisation numbers.

- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

  Yes. Baseline characteristics appear similar in all treatment arms.

- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

  No, this was an open-label trial; therefore after randomisation, the investigator, pharmacist and patient were aware of the treatment

administered to the patient. The investigator however, withheld the treatment assignment from the local pathologist interpreting the biopsies. The local pathologist provided the investigator with their interpretation for clinical management of the patient. The manufacturer's core clinical team and data analysts remained blinded to patient treatment from the time of randomisation until database lock after all patients finished the first year of the study.

- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

  Yes. The tacrolimus elimination group was terminated prematurely based on a recommendation of the Data Monitoring Committee due to a higher incidence of acute rejection versus the other cohorts.

- Is there any evidence to suggest that the authors measured more outcomes than they reported?

  No. All pre-specified outcomes appear to have been reported.

- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

  Yes. All randomised patients were included in the intent-to-treat population. This was appropriate but the methods used to account for missing data are unclear.

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

Please see Section 10 in Appendix 3 for quality assessment of the RCT H2304.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Only one RCT is available, therefore no table is presented.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.

The efficacy results for the outcomes in Study H2304 are summarised in Table 9 and Table 10 for 12 months and 24 months post-transplant respectively (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]). Where reported, odds ratios or risk ratios are presented in the tables. The tables are based on the number of patients in the ITT analysis.

Table 9: Summary of efficacy results for outcomes at 12 months

	EVR+ Reduced TAC (N=245)	**TAC Control (N=243)**	**Difference (SE) (95% CI)**	**p Value**
Time to death				
KM survival probabilities (%)	96.3	97.5	1.2 (NR) (-7.8 to 10.1)	p=0.60
Number of deaths*	9	6		
Crude death (%)*	3.7	2.5		
Time to graft loss or death				
KM graft survival probabilities (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with graft loss*	[redacted]	[redacted]		
Time to tBPAR or death				
KM tBPAR free probabilities (%)	97.1	93.0	-4.1 (NR) (-8.0 to -0.3)	p=0.035
Number of patients with tBPAR reported	7	17		
Time to acute rejection				
KM tBPAR free probabilities (%)	96.3	89.3	-7.0 (NR) (-11.6 to -2.5)	p=0.003
Number of patients with acute rejection reported*	9	26		
Severity of rejection				
Number of moderate or severe treated tBPAR as measured by RAI scores (score:n)	3:3; 4-5:4; 6-7:0; 8-9:0	3:4; 4-5: 4; 6-7:7; 8-9:2	NR	NR
Time to death or loss graft loss or tBPAR				
KM composite efficacy survival probabilities (%)	93.3	90.3	-3.0 (NR) (-8.7 to 2.6)	p ≤0.001

Number of composite events*	16	23		
Change in eGFR from randomisation				
Change in renal function from baseline*	-2.23 (se=1.54)	-10.73 (se=1.54)	8.5 (2.12) (3.74 to 13.27)	p ≤0.001 (superiority and non-inferiority)
HCC outcomes				
Number of patients with HCC recurrence*	0	1	NR	NR
HCV outcomes				
Number of patients with HCV recurrence	28	19	NR	NR
Change in viral load from baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change in fibrosis (Ishak-Knodell score) from baseline			[redacted]	[redacted]

Notes: * +/- 2 months; † measured in terms of differences between survival probabilities; ‡ A vs. B or B vs. A.; § measured in terms of HR; # Measurement by MDRD4 formula was used if reported, otherwise any of the following methods of measurements: CKD-EPI (mL/min/1.73m2), Nankivell (mL/min/1.73m2), Cockcroft-Gault (mL/min), Serum creatinine (µmol/L)

Abbreviations: CI, confidence interval; SE, standard error, SD, standard deviation; KM, Kaplan-Meier; HR, hazard ratio; NR, not reported; tBPAR, treated biopsy proven acute rejection; eGFR, estimated glomerular filtration rate; MDRD4, four-variable modification of diet in renal disease; RAI, Rejection Activity Index

Source: (de Simone *et al.*, 2012[7], Hexham *et al.*, 2011[39])

Table 10: Summary of efficacy results for outcomes at 24 months

	EVR+ Reduced TAC	TAC Control	Difference (SE) (95% CI)	p Value
Time to death				
KM survival probabilities (%)	94.8	95.6	0.8 (NR) (-3.7 to 5.2)	p=0.70
Number of deaths*	12	10		
Time to graft loss or death				
KM graft survival probabilities (%)	92.7	93.8	1.1 (NR) (-4.2 to 6.4)	p=0.64
Number of patients with graft loss*	17	14		
Time to tBPAR or death				
KM tBPAR free probabilities (%)	95.2	92.3	-2.9 (NR) (-7.9 to 2.2)	p=0.20
Number of patients with tBPAR reported	11	18		
Time to acute rejection (incidence of BPAR)				
KM tBPAR free probabilities (%)	93.9	86.7	-7.2 (NR) (-13.5 to -0.9)	p=0.01
Number of patients with acute rejection reported*	14	30		
Time to death or loss graft loss or tBPAR				
KM composite efficacy survival probabilities (%)	89.7	87.5	-2.2 (NR) (-8.8 to 4.4)	p=0.45
Number of composite events*	24	29		
Change in eGFR (MDRD4) from randomisation				
Change in renal function from baseline*	-7.9 (se=1.5)	-14.6 (se=1.5)	6.7 (2.1) (1.9 to11.4)	p ≤0.0001
Severity of rejection				
Number of moderate or severe treated tBPAR as measured by RAI scores (score:n)	0	10		
HCC outcomes				
Number of patients with HCC	5	4		

recurrence*				
HCV outcomes				
Number of patients with HCV recurrence	33	24		
Change in viral load from baseline	[redacted]	[redacted]	[redacted]	
Change in fibrosis (Ishak-Knodell score) from baseline	[redacted]	[redacted]	[redacted]	[redacted]

Notes: * +/- 2 months; † measured in terms of differences between survival probabilities; ‡ A vs. B or B vs. A.; § measured in terms of HR; # Measurement by MDRD4 formula was used if reported, otherwise any of the following methods of measurements: CKD-EPI (mL/min/1.73m2), Nankivell (mL/min/1.73m2), Cockcroft-Gault (mL/min), Serum creatinine (µmol/L)

Abbreviations: CI, confidence interval; SE, standard error; SD, standard deviation; KM, Kaplan-Meier; HR, hazard ratio; NR, not reported; BPAR, biopsy proven acute rejection; tBPAR, treated biopsy proven acute rejection; eGFR, estimated glomerular filtration rate; MDRD4, four-variable modification of diet in renal disease; RAI, Rejection Activity Index

Sources: (Saliba, 2013[8], Lopez *et al.*, 2013[42])

Subgroup baseline results:

Table 11: Kaplan-Meier incidence rates of primary composite efficacy failure (time to treated BPAR, graft loss or death) by treatment; Subgroup analysis (ITT population – 12 month analysis)

Variable	Subgroup	EVR + Reduced TAC (N=245) n (KM %)	TAC Control (N=243) n (KM %)	Diff Risk % (95% CI)
Age group	< 60 years	[redacted]	[redacted]	[redacted]
	≥ 60 years	[redacted]	[redacted]	[redacted]
Gender	Female	[redacted]	[redacted]	[redacted]
	Male	[redacted]	[redacted]	[redacted]
Race	Caucasian	[redacted]	[redacted]	[redacted]
	Black	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]
	All others	[redacted]	[redacted]	[redacted]
Region	North America	[redacted]	[redacted]	[redacted]
	Europe	[redacted]	[redacted]	[redacted]
	Rest of the world	[redacted]	[redacted]	[redacted]
eGFR (MDRD) (mL/min/1.73m2)	< 30	[redacted]	[redacted]	[redacted]
	30 – < 55	[redacted]	[redacted]	[redacted]
	55 – < 70	[redacted]	[redacted]	[redacted]
	70 – < 90	[redacted]	[redacted]	[redacted]
	≥ 90	[redacted]	[redacted]	[redacted]

Source: (de Simone *et al.*, 2012[7], Hexham *et al.*, 2011[39])

Table 12: Incidence rates of primary composite efficacy failure (time to treated BPAR, graft loss or death) by treatment; Subgroup analysis (ITT population – 12 month analysis)

Variable	Subgroup	EVR + Reduced TAC (N=245) n (%)	TAC Control (N=243)	Diff Risk % (95% CI)
eGFR (MDRD) at randomisation (mL/min/1.73m^2)	70 - < 90	[redacted]	[redacted]	[redacted]
	≥ 90	[redacted]	[redacted]	[redacted]
HCV status	Negative	[redacted]	[redacted]	[redacted]
	Positive	[redacted]	[redacted]	
MELD score	≤ 14	[redacted]	[redacted]	[redacted]
	15 – 19	[redacted]	[redacted]	
	20 – 24	[redacted]	[redacted]	

	25 – 29	[redacted]	[redacted]	
	≥ 30	[redacted]	[redacted]	
End-stage disease leading to transplantation *	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	
	4	[redacted]	[redacted]	
	5	[redacted]	[redacted]	

Source: (de Simone *et al.*, 2012[7], Hexham *et al.*, 2011[39])*End stage diseases: (1) Alcoholic cirrhosis, Cryptogenic cirrhosis, (2) Hepatitis B, Hepatitis C, Other viral hepatitis, (3) Primary biliary cirrhosis, Sclerosing cholangitis, Autoimmune liver hepatitis, (4) Hepatocellular carcinoma, (5) Biliary atresia, Metabolic disease, Acute hepatic failure, Other. Abbreviations: NR, not reported

Table 13: Change of eGFR (MDRD4) (mL/min/1.73m2) to Month 12 (ITT population – 24 month analysis)

Variable	**Subgroup**	**EVR + Reduced TAC (N=245) n, mean (SD)**	**TAC Control (N = 243) n, mean (SD)**
Age group	<60 years	[redacted]	[redacted]
	≥ 60 years	[redacted]	[redacted]
Gender	Female	[redacted]	[redacted]
	Male	[redacted]	[redacted]
Race	Caucasian	[redacted]	[redacted]
	Black	[redacted]	[redacted]
	Asian	[redacted]	[redacted]
	All others	[redacted]	[redacted]
Region	North America	[redacted]	[redacted]
	Europe	[redacted]	[redacted]
	Rest of the World	[redacted]	[redacted]
HCV status	Negative	[redacted]	[redacted]
	Positive	[redacted]	[redacted]
eGFR (MDRD4) strata (mL/min/1.73m2)	< 30	[redacted]	[redacted]
	30 – <55	[redacted]	[redacted]
	55 – <70	[redacted]	[redacted]
	70 – <90	[redacted]	[redacted]
	≥ 90	[redacted]	[redacted]
eGFR (MDRD4) ranges at randomisation (mL/min/1.73m2)	< 30	[redacted]	[redacted]
	30 – <45	[redacted]	[redacted]
	45 – <60	[redacted]	[redacted]
	≥ 60	[redacted]	[redacted]

Source: (Saliba, 2013[8], Lopez *et al.*, 2013[42])

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable. Please see section 6.6.2.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

A meta-analysis was not undertaken as there was only one RCT of interest.

6.7 *Indirect and mixed treatment comparisons*

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

The ISPOR task force for Network Meta-analysis (NMA) recognised that the terms indirect treatment comparison (ITC), mixed treatment comparison (MTC), and NMA are sometimes used interchangeably and proposed specific definitions which are used in this section (Section 6.7). The term NMA refers to where the evidence base consists of more than two RCTs connecting more than two interventions. If the network consists of at least one closed loop then this is referred to as an MTC. Any analysis of an open-loop network is referred to as an ITC (Jansen *et al.*, 2011[58]).

In line with the decision problem outlined in Section A, a clinical systematic review of the literature was conducted for relevant RCT evidence to inform the NMA (see Section 6.2). As only one study was identified in the clinical review, an investigation into the feasibility of conducting a NMA was undertaken in order to assess the comparative efficacy and safety of everolimus (in combination with reduced dose tacrolimus) versus the two immunosuppressive therapies in the decision problem currently used for the prevention of allogeneic liver transplantation rejection.

The following steps were taken to identify and retrieve relevant clinical data on comparators:

1. Search based on NICE decision problem.
2. Study selection:
   - Defining the comparator set;
   - Feasibility assessment.

Network meta-analysis systematic literature review

A search strategy was developed in line with the NICE final scope for everolimus in combination with reduced dose tacrolimus as described in Section 6.2. To ensure that relevant RCTs were identified in line with both the anticipated licence of everolimus and the NICE scoping report, PICOS criteria (see Table 14) were developed based on the following assumptions that were derived from clinical expert opinion:

- Everolimus in combination with reduced dose tacrolimus would be used in the maintenance phase of treatment instead of everolimus in combination with a calcineurin inhibitor in line with the anticipated license (expected before end 2014).
- The inclusion of interventions with or without corticosteroids was added after clinical expert advice and in line with H2304, which is broader than the NICE scope.
- Induction therapies were excluded as the review is focused on maintenance immunosuppressive therapy following allogeneic liver transplantation and induction therapies are currently not licensed in liver transplantation in the United Kingdom.
- Exclusion of studies where CNIs were included but did not distinguish between tacrolimus and ciclosporin.

Study selection

The same study selection methodology as outlined in Section 6.2.1 was used to conduct the selection of studies relevant to the NMA. However, different PICOS criteria were developed to capture relevant studies for comparators beyond everolimus plus reduced dose tacrolimus. The inclusion and exclusion criteria are outlined in Table 14.

Table 14: Eligibility criteria for NMA study selection

	Inclusion	Exclusion
Population	• Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.
Intervention/ Comparator	• Any of the following interventions: 1. Everolimus in combination with reduced dose tacrolimus with or without a corticosteroid. 2. Any combination of MMF and a calcineurin inhibitor with or without a corticosteroid. 3. Any combination of azathioprine and a calcineurin inhibitor with or without a corticosteroid.	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.
Outcomes	• Patient survival. • Graft survival. • Time to acute rejection. • Renal function. • Time to end-stage renal disease. • Time to recurrence of hepatocellular carcinoma. • Adverse effects of treatment. • Health Related Quality of Life (HRQL).	• Studies that do not focus on rejection of the liver as an outcome (efficacy), or safety data related to the intervention(s) of interest, or HRQL. • Studies with only cost and no clinical outcomes.
Study design	• Eligible study types were RCTs of any duration, including cross-over RCTs if data were presented at cross-over. Studies published as abstracts or conference presentations were eligible for the primary analysis of clinical effectiveness if adequate data are provided.	• Non-RCT study designs or articles reporting results of RCTs published elsewhere, e.g. reviews, meta-analyses/pooled analyses, editorials, notes, comments or letters.
Language restrictions	• All languages.	• None.

A total of 8,416 titles and abstracts were found. After the title and abstract screen, 478 full-text records were retrieved. At full-text review stage, it was observed that many studies compared against tacrolimus monotherapy (with or without corticosteroids) and it was decided that this comparator could potentially provide useful links in the NMA.

Comparator synthesis set

The value of providing a further iteration of the search strategy to extend for the ciclosporin monotherapy was considered in line with recommendations provided for this in the literature for searching for evidence to inform the networks (Hawkins *et al.*, 2009[59]). However, a further search was not undertaken following published evidence and consultation with a clinical expert. Tacrolimus is the most commonly used immunosuppressant after liver transplantation as it is associated with fewer episodes of rejection when compared to ciclosporin (de Mare-Bredemeijer *et al.*, 2012[19]). The clinical expert advised that ciclosporin was an older treatment with changes in clinical practice (approximately 30 years) which would make the comparison inappropriate as it is rarely used in the maintenance phase as a monotherapy. This provided a refined comparator set defined as to include any study that included two or more of the following comparators within the study (see Table 15):

1. Everolimus plus reduced dose tacrolimus with or without a corticosteroid.
2. Any combination of MMF and a calcineurin inhibitor (reduced/standard ciclosporin or reduced/standard dose tacrolimus monotherapy) with or without a corticosteroid.
3. Any combination of azathioprine and a calcineurin inhibitor (reduced/standard dose ciclosporin or reduced/standard dose tacrolimus monotherapy) with or without a corticosteroid.
4. Tacrolimus monotherapy with or without corticosteroid.

After full-text review, a set of 61 records were selected. These 61 records reported the results of 22 RCTs. A study flow diagram for the NMA systematic literature review is presented in Figure 6.

Following an assessment of the comparators in the 22 RCTs, it was identified that the following comparator arms were found to enable a network of studies:

- Everolimus plus reduced dose tacrolimus (EVR + reduced TAC);
- Mycophenolate mofetil plus standard dose tacrolimus (MMF + standard TAC);
- Mycophenolate mofetil plus reduced dose tacrolimus (MMF + reduced TAC);
- Mycophenolate mofetil plus standard dose ciclosporin (MMF + CIC);
- Azathioprine plus standard dose tacrolimus (AZA + standard TAC);
- Azathioprine plus standard dose ciclosporin (AZA + CIC);
- Standard dose tacrolimus (Standard TAC).

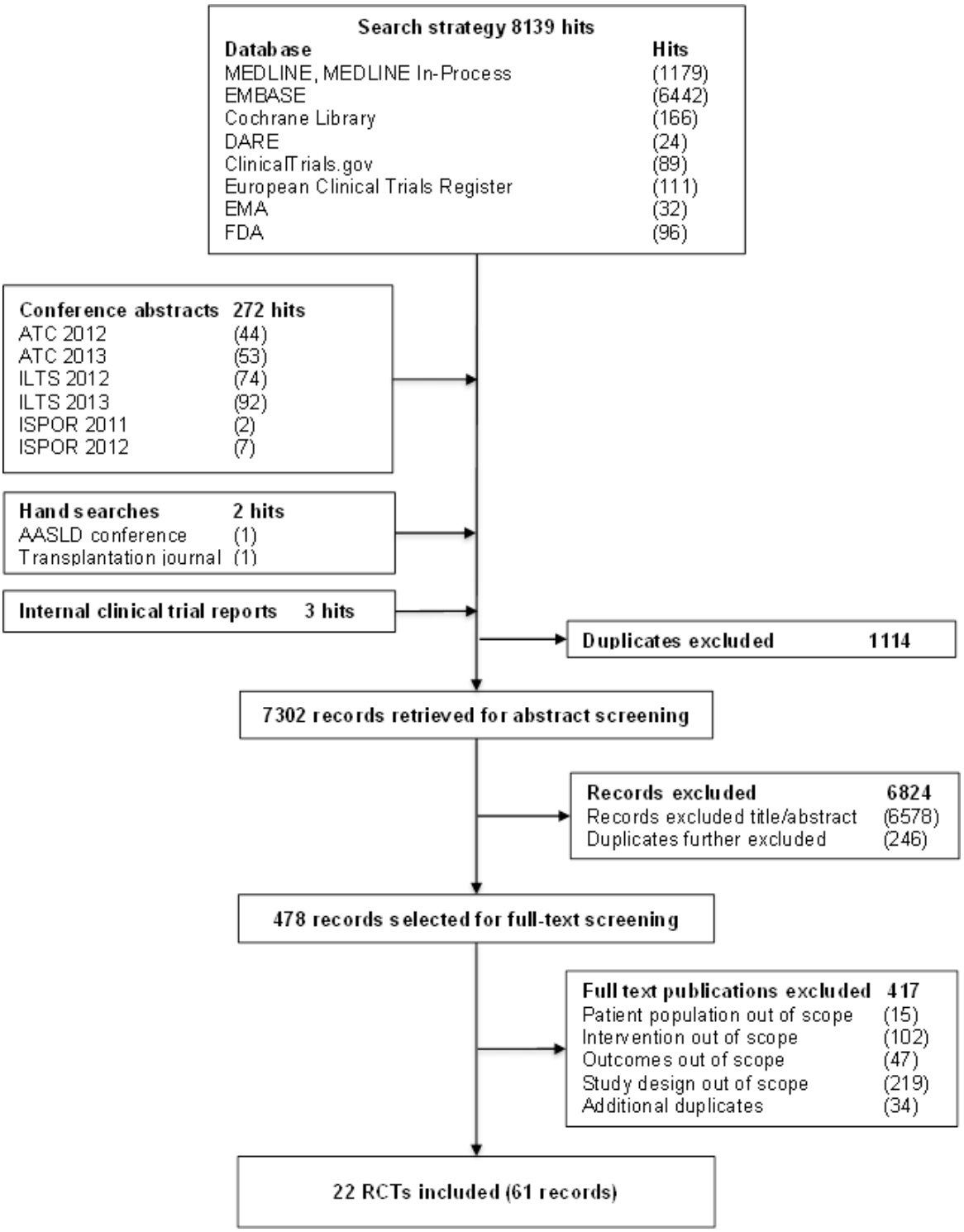
Where the tacrolimus dose was not stated as 'reduced' dosage (<7ng/ml immediately post transplantation) in the study, it was assumed that standard tacrolimus dosing (≥7ng/ml immediately post transplantation) was administered. Studies were excluded where CNIs were grouped into one category and therefore it was not possible to distinguish between tacrolimus and ciclosporin. Two studies were identified (Cicinnati *et al.*, 2007[60], Pageaux *et al.*, 2006[61]) as containing a grouped CNI.

Table 15: Refined eligibility for NMA study selection

	Inclusion	**Exclusion**
Population	• Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.
Intervention/ Comparator	At least two of the interventions in the comparator set which includes: 1. Everolimus in combination with reduced dose tacrolimus with or without a corticosteroid. 2. Any combination of MMF and a calcineurin inhibitor (reduced/standard dose ciclosporin, reduced/standard dose tacrolimus) with or without a corticosteroid. 3. Any combination of azathioprine and a calcineurin inhibitor (reduced/standard dose ciclosporin, reduced/standard dose tacrolimus monotherapy) with or without a corticosteroid.	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.

	4. Tacrolimus monotherapy with or without a corticosteroid.	
Outcomes	• Patient survival. • Graft survival. • Time to acute rejection. • Renal function. • Time to end-stage renal disease. • Time to recurrence of hepatocellular carcinoma. • Adverse effects of treatment. • Health Related Quality of Life (HRQL).	• Studies that do not focus rejection of the liver as an outcome (efficacy), or safety data related to the intervention(s) of interest, or HRQL. • Studies with only cost and no clinical outcomes.
Study design	• Eligible study types were RCTs of any duration, including cross-over RCTs if data were presented at cross-over. Studies published as abstracts or conference presentations were eligible for the primary analysis of clinical effectiveness if adequate data are provided.	• Non-RCT study designs or articles reporting results of RCTs published elsewhere, e.g. reviews, meta-analyses/pooled analyses, editorials, notes, comments or letters.
Language restrictions	• All languages.	• None.

Figure 6: Clinical Study flow diagram for the NMA search



Critical appraisal of NMA studies

While it was unclear if randomisation or concealment of treatment allocation was appropriate in most studies, no studies were excluded due to risk of bias. A summary of the critical appraisal can be found in Table 16.

Table 16: Critical appraisal of studies included in NMA

Author and year	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
(de Simone *et al.*, 2012[7])	Yes	Yes	Yes	No	Yes	No	Yes
(Garcia-Gonzalez *et al.*, 2005[62], Serrano *et al.*, 2002[63])	Unclear	Unclear	No	No	No	No	Yes
(Neuberger *et al.*, 2007[64], Neuberger *et al.*, 2009[65])	Unclear	Unclear	Yes	No	Yes	No	Yes
(Klintmalm *et al.*, 2011[66], Klintmalm *et al.*, 2007[67], Sher *et al.*, 2012[68])	Unclear	Unclear	Unclear	No	Unclear	No	Yes
(Boillot *et al.*, 2001[69], Samuel *et al.*, 1998[70])	Yes	Unclear	Yes	Unclear	No	No	Yes
(Fisher *et al.*, 1998[71], Fisher *et al.*, 2004[72])	Unclear	Unclear	Yes	No	Unclear	No	Yes
(Jain *et al.*, 2002[73], Jain *et al.*, 2001[74], Jain *et al.*, 2001[75], Jain *et al.*, 1998[76])	Yes	Yes	Yes	No	Unclear	No	Yes
(Junge *et al.*, 2005[77])	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear
(Wiesner *et al.*, 2001[78])	Unclear	Unclear	Yes	Unclear	No	No	Yes
(Nashan *et al.*, 2009[79])	Unclear	Unclear	Unclear	No	No	No	Yes
(Greig *et al.*, 2003[80])	Unclear	Unclear	Yes	No	Unclear	No	Yes
(Marin Gomez *et al.*, 2011[81])	Unclear	Unclear	Yes	No	Unclear	No	Yes

(Neuhaus *et al.*, 1997[82])	Unclear	Unclear	Yes	No	Unclear	No	Unclear
(Boudjema *et al.*, 2011[83], ClinicalTrials.gov, 2005[84])	Yes	Unclear	Unclear	No	No	Yes	Yes
(Takada *et al.*, 2013[85], ClinicalTrials.gov, 2001[86])	Unclear	Unclear	Yes	No	No	No	Yes
(Dmitrewski *et al.*, 1994[87])	Unclear	Unclear	Yes	Unclear	No	Unclear	No
(Porayko *et al.*, 1994[88])	Unclear	Unclear	Yes	No	No	No	Yes
(Therapondos *et al.*, 2002[89])	Unclear	Unclear	Yes	Unclear	No	No	Yes
(Salizzoni *et al.*, 2001[90])	Yes	Unclear	Unclear	No	No	No	Yes
(Manousou *et al.*, 2009[91])	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes
(Samonakis *et al.*, 2006[92])	Yes	Unclear	Yes	Unclear	No	No	Yes
(McDiarmid *et al.*, 1993[93])	Unclear	Unclear	Unclear	No	Unclear	No	Unclear

Feasibility assessment

After final study selection, sixteen clinical endpoints were extracted and were considered in the feasibility analysis. These endpoints are described in Table 17 below.

Table 17: Description of the 16 endpoints considered for the NMA

Endpoints	Definitions
Efficacy	
Survival at 12 months	• The event is defined as death from any causes. • The Kaplan-Meier method should be used to calculate the event free probabilities.
Survival at 24 months	
Graft survival at 12 months	• The event is defined as death from any causes or graft loss. • The Kaplan-Meier method should be used to calculate the event free probabilities.
Graft survival at 24 months	
Acute rejection at 3 months	• The event is defined as Biopsy Proven Acute Rejection (BPAR). • The Kaplan-Meir method should be used to calculate the event free probabilities.
Acute rejection at 6 months	
Acute rejection at 12 months	
Acute rejection at 24 months	
Renal function at 12 months	• The renal function could be measured by the estimated Glomerular Filtration Rate (eGFR) using any formula, e.g. MDRD4, or by the estimated Creatinine Clearance Rate (eCCR) using the Cockcroft–Gault formula. • For any measurement tool, Change from Baseline (CFB) should be used.
Renal function at 24 months	
Safety	
Withdrawals due to Adverse Events (AEs)	• Number of withdrawals due to AEs.
Hypertension	• Number with hypertension.
Diabetes	• Number of general diabetes or new-onset or de novo diabetes or new-onset and worsening of pre-existing diabetes.
Infections	• Number of any infections. • If multiple kinds of infections are reported, the highest number was extracted.
Hepato-Cellular Carcinoma (HCC)	• Number of recurrent HCC.
Hepatitis C Virus (HCV)	• Number of new-onset or recurrent HCV.

After data from the systematic literature review had been extracted and critically appraised, a feasibility assessment for the NMA was conducted. This assessment consisted of two research questions;

1. Is there one network of interlinked RCTs to allow the comparisons of interest?

2. Are there any differences in study and patient characteristics across comparisons that affect the treatment effects of the interventions of interest relative to a reference treatment?

Results of the feasibility assessment

***Question 1:* Is there one network of interlinked RCTs to allow the comparisons of interest?**

There was heterogeneity and variation between studies that provided challenges to building a feasible network and assumptions were defined in discussion with the manufacturer's clinical team. The main variation across studies was with respect to:

- Lack of reporting in studies of the characteristics that could be potential treatment effect modifiers to enable assessment to be made across the set of studies.
- Variation in the definition of the tacrolimus and ciclosporin arms with respect to dosage across the studies (definitions between standard dose and reduced dose).
- Variations in the definitions for the outcomes included across studies, for renal function, diabetes and infections.
- Variation in the duration of use of corticosteroid therapy in combination with the interventions of interest.

The evidence identified in the SLR was sufficient to draw feasible networks for thirteen out of the sixteen outcomes in Table 17. It was not deemed feasible to create a network for HCC data as only two RCTs reported data and events were very rare (≤ 3 events in (de Simone *et al.*, 2012[7], Boudjema *et al.*, 2011[83])), which it was anticipated would lead to convergence issues when analyses were run. For tBPAR KM probabilities at 24 months, only 3 studies reported data (de Simone *et al.*, 2012[7], Jain *et al.*, 2001[75], Dmitrewski *et al.*, 1994[87]) and only a reduced set of comparators (MMF + Standard TAC and AZA + CIC) could be conducted, which would not contribute to the decision problem. As acute rejections usually occur within 3 months post-transplantation (Wiesner *et al.*, 1998[94]), it was assumed that an NMA of tBPAR KM probabilities at 3, 6, and 12 months would be more informative. Finally, mean eGFR at 24 months was reported in H2304 only and therefore no analysis is possible for this outcome measure.

Studies reported adverse events at a variety of time points and the feasibility of running an analysis of studies reporting adverse event data at any time point within the same model was assessed. However, the assumption of a

constant hazard for the AEs did not seem valid and therefore it was concluded that safety outcomes should be analysed at 12 months.

Furthermore, a key outcome measure of interest, renal function, was measured by eGFR or by estimated creatinine clearance rate (eCRR). As both measures are useful to monitor renal function, the clinical experts consulted suggested to analyse the data together using the standardised mean difference between treatment arms, with a scenario analysis using only eGFR measures.

***Question 2:* Are there any differences in study and patient characteristics across comparisons that affect the treatment effects of the interventions of interest relative to a reference treatment (everolimus plus reduced dose tacrolimus)?**

The potential treatment effect modifiers were identified in discussion with a clinical expert during the feasibility assessment stage. The feasibility assessment identified some discrepancies between H2304 and the other trials (see Table 18 for the potential treatment modifiers); more H2304 patients had diabetes and hypertension at baseline than in the other studies (although only 8/22 and 5/22 studies reported information on respectively diabetes and hypertension at baseline) and the standard TAC arm of H2304 presented better overall survival, graft survival and free from tBPAR probabilities at 12 and 24 months than the standard TAC arms of the other studies. The feasibility assessment did not identify any reason that could explain the differences between results. As H2304 is the only study including everolimus in combination with reduced dose tacrolimus, it was not feasible to conduct subgroup analyses excluding this study. It was assumed that the H2304 study is comparable with the rest of the evidence and that the efficacy differences observed between the H2304 standard TAC arm and the other standard TAC arms are only due to chance.

The assessment also identified that there may be differences in the labelling of the treatment comparators, which can potentially influence the NMA results. At present, the immunosuppressant combinations are various. A CNI is recommended; however, no guidelines are available by NICE on the choice between ciclosporin and tacrolimus and at what dosages or target doses. In addition, a corticosteroid is often used but no guideline specifies whether and when it should be withdrawn.

Table 18: Potential treatment modifiers identified

Potential treatment effect	Potential treatment modifiers
Efficacy and safety	• Exclusion of concomitant steroids in the first 3 months (BPAR KM probabilities) • HCC • Cold ischaemic time (organ quality) • Donor age (organ quality)
Safety results	• Diabetes and hypertension

BPAR, biopsy proven acute rejection; KM, Kaplan Meier; HCC, hepatocellular carcinoma

6.7.2 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table 19 gives a summary of the trials used to conduct the NMA and indicates the comparisons made within each RCT. Please see Appendix 14 for the network diagrams used for each outcome assessed.

Table 19: Summary of the trials used to conduct the NMA

No. Trials	References of trials	EVR + reduced TAC	Standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC
1	(de Simone *et al.*, 2012[7])	√	√					
1	(Garcia-Gonzalez *et al.*, 2005[62], Serrano *et al.*, 2002[63])		√					
1	(Neuberger *et al.*, 2007[64], Neuberger *et al.*, 2009[65])		√					√
1	(Klintmalm *et al.*, 2011[66], Klintmalm *et al.*, 2007[67], Sher *et al.*, 2012[68])		√				√	
1	(Boillot *et al.*, 2001[69], Samuel *et al.*, 1998[70])		√		√			
1	(Fisher *et al.*, 1998[71], Fisher *et al.*, 2004[72])					√	√	
1	(Jain *et al.*, 2002[73], Jain *et al.*, 2001[74], Jain *et al.*, 2001[75], Jain *et al.*, 1998[76])		√				√	
1	(Junge *et al.*,		√				√	

	2005[77])							
1	(Wiesner *et al.*, 2001[78])			√		√		
1	(Nashan *et al.*, 2009[79])						√	√
1	(Greig *et al.*, 2003[80])			√	√			
1	(Marin Gomez *et al.*, 2011[81])		√	√				
1	(Neuhaus *et al.*, 1997[82])		√		√			
1	(Boudjema *et al.*, 2011[83], ClinicalTrials.gov, 2005[84])		√					√
1	(Takada *et al.*, 2013[85], ClinicalTrials.gov, 2001[86])		√				√	
1	(Dmitrewski *et al.*, 1994[87])		√	√				
1	(Porayko *et al.*, 1994[88])		√	√				
1	(Therapondos *et al.*, 2002[89])			√	√			
1	(Salizzoni *et al.*, 2001[90])		√		√			
1	(Manousou *et al.*, 2009[91])		√		√			
1	(Samonakis *et al.*, 2006[92])		√		√			
1	(McDiarmid *et al.*, 1993[93])		√	√				

Note: Each arm is labelled as per the trial definition. Abbreviation: AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus; CIC, ciclosporin; EVR, everolimus.

6.7.3 For the selected trials, provide a summary of the data used in the analysis.

The full description of the study data used in the analyses are presented in Appendices 2 and 16.

Study design

All studies were RCTs as expected by the defined systematic literature review inclusion criteria; additionally all studies were open label or the blinding was not reported with the exception of (Wiesner *et al.*, 2001[78]), which was a double blinded trial. Trial duration ranged from 3 months to 60 months with the duration of 5 trials not reported. The studies identified included 6 studies lasting 24 months or longer. The critical appraisal checklist used to assess the relevant studies for the NMA indicated that (Saliba *et al.*, 2014[3], de Simone *et al.*, 2012[7], Saliba, 2013[8]) had the lowest risk of bias and highest validity on the basis of reporting.

Patient characteristics

ITT numbers were present for all studies with the results ranging from 14 to 287, only the (de Simone *et al.*, 2012[7], Saliba, 2013[8]) analysed groups of patients larger in size than 200. Mean age was similar across all studies and ranged from 43.5 to 55.5 years, with a mean weighted age of 51.3 years. The weighted average proportion of males included in each study was 65 percent and this ranged from 13.3 to 80.2 percent between studies. The donor age was reported in 11 of the 22 studies (de Simone *et al.*, 2012[7], Boillot *et al.*, 2001[69], Fisher *et al.*, 2004[72], Jain *et al.*, 2001[75], Wiesner *et al.*, 2001[78], Greig *et al.*, 2003[80], Boudjema *et al.*, 2011[83], Therapondos *et al.*, 2002[89], Salizzoni *et al.*, 2001[90], Manousou *et al.*, 2009[91], Samonakis *et al.*, 2006[92]). Mean donor age ranged from 33 to 52 years between studies, with a weighted average of 42.7 years. All studies are expected to be comparable with respect to this characteristic.

HCV prevalence at baseline varied between studies with a mean weighted average of 36.4 percent and a range of 7 to 100 percent respectively. Three studies (Sher *et al.*, 2012[68], Takada *et al.*, 2013[85], Manousou *et al.*, 2009[91]) only included HCV positive patients.

The weighted average of eGFR in patients at baseline was 80.5mL/minute/1.73m^2 and ranged from 75 to 90 mL/minute/1.73m^2. This patient characteristic was reported in 3 of the 22 relevant studies (de Simone *et al.*, 2012[7], Fisher *et al.*, 2004[72], Therapondos *et al.*, 2002[89]). The weighted average of eCRR in patients at baseline was 99.2mL/minute and ranged from 69.6 to 104.31 mL/minute. This patient characteristic was only reported in 3 of the 22 relevant studies (Neuberger *et al.*, 2009[65], Nashan *et al.*, 2009[79], Boudjema *et al.*, 2011[83]).

Diabetes was reported in 8 of the 22 studies of which the weighted mean with diabetes present across the studies was 23.7 percent of patients (de Simone *et al.*, 2012[7], Fisher *et al.*, 2004[72], Greig *et al.*, 2003[80], Marin Gomez *et al.*, 2011[81], Boudjema *et al.*, 2011[83], Therapondos *et al.*, 2002[89], Manousou *et al.*, 2009[91], Samonakis *et al.*, 2006[92]). Two studies (Neuberger *et al.*, 2009[65], Boillot *et al.*, 2001[69]) did not report the type of diabetes, whereas the other studies reported new onset/*de novo* diabetes. Reported values ranged from 0 to 41.6 percent between studies, with the highest values reported in the H2304 trial.

Hypertension was reported in 5 of the 22 studies (de Simone *et al.*, 2012[7], Fisher *et al.*, 2004[72], Greig *et al.*, 2003[80], Marin Gomez *et al.*, 2011[81], Therapondos *et al.*, 2002[89]). The weighted average of hypertension at baseline was 25.1 percent with a range of 3.9 to 34.7 percent reported in the five studies.

The proportion of patients with HCC at baseline appears similar with respect to this patient characteristic, with a weighted average of 20.2 percent and a range of 6 to 40.7 percent. HCC was reported in 9 of the 22 studies (de Simone *et al.*, 2012[7], Garcia-Gonzalez *et al.*, 2005[62], Neuberger *et al.*, 2009[65], Boillot *et al.*, 2001[69], Nashan *et al.*, 2009[79], Boudjema *et al.*, 2011[83], Salizzoni *et al.*, 2001[90], Manousou *et al.*, 2009[91], Samonakis *et al.*, 2006[92]).

There was some variation in the cold ischaemic time between studies with a weighted average of 9.0 hours and a range from 7.3 to 11.6 hours. Cold ischaemic time was reported in 10 of the 22 studies (de Simone *et al.*, 2012[7], Boillot *et al.*, 2001[69], Fisher *et al.*, 2004[72], Wiesner *et al.*, 2001[78], Greig *et al.*, 2003[80], Boudjema *et al.*, 2011[83], Therapondos *et al.*, 2002[89], Salizzoni *et al.*, 2001[90], Manousou *et al.*, 2009[91], Samonakis *et al.*, 2006[92]). The mean cold ischaemic time stayed below 13 hours in all studies.

Outcomes

Twelve studies (de Simone *et al.*, 2012[7], Garcia-Gonzalez *et al.*, 2005[62], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2007[67], Boillot *et al.*, 2001[69], Fisher *et al.*, 2004[72], Jain *et al.*, 2001[75], Wiesner *et al.*, 2001[78], Greig *et al.*, 2003[80], Neuhaus *et al.*, 1997[82], Boudjema *et al.*, 2011[83], Takada *et al.*, 2013[85]) reported data at 12 months, and 8 studies (Saliba, 2013[8], Garcia-Gonzalez *et al.*, 2005[62], Klintmalm *et al.*, 2011[66], Fisher *et al.*, 2004[72], Jain *et al.*, 2001[75], Junge *et al.*, 2005[77], Takada *et al.*, 2013[85], Samonakis *et al.*, 2006[92]) reported data at 24 months. At 12 months, the overall survival is lower in the TAC arm of (Neuhaus *et al.*, 1997[82]) (79.4%) and higher in the TAC arm of (de Simone *et al.*, 2012[7]) (97.5%) compared to 81.3 to 95.9 percent in the 8 other TAC arms. At 24 months, the overall survival in the 8 TAC arms varied between 76.9 and 95.9 percent. No obvious outlier data were identified.

Graft survival KM probabilities were reported in 11 studies (de Simone *et al.*, 2012[7], Garcia-Gonzalez *et al.*, 2005[62], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2007[67], Boillot *et al.*, 2001[69], Fisher *et al.*, 2004[72], Jain *et al.*, 2001[75], Wiesner *et al.*, 2001[78], Greig *et al.*, 2003[80], Neuhaus *et al.*, 1997[82], Boudjema *et al.*, 2011[83]) at 12 months, and 6 studies (Saliba, 2013[8], Garcia-Gonzalez *et al.*, 2005[62], Klintmalm *et al.*, 2011[66], Fisher *et al.*, 2004[72], Jain *et al.*, 2001[75], Samonakis *et al.*, 2006[92]) at 24 months. At 12 months, graft survival is reported as higher in the TAC arm of (de Simone *et al.*, 2012[7]) (97%) compared to 76.5 to 94.3 percent reported in the 8 other TAC arms. No reason was identified that could explain the variation observed in the TAC arms. At 24 months, graft survival was observed to be lower in the TAC arm of (Samonakis *et al.*, 2006[92]) (70.4%) and higher in the TAC arm of (Saliba, 2013[8]) (93.8%) compared to 73.5 to 92.5 percent in the TAC arms of the 4 other studies. No reason was identified that could explain these differences.

Time to BPAR KM probabilities were present in:

- 11 studies at 3 months (Hexham *et al.*, 2011[39], Garcia-Gonzalez *et al.*, 2005[62], Klintmalm *et al.*, 2007[67], Boillot *et al.*, 2001[69], Jain *et al.*, 2001[75], Wiesner *et al.*, 2001[78], Nashan *et al.*, 2009[79], Greig *et al.*, 2003[80], Boudjema *et al.*, 2011[83], Salizzoni *et al.*, 2001[90], Samonakis *et al.*, 2006[92])
- 7 studies at 6 months (Hexham *et al.*, 2011[39], Neuberger *et al.*, 2009[65], Fisher *et al.*, [72], Wiesner *et al.*, 2001[78], Nashan *et al.*, 2009[79], Greig *et al.*, 2003[80], Boudjema *et al.*, 2011[83])
- 9 studies at 12 months (Hexham *et al.*, 2011[39], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2011[66], Boillot *et al.*, 2001[69], Jain *et al.*, 2001[75], Greig *et al.*, 2003[80], Neuhaus *et al.*, 1997[82], Boudjema *et al.*, 2011[83], Porayko *et al.*, 1994[88])
- 3 studies at 24 months (Lopez *et al.*, 2013[42], Jain *et al.*, 2001[74], Dmitrewski *et al.*, 1994[87]).

At 3 months, high probabilities of free from tBPAR were reported in the TAC arm of H2304 (Hexham *et al.*, 2011[39]), and (Klintmalm *et al.*, 2011[66]) compared to the 6 other TAC arms (between 59.3 and 70%). The lowest probability of free from tBPAR at 3 months in the TAC arms was reported in (Garcia-Gonzalez *et al.*, 2005[62]); 59.3%). An explanation for these differences could not be identified from the study design and patient characteristics of the studies.

At 6 months, the probabilities of free from tBPAR in the 3 TAC arms varied: 91.1% in H2304 (Hexham *et al.*, 2011[39]), 73.5% in (Neuberger *et al.*, 2009[65]) and 57.5% in (Boudjema *et al.*, 2011[83]). At 12 months, the probabilities of free from tBPAR reported in the 8 TAC arms were again diversified from 50% in (Dmitrewski *et al.*, 1994[87]) (not used in the network) to 88.4% in H2304 (Hexham *et al.*, 2011[39]). The evidence at 24 months is very limited.

Renal function[1] data were present in 5 studies (Hexham *et al.*, 2011[39], Neuberger *et al.*, 2009[65], Boudjema *et al.*, 2011[83], Porayko *et al.*, 1994[88], McDiarmid *et al.*, 1993[93]) at 12 months and 1 study at 24 months (de Simone *et al.*, 2012[7]). Mean change from baseline (CFB) was reported in 2 studies at 12 months (Hexham *et al.*, 2011[39], Neuberger *et al.*, 2009[65]) and in 1 study at 24 months (Saliba, 2013[8]). The decrease in the eGFR mean values at 12 months compared to the baseline in the TAC arms were higher for (Porayko *et al.*, 1994[88]); -38.0) and for (McDiarmid *et al.*, 1993[93]); -46.0) than for (de Simone *et al.*, 2012[7]); -10.73). Very few patient characteristics are reported in

1 Renal function is measured using eGFR or eCRR. In order to combine the results of the eGFR and eCRR measures in one analysis, effect size (ES) analyses were conducted. The difference between the least square mean at follow-up (LS mean at FU) or the CFB for the baseline comparator versus the active treatment was divided by the pooled standard deviation (SD) so that both measurements were standardised and were combined in one analysis.

(Porayko *et al.*, 1994[88]) and (McDiarmid *et al.*, 1993[93]) – only mean eGFR at baseline and mean age; therefore it is difficult to assess whether the high decrease of the mean eGFR CFB in the TAC arms of these 2 studies is due to some potential treatment effect modifier or due to chance. The eCRR in the 2 TAC arms were more homogeneous: -24.89 for (Neuberger *et al.*, 2009[65]) and -21.0 for (Boudjema *et al.*, 2011[83]).

Adverse events

The number of withdrawals due to adverse events was reported in 6 studies (de Simone *et al.*, 2012[7], Neuberger *et al.*, 2009[65], Boillot *et al.*, 2001[69], Nashan *et al.*, 2009[79], Greig *et al.*, 2003[80], Porayko *et al.*, 1994[88]). The withdrawals due to adverse events in the 4 TAC arms were varied, from 7 percent in (Boillot *et al.*, 2001[69]) to 30 percent in (Neuberger *et al.*, 2009[65]).

The number of patients with hypertension was reported in 6 studies (de Simone *et al.*, 2012[7], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2007[67], Nashan *et al.*, 2009[79], Boudjema *et al.*, 2011[83], Porayko *et al.*, 1994[88]). Hypertension was a frequent adverse event. In the TAC arms, the percentage of patients experiencing hypertension at 12 months varied from 15.8 percent in (de Simone *et al.*, 2012[7]) to 56.0 percent in (Boudjema *et al.*, 2011[83]).

The number of patients with diabetes was reported in 6 studies (de Simone *et al.*, 2012[7], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2007[67], Boillot *et al.*, 2001[69], Neuhaus *et al.*, 1997[82], Boudjema *et al.*, 2011[83]). The networks included all reported definitions of diabetes (diabetes, new onset diabetes and *de novo* diabetes). The percentage of patients experiencing diabetes at 12 months in the TAC arms was quite high in (Neuberger *et al.*, 2009[65]); 47.8% and in (Boudjema *et al.*, 2011[83]); 35.0% compared to the 4 other TAC arms (between 2.9 and 16.6 percent).

The number of patients with infection was reported in 9 studies (de Simone *et al.*, 2012[7], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2007[67], Boillot *et al.*, 2001[69], Wiesner *et al.*, 2001[78], Nashan *et al.*, 2009[79], Greig *et al.*, 2003[80], Neuhaus *et al.*, 1997[82], Boudjema *et al.*, 2011[83]). The network included all reported definitions of infection (overall infections, opportunistic infections, cytomegalovirus [CMV] infection plus extra-hepatic infections, bacterial infection and non-defined infections). The percentage of patients experiencing infection at 12 months in the TAC arms was quite high in (Neuhaus *et al.*, 1997[82]); 94.1% and in (Boillot *et al.*, 2001[69]); 82.0% compared to the 4 other TAC arms (between 22.0 and 52.0 percent).

The number of patients with HCV recurrence was reported in 6 studies (de Simone *et al.*, 2012[7], Garcia-Gonzalez *et al.*, 2005[62], Neuberger *et al.*, 2009[65], Klintmalm *et al.*, 2011[66], Nashan *et al.*, 2009[79], Takada *et al.*, 2013[85]). The percentage of patients experiencing HCV recurrence at 12 months in the TAC

arms was quite low in H2304 (7.9%) and in (Neuberger *et al.*, 2009[65]); 3.8%) compared to the 3 other TAC arms (between 34.1 and 59.4 percent).

A HCC recurrence network at 12 months was not feasible.

It was therefore possible to form a network for 13 of the 16 outcomes. It was not possible to form networks for HCC at 12 months, or renal function and BPAR at 24 months.

6.7.4 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

A NMA in the form of a MTC was performed for these outcomes:

- Overall survival at 12 months
- Graft survival at 12 months
- Time to BPAR 3 months
- Time to BPAR 12 months
- Withdrawals due to adverse events 12 months
- Hypertension 12 months
- Infection 12 months
- HCV recurrence 12 months.

A NMA in the form of an ITC was performed for these outcomes:

- Overall survival at 24 months
- Graft survival at 24 months
- Time to BPAR 6 months
- Renal function 12 months
- New onset diabetes 12 months.

Models

All models were based upon NICE Decision Support Unit (DSU) guidance (Dias *et al.*, 2011[95]). The parameters of the different models was estimated within a Bayesian framework using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS/OpenBUGS software package (Lunn *et al.*, 2000[96]). A first series of iterations from the WinBUGS/OpenBUGS sampler was discarded as 'burn-in' and the inferences were based on additional iterations. Coding is available in Section 10.14.3 in Appendix 14. An inconsistency model (Dias *et al.*, 2011[95]) was performed each time that a closed loop was present in the network (i.e. for overall survival [OS] at 12 months, tBPAR at 3 and 12 months, withdrawals due to AEs at 12 months, hypertension, infections, and HCV recurrence at 12 months). To assess for heterogeneity in the treatment effects for a particular

pair-wise comparison caused by treatment effect modifiers, both fixed effects and random effects model were assessed.

Likelihood and link functions were defined for the different types of outcome data in the available evidence base and can be seen in Table 20.

Table 20: Likelihood and link functions for different types of outcome data

	Likelihood	**Link function**
Normally distributed continuous data	$y_{jk} \sim normal(\theta_{jk}, \sigma_{jk}^2)$	Identity
Binary data	$r_{jk} \sim binomial(p_{jk}, n_{jk})$	$\text{logit}(p_{jk})$

A non-informative prior distribution was used for the model parameters to ensure observed results were not influenced by the prior distribution (a common criticism of the Bayesian approach). Using a flat prior ensures that any parameter value is 'equally' likely before seeing the data. This approach is consistent with NICE DSU guidance (Dias *et al.*, 2011[97]). Table 21 provides an overview of the prior distributions used in the analysis.

Table 21: Prior distributions for model parameters

Model parameters	**Prior distribution**
Nuisance parameters	$\mu_{jb} \sim normal(0, 10\,000)$
Treatment effect parameters	$d_{Ak} \sim normal(0, 10\,000)$
Heterogeneity parameters	$\sigma \sim uniform(0, 5)$

In order to identify the most appropriate model given the evidence base, goodness-of-fit was measured by the deviance information criterion (DIC). The model with the lowest DIC was assumed to provide the 'best' fit and was considered the base-case model with the data set used.

6.7.5 Please present the results of the analysis.

The NMA results (i.e. the results of the consistency model where direct and indirect evidence are assumed consistent for any 'closed loops' in the evidence network) are provided in the bottom left hand side of the relative results tables. The inconsistency model results, i.e. estimates for the comparisons where direct evidence is available, are presented in the upper

right hand side of the relative results tables. The inconsistency results are only presented when a closed loop was present in the network.

Only the results for the best fit models are presented in this section. In the circumstances where the results of the DIC statistic for the two models are similar (tBPAR 6 and 12 months, withdrawals due to AEs at 12 months), both analyses are presented (Table 22). Details of all model results can be provided upon request.

Table 22: Summary of model fit (DIC) scores

Outcome Measure	**Fixed Effects**	**Random Effects**	**Model presented***
Overall Survival 12 months	133.3	134.8	FE
Overall Survival 24 months	83.2	85.0	FE
Graft survival 12 months	127.8	129.6	FE
Graft survival 24 months	71.6	73.3	FE
tBPAR 3 months	138.3	139.9	FE/RE
tBPAR 6 months	79.9	79.5	RE/FE
tBPAR 12 months	119.7	119.3	RE/FE
Renal function (eGFR) 12 months	-0.8	0.3	FE/RE
Withdrawals due to AEs 12 months	68.6	68.0	RE/FE
Hypertension 12 months	75	76.9	FE
New onset diabetes 12 months	72.1	74.0	FE
Infections 12 months	117.0	119.1	FE
HCV recurrence 12 months	71.5	73.1	FE

*FE: Fixed effects model; RE: Random effects model; model presented first is the preference based on the DIC.

Overall survival at 12 and 24 months

At 12 months, EVR + reduced TAC is expected to be comparable to all other treatments in the comparator set (see Table 23).

Table 23: Overall Survival at 12 months (Odds Ratios, fixed effect model)

			Results of the inconsistency model						
	Intervention		Comparator						
			standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate			1.2		1.1	1.0	0.6
		95% CrI			0.8 2.0		0.7 1.9	0.5 1.8	0.2 1.9
		P(better)							
	AZA + CIC	estimate	0.3		4.9	1.1			
		95% CrI	0.1 1.2		1.1 37.1	0.7 1.8			
		P(better)	4%						
	AZA + standard TAC	estimate	1.2	4.1					
		95% CrI	0.8 2.0	1.1 21.3					
		P(better)	81%	98%					
	MMF + CIC	estimate	0.3	1.1	0.3		2.3		
		95% CrI	0.1 1.4	0.7 1.8	0.0 1.1		0.2 75.7		
		P(better)	7%	67%	3%				
	MMF + standard TAC	estimate	1.1	3.6	0.9	3.2			
		95% CrI	0.7 1.8	0.9 20.1	0.4 1.8	0.8 18.6			
		P(better)	64%	96%	37%	94%			
	MMF + reduced TAC	estimate	1.0	3.2	0.8	2.9	0.9		
		95% CrI	0.5 1.8	0.7 19.4	0.4 1.7	0.6 18.0	0.4 2.0		
		P(better)	46%	94%	27%	91%	38%		
	EVR + reduced TAC	estimate	0.6	2.2	0.5	1.9	0.6	0.7	
		95% CrI	0.2 1.9	0.4 15.5	0.2 1.7	0.3 14.4	0.2 1.9	0.2 2.3	
		P(better)	21%	80%	14%	76%	19%	26%	

At 24 months, EVR + reduced TAC is expected to be comparable to all other treatments. The inconsistency model was not performed as there was no closed loop in the network. The results of all scenario analyses are in line with the base case results. Table 24 summarises the results of the 24 month OS analysis.

Table 24: Overall Survival at 24 months (Odds Ratio, fixed effects model)

Intervention		**Comparator**			
		standard TAC	AZA + standard TAC	MMF + CIC	MMF + standard TAC
AZA + standard TAC	estimate	0.9			
	95% CrI	0.5 1.6			
	P(better)	33%			
MMF + CIC	estimate	1.2	1.3		
	95% CrI	0.1 12.2	0.1 15.1		
	P(better)	55%	59%		
MMF + standard TAC	estimate	1.1	1.3	1.0	
	95% CrI	0.7 1.7	0.6 2.7	0.1 9.8	
	P(better)	66%	72%	48%	
EVR + reduced TAC	estimate	0.8	1.0	0.7	0.8
	95% CrI	0.4 1.9	0.3 2.7	0.1 9.0	0.3 2.0
	P(better)	34%	47%	39%	29%

Graft Survival at 12 and 24 months

At 12 months, EVR + reduced TAC is expected to be comparable to all treatments in the comparator set (see Table 25). At 24 months, EVR + reduced TAC is expected to be comparable to all other treatments in the comparator set (see Table 26). The inconsistency model was not performed at 24 months as there was no closed loop in the network.

Table 25: Graft survival at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model						
			Comparator						
	Intervention		standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate			1.1		1.4	1.1	0.6
		95% CrI			0.7 1.7		0.9 2.2	0.6 2.3	0.2 1.5
		P(better)							
	AZA + CIC	estimate	0.3		6.4	1.0			
		95% CrI	0.1 1.0		1.5 48.2	0.6 1.6			
		P(better)	3%						
	AZA + standard TAC	estimate	1.2	3.6					
		95% CrI	0.7 1.8	1.2 13.6					
		P(better)	75%	99%					
	MMF + CIC	estimate	0.3	1.0	0.3		1.4		
		95% CrI	0.1 1.1	0.7 1.7	0.1 0.9		0.9 2.2		
		P(better)	4%	57%	2%				
	MMF + standard TAC	estimate	1.3	4.1	1.1	3.9			
		95% CrI	0.8 2.1	1.2 16.3	0.6 2.1	1.2 16.1			
		P(better)	88%	>99%	65%	99%			
	MMF + reduced TAC	estimate	1.1	3.5	1.0	3.4	0.9		
		95% CrI	0.6 2.3	0.9 16.3	0.4 2.2	0.8 16.1	0.4 2.0		
		P(better)	63%	97%	47%	96%	36%		
	EVR + reduced TAC	estimate	0.6	1.8	0.5	1.7	0.4	0.5	
		95% CrI	0.2 1.5	0.4 9.2	0.2 1.4	0.4 9.1	0.1 1.2	0.1 1.6	
		P(better)	12%	76%	9%	74%	6%	12%	

Table 26: Graft survival at 24 months (Odds Ratio, fixed effects model)

Intervention		Comparator			
		standard TAC	AZA + standard TAC	MMF + CIC	MMF + standard TAC
AZA + standard TAC	estimate	0.9			
	95% CrI	0.5 1.6			
	P(better)	35%			
MMF + CIC	estimate	1.3	1.5		
	95% CrI	0.2 8.3	0.2 10.2		
	P(better)	61%	65%		
MMF + standard TAC	estimate	1.2	1.4	1.0	
	95% CrI	0.8 1.9	0.7 2.9	0.2 5.8	
	P(better)	83%	81%	48%	
EVR + reduced TAC	estimate	0.8	0.9	0.6	0.7
	95% CrI	0.4 1.7	0.4 2.4	0.1 4.6	0.3 1.5
	P(better)	30%	44%	33%	18%

BPAR at 3, 6 and 12 months

At 3 months, EVR + reduced TAC is expected to be more efficacious than all comparators included in the analysis. The credible intervals for the comparisons versus EVR + reduced TAC are wide. Table 27 reports the results of the 3-month analysis using the fixed effects model.

Table 27: BPAR free at 3 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model						
	Intervention		**Comparator**						
			standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate			1.4		1.7	2.4	11.4
		95% CrI			1.0 1.9		1.1 2.6	1.3 4.5	3.0 83.7
		P(better)							
	AZA + CIC	estimate	0.9		1.6	1.4			
		95% CrI	0.4 1.8		0.8 3.3	0.9 2.0			
		P(better)	35%						
	AZA + standard TAC	estimate	1.4	1.6					
		95% CrI	1.0 1.9	0.8 3.3					
		P(better)	98%	91%					
	MMF + CIC	estimate	1.2	1.4	0.8				
		95% CrI	0.5 2.7	0.9 2.0	0.4 1.8				
		P(better)	65%	95%	34%				
	MMF + standard TAC	estimate	1.8	2.0	1.3	1.5		0.9	
		95% CrI	1.2 2.6	0.9 4.8	0.8 2.1	0.6 3.8		0.2 3.9	
		P(better)	>99%	95%	82%	80%			
	MMF + reduced TAC	estimate	2.2	2.6	1.6	1.9	1.3		
		95% CrI	1.3 4.0	1.0 6.8	0.8 3.1	0.7 5.3	0.6 2.5		
		P(better)	>99%	97%	92%	89%	75%		
	EVR + reduced TAC	estimate	11.4	13.4	8.2	9.8	6.5	5.2	
		95% CrI	3.0 81.5	2.8 108.2	2.1 59.3	2.0 80.9	1.6 47.5	1.2 40.0	
		P(better)	>99%	>99%	>99%	>99%	>99%	99%	

At 6 months, the random effects model was preferred based on DIC, although there was only a small difference in the statistic so both models are presented. In the random effects model, EVR + reduced TAC is expected to be comparable to all other treatments (see Table 28). The credible intervals for all comparisons are wide. Table 29 provides the results of the fixed effects model for BPAR free at 6 months.

Table 28: BPAR free at 6 months (Odds Ratio, random effects model)

Intervention		**Comparator**					
		standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC
AZA + CIC	estimate	0.6					
	95% CrI	0.0 4212.0					
	P(better)	41%					
AZA + standard TAC	estimate	0.9	1.5				
	95% CrI	0.0 18600.0	0.0 173.0				
	P(better)	49%	66%				
MMF + CIC	estimate	0.9	1.5	1.0			
	95% CrI	0.0 1733.0	0.0 171.6	0.0 907.9			
	P(better)	49%	68%	50%			
MMF + standard TAC	estimate	1.4	2.2	1.5	1.5		
	95% CrI	0.0 512.7	0.0 1852.0	0.0 5935.0	0.0 176.7		
	P(better)	59%	70%	59%	63%		
MMF + reduced TAC	estimate	1.3	2.1	1.4	1.4	0.9	
	95% CrI	0.0 38.5	0.0 7131.0	0.0 17830.0	0.0 1204.0	0.0 107.4	
	P(better)	67%	64%	56%	58%	48%	
EVR + reduced TAC	estimate	4.2	6.6	4.5	4.4	3.0	3.2
	95% CrI	0.0 501.3	0.0 137200.0	0.0 267900.0	0.0 29800.0	0.0 4889.0	0.0 1026.0
	P(better)	84%	76%	71%	74%	71%	78%

Table 29: BPAR free at 6 months (Odds Ratio, fixed effects model)

Intervention		Comparator					
		standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC
AZA + CIC	estimate	0.6					
	95% CrI	0.1 3.4					
	P(better)	28%					
AZA + standard TAC	estimate	0.9	1.5				
	95% CrI	0.1 5.9	0.8 3.0				
	P(better)	46%	88%				
MMF + CIC	estimate	0.9	1.5	1.0			
	95% CrI	0.1 5.0	1.1 2.1	0.5 2.1			
	P(better)	45%	99%	50%			
MMF + standard TAC	estimate	1.3	2.3	1.5	1.5		
	95% CrI	0.3 5.5	0.7 7.3	0.4 5.8	0.5 4.6		
	P(better)	66%	92%	73%	78%		
MMF + reduced TAC	estimate	1.3	2.1	1.4	1.4	0.9	
	95% CrI	0.9 1.8	0.4 13.0	0.2 9.8	0.3 8.3	0.2 3.8	
	P(better)	89%	80%	64%	65%	46%	
EVR + reduced TAC	estimate	4.1	7.0	4.7	4.7	3.1	3.3
	95% CrI	1.7 11.6	1.0 57.3	0.6 42.7	0.7 37.1	0.6 18.0	1.3 9.9
	P(better)	>99%	97%	93%	94%	91%	>99%

At 12 months, the random effects model was preferred based on DIC, although there was only a small difference. At 12 months, EVR + reduced TAC is expected to be comparable to all comparator treatments in the random effects model (see Table 30). All direct estimates are in line with those obtained from the consistency model. Table 31 shows the fixed effect model results for the 12 month BPAR free analysis. The fixed effect model shows that EVR + reduced TAC is expected to be more efficacious than standard TAC, AZA + CIC, and MMF + reduced TAC, and comparable to the other comparator treatments.

Table 30: BPAR free at 12 months (Odds Ratio, random effects model)

			Results of the inconsistency model					
	Intervention		Comparator					
			standard TAC	AZA + CIC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		1.4	0.9	1.7	1.3	2.6
		95% CrI		0.1 14.7	0.2 3.6	0.4 7.9	0.3 5.7	0.3 20.1
		P(better)						
	AZA + CIC	estimate	0.9		1.4			
		95% CrI	0.2 3.7		0.2 11.0			
		P(better)	38%					
	AZA + standard TAC	estimate	1.0	1.1				
		95% CrI	0.4 2.7	0.3 3.7				
		P(better)	44%	59%				
	MMF + standard TAC	estimate	1.7	2.0	1.7			
		95% CrI	0.6 5.7	0.3 11.0	0.4 8.6			
		P(better)	89%	84%	85%			
	MMF + reduced TAC	estimate	1.3	1.6	1.4	0.8		
		95% CrI	0.5 4.1	0.3 8.0	0.3 6.0	0.2 3.5		
		P(better)	78%	75%	74%	33%		
	EVR + reduced TAC	estimate	2.6	3.0	2.7	1.6	2.0	
		95% CrI	0.5 13.0	0.3 22.4	0.4 17.4	0.2 10.3	0.3 13.3	
		P(better)	92%	89%	90%	74%	83%	

Table 31: BPAR free at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model					
	Intervention		Comparator					
			standard TAC	AZA + CIC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		1.5	0.9	1.5	1.3	2.6
		95% CrI		0.4 5.7	0.6 1.4	1.0 2.2	0.9 1.8	1.3 5.4
		P(better)						
	AZA + CIC	estimate	0.8		1.4			
		95% CrI	0.4 1.6		0.7 2.8			
		P(better)	25%					
	AZA + standard TAC	estimate	0.9	1.2				
		95% CrI	0.6 1.4	0.6 2.2				
		P(better)	38%	71%				
	MMF + standard TAC	estimate	1.5	1.9	1.6			
		95% CrI	1.0 2.2	0.9 4.3	0.9 2.9			
		P(better)	98%	94%	95%			
	MMF + reduced TAC	estimate	1.3	1.6	1.3	0.8		
		95% CrI	0.9 1.8	0.7 3.5	0.8 2.3	0.5 1.4		
		P(better)	89%	88%	85%	25%		
	EVR + reduced TAC	estimate	2.6	3.3	2.8	1.7	2.1	
		95% CrI	1.3 5.4	1.2 9.0	1.2 6.4	0.8 3.9	0.9 4.7	
		P(better)	>99%	>99%	>99%	91%	96%	

Renal function results at 12 months

At 12 months, EVR + reduced TAC is expected to be more efficacious than MMF + reduced TAC and more efficacious than standard TAC, and expected to be comparable to AZA + CIC. The inconsistency model was not performed as there was no closed loop in the network (see Table 32).

Table 32: Renal function at 12 months (Difference in effect size, fixed effects model)

Intervention		**Comparator**		
		standard TAC	AZA + CIC	MMF + reduced TAC
AZA + CIC	estimate	0.7		
	95% CrI	0.3 1.1		
	P(better)	>99%		
MMF + reduced TAC	estimate	0.1	-0.6	
	95% CrI	0.0 0.3	-1.0 -0.1	
	P(better)	95%	1%	
EVR + reduced TAC	estimate	0.4	-0.4	0.2
	95% CrI	0.2 0.5	-0.8 0.1	0.0 0.5
	P(better)	>99%	6%	96%

The differences in effect size were translated into difference in CFB by multiplying the effect sizes by the typical standard deviation for an eGFR measurement. The results obtained are reported in Table 33 below. At 12 months, EVR + reduced TAC is expected to reduce the eGFR deterioration by 8.5 ml/min/1.73m^2 [95CrL% 4.2; 12.8] compared to standard TAC. Although EVR + reduced TAC point estimate reduces eGFR deterioration by 5.1 ml/min/1.73m^2 in comparison with MMF + reduced TAC, it is considered comparable, because the credible interval [95CrL% -0.8; 11.0] passes zero. EVR + reduced TAC is expected to be comparable to AZA + CIC.

Table 33: Renal function at 12 months (Difference in eGFR change from baseline, fixed effects model)

Intervention		**Comparator**		
		standard TAC	AZA + CIC	MMF + reduced TAC
AZA + CIC	estimate	17.1		
	95% CrI	7.5 26.6		
MMF + reduced TAC	estimate	3.4	-13.7	
	95% CrI	-0.7 7.4	-24.0 -3.3	
EVR + reduced TAC	estimate	8.5	-8.6	5.1
	95% CrI	4.2 12.8	-19.1 2.0	-0.8 11.0

Withdrawals due to AEs at 12 months

The random effects model was preferred based on the DIC, though there was little difference between the model statistics. Therefore, both models are presented in this section. Withdrawals due to AEs for EVR + reduced TAC are expected to be comparable to all comparator treatments (see Table 34). The credible intervals for all comparisons are wide (potentially caused by lower number of events in four studies) and should be interpreted with caution. In the fixed effects model (see Table 35), the tolerability of EVR + reduced TAC is found to be lower than with standard TAC, AZA + CIC, MMF + standard TAC and MMF + reduced TAC, and comparable to AZA + standard TAC.

Table 34: Withdrawals due to AEs at 12 months (Odds Ratio, random effects model)

			Results of the inconsistency model					
			Comparator					
	Intervention		standard TAC	AZA + CIC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		0.0	1.2		0.6	1.9
		95% CrI		0.0 0.0	0.0 714.8		0.0 323.4	0.0 1061.0
		P(better)						
	AZA + CIC	estimate	0.0		4.6			
		95% CrI	0.0 5.3		0.0 3041.2			
		P(better)	93%					
	AZA + standard TAC	estimate	0.5	13.3				
		95% CrI	0.0 57.2	0.1 12580.0				
		P(better)	64%	11%				
	MMF + standard TAC	estimate	0.3	6.4	0.5		2.3	
		95% CrI	0.0 2261.0	0.0 7548000.0	0.0 74520.0		0.0 1303.7	
		P(better)	68%	30%	58%			
	MMF + reduced TAC	estimate	0.6	15.0	1.1	2.3		
		95% CrI	0.0 360.3	0.0 1898000.0	0.0 19420.0	0.0 1532.0		
		P(better)	62%	17%	49%	35%		
	EVR + reduced TAC	estimate	1.9	47.7	3.5	7.3	3.2	
		95% CrI	0.0 1149.0	0.0 5863000.0	0.0 56920.0	0.0 552300.0	0.0 27320.0	
		P(better)	35%	10%	29%	29%	32%	

Table 35: Withdrawals due to AEs at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model					
			Comparator					
	Intervention		standard TAC	AZA + CIC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		0.1	1.2		0.6	1.9
		95% CrI		0.0 0.8	0.4 3.7		0.4 1.0	1.2 3.2
		P(better)						
	AZA + CIC	estimate	0.1		4.3			
		95% CrI	0.0 0.7		1.0 31.4			
		P(better)	>99%					
	AZA + standard TAC	estimate	1.0	7.1				
		95% CrI	0.4 2.8	1.6 56.1				
		P(better)	49%	0%				
	MMF + standard TAC	estimate	0.3	1.9	0.3		2.2	
		95% CrI	0.1 1.1	0.2 24.7	0.0 1.5		0.6 10.0	
		P(better)	96%	29%	93%			
	MMF + reduced TAC	estimate	0.6	4.2	0.6	2.3		
		95% CrI	0.4 1.0	0.8 38.5	0.2 1.9	0.6 9.9		
		P(better)	98%	5%	82%	12%		
	EVR + reduced TAC	estimate	1.9	13.5	1.9	7.2	3.2	
		95% CrI	1.1 3.2	2.5 124.0	0.6 6.0	1.6 37.4	1.6 6.5	
		P(better)	1%	0%	14%	1%	0%	

Hypertension at 12 months

The safety in terms of hypertension at 12 months for EVR + reduced TAC is expected to be worse in comparison to MMF + standard TAC and MMF + reduced TAC and is expected to be comparable to standard TAC and AZA + CIC. Table 36 presents the results of the fixed effects models. All direct estimates are in line with the estimates obtained by the inconsistency model.

Table 36: Hypertension at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model				
	Intervention		Comparator				
			standard TAC	AZA + CIC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		2.2	0.5	0.6	1.1
		95% CrI		0.6 9.0	0.2 1.1	0.4 0.9	0.7 1.8
		P(better)					
	AZA + CIC	estimate	2.2				
		95% CrI	0.6 9.0				
		P(better)	12%				
	MMF + standard TAC	estimate	0.5	0.2		1.2	
		95% CrI	0.3 1.0	0.0 1.0		0.4 3.4	
		P(better)	98%	97%			
	MMF + reduced TAC	estimate	0.6	0.3	1.2		
		95% CrI	0.4 0.9	0.1 1.1	0.6 2.4		
		P(better)	>99%	97%	29%		
	EVR + reduced TAC	estimate	1.1	0.5	2.2	1.8	
		95% CrI	0.7 1.8	0.1 2.0	1.0 4.9	1.0 3.2	
		P(better)	34%	84%	3%	3%	

Diabetes (assumed new onset) at 12 months

Safety of EVR + reduced TAC with respect to new onset diabetes at 12 months is expected to be comparable to standard TAC, AZA + standard TAC and MMF + standard TAC (Table 37). The inconsistency model was not performed as there was no closed loop in the network.

Table 37: Diabetes at 12 months (Odds Ratio, fixed effects model)

Intervention		**Comparator**			
		standard TAC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC
AZA + standard TAC	estimate	1.5			
	95% CrI	0.5 4.6			
	P(better)	25%			
MMF + standard TAC	estimate	1.6	1.1		
	95% CrI	0.5 4.9	0.2 5.2		
	P(better)	21%	47%		
MMF + reduced TAC	estimate	0.9	0.6	0.5	
	95% CrI	0.6 1.2	0.2 1.9	0.2 1.7	
	P(better)	80%	82%	85%	
EVR + reduced TAC	estimate	1.2	0.8	0.8	1.4
	95% CrI	0.8 2.0	0.2 2.8	0.2 2.5	0.8 2.5
	P(better)	19%	62%	66%	12%

Infections at 12 months

The safety of EVR + reduced TAC with respect to infections at 12 months is expected to be comparable in comparison to all other treatments. All direct estimates are in line with the estimates obtained from the inconsistency model. Table 38 presents the results of the fixed effects model.

Table 38: Infections at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model						
	Intervention		Comparator						
			standard TAC	AZA + CIC	AZA + standard TAC	MMF + CIC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate			1.0		1.0	1.2	1.3
		95% CrI			0.5 2.1		0.5 2.0	0.8 1.7	0.9 1.9
		P(better)							
	AZA + CIC	estimate	0.8		1.3	1.1			
		95% CrI	0.3 2.1		0.6 2.8	0.8 1.5			
		P(better)	68%						
	AZA + standard TAC	estimate	1.0	1.3					
		95% CrI	0.5 2.0	0.6 2.8					
		P(better)	45%	22%					
	MMF + CIC	estimate	0.9	1.1	0.8				
		95% CrI	0.3 2.4	0.8 1.5	0.4 1.8				
		P(better)	61%	30%	68%				
	MMF + standard TAC	estimate	1.1	1.5	1.1	1.3		0.8	
		95% CrI	0.6 2.0	0.5 4.7	0.5 2.6	0.4 4.5		0.3 2.1	
		P(better)	33%	26%	42%	32%			
	MMF + reduced TAC	estimate	1.1	1.4	1.1	1.3	1.0		
		95% CrI	0.8 1.6	0.5 4.2	0.5 2.3	0.4 4.1	0.5 1.8		
		P(better)	25%	25%	42%	31%	51%		
	EVR + reduced TAC	estimate	1.3	1.7	1.3	1.5	1.1	1.2	
		95% CrI	0.9 1.9	0.6 4.9	0.6 2.7	0.5 4.7	0.6 2.3	0.7 1.9	
		P(better)	7%	17%	28%	22%	35%	28%	

HCV recurrence at 12 months

The safety of EVR + reduced TAC with respect to HCV recurrence is worse in comparison to AZA + standard TAC, and is expected to be comparable to the other treatments in the comparison. All direct estimates are in line with the estimates obtained from the consistency model. Table 39 gives the results of the fixed effects model.

Table 39: HCV recurrence at 12 months (Odds Ratio, fixed effects model)

			Results of the inconsistency model				
	Intervention		Comparator				
			standard TAC	AZA + standard TAC	MMF + standard TAC	MMF + reduced TAC	EVR + reduced TAC
Results of the consistency model	standard TAC	estimate		0.6	1.3	1.6	1.5
		95% CrI		0.3 1.1	0.8 2.2	0.6 4.6	0.8 2.9
		P(better)					
	AZA + standard TAC	estimate	0.6				
		95% CrI	0.3 1.1				
		P(better)	95%				
	MMF + standard TAC	estimate	1.3	2.3		1.0	
		95% CrI	0.8 2.2	1.0 5.2		0.2 6.4	
		P(better)	15%	3%			
	MMF + reduced TAC	estimate	1.5	2.6	1.2		
		95% CrI	0.6 3.7	0.9 7.9	0.5 3.0		
		P(better)	18%	4%	38%		
	EVR + reduced TAC	estimate	1.5	2.6	1.2	1.0	
		95% CrI	0.8 2.8	1.1 6.5	0.5 2.6	0.3 2.9	
		P(better)	9%	2%	36%	50%	

6.7.6 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Please see Section 6.7.4 Table 22. The assessment of heterogeneity was conducted by running both fixed and random effects models. Best fit was determined by the use of the DIC. Random effects models were selected for BPAR at 6 months, 12 months and withdrawals due to AEs at 12 months. However, it was difficult to select between the statistical models, particularly for BPAR outcomes and withdrawal due to AEs because of a small difference between the DIC.

It was challenging to assess the similarity assumption across studies because three studies included in the networks only reported sparse information on patient characteristics (Neuhaus *et al.*, 1997[82], Porayko *et al.*, 1994[88], McDiarmid *et al.*, 1993[93]). Potential treatment effect modifiers were identified in the NMA feasibility assessment and impact on the basecase results of the potential treatment effect modifiers considered:

- The exclusion of concomitant steroids in the first three months, which impact upon BPAR at 3, 6 and 12 months. All arms in all studies included steroids for at least three months with the exception of the MMF + standard TAC arm in (Takada *et al.*, 2013[85]), the MMF + standard TAC arm in (Junge *et al.*, 2005[77]), the TAC arm in (Manousou *et al.*, 2009[91]) and the TAC arm in (Samonakis *et al.*, 2006[92]). A scenario analysis was considered to assess this potential treatment effect modifier.
- BMI as a treatment effect modifier was difficult to assess following the analysis because it was only reported in 4 of the 22 studies. In these 4 studies, the weighted mean average of BMI was 25.2, with a small range from 24.0 to 29.0. No further analysis was considered.
- Diabetes was reported in 8 of the 22 studies. There was wide variation with reported values ranging from 0 to 41.6 percent and the highest values reported in H2304 (de Simone *et al.*, 2012[7], Saliba, 2013[8]) and (Boudjema *et al.*, 2011[83]). A scenario analysis was considered to further assess the impact of the potential treatment effect modifier.
- Hypertension was sparsely reported across studies at baseline. The highest values were found in H2304 (de Simone *et al.*, 2012[7], Saliba, 2013[8]) and could potentially be considered an outlier in comparison to the four other studies. As H2304 was the only everolimus trial, a subgroup analysis could not be performed. It was also considered inappropriate to include hypertension at baseline as a covariate because of the sparse number of studies in the network. No scenario or further analysis was considered.
- HCC proportion at baseline varied across studies. There were also some imbalances between the treatment arms of (Nashan *et al.*, 2009[79]); 6 versus 27 percent) and (Salizzoni *et al.*, 2001[90]); 11.8 versus 24.4 percent). The impact of this was further considered in a scenario analysis.
- Cold ischaemic time varied from 7.3 to 11.6 hours and was reported in 10 of the 22 studies considered relevant but below 13 hours in all studies. It was assumed that 13 hours was a possible cut-off point to determine organ damage and therefore all studies included were considered comparable with respect to this characteristic. No further analysis was undertaken.
- Donor age varied between 33 to 52 years and this potential treatment effect modifier was not considered to impact the results of the base case analysis presented. No further analysis was undertaken.

6.7.7 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

While all trials were relevant, most reported only limited data or assumptions were made to allow networks to be created. Therefore, several scenario analyses were conducted to investigate the impact of excluding trials including (Table 40):

1. Grouping CNIs:

   In this scenario the treatment arms would be:

   - EVR + reduced TAC
   - AZA + standard CNI
   - MMF + standard CNI
   - MMF + reduced TAC
   - Standard TAC.

2. Excluding studies that included treatment arms with steroids < 3 months:

   The exclusion of concomitant steroids treatment in the first 3 months may be a potential treatment effect modifier. In this scenario analysis, three studies (Junge *et al.*, 2005[77], Takada *et al.*, 2013[85], Manousou *et al.*, 2009[91]) would be excluded from the analysis.

3. Excluding studies where TAC could be reclassified:

   After clinical expert opinion, the analysis assumed that standard tacrolimus should be defined by a target dose with a maximum range ≥7ng/ml immediately after transplant and reduced dose tacrolimus should be defined by a target dose with a maximum range < 7ng/ml immediately after transplant. Using these criteria, six studies (Neuberger *et al.*, 2009[65], Nashan *et al.*, 2009[79], Boudjema *et al.*, 2011[83], Dmitrewski *et al.*, 1994[87], Porayko *et al.*, 1994[88], McDiarmid *et al.*, 1993[93]) had a TAC treatment arm that should be reclassified.

4. Excluding studies with HCC imbalances at baseline:

   (Nashan *et al.*, 2009[79], Salizzoni *et al.*, 2001[90]) report imbalances between their treatment arms for the proportion of patients with HCC at baseline and are excluded in this analysis.

5. Excluding studies in which patients with diabetes are excluded at baseline:

One component of the exclusion criteria in the (Boudjema *et al.*, 2011[81]) study was to exclude diabetic patients at baseline; this scenario removes this study from the analysis.

6. Excluding studies that use a comparator as a rescue medication:

   (Klintmalm *et al.*, 2011[66], Samonakis *et al.*, 2006[92]) both offered MMF as a rescue medicine. As MMF is one of the comparators outlined in the NICE scoping document, the inclusion of MMF as a rescue medicine may be a potential treatment effect modifier. For this reason a scenario analysis was carried out excluding these two studies.

7. Including only eGFR measures for renal function CFB at 12 months:

   There are three studies that report renal function using eGFR: the (de Simone *et al.*, 2012[7], Neuberger *et al.*, 2009[65], McDiarmid *et al.*, 1993[93]). This scenario restricted the network to EVR + reduced TAC, MMF + reduced TAC and AZA + CIC, i.e. removing MMF + standard TAC arm from the network.

Table 40: Base case and scenario analyses conducted by outcome

Analysis	**Base case**	**Scenar-io 1**	**Scenar-io 2**	**Scenar-io 3**	**Scenar-io 4**	**Scenar-io 5**	**Scenar-io 6**	**Scenar-io 7**
Description	**All studies**	**Grouping CNIs**	**Steroids < 3 months**	**TAC reclassi-fication**	**HCC imbalances at baseline**	**Diabetes excluded at baseline**	**Comparator as rescue medication**	**Only eGFR measures for renal function**
Survival KM probabilities at 12 months (OR)	√	√	√			√	√	
Survival KM probabilities at 24 months (OR)	√	√	√				√	
Graft survival KM probabilities at 12 months (OR)	√	√				√	√	
Graft survival KM probabilities at 24 months (OR)	√	√					√	
tBPAR KM probabilities at 3 months (OR)	√	√		√	√	√	√	

tBPAR KM probabilities at 6 months (OR)	√	√				√		
tBPAR KM probabilities at 12 months (OR)	√	√		√		√	√	
Renal function at 12 months (difference)	√					√		√
Withdrawals due to AEs at 12 months (OR)	√	√						
Hypertension at 12 months (OR)	√					√		
Diabetes at 12 months (OR)	√					√		
Infections at 12 months (OR)	√	√				√		
HCV at 12 months (OR)	√		√	√	√		√	

Results of scenario analyses:

For BPAR free at 3 and 6 months, the only scenario that had an impact was scenario 5, which indicated that EVR + reduced TAC had an improved effectiveness versus all other treatment arms. For BPAR at 12 months in scenarios 3 and 5, EVR + reduced TAC was found to have a higher chance of producing BPAR free patients than standard TAC, AZA + CIC, and AZA + standard TAC and an improved odds ratio versus MMF + standard TAC.

All other outcomes were insensitive to changes in the included or excluded studies.

6.7.8 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

See Section 6.7.5 and 6.7.6 for heterogeneity between individual outcome results.

There were 8 networks for outcomes with closed loops (MTC) for which the inconsistency between the direct and indirect evidence on the treatment combinations was assessed. There was no evidence of inconsistency identified for BPAR at 3 and 12 months, hypertension at 12 months, infection at 12 months and HCV recurrence at 12 months. The inconsistency model estimates available were in line with those obtained from the consistency model for each of these outcomes, suggesting that no significant inconsistencies are present between the direct and indirect treatment estimates.

There was some evidence of inconsistency between the results for the following outcome comparisons:

- Overall Survival at 12 months: There is a small difference for AZA + CIC versus AZA + standard TAC between the consistency model (bottom left-hand side) and the inconsistency model (upper right hand side). The point estimates are respectively 4.1 and 4.9; however in both models, AZA + standard TAC was found to be more efficacious than AZA + CIC. Therefore, all available estimates are in line with those obtained from the consistency model, suggesting that no significant inconsistencies are present between the direct and indirect treatment estimates.
- Graft Survival at 12 months: There is a small difference for AZA + CIC versus AZA + standard TAC between the consistency model (bottom left-hand side) and the inconsistency model (upper right hand side). The point estimates are respectively 3.6 and 6.4; however in both models, AZA + standard TAC was found to be more efficacious than AZA + CIC. Therefore, all available estimates are in line with those obtained from the consistency model, suggesting that no significant inconsistencies are present between the direct and indirect treatment estimates.
- Withdrawals due to AEs at 12 months: There are differences for the AZA + CIC versus AZA + standard TAC between the consistency model and the inconsistency model. The point estimates in the random effects model are respectively 13.3 and 4.6; however in both models AZA + standard TAC is expected to have more withdrawals due to AEs in comparison to AZA + CIC. This suggests that no significant inconsistencies are present between the direct and indirect treatment estimates. However the analyses for the random effects model should be treated with caution because of the very wide credible intervals. The

reasons for these results could be because the direct pairwise comparisons rely only on one study (six studies for six treatments). The second reason is the low number of events reported in four of these studies: (Boillot *et al.*, 2001[69]), (7 withdrawals due to AEs for standard TAC; 8 for AZA + standard TAC); (Nashan *et al.*, 2009[79]), (4 for MMF + standard TAC; 7 for MMF + reduced TAC); (Greig *et al.*, 2003[80]), (2 for AZA + CIC; 7 for AZA + standard TAC); (Porayko *et al.*, 1994[88]), (4 for standard TAC; 0 for AZA + CIC). A small change of one or two events in one of the treatment arms could dramatically impact the odds ratios.

For time-to-event outcomes, analyses were performed at fixed time points separately using the cumulative number of events provided by the Kaplan-Meier estimates. Complementary analyses using the Kaplan-Meier curves when reported could provide better estimates on the relative effect of EVR + reduced TAC versus other comparators. Survival or time-to-event is a function of the underlying hazard of the event of interest (i.e. BPAR or graft loss or death) at a given point in time.

For renal function, the mean change from baseline at 12 months and its uncertainty were not reported but estimated for (Boudjema *et al.*, 2011[83], Porayko *et al.*, 1994[88], McDiarmid *et al.*, 1993[93]). This may have impacted the results, especially the comparisons versus AZA + CIC.

For safety outcomes, variation in the definition of diabetes and infections may have influenced the results. In two studies (Neuberger *et al.*, 2009[65], Boillot *et al.*, 2001[69]) out of six studies included, the definition of diabetes was not reported. By pooling new onset diabetes with overall diabetes, some bias may have been introduced in the analysis. For infections, varying definitions were used across the studies. Overall number of infections, opportunistic infections, CMV plus extra-hepatic infections, bacterial infections and undefined infections were all pooled in the analysis. Pooling of all these different terms might have introduced some bias in the analysis.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

Systematic review for non-RCT data

The search strategy, databases, and registries searched are as described in section 6.1.

Study selection

The process of study selection in terms of abstract screening and full text review was the same as is detailed in section 6.2. However, different PICOS criteria were developed to capture non-RCT data. The PICOS criteria used can be found in Table 41.

Table 41: Eligibility criteria used in the search for non-RCTs

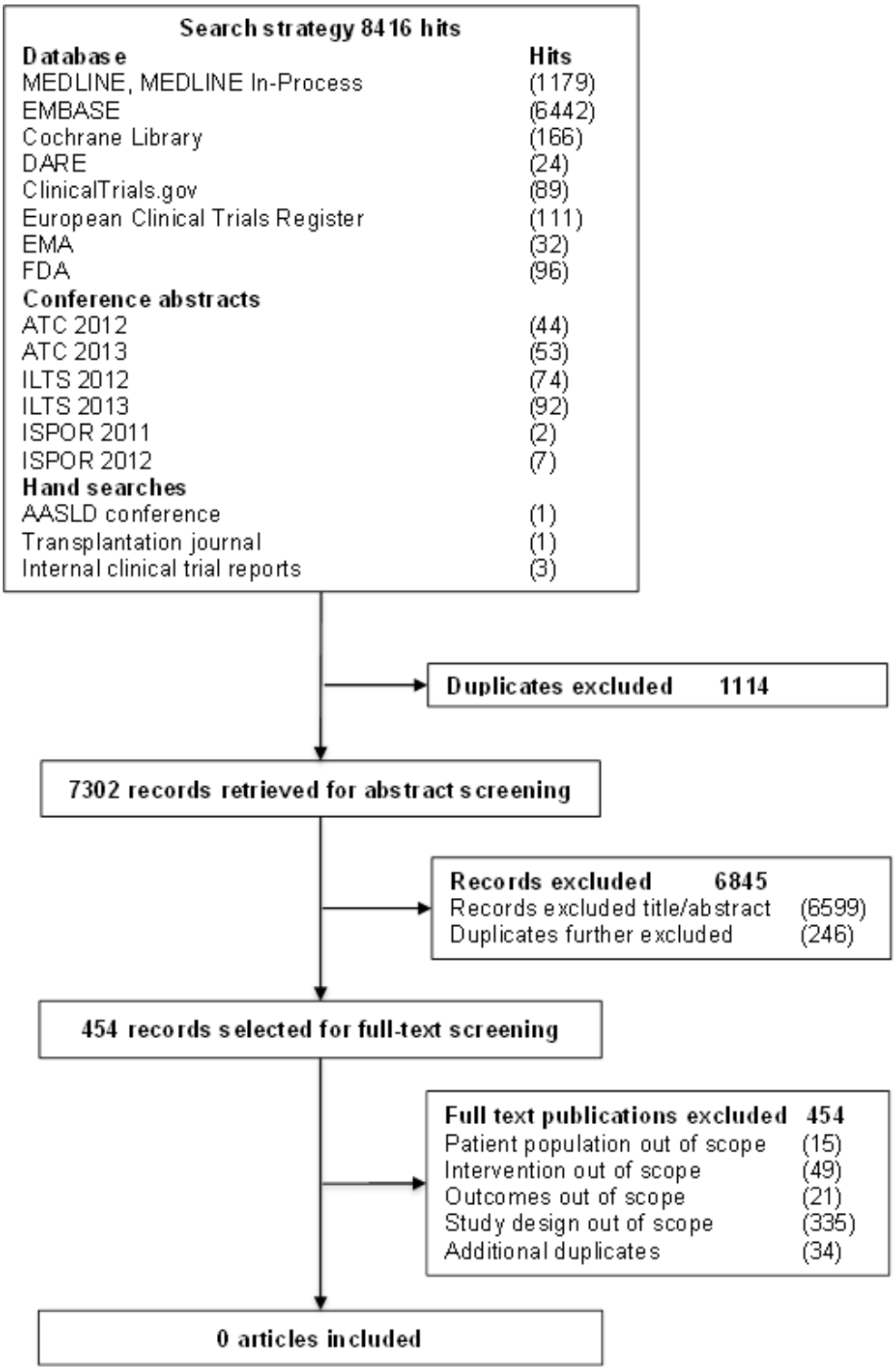
Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.
Intervention/ Comparator	• Everolimus in combination with reduced dose tacrolimus with or without corticosteroids.	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.

Outcomes	• Patient survival. • Graft survival. • Time to acute rejection. • Renal function. • Time to end-stage renal disease. • Time to recurrence of hepatocellular carcinoma. • Adverse effects of treatment. • Health Related Quality of Life (HRQL).	• Studies that do not focus rejection of the liver as an outcome (efficacy) or HRQL. • Studies with only cost and no clinical outcomes.
Study design	• Non-RCT studies including observational studies, experimental studies and single arm prospective trials.	• RCTs. • Reviews. • Meta-analyses/pooled analyses. • Case studies (sample size not significant). • Editorials, notes, comments or letters.

Abbreviations: HRQL, Health Related Quality of Life; RCT, Randomised Controlled Trial

The search identified 8,416 hits from databases and registries plus additional papers identified through hand searching and conference abstracts (as described in section 6.1). Following title and abstract screening of the records, 454 full-texts were retrieved. Seven full text studies were identified for everolimus; however, upon full text review for eligibility, these were excluded as they were not in combination with reduced dose tacrolimus (Figure 6).

Figure 7: Flowchart of the article selection process for non-RCT studies (PRISMA diagram)



6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Systematic review for safety data

The search strategy, databases, and registries searched are as described in section 6.1.

Study selection

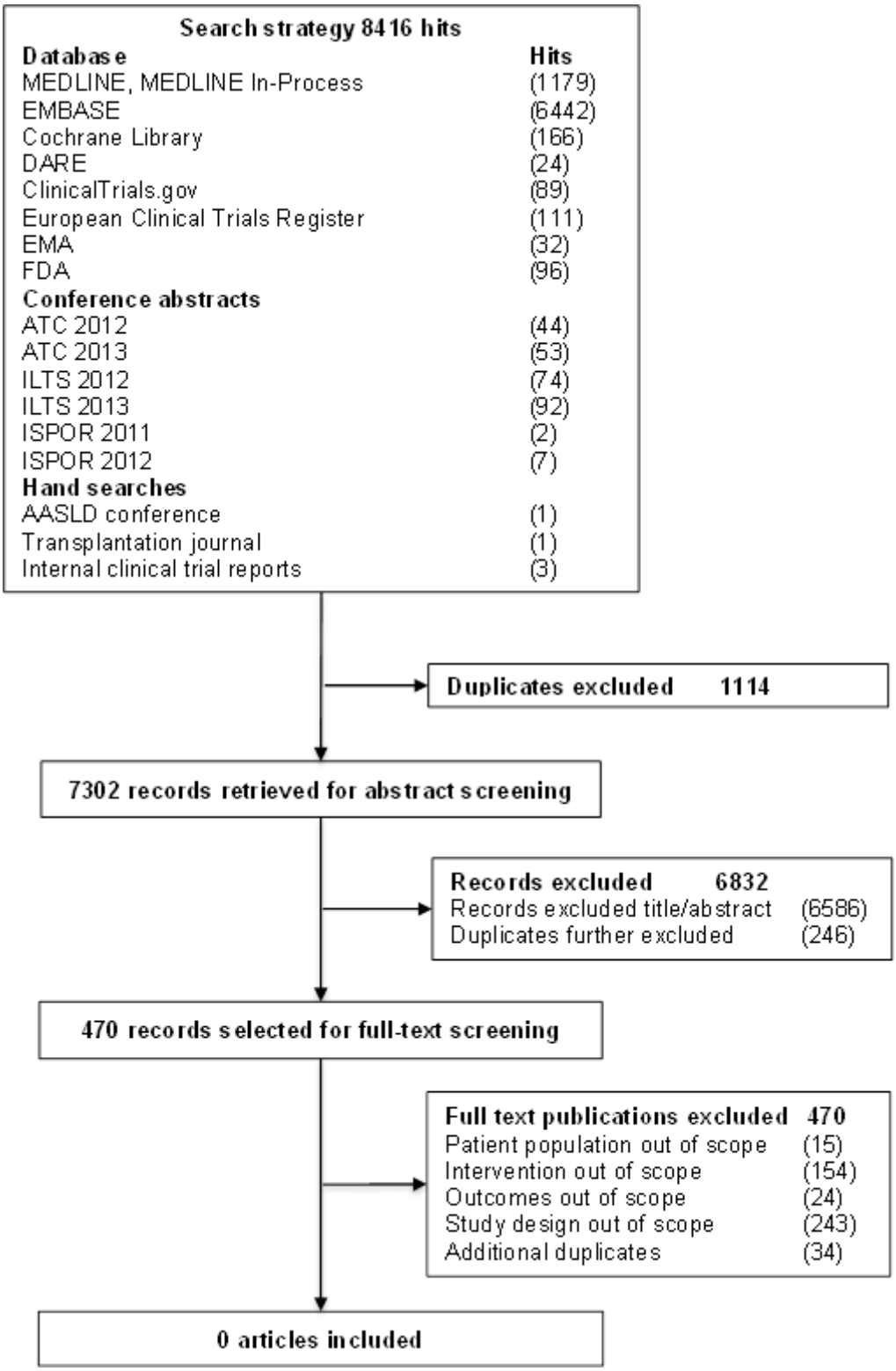
The process of study selection in terms of abstract screening and full text review was the same as is detailed in section 6.2. The same PICOS criteria were used as in the RCT search (see Table 42).

Table 42: Eligibility criteria used in the search for adverse events

Criteria	Inclusion criteria	Exclusion criteria
Population	• Adult on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients. • Pre-liver transplant patients including induction therapy. • Non-human. • Paediatric.
Intervention/ Comparator	• Everolimus in combination with reduced dose tacrolimus with or without corticosteroids.	• Sirolimus regimens. • Any regimen in combination with an induction treatment. • Any study without information on dosages.
Outcomes	• Safety as primary outcome.	• Studies that do not assess safety as a primary outcome.
Study design	• RCTs. • Non-RCTs.	• Case studies (sample size not significant). • Editorials, notes, comments or letters. • Reviews. • Meta-analyses/pooled analyses.

The search identified 8,416 hits from databases and registries plus additional papers identified through hand searching and conference abstracts (as described in Section 6.1). Following title and abstract screening of the records, no studies were found that were designed primarily to assess safety outcomes and was therefore excluded from further analysis. One study was identified containing the intervention of interest (everolimus in combination with reduced dose tacrolimus with corticosteroids). However, this RCT was not designed to primarily assess safety although reported in the next section. The flow diagram is presented in Figure 8.

Figure 8: Study flow diagram for Adverse Event study selection (PRISMA diagram)



6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Table 43 displays the prevalence data for key adverse events identified in the H2304 study. It should be noted that the third treatment arm (the TAC Elimination arm) is excluded from Table 43. This is due to enrolment in this arm being stopped due to a high incidence of acute rejection following an independent Data Monitoring Committee recommendation (see section 6.2.6).

Table 43: Key adverse events across randomised groups from H2304

System organ / class / adverse events	12 months			24 months		
	EVR+ rTAC (N = 245) n (%)	TAC control (N = 241) n (%)	Relative risk, % (95% CI)	EVR+ rTAC (N = 245)	TAC control (N = 241)	Relative risk, % (95% CI)
Diarrhoea	47 (19.2)	50 (20.7)	0.92 (0.65-1.32)	[redacted]	[redacted]	[redacted]
Headache	47 (19.2)	46 (19.1)	1.01% (0.70-1.45)	[redacted]	[redacted]	[redacted]
Hypertension	42 (17.1)	38 (15.8)	NR	[redacted]	[redacted]	[redacted]
Wound healing/ biliary leaks	27 (11)	19 (7.9)	1.4 (0.80-2.45)	27 (11)	20 (8.3)	2.8 (2.5-8.0)
New onset diabetes mellitus	48 (19.6)	40 (16.6)	NR	51 (20.8)	40 (16.5)	4.3 (2.6-11.2)
Lipid changes	58 (23.7)	23 (9.5)	2.48 (1.58-3.89)	66 (26.9)	28 (11.6)	15.4 (8.5- 22.2)
Infections	123 (50.2)	105 (43.6)	1.15 (0.95-1.39)	[redacted]	[redacted]	[redacted]
Renal failure	15 (6.1)	21 (8.7)	NR	[redacted]	[redacted]	[redacted]

CI, confidence interval; NR, not reported

EVR + rTAC, everolimus with reduced dose tacrolimus and corticosteroids

TAC control, tacrolimus with corticosteroids control arm

Adapted from European Public Assessment Reports published by the European Medicines Agency

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Safety results were favourable and were consistent with the known class effects of mTOR inhibitors. Approximately three-quarters (74.3%) of patients tolerated the everolimus in combination with reduced dose tacrolimus with corticosteroids regimen to Month 12. No patient developed severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2). While there is no direct evidence between everolimus + reduced dose tacrolimus in comparison to the comparators in the scope, evidence from the NMA indicated that the treatments were comparable in terms of safety.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Introduction of everolimus plus reduced dose tacrolimus four weeks post-transplant provides superior renal function (renal sparing) at 1 year, 2 and 3 years after liver transplantation compared to a standard dose tacrolimus regimen, with effective immunosuppression despite reduced tacrolimus concentrations.

- Study H2304 showed that for the primary composite efficacy endpoint of tBPAR, graft loss or death, the everolimus plus reduced dose tacrolimus arm was statistically non-inferior to the control tacrolimus arm at 12 and 24 months after liver transplantation (de Simone *et al.*, 2012[7], Saliba, 2013[8], Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]).
- Study H2304 showed that introduction of everolimus plus reduced dose tacrolimus arm at 30 days post-transplant provided superior renal function compared with a standard dose tacrolimus regimen, at 12 and 24 months after liver transplantation (de Simone *et al.*, 2012[7], Saliba, 2013[8], Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]).
- Within the subgroup analyses in H2304, it was found that there were no significant differences in the incidence of HCC/HCV recurrence or HCV-related fibrosis progression between everolimus plus reduced dose tacrolimus and the control tacrolimus arm.

Additionally, the evidence from the NMA indicated the relative treatment effects for everolimus plus reduced dose tacrolimus in comparison to azathioprine and MMF (both in combination with standard dose tacrolimus) with respect to the following outcomes at 12 and 24 months after liver transplantation:

- *Overall survival:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable at 12 and 24 months against standard dose tacrolimus, azathioprine plus ciclosporin, azathiopine plus standard dose tacrolimus, MMF plus ciclosporin, MMF plus standard dose tacrolimus, and MMF plus reduced dose tacrolimus (herein referred to as *all* comparator treatments) with respect to the efficacy outcome of overall survival.
- *Graft survival:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable to *all* comparator treatments.
- *tBPAR:* Everolimus plus reduced dose tacrolimus arm is expected to be more efficacious than *all* comparators at 3 months, and either comparable or more efficacious against all comparator treatments at 6 and 12 months.
- *Renal function:* The results of the NMA (Section 6.7) indicate that everolimus plus reduced dose tacrolimus arm compared with a standard dose tacrolimus regimen is potentially more efficacious with respect to preserving renal function at 12 months after liver transplantation.
- *Withdrawals due to adverse events:* The tolerability of everolimus plus reduced dose tacrolimus arm is expected to be comparable to azathioprine plus standard dose tacrolimus, and MMF plus ciclosporin, and worse than the other comparators in the *all* comparator set. However, the analysis found wide credible intervals for this comparison, indicating that the results should be interpreted with caution.
- *Hypertension:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable to *all* comparators with the exception of MMF plus standard dose tacrolimus and MMF plus reduced dose tacrolimus.
- *New onset diabetes:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable to *all* treatment comparators at 12 months.
- *Infections:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable to *all* comparator treatments at 12 months.
- *HCV recurrence:* Everolimus plus reduced dose tacrolimus arm is expected to be comparable to all comparator treatments at 12 months with the exception of azathioprine plus ciclosporin where it is expected to be worse.
- *HCC recurrence:* A network was not feasible with the available evidence.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths of the evidence base

Evidence of preservation of renal function: The timing of everolimus introduction (Day 30) was selected to ensure tacrolimus dose reduction could be undertaken before irreversible kidney damage occurred and also to minimise the risks of wound healing complications and potential vascular complications such as hepatic artery thrombosis. The NMA demonstrated a reduction in the deterioration of renal function is expected with everolimus plus reduced dose tacrolimus in comparison to standard dose tacrolimus (monotherapy) and MMF plus reduced dose tacrolimus. Future studies may help with understanding if earlier introduction of everolimus (10–15 days after transplantation) can achieve even greater renal benefits while maintaining safety and tolerability.

Novel evidence synthesis: The NMA conducted provides a comprehensive assessment of comparative effectiveness between everolimus in combination with reduced dose tacrolimus and comparators relevant to UK clinical practice. The analysis brought together a range of relevant efficacy and safety outcomes that were then used to populate the *de novo* cost-effectiveness model. The NMA analyses provided evidence that everolimus plus reduced dose tacrolimus had favourable efficacy against a number of the comparators for tBPAR at 3, 6 and 12 months. The analyses demonstrated expected comparability of everolimus plus reduced dose tacrolimus against all of the comparators for overall survival and graft survival at 12 and 24 months. The robustness of the NMA analyses were tested by performing extensive scenario analyses that demonstrated limited impact on the results. The consistency analyses showed that all but withdrawals due to adverse events were consistent with head to head trial data.

Large trial sample size and length of follow-up for everolimus combination: H2304 is the largest trial in immunosuppression for post-liver transplantation patients (N=719 ITT). Many of the trials identified in the systematic literature review for the comparator set in the NMA have relatively small sample sizes. H2304 also followed up patients for up to 36 months, which was longer than any other trial identified in the evidence base. The H2304 trial also compared favourably to the other trial evidence in the critical appraisal.

Active comparator arm: The inclusion of an active comparator arm gives the trial real-world applicability as well as allowing for an NMA with other treatments where a head-to-head trial is not available.

Baseline characteristics: Patients were stratified according to HCV status and renal function at the time of randomisation helping to achieve balance between the treatment arms in terms of the likely evolution of renal function.

Limitations of the evidence base

Open-label: Use of an open-label design was mandated by the need for careful adjustments in everolimus and tacrolimus exposure. Although the absence of blinding introduces the possibility of bias in adverse event reporting, this would not have influenced laboratory measurements of renal function. The interpretation of local biopsy readings for evaluation of tBPAR would not have been affected as the treatment assignment was withheld from the local pathologist interpreting the biopsies.

UK clinical practice: There were a few limitations with regards to the number of UK patients in the trial, dose of tacrolimus and the baseline eGFR:

- Limited number of UK patients: The study was conducted predominantly with patients in the US (190 patients in 29 centres were randomised); a total of 719 patients were randomised from North America, Europe and the Rest of the World. The study included eight UK patients in two centres.
- The H2304 study had a majority of Caucasian patients: Only 19 (2.6%) of patients were black, which limits the applicability of the data in these patients. The MHRA assessment noted that black individuals require, on average, two times the dose of tacrolimus to achieve target blood concentrations, have a higher risk of acute rejections, and a significantly higher incidence of new onset diabetes after transplantation.
- UK comparator dose: The target ranges for tacrolimus dose in H2304 are higher than in standard UK clinical practice (a blood concentration of <5ng/mL would be considered low-dose tacrolimus in the UK, and a standard dose of tacrolimus is in line with the Prograf SpC (5–20ng/mL)). This is due to the study being conducted predominantly in the US, as well as due to changes in clinical practice since protocol development in 2007.
- Baseline eGFR: The inclusion criterion for baseline eGFR stipulated eGFR ≥30 mL/min/1.73 m2; however, randomised patients had a mean eGFR of 81 mL/min/1.73 m2, which is close to normal. Although this may not accurately reflect UK clinical practice, it gives greater weighting to the inference that the deterioration in renal function in the TAC control arm is due to tacrolimus dose.

NMA limitations: There were some limitations with respect to the paucity of data, similarity assumption and variation in outcome measurement with details provided below:

- Paucity of data: Only a maximum of 12 studies were included in the networks to estimate comparisons between seven treatments of interest for each outcome.
- Similarity and consistency assumptions: Similarity assumptions were investigated by running 7 different scenarios based on differences observed in study design, patient characteristics or measurement tool; however some studies do not report information on these characteristics e.g. (Neuhaus *et al.*, 1997[82], Porayko *et al.*, 1994[88], McDiarmid *et al.*, 1993[93]). There is a possibility that the similarity assumption was not valid for these studies.
- Variation in outcome measurement: For safety outcomes, variation in the definition of diabetes and infections may have influenced the results. In two studies (Neuberger *et al.*, 2009[65], Boillot *et al.*, 2001[69]), the definition of diabetes was not reported. Overall number of infections, opportunistic infections, CMV plus extra-hepatic infections, bacterial infections and undefined infections were all pooled in the analysis. Pooling of all these different terms might have introduced some bias in the analysis. As different studies measured the change in renal function in different ways (eCRR and eGFR) a combination of these measures was undertaken using established formulae (see Section 6.7).

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Immunosuppression after liver transplantation has evolved from improving short-term survival of allografts and patient survival through reduction of acute rejection rates to improving rates of other clinical endpoints that were associated with the risk for longer term allograft failure. The level of renal function is one such clinical parameter that has gained attention in the last several years as an important prognostic risk among patients with progressive liver failure. A major contributor to renal dysfunction in a recipient of a liver allograft is the use of and exposure to CNIs e.g. tacrolimus. Reducing exposure to CNIs following solid organ transplantation is therefore a well-established clinical objective. The evidence base supports the early introduction of the mTOR inhibitor everolimus to facilitate tacrolimus minimisation for long-term maintenance of therapy with low exposure to tacrolimus.

The relevance of the outcomes assessed in the clinical trials are detailed below:

- *tBPAR:* tBPAR was determined as acute rejection with a locally confirmed RAI ≥3 according to Banff 1997 criteria treated with antirejection therapy. Banff schema is a consensus document that was designed to provide an internationally accepted standard for the purpose of grading acute liver allograft rejection. The Banff RAI comprises 3 components scored from 0 to 3: venous endothelial inflammation (E); bile duct damage (B); and portal inflammation (P); the scores are combined to an overall score (the RAI).
- *Progression to renal failure (estimated by eGFR)*: The importance of renal dysfunction for liver transplant recipients was illustrated by an analysis of data collected by the United Network for Organ Sharing (UNOS) in the States (Ojo *et al.*, 2003[98]). In this registry, chronic renal failure, defined by an eGFR ≤29 mL/min/1.73m^2, had a cumulative incidence rate approaching around 15% by 3 and 20% by 5 years post-liver transplantation; this was associated with a four-fold increased risk for patient death among recipients of solid organ transplants.
- *Renal function:* The evidence base included consideration of the evolution of renal function over time as assessed by the change in eGFR, using the MDRD4 if available, which is widely used in research and clinical practice.
- *Safety outcomes:* Safety evaluations included treatment-related side effects such as new onset diabetes mellitus, evolution in lipid parameters, and infections.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Eligibility of patients for treatment

Transplant status: All patients who have post-liver transplant status would be eligible for treatment with everolimus; patients will have eGFR ≥30 mL/min/1.73m^2 at start of treatment.

Tacrolimus dose: The target ranges for tacrolimus exposure in both arms of the study were higher than those typically used in UK clinical practice. In the UK, a blood concentration of <5ng/mL would be considered low-dose tacrolimus, and a standard dose of tacrolimus is in line with the Prograf SpC (5–20ng/mL). It should also be noted that the assay method selected should

be sufficiently sensitive to distinguish the low blood concentration levels of tacrolimus described in the anticipated license.

Use of MMF: MMF administered to patients (according to local practice) was discontinued at randomisation in H2304. However, MMF is often used in liver transplant patients in clinical practice including co-administration with tacrolimus.

Baseline eGFR: Patients enrolled in the trial had baseline eGFR higher (mean 81 mL/min/1.73m^2) than the eGFR levels typically observed in patients in clinical practice in the UK (usually in the range of 50–65 mL/min/1.73m^2 at the time of liver transplant).

Everolimus dose

In Study H2304, which is the only relevant RCT and the only study in the MTC that contains everolimus, everolimus therapy was initiated at a dose of 1.0 mg b.i.d. in all patients. This will be the dose stated in the SPC. It is expected that in most patients, therapy will be stabilised at this dose, but it can be adjusted to achieve target trough concentration of 3 to 8 ng/mL.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A systematic literature review was conducted in order to identify existing cost-effectiveness analyses evaluating everolimus in combination with reduced dose tacrolimus relative to the decision problem comparators (azathioprine plus standard dose tacrolimus and MMF plus standard dose tacrolimus).

Everolimus and its alternative names were included in a search strategy that incorporated disease and patient population terms consistent with the clinical searches in section 6. In addition to these terms, database-specific search filters were added to capture cost-effectiveness analysis based upon the validated filter terms published by the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009[18]).

The searches were limited to human studies, but were not restricted by either language or geographical scope. The date limit decision was informed following advice from experts that highlighted that because of changes in clinical practice over the last 20 years studies before 1990 would not be relevant to the decision problem. The search strings by database are reported in Appendix 10.

Computerised bibliographic databases recommended by the CRD (Centre for Reviews and Dissemination, 2009[18]) were searched, including MEDLINE, MEDLINE In-Process, EMBASE, EconLit NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), and the NIHR Health Technology Assessment (NIHR HTA). ISPOR (Europe) conference was also searched. An initial search was conducted on the 7th August, 2013, and updated on 18th August 2014. Eighty-nine records were retrieved.

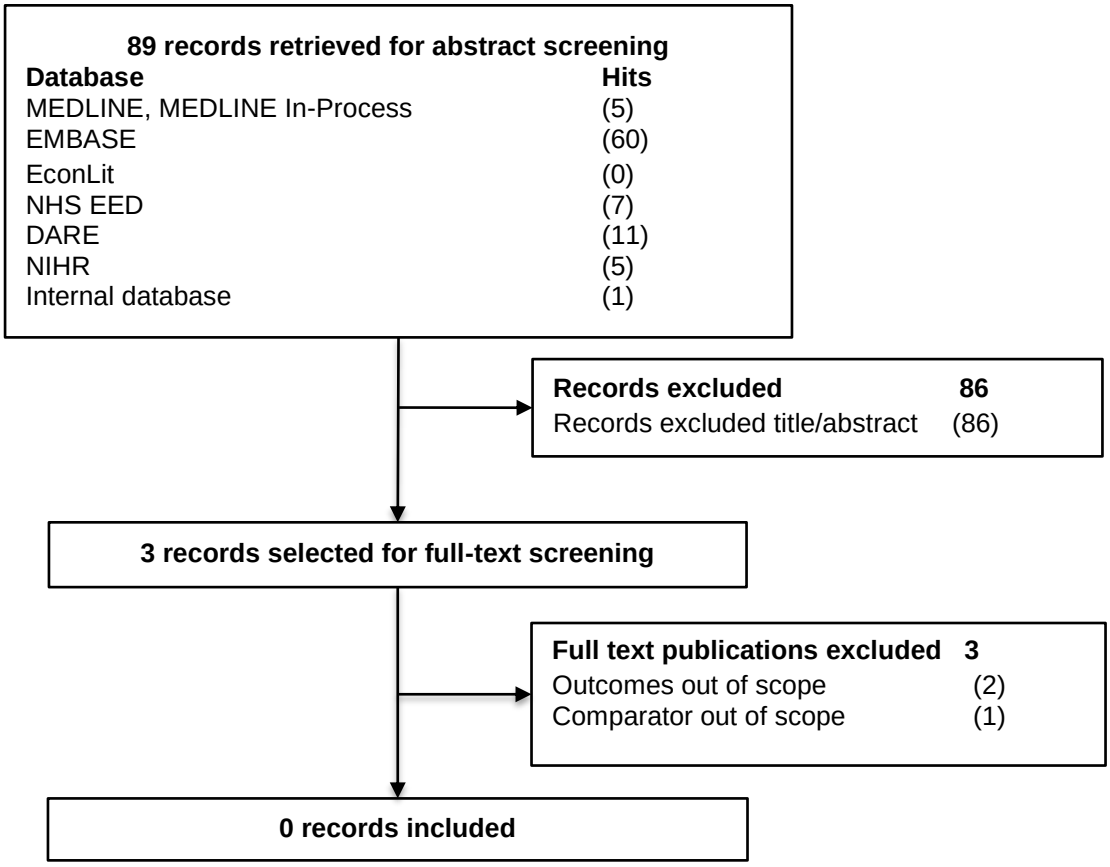
Study selection

The process of study selection was performed in two stages. The first stage was performed by a primary reviewer that screened the titles and abstracts on the basis of the inclusion criteria which was then checked by a second reviewer. Following the selection of relevant abstracts, full-texts were retrieved in the second stage and assessed in line with the eligibility criteria by the primary reviewer and checked by a secondary reviewer (study selection flow diagram in Figure 9). This was conducted in line with pre-set criteria for Population, Intervention(s), Outcome(s)/Comparator(s) and Study design (PICOS), as set out in Table 44. Upon disagreement on the relevance of an abstract or full text between the two reviewers, a third reviewer assisted in the attainment of a consensus decision, as recommended in the CRD guidelines for systematic reviews.

Table 44: Inclusion and exclusion criteria for the review of cost-effectiveness studies

Criteria	**Inclusion criteria**	**Exclusion criteria**
Population	• Adults on maintenance immunosuppressive therapy following allogeneic liver transplantation.	• Any non-liver related transplant patients • Pre-liver transplant only patients ('induction' phase), that are not part of an overall regimen that includes post-transplant treatment • Non-human • Paediatric
Intervention/ Comparator	• Everolimus in combination with reduced dose tacrolimus with or without a corticosteroid	• Non-everolimus regimens (in combination with tacrolimus +/- a corticosteroid) • MMF regimens • Azathioprine regimens
Outcomes	• Cost-effectiveness (CEA) results / cost-utility (CUA) results / cost-benefit (CBA) results • ICER (cost per QALY, cost per clinical event). • Cost-benefit ratio. • Cost-consequence (CCA) results / cost-minimisation (CMA) results • ICER (cost per QALY, cost per clinical event).	• Outcomes not related to economic evaluations (i.e. only costs or only effects) • Budget impact
Study design	• Economic evaluations; CUA, CBA, CEA, CCA, CMA.	• Budget impact analyses.

Figure 9: Flow diagram for the selection of cost-effectiveness evaluations



Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The search obtained 89 records and 86 records were excluded on the basis of an assessment of the title and abstracts against the inclusion criteria. In the second stage of study selection, three full text records reporting on three studies were reviewed. Two studies were excluded as they were not economic evaluations. The third study was a poster presentation at ISPOR 2013 which provided an analysis of the costs and effects in a Markov model associated with immunosuppressant therapy following liver transplantation. The cost-consequence analysis investigated tacrolimus monotherapy for a US

population but did not include the everolimus plus reduced dose tacrolimus and was therefore excluded based on the intervention study eligibility criteria.

Since the studies reporting cost-effectiveness analyses did not include an everolimus based regimen in the population of interest all were excluded and there are no cost-effectiveness analyses presented.

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

There were no suitable studies identified on which to perform a quality assessment.

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Everolimus in combination with reduced dose tacrolimus with or without corticosteroids is expected to be indicated for maintenance immunosuppressive therapy (commencing 4 weeks post-surgery) for adult patients who have undergone allogeneic liver transplantation.

Liver transplantation is used to treat liver failure for any reason. The *de novo* cost-effectiveness analysis considers patients who have undergone a liver transplantation for any reason such as drug-induced failure (such as overdoses or idiosyncratic drug reactions), hepatitis C virus (HCV), Acute Budd-Chiari syndrome metabolic diseases, alcoholic-related liver disease malignancy (such as hepatocellular carcinoma [HCC]), non-alcoholic steato-hepatitis (NASH), or other causes of cirrhosis (such as biliary cirrhosis, sclerosing cholangitis, haemochromatosis and cryptogenic cirrhosis) (Patient, 2013[99]).

The NICE scope statement of the decision problem includes two subgroups to be considered: people with hepatitis C infection, and people with renal dysfunction. The inclusion of a hepatitis C patient sub-group analysis was not conducted after clinical expert opinion indicated that there is unlikely to be a difference between treatment arms in terms of recurrence rates or treatment of HCV. Additionally, the pivotal H2304 trial indicated there were no significant differences in primary outcomes in these patients (Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]). Therefore, no incremental differences would be expected in this sub-population. The model does consider patient renal function because of the design of the *de novo* model including a renal sub-model, which allows patients to transition through the stages of chronic kidney disease. However, the model does not include a specific cost-effectiveness argument for this group of patients alone. Please see section 7.2.2 and 7.2.3 for further explanation of how this sub-population is modelled.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The core cost-effectiveness model (Figure 10) schematic outlines the main hepatic health states and/or complications of a post-transplant patient. The health states are defined in Table 45.

Evidence from the pivotal phase III trial H2304 (de Simone *et al.*, 2012[7], Saliba, 2013[8]), as well as the evidence synthesised from the network meta-analysis (see Section 6.7) indicates that patients treated with calcineurin inhibitors such as tacrolimus have an increased risk of impaired renal function. However, H2304 (de Simone *et al.*, 2012[7], Saliba, 2013[8]) has shown that the use of everolimus with reduced dose tacrolimus and corticosteroids can produce a 'renal sparing' effect. Hence, to demonstrate this clinically relevant effect, a sub-model (Figure 10) was used to analyse the renal dysfunction of a patient alongside the main model. The sub-model includes states defined by stages of chronic kidney disease (CKD) as defined in NICE's CKD guidelines (NICE, 2014[100]).

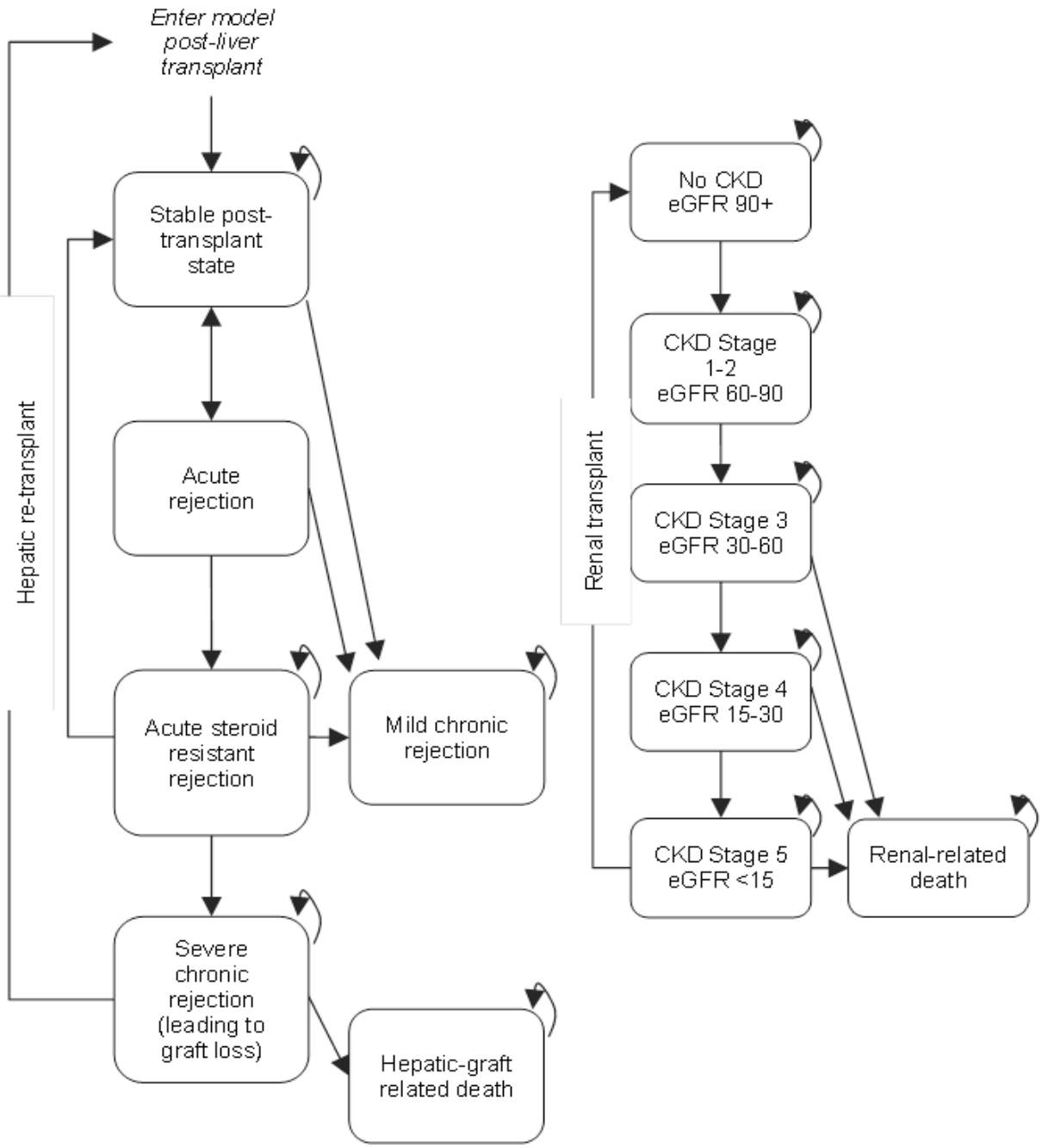
This structural approach to modelling by including a core cost-effectiveness model and a renal sub-model was considered important because the treatment effect has an impact on more than one aspect of a patients' health (either negatively or positively). Previously validated models utilising this approach include the CORE diabetes model, which uses a base model with various sub-models (Palmer *et al.*, 2004[101]). In addition, ISPOR good research practice guidelines encourage the design option of using sub-models to simplify the model structure (Karnon *et al.*, 2012[102]).

A patient simulation model was selected in line with (Davis *et al.*, 2014[103]) recommendations which suggest this modelling approach to be used when patient flow is determined by time since last event or a history of a previous event. For example, time in state is used to determine the probability of acute rejection which is a function of time since transplant and the risk of death in the graft loss state is different between for example, the first 3 months and the second 3 months (3 - 6 months post transplantation). Additionally, as the model structure includes a sub-model for renal patients, patient level simulation allows the application of between-model calculations to be made more easily. In the patient simulation, events that occur in the core cost-effectiveness model do not impact on progression through the renal sub-model. The exception to this is death, which can occur as a result of progression in either model, and is considered an absorbing state in both models.

A lifetime time horizon was chosen as patients are required to take immunosuppression for their entire lifetime (BTS, 2011[104]). Each model cycle

is three months. The cycle length was chosen after consultation with clinical experts who stated that most acute rejection occurs after three months post transplantation and therefore this cycle length was appropriate to capture relevant clinical events.

Figure 10: Core (hepatic rejection) cost-effectiveness model and renal sub-model, reflecting the potential patient pathways



*Patients are at risk of natural mortality at any time throughout both models.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The structure of the core cost-effectiveness (hepatic rejection) was chosen following consideration of clinical guidelines for immunosuppression post-liver transplantation in the UK and existing clinical literature that was identified in the clinical systematic literature search (section 6) (BTS, 2011[104]). The model structure was subsequently verified by a Consultant Hepatobiliary and Transplant Surgeon and a Consultant Hepatologist prior to model construction.

Existing clinical guidelines

A search was undertaken to identify UK clinical guidelines for the immunosuppression of adult patients with allogeneic liver transplants to inform the model structure and patient pathway, but no single guideline was identified for all. The National Clinical Guideline Centre (NCGC), NICE's Clinical Guidelines in Development, the Scottish Intercollegiate Guidelines Network (SIGN), NICE Pathways, the Guidelines International Network, the Guidelines and Audit Implementation Network (GAIN) or Clinical Research Est. Northern Ireland (CREST) have not, to-date, published guidelines for immunosuppression post-liver transplantation. The British Transplantation Society (BTS) (BTS, 2011[104]) has published guidelines for the management of liver transplantation for patients with non-alcoholic steato-hepatitis (NASH) before and after liver transplantation. In addition, the American Society of Transplantation published guidelines for the primary care doctors in 2009, but state that: "no official document has been published for primary care physicians regarding the management of liver transplant patients" (McGuire *et al.*, 2009[105]).

Although published guidelines were limited, it is clear that the main goal of post-transplant immunosuppression is to prevent hepatic graft rejection (BTS, 2011[104], McGuire *et al.*, 2009[105], Charlton *et al.*, 2009[106]). If rejection of the graft occurs it can be categorised into hyperacute rejection, acute (cellular) or chronic (ductopenic) rejection (Charlton *et al.*, 2009[106]).

Hyperacute rejection

Hyperacute rejection occurs within the first minutes/hours post-transplantation and is a result of host antibodies reacting with the new liver, resulting in organ failure. Hyperacute rejection takes place prior to the impact of post-induction phase immunosuppressive medication and is thus not attributable to (post-induction phase) immunosuppressive medication (as is the case for everolimus plus reduced dose tacrolimus). As the decision problem defines the incremental cost-effectiveness between post-induction immunosuppressive medications, hyperacute rejection is not relevant to this model.

Acute rejection

Acute rejection usually occurs within 4 weeks/1 month of transplantation, but late acute rejection can occur past this point (Charlton *et al.*, 2009[106], Neuberger, 1999[107], Neuberger *et al.*, 1998[108]). The gold standard for testing for acute rejection is liver biopsy and treatment for acute rejection is typically a course of high-dose corticosteroids (Neuberger *et al.*, 1998[108]) with between 80% and 90% of acute rejection episodes responding to high-dose intravenous bolus corticosteroid therapy (Charlton *et al.*, 2009[106], Aydogan *et al.*, 2010[109]). In the event that corticosteroid therapy fails because patients are resistant to bolus intravenous corticosteroid therapy, they instead may require anti-lymphocyte therapy (Aydogan *et al.*, 2010[109]).

Chronic rejection

Inadequately treated acute rejection can progress to steroid-resistant acute rejection and (severe chronic rejection leading to) graft loss (Neuberger, 1999[107]). Chronic rejection can be defined as immunology injury to the hepatic graft due to persistent acute rejection (Neil *et al.*, 1997[110], Neumann *et al.*, 2003[111]). If patients do not respond to acute rejection therapy, they may advance to a status of chronic rejection (Aydogan *et al.*, 2010[109]). Chronic rejection is almost always preceded by one or more episodes of acute rejection that are often resistant to bolus intravenous corticosteroid therapy and anti-lymphocyte therapy (Charlton *et al.*, 2009[106]).

After clinical expert opinion was sought, it was assumed that chronic hepatic rejection develops following acute hepatic rejection that has persisted for 3 successive months and the patient has failed consecutive first line high dose steroid therapy followed by 3 successive months of acute steroid resistant rejection and failed second line anti-lymphocyte therapy had occurred (a total of 6 months.

The derived core (hepatic rejection) model states are described in Table 45.

Renal sub-model

Renal dysfunction is a common and significant problem after liver transplantation. Declining renal function can have a major impact on graft and patient survival. In transplant patients, chronic kidney disease is associated with an increased predisposition to cardiovascular events, an increased risk of hospitalisation, hepatic allograft dysfunction and an increase in mortality when compared with patients with preserved renal function (Ojo *et al.*, 2003[98], McGuire *et al.*, 2009[105], Charlton *et al.*, 2009[106]). Therefore, one of the key aims of effective immunosuppression post-transplant is to preserve renal function.

Chronic kidney disease (CKD) describes abnormal kidney function and/or structure (NICE, 2014[100]). The estimated glomerular function rate (eGFR) is a measure than can be used to determine renal dysfunction. The eGFR is calculated using a specified formula, typically the Modified Diet of Renal Disease (MDRD4) formula which uses the patient's age, sex, ethnicity and an equation based on epidemiological data (Rule *et al.*, 2006[112]). The MDRD4 equation is the "best estimate of GFR", with the older Cockcroft–Gault (providing an eGFR based on plasma creatinine, sex, age and body weight) being the second most accurate measure as judged by one study (Gonwa *et al.*, 2004[113]).

Normal eGFR is around 120 mL/min/1.73 m^2 but once a patient's eGFR falls below 90 mL/min/1.73 m^2, the risk of kidney disease increases. Once eGFR falls below 60 mL/min/1.73 m^2 complications should be treated (Table 48). Patients will progress through the renal sub-model as their eGFR falls, in accordance to the latest NICE clinical guideline (NICE, 2014[100]).

Approximately 98% of patients with kidney failure begin dialysis when their eGFR is less than 15 mL/min/1.73 m^2 (Obrador *et al.*, 1999[114]) and the development of chronic kidney failure is associated with a 4.5 greater probability of death compared to organ recipients with no CKD and normal renal function (Ojo *et al.*, 2003[98]).

7.2.4 Please define what the health states in the model are meant to capture.

Table 45: Core cost-effectiveness (hepatic rejection) model health state definitions

Health state	Description
Stable post-transplant state	Patients enter the model four weeks after their transplant in this state which reflects being stable on immunosuppressive regimens with no clinical signs of rejection. Patients who successfully treat acute rejection episodes return to this state.
Acute rejection	Patients with acute rejection episodes (as diagnosed by biopsy) enter this state and can either return to the stable post-transplant state through successful high-dose steroid treatment. If steroid treatment is unsuccessful the patient progresses to the steroid-resistant acute rejection state after 3 months.
Acute steroid resistant rejection	If steroid treatment is unsuccessful after three months, patients enter this state where they undergo second line anti-lymphocyte therapy.
Severe chronic rejection (leading to graft loss)	If a patient fails both first line (high-dose steroid) and second line (anti-lymphocyte) therapy for acute rejection, a patient enters a state of severe chronic rejection. Severe chronic rejection will lead to failure of the transplanted organ and the patient will require a further transplant.
Mild chronic rejection	After year 1 post-transplant, a patient can develop a mild form of chronic rejection from any state except severe chronic rejection and death. This state is largely asymptomatic. It is not clear what causes this state of rejection, and a patient can also recover naturally and return to a stable post-transplant state with no rejection (Hirschfield *et al.*, 2009[114]).
Death	Patients have increased mortality risk in a state of severe chronic rejection (leading to graft loss) and this is captured by the liver-related death state in the model. Natural (background) mortality risk (absent from Figure 10) is applied at all stages of the model.

Health states in the renal sub-model are defined by the latest NICE clinical guideline on CKD progression (NICE, 2014[100]) (see Table 46). The renal sub-model consists of five health states of varying severity, with CKD5 being the most severe. Patients leave the model upon CKD related, hepatic related death, or from natural (background) mortality. The health states for the core cost-effectiveness model and the renal sub-model are designed to capture the important health service costs and health consequences arising from potential post-transplant complications.

Table 46: Renal sub-model health state definitions

Health state	eGFR	Definition (from the NICE guideline for CKD)
No CKD	≥90 mL/min/1.73m^2	Normal or increased GFR, with other evidence of kidney damage.
Stages 1-2	60-89 mL/min/1.73m^2	Slight decrease in GFR, with other evidence of kidney damage.
Stage 3	30-59 mL/min/1.73m^2	Moderate decrease in GFR, with or without other evidence of kidney damage.
Stage 4	15-29 mL/min/1.73m^2	Severe decrease in GFR, with or without other evidence of kidney damage.
Stage 5	0-15 mL/min/1.73m^2	Established renal failure, in need of dialysis or transplant.
Death		Patients have increased mortality risk in a state of severe chronic rejection (leading to graft loss) and this is captured by the liver-related death state in the model. Natural (background) mortality risk (absent from Figure 10) is applied at all stages of the model.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As described in Section 2.1, liver transplantation requires immunosuppressive therapy to prevent graft loss. The economic model attempts to track patients post-transplant. Section 7.2.3 discusses the stages of potential hepatic rejection included in the model: acute, acute steroid resistant, mild chronic, severe chronic leading to graft loss) and their relevance to the decision problem is set out. In the core cost-effectiveness (hepatic rejection) model, disease progression from the state *Stable Post-Transplant State* to *Acute Rejection* was completely dependent on the immunosuppressive regimen (the treatment arm). This probability of progression was derived from the probability of freedom from biopsy proven acute rejection (BPAR) for each comparator, calculated in the NMA (see section 6.7). Beyond this stage in the core cost-effectiveness (hepatic rejection) model, progression was not dependent on the patient's treatment arm as no other outcome measures (e.g. overall survival) were assumed to impact disease progression. The underlying disease progression beyond *Acute Rejection* is described in Table 47.

Table 47: Underlying disease progression in the main (hepatic rejection) model

From health state	To health state	Cause of progression
Acute rejection	Acute steroid resistant rejection	Probability of unsuccessful corticosteroid therapy (courses of high dose methylprednisolone).
Acute steroid resistant rejection	Severe chronic rejection (leading to graft loss)	Probability of unsuccessful anti-lymphocyte therapy (second line therapy following failed methylprednisolone therapy).
Any (after year 1)	Mild chronic rejection	A state of rejection (for which few studies are found in the literature) with around 3 - 5% of patients progressing to this state annually, irrelevant of their starting state.
Severe chronic rejection (leading to graft loss)	Stable post-transplant	Progression back to the start of the model is via a re-transplant. It was assumed that patients wait two cycles (6 months) on the waiting list before progressing (OrganDonation, 2014[115]).

In the renal sub-model, all stages of CKD are captured in the model health states. Progression occurs according to eGFR decrease in the first year after transplantation, which is dependent upon the patient's immunosuppressive regimen. Following year one, a patient's decline through the stages of worsening eGFR (stages of CKD) is assumed constant and dependent on underlying disease probabilities as set out in Table 48.

Table 48: Underlying CKD progression

State	Annual progression rate to next state (Lamattina *et al.*, 2011[116])	Increased risk of mortality in state (Keith *et al.*, 2004[117])
No CKD	7.0%	+ 0.0%
CKD stages 1/2	34.0%	+ 0.74%
CKD stage 3	56.0%	+ 1.22%
CKD stage 4	3.0%	+ 2.29%
CKD stage 5	-	+ 4.57%

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Additional features of the model are reported in Table 49.

Table 49: Key features of analysis in the cost-effectiveness model

Factor	Chosen values	Justification	Reference
Half-cycle correction	Not applied	A lifetime time horizon modeling approach is used and therefore the need for half-cycle correction is unnecessary	(Siebert, 2012[115])
Were health effects measured in QALYs; if not, what was used?	Yes	NICE Reference case	(NICE, 2013[116])
Discount of 3.5% for utilities and costs	Yes	NICE Reference case	(NICE, 2013[116])
Perspective (NHS/PSS)	Yes	NICE Reference case	(NICE, 2013[116])
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The treatment regimens and their dosages used in the model are in line with the existing SPCs (and Certican's® upcoming SPC) and as set out in sections 1.3 and 1.5.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.

- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

There is no treatment continuation rule assumed in the model.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

In the core (hepatic rejection) model, time to BPAR free was the main clinical efficacy input data, with the probability of incurring acute rejection episodes determining the probability of moving from the first state *Stable Post-transplant* to a state of *Acute Rejection.* The NMA (see section 6.7) provided BPAR data at 3, 6 and 12 months post-transplant; this data was used in the model to derive time dependent transition probabilities. An alternative approach to modelling time to BPAR data would be to model these effects as parametric survival distributions. However, as Kaplan Meier plots were not available for all comparators for this outcome measure, this approach was not feasible.

Common (i.e. not treatment-specific) progression probabilities determined a patient's transitions between states beyond *Acute Rejection*. Clinical variables affecting these subsequent transitions are displayed in Table 50.

Table 50: Clinical parameters driving non-treatment specific progression through the core (hepatic rejection) cost-effectiveness model

Treatment of acute rejection (AR)	**Value**	**Source**
Probability of successful 1st line* steroid therapy	86.3%	(Aydogan *et al.*, 2010[109])
Number of consecutive 1st line* steroid therapy courses in one cycle	3	Clinical expert opinion
Probability of successful 2nd line* anti-lymphocyte therapy in steroid resistant patients	83.3%	(Aydogan *et al.*, 2010[109])
Number of consecutive 3-month cycles of 2nd line* therapy	1	(Aydogan *et al.*, 2010[109])
Percentage of patients who develop mild chronic rejection**	4% annually	Clinical expert opinion
Percentage of patients who develop severe chronic rejection after acute steroid resistant rejection***	16.7%	(Aydogan *et al.*, 2010[109])
Increased chance of mortality in a state of graft loss on waiting list for a new graft	+ 12% annually	(Organ Donation, 2014[15])
Expected number of cycles patient remains in state before requiring re-transplant (affects time spent in the model in a state of graft loss before re-starting the model)†	2 cycles	(Organ Donation, 2014[15])
Probability of operative death at liver re-transplantation	0.7%	(Aylin *et al.*, 2013[117])

1st line therapy is a course of high dose methylprednisolone, 2nd line therapy is a course of anti-lymphocyte therapy for those who are resistant to steroid therapy. Clinical expert opinion of between 3-5% annually. ***16.7% fail Antilymphocyte therapy for acute steroid resistant rejection. † 147 days is the median time spent on the waiting list for a transplant.*

In the renal sub-model, the decrease from baseline in a patient's eGFR in the first year post-transplant was used to determine their CKD stage at the end of year one. Potential nephrotoxicity of tacrolimus (and calcineurin inhibitors) was captured by determining the patients mean change from baseline renal function as measured by change in eGFR. At the end of year one, the modelled patient's renal function follows a natural progressive decline (i.e. independent of immunosuppressive treatment option) (see underlying disease probabilities section 7.2.5). This is the same in both treatment arms, as seen in H2304 (de Simone *et al.*, 2012[7]), where everolimus plus reduced dose tacrolimus versus standard dose tacrolimus showed that the relative difference in eGFR between these two arms was constant after year one.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The probabilities of moving through the core cost-effectiveness (hepatic rejection) model vary with respect to whether these are treatment dependent. Probabilities for transition and for each treatment where applicable will be elicited to the model states and were derived from the clinical input data as stated in section 7.3.1.

Table 51 describes the assumptions and sources for each transition, with time dependent probability data set out in **Error! Reference source not found.**-134 in Appendix 10.15, respective to the time points stated in section 7.3.3.

Table 51: The derivation of the transition probabilities from clinical data in the core (hepatic rejection) model

From health state	To health state	Assumption	Source
Stable post-transplant state	Stable post-transplant state	1 - P(leaving state)	*Calculation*
	Acute rejection	Probability constant over this period	Treatment arm specific data from the NMA
	Mild chronic rejection	Only possible after 1 year in state	(Hirschfield *et al.*, 2009[118])
	Death	Natural mortality only	(ONS, 2012[119])
Acute rejection	Stable post-transplant state	Three courses of steroid therapy to treat acute rejection	(Aydogan *et al.*, 2010[109])
	Acute steroid resistant rejection	1 - P(leaving state)	*Calculation*
	Mild chronic rejection	Only after possible after 1 year in state	(Hirschfield *et al.*, 2009[118])
	Death	Natural mortality only	(ONS, 2012[119])
Acute steroid resistant rejection	Stable post-transplant state	Anti-lymphocyte therapy	(Aydogan *et al.*, 2010[109])
	Acute steroid resistant rejection	1 - P(leaving state)	*Calculation*
	Graft loss (severe chronic rejection)	Progression to chronic severe rejection if steroid therapy failed	(Aydogan *et al.*, 2010[109])
	Liver-related death	Natural mortality only	(ONS, 2012[119])
Mild chronic rejection	Stable post-transplant state	Chronic rejection spontaneously resolves patient becomes stable 0% probability in the base case	(Hirschfield *et al.*, 2009[118])
	Mild chronic rejection	Patient persists in this state unless they die	(Hirschfield *et al.*, 2009[118])
	Liver-related death	Natural mortality only	(ONS, 2012[119])
Graft loss (severe chronic rejection)	Stable post-transplant (via re-transplant)	Patients automatically transplanted after 2 cycles (6 months)	(Organ Donation, 2014[15])
	Graft loss (severe chronic rejection)	1 - P(leaving state)	*Calculation*
	Death	12% patients die per year on the waiting list	(Organ Donation, 2014[15])

Table 52: Renal sub-model 3-monthly cycle transition probabilities from year 1 onwards

From health state	To health state	P (all regimens)	Assumption	Reference / source
No CKD	No CKD	98.25%	1 - P(leaving state)	*Calculation*
	CKD stages 1 to 2	1.75%	Annual probability of progression converted to rates and adjusted for cycle length, then re-converted to probability	(La Mattina *et al.*, 2011[120])
	Death (non-kidney related)	0.00%	Natural mortality is assumed and is already accounted for in the main hepatic model	(ONS, 2012[119])
CKD stages 1 to 2	CKD stages 1 to 2	90.76%	1 - P(leaving state)	*Calculation*
	CKD stage 3	8.50%	Annual probability of progression converted to rates and adjusted for cycle length, then re-converted to probability	(La Mattina *et al.*, 2011[120])
	Kidney-related death	0.74%	Added mortality risk assumed in CKD stage 2	(Keith *et al.*, 2004[121])
CKD stage 3	CKD stage 3	84.79%	1 - P(leaving state)	Calculation
	CKD stage 4	14.00%	Annual probability of progression converted to rates and adjusted for cycle length, then re-converted to probability	(La Mattina *et al.*, 2011[120])
	Kidney-related death	1.21%	Added mortality risk assumed in CKD stage 3	(Keith *et al.*, 2004[121])
CKD stage 4	CKD stage 4	96.97%	1 - P(leaving state)	*Calculation*
	CKD stage 5	0.75%	Annual probability of progression converted to rates and adjusted for cycle length, then re-converted to probability	(La Mattina *et al.*, 2011[120])
	Kidney-related death	2.28%	Added mortality risk assumed in CKD stage 4	(Keith *et al.*, 2004[121])
CKD stage 5	CKD stage 5	95.43%	1 - P(leaving state)	Calculation
	Kidney-related death	4.57%	Added mortality risk assumed in CKD stage 5	(Keith *et al.*, 2004[121])

CKD stage 5 (after 14 cycles)	CKD stage 5 (in cycle 14 only)	0.00%	1 - P(leaving state)	*Calculation*
	No CKD via renal transplant (in cycle 14 only)	99.33%	Patients transplanted between 32 - 35 mths on waiting list	(Organ Donation, 2014[122])
	Operative Death	0.67%	Operative death rate	(Aylin *et al.*, 2013[117])
Post-renal transplant ("No CKD [T]")	No CKD (T)	98.25%	Move back into start of model	*Assumption*
	CKD stages 1 to 2	1.75%	Same progression chance as before transplant	(Abad *et al.*, 2011[123])
	Death (non-kidney related)	0.00%	Natural mortality is assumed and is already accounted for in the hepatic model	(Organ Donation, 2014[122])

*(Abad., 2011[123]) found that there were no differences between patients with first transplantation and those with a repeat transplantation in 419 renal transplant patients.

Transition probabilities for the renal sub-model are constant (as previously described) post year one. These are displayed in Table 52 and are not time dependent or treatment arm dependent and are based on underlying disease progression probabilities.

Prior to this (in the first year post-transplant), renal function is directly derived from the expected decrease in eGFR from baseline (from the NMA, see Table 53). The model randomly samples selected patient baseline characteristics including their starting eGFR level (mean patient level at baseline was 81 mL/min per 1.73 m^2 (Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]). The expected decrease (as displayed in Table 53) was then applied to the patient in the first year post transplant and their eGFR level after 12 months was then calculated and a patient was assigned to the appropriate CKD state as per the model schematic (section 7.2.2).

The estimates in Table 53 are derived from the NMA (section 6.7), which found that everolimus plus reduced dose tacrolimus was expected to be more effective at reducing renal function decline against standard dose tacrolimus, and was expected to be comparable to azathioprine plus ciclosporin and MMF plus reduced dose tacrolimus. As azathioprine plus ciclosporin and MMF + reduced dose tacrolimus are not commonly used in UK clinical practice (approximately 5% of current market) (Novartis data on file 2014), and are more likely to be used in combination with standard dose tacrolimus, the decision was taken that the estimate for standard dose tacrolimus would be used for a comparison between everolimus plus reduced dose tacrolimus and

azathioprine plus standard dose tacrolimus and MMF plus standard dose tacrolimus.

As the occurrence of renal failure is due to calcineurin inhibitor (tacrolimus) nephrotoxicity and is the most common complication following orthotopic liver transplantation transplantation (Ziolkowski *et al.*, 2003[124]), the advantage of a renal sparing effect of everolimus allows for reduced dose tacrolimus in comparison to azathioprine or MMF based treatments which include standard dose tacrolimus. The azathioprine and MMF SPC note that renal dysfunction is a very rare side effect (FDA, 1998[125]). Hence, Table 53 displays the same eGFR decrease data for both regimens as they both use standard tacrolimus dosing. Data from the H2304 trial (de Simone *et al.*, 2012[7], Lopez *et al.*, 2013[42]) indicates that EVR plus reduced dose tacrolimus saw an 8.5 point reduction in eGFR relative to standard TAC over 12 months. However, the relative difference is drawn from the NMA and the absolute eGFR decrease provided in Table 53 is used in the model.

Table 53: Absolute eGFR decrease at 12 months as used in the model from the NMA

Event	Base case	Low CI	High CI
Everolimus + reduced dose tacrolimus + corticosteroids	-23.1	-27.4	-18.7
Azathioprine + standard dose tacrolimus + corticosteroids	-31.6	-32.3	-30.9
MMF + standard dose tacrolimus + corticosteroids	-31.6	-32.3	-30.9

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There is evidence that the transition probabilities for acute rejection vary over time in the (Charlton *et al.*, 2009[106], Neuberger, 1999[107], Neuberger *et al.*, 1998[108]) and therefore the core cost-effectiveness model (hepatic rejection) transition probabilities are time varying in this model. Time dependent transition probabilities were used in the model until after year one, when transition probabilities were assumed constant. Transition probabilities for the core cost-effectiveness (hepatic rejection) model were drawn from a table of 5 different time points as follows:

- First 3 months post-transplant / in the current health state (cycle 1)
- Months 4-6 post-transplant / in the current health state (cycle 2)
- Months 7-9 post-transplant / in the current health state (cycle 3)

- Months 10-12 post-transplant / in the current health state (cycle 4)
- Months 13 onwards post-transplant / in the current health state (cycles 5 and onwards)

This enabled the model to take account of when a patient could no longer stay in a health state given the time they had already spent there (as in severe chronic rejection), or to allow patients to move into another state, such as mild-chronic rejection, after a certain time period.

In the renal sub-model, transitions were not time-dependent. Transition probabilities were based upon annual eGFR decrease dependent on the treatment in year one, and assumed to be constant thereafter (see section 7.3.2).

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Yes, to evaluate the progression of CKD, kidney failure (GFR <15 ml/min per 1.73 m^2 or the initiation of dialysis or transplantation) is an accepted clinical end point for clinical trials. However it is impractical due to the generally slow progress of CKD, requiring a long duration of follow-up, during which many patients would die of other complications of CKD, such as cardiovascular disease, before reaching kidney failure. Hence, surrogate endpoints are usually used, particularly in earlier stages of CKD. GFR is widely accepted to be the best overall marker of kidney function. Substantial GFR decline is an intermediate outcome for the clinical end point of kidney failure and an accepted surrogate end point for clinical trials (Stevens *et al.*, 2006[126]). In the H2304 study, GFR was estimated using the MDRD4 formula, which is valid globally in clinical practice, and confirmed using other methods of assessing renal function (serum creatinine, Cystatin C, other formulae for eGFR calculation [MDRD-6, Nankivell, Cockcroft-Gault and Hoek formulae], and proteinuria as determined by a spot urine protein/creatinine ratio).

The core cost-effectiveness model (and renal sub-model) links intermediate and final outcomes by taking into account baseline patient characteristics and changes in these characteristics over time (e.g. eGFR). Also, quality-adjusted life years (QALYs) are used in this submission as final outcomes. These are calculated as functions of the health states which occur in each cycle. Disutility associated with adverse events is calculated by the frequency of occurrence in each cycle. The utilities are accounted by year and are cumulative. The utility and disutility values used in the model can be found in section 7.5.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Three clinical experts were consulted, two externally from the manufacturer and one internally. Two external experts were approached and two participated. These two were experts were selected for their expertise in UK liver transplantation practice. Declarations of conflicts of interest were obtained. A telephone and interactive WebEx sharing meeting was held on 24th March 2014. The decision problem was provided, and they were shown the proposed model schematics for both the core cost-effectiveness model and the renal sub-model, and the key assumptions that had been made at that point in the model development were presented. The experts were sent a document describing the project and the topics for discussion in the meeting the week prior to the meeting.

In the meeting, the clinical experts were asked questions on the following topics (with their answers sub-bulleted):

- The availability of existing clinical guidelines:
  - Experts confirmed that no national UK clinical guidelines for the use of immunosuppression in liver transplantation patients are currently published.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- Acute rejection:
  - Hyperacute rejection is affected by immunosuppression regimens.
  - Acute rejection is highest during the first month post-transplantation, with the probability then falling.
  - The advantage of competing immunosuppression regimens is not through limiting rejection (as this is managed very well currently) but it is obtained by improvements in side-effects such as renal functioning.
  - Three days of high dose steroids are used to treat detected acute rejection (for example, 1000mg of methylprednisolone) with around 85 to 90 percent success rates of therapy.
  - If this therapy fails, it is repeated again 3 days later with the same success rate.
  - Patients who are 'steroid resistant' may be given monoclonal antibody therapy such as anti-lymphocyte globulin (ATG) therapy.
- Chronic rejection and graft loss:
  - The loss of bile ducts can determine chronic rejection.
  - Jaundice is a visible symptom that signals chronic rejection.
  - Mild chronic rejection bears similar health-related quality of life to those with steroid resistant acute rejection.
  - Severe chronic rejection could be grouped in the model with the state graft loss.
  - Severe chronic rejection often requires hospitalisation for a number of weeks with repeated biopsies.
  - There is sparse evidence that immunosuppression affects the probability of recurrent diseases such as HCC, HCV, HBV, CMV, PBC, PSC, ETOH.
- Renal dysfunction:
  - The tacrolimus dose is the major influence on renal dysfunction.
  - The movement of a patient through the renal sub-model is independent of the patient's position in the core cost-effectiveness (hepatic rejection) model.
  - It is appropriate to assume once the initial eGFR drop has occurred (i.e. by year 1 post-transplant), the choice of immunosuppression does not then accelerate the progression to worse stages of CKD, but rather this is then down to underlying disease progression.
- Specific input data:
  - There is no increased chance of mortality in states of acute rejection or mild rejection.

  - Patients in a state of severe chronic rejection that leads to graft loss can have increased probability of death as the liver fails once the graft is lost.
- Hepatitis C and Hepato-cellular carcinoma sub-groups:
  - It would be unlikely that the choice of immunosuppressive regimen would impact patient outcomes in these subgroups.
- Corticosteroid use:
  - Corticosteroid use gradually tapered and usually eliminated after six months (the definition used in this submission for with or without corticosteroids).

As the clinical experts were in the same telephone meeting together (but in separate locations), no iteration was used to collate the feedback as they discussed topics with one another in real time.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 54 contains the clinical input data used in the model. Please note that utility input data, resource use and cost input data are tabulated in sections 7.4 and 7.5. The data in this section is efficacy and safety data pertaining to the treatment arms and is supplemented by cost, resource use, and utility data in Table 58, Table 63, Table 64, Table 65, and Table 66.

Besides the impact on renal functioning, other treatment related adverse events include disease recurrences (such as HCV and HCC), hypertension, diabetes mellitus and infections (bacterial, opportunistic, cytomegalovirus [CMV] and fungal). The recurrence of HCV and HCC were not considered in the model as the clinical literature (see section 6.7) and consultation with clinical experts indicated that there was no effect of the immunosuppressive regimen on these variables; hence they are of no relative interest to our analysis. The NMA provides synthesised point estimates for hypertension, diabetes and infections, with other serious event prevalence data sourced from respective SPCs.

Table 54: Summary of clinical input variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Baseline characteristics for all treatment arms			
Baseline age	53.8 years	18.0 to 70.0 range (Lopez *et al.*, 2013[40]) (Normal distribution)	Trial results section 6.5
Baseline gender	50%	45% to 55% (Normal distribution)	Trial results section 6.5
Baseline life expectancy	78.7 years	18 to 101 age (Lopez *et al.*, 2013[40]) (Normal distribution)	Trial results section 6.5
Baseline body weight (kg)	82.6	Range 59.1 to 89.7 (Standard deviation 14.82) (Lopez *et al.*, 2013[40]) (Normal distribution)	Trial results section 6.5
Baseline mean eGFR immediately post-liver transplant	81 mL/min/1.73m^2	17.5 to 259.1 range (Lopez *et al.*, 2013[40]) (Normal distribution)	Trial results section 6.5
Everolimus + reduced dose tacrolimus			
BPAR free at 3 months	98.1%	93.5% to 99.7% (Beta distribution)	Absolute values derived from NMA results section 6.7
BPAR free at 6 months	94.4%	88.5% to 97.9% (Beta distribution)	Absolute values derived from NMA results section 6.7
BPAR free at 12 months	89.5%	82.3% to 94.4% (Beta distribution)	Absolute values derived from NMA results section 6.7
eGFR decrease at 12 months	-23.1 mL/min/1.73m^2	-27.4 to -18.7 (Log-normal distribution)	Absolute values derived from NMA results section 6.7
Hypertension 12 month prevalence	40.3%	29.1% to 52.4% (Beta distribution)	Absolute values derived from NMA results section 6.7
New onset diabetes 12 month prevalence	15.7%	9.7% to 24.0% (Beta distribution)	Absolute values derived from NMA results section 6.7
Infection 12 month prevalence	65.7%	56.4% to 74.1% (Beta distribution)	Absolute values derived from NMA results section 6.7

Herpes 12 month prevalence	0.4%	0.36% to 0.44% (Beta distribution)	(Lopez *et al.*, 2013[42])
Tremor 12 month prevalence	10.2%	9.2% to 11.2% (Beta distribution)	(Lopez *et al.*, 2013[42])
Insomnia 12 month prevalence	6.9%	6.2% to 7.6% (Beta distribution)	(Lopez *et al.*, 2013[42])
CMV 12 month prevalence	4.1%	3.7% to 4.5% (Beta distribution)	(Lopez *et al.*, 2013[42])
Azathioprine + standard dose tacrolimus			
BPAR free at 3 months	86.2%	80.2% to 90.6% (Beta distribution)	NMA results section 6.7
BPAR free at 6 months	78.7%	33.6% to 96.0% (Beta distribution)	NMA results section 6.7
BPAR free at 12 months	75.6%	65.3% to 83.7% (Beta distribution)	NMA results section 6.7
eGFR decrease at 12 months	-31.6	-32.3 to -30.9 (Log-normal distribution)	NMA results section 6.7
Hypertension 12 month prevalence	57.8%	28.7% to 83.2% (Beta distribution)	NMA results section 6.7
New onset diabetes 12 month prevalence	18.3%	7.8% to 36.1% (Beta distribution)	NMA results section 6.7
Infection 12 month prevalence	60.3%	45.9% to 73.8% (Beta distribution)	NMA results section 6.7
Herpes 12 month prevalence	5.9%	5.3% to 6.5% (Beta distribution)	(FDA, 1998[125])
Tremor 12 month prevalence	35.5%	32.0% to 39.1% (Beta distribution)	(FDA, 1998[125])
Insomnia 12 month prevalence	47.0%	42.3% to 51.7% (Beta distribution)	(FDA, 1998[125])
CMV 12 month prevalence	8.0%	7.2% to 8.8% (Beta distribution)	(FDA, 1998[125])
MMF + standard dose tacrolimus			
BPAR free at 3 months	88.7%	82.7% to 92.9% (Beta distribution)	NMA results section 6.7
BPAR free at 6 months	84.6%	56.3% to 95.8% (Beta distribution)	NMA results section 6.7
BPAR free at 12 months	83.4%	75.8% to 88.9% (Beta distribution)	NMA results section 6.7

eGFR decrease at 12 months	-31.6	-32.3 to -30.9 (Log-normal distribution)	NMA results section 6.7
Hypertension 12 month prevalence	23.9%	14.2% to 37.0% (Beta distribution)	NMA results section 6.7
New onset diabetes 12 month prevalence	11.6%	7.6% to 16.7% (Beta distribution)	NMA results section 6.7
Infection 12 month prevalence	62.6%	48.8% to 74.6% (Beta distribution)	NMA results section 6.7
Herpes 12 month prevalence	10.1%	9.1% to 11.1% (Beta distribution)	(FDA, 1998[125])
Tremor 12 month prevalence	33.9%	30.5% to 37.3% (Beta distribution)	(FDA, 1998[125])
Insomnia 12 month prevalence	52.3%	47.1% to 57.5% (Beta distribution)	(FDA, 1998[125])
CMV 12 month prevalence	5.8%	5.2% to 6.4% (Beta distribution)	(FDA, 1998[125])
CI, confidence interval; *where data is from a label, only a point estimate was available. A beta distribution was fit to these and a standard error calculated on the basis of +/- 20% of the point estimates which are similar to NMA synthesised adverse event.			

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Costs and outcomes are extrapolated beyond the trial time horizon. The core cost-effectiveness model (and sub-model) uses a lifetime time horizon, while the trial data used in the model is based upon 12 month follow-up data. While the H2304 trial had 36-month data available (Saliba *et al.*, 2014[3], Rauer *et al.*, 2014[45]), the NMA feasibility assessment did not find sufficient networks at the 36-month time period to conduct comparisons between treatments (see Section 6.3). For subsequent cycles, no further changes in this clinical outcome were assumed.

In the core cost-effectiveness model, the transition probabilities remain constant after year two. In the renal sub-model, the first year of treatment is based upon trial data. Afterwards, decline in renal function is subject to the risk of progression by CKD stage for all patients, regardless of therapy.

Adverse event rates were taken from NMA and trial data. These rates are assumed constant over time and no additional extrapolation criteria were applied to these parameters.

Tacrolimus and corticosteroids are titrated over time and the model considers these changing doses up to the end of the first year post-transplant, after which the doses are assumed constant and extrapolated for the rest of the time horizon. In all regimens the tacrolimus dose is decreased over time as a patient's target blood trough levels change, but the difference between the reduced dose regimen (the everolimus based regimen) and the standard dose regimen (the azathioprine and MMF based regimens) can be seen in the starting dose differences (Table 55). Clinical expert advice led to the assumption that corticosteroids are usually eliminated after 6 months of use. It was assumed that drug dosing becomes constant from month 12 onwards.

Table 55: Mean daily dose of immunosuppression over time

Everolimus regimen	**Starting**	**Month 3+**	**Month 6+**	**Month 9+**	**Month 12+**
Everolimus	2.0 mg	2.0 mg	2.0 mg	2.0 mg	2.0 mg
Reduced dose tacrolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Corticosteroid	15.0 mg	7.5 mg	0.0 mg	0.0 mg	0.0 mg
Azathioprine regimen	**Starting**	**Month 3+**	**Month 6+**	**Month 9+**	**Month 12+**
Azathioprine	1.0 mg/kg	1.0 mg/kg	1.0 mg/kg	1.0 mg/kg	1.0 mg/kg
Tacrolimus	0.12 mg/kg	0.09 mg/kg	0.08 mg/kg	0.07 mg/kg	0.07 mg/kg
Corticosteroid	15.0 mg	7.5 mg	0.0 mg	0.0 mg	0.0 mg
MMF regimen	**Starting**	**Month 3+**	**Month 6+**	**Month 9+**	**Month 12+**
MMF IV	2000 mg*	0 mg	0 mg	0 mg	0 mg
MMF oral	3000 mg*	3000 mg	3000 mg	3000 mg	3000 mg
Tacrolimus	0.12 mg/kg	0.09 mg/kg	0.08 mg/kg	0.07 mg/kg	0.07 mg/kg
Corticosteroid	15.0 mg	7.5 mg	0.0 mg	0.0 mg	0.0 mg

*IV MMF should be used in the first four days following hepatic transplant, and oral MMF started as soon as possible afterwards. This was taken into account in the model by dividing the resource use by the relevant proportion of the cycle. Dosages for everolimus and reduced dose tacrolimus were taken from the clinical trial report (Lopez *et al.*, 2013[42]). All other dosing assumptions were made using the BNF 67 (BNF, 2014[127]).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The following key assumptions have been made:

1) Hyperacute rejection only occurs within the first day following patient's transplant; therefore it is not an event that can occur once a patient has entered the model. Only the probability of acute rejection is thus treatment related.

    a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014.

2) There is a positive probability that patients can be successfully treated for acute rejection with a course of high-dose steroids, subsequently returning to a stable post-transplant state.

a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014, and also supported by literature (Aydogan *et al.*, 2010[109]).

3) If patients fail three courses of first line steroid therapy for acute rejection, they then progress to a state of acute steroid resistant rejection whereby they have second line anti-lymphocyte therapy administered.

   a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014, and also supported in the literature (Aydogan *et al.*, 2010[109]).

4) Patients who have acute rejection episodes and then return to a stable post-transplant state have the same probability of another acute rejection occurring when they entered the stable post-transplant state initially.

   a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014.

5) Patients cannot return to an earlier state from a state of severe chronic rejection leading to graft loss unless they undergo a new transplantation.

   a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014.

6) The probability of incurring treatment related adverse events (including a reduction in eGFR) is entirely treatment related and is independent of the state of hepatic rejection a patient is in. Probabilities are the same in a state of stable post-transplant state as they are in a state of graft loss.

   a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014.

7) The immunosuppressive regimen determines the eGFR decrease during year 1, but the difference between regimens on further renal dysfunction is assumed constant (following 'natural' CKD progression).

   a. Assumption confirmed by clinical experts in expert consultation meeting on 24th March 2014.
   b. Data in the H2304 trial (at 12 and 24 months) for everolimus with reduced dose tacrolimus and the standard dose tacrolimus control arm shows that the relative difference between these two arms in terms of eGFR becomes constant after year 1 (Lopez *et al.*, 2013[42]).

8) Mild chronic rejection cannot occur in the first year post-transplant, it is not dependant on immunosuppressive regimen, and the percentage of patients who develop mild chronic rejection annually is around 3% - 5%.

    a. Literature of mild chronic rejection is sparse, but the assumption was confirmed by clinical experts in expert consultation meeting on 24th March 2014, and in August 2014.

9) No administration or monitoring costs were assumed for the immunosuppressive regimens as once discharged from transplantation surgery, all treatments are administered orally by the patients themselves and monitoring is conducted during regular check-ups with doctors.

    a. Assumption made from administration information from the British National Formulary (BNF, 2014[127]) and monitoring of patients would be the same regardless of regimen and therefore is not included in the model (as part of regular post-transplant monitoring).

10) It was assumed that drug dosing becomes constant from month 12 onwards.

    a. The British National Formulary does not advise a change in dosage after initiation of oral therapy for azathioprine, MMF or tacrolimus (BNF, 2014[127]).

11) Patients who have failed three successive courses of high dose steroid therapy for acute rejection and go on to fail subsequent anti-lymphocyte therapy for acute rejection and have had persistent acute rejection episodes for at least 6 months are to enter either a mild chronic rejection or severe chronic rejection state.

    a. Experts suggested that a specific time in which chronic rejection develops following persistent acute rejection is difficult to provide, but that patients who have failed both lines of successive therapy will enter a state of chronic rejection, and not mild chronic rejection.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Undergoing a liver transplantation can have various impacts on HRQL, including recurrent headaches, muscle wasting, fatigue and osteoporosis (Bryan *et al.*, 1998[128]). However, some studies have found large improvements in the physical domains of various quality of life measures (including SF-36) and in improvements of sexual function (due to liver disease causing sex hormone imbalances) (Tome *et al.*, 2008[129]).

The impact of life-long immunosuppression and the associated side-effects (such as kidney dysfunction) can also reduce quality of life. A 2012 review by (Lim *et al.*, 2012[130]) noted that while immunosuppression has improved overall survival, they are associated potentially significant side-effects including: diabetes, gastrointestinal toxicity, infections, growth retardation, hyperkalaemia and hypomagnesaemia, hyperlipidaemia, bone marrow suppression, and hypersensitivity. The authors' note that as care improves for transplant patients, improving quality of life in these patients would require a multidisciplinary team approach with involvement of the primary care physician.

The core cost-effectiveness (and sub-model) attempts to take account of the changes in health related quality of life (HRQL) by using data from utility studies (outlined below) and the following assumptions:

- Living with a liver transplant without rejection

  - A recent systematic review (Tome *et al.*, 2008[129]) shows that there is an impact on a patient's HRQL post-liver transplant.
- Suffering from acute rejection episodes:
  - It was assumed based on suggestions from clinical experts (section 7.4.10) that patients with acute rejection episodes can be considered asymptomatic and are thus unlikely to have any health-related quality of life impact.
- Suffering from mild chronic rejection:
  - Literature is scarce on the exact nature of mild chronic rejection, although consultation with clinical experts highlighted that patients may present with jaundice but not have their HRQL impacted severely beyond that of an acute rejection patient.
- Suffering from severe chronic rejection that leads to graft loss:
  - Liver failure and graft loss are documented to impact HRQL and patients on the waiting list for new livers have poor quality of life (Hartwell *et al.*, 2011[131], Longworth *et al.*, 2003[132]), and reaching this state in the model is a product of chronic rejection.
- Treatment related adverse events that impact quality of life:
  - See section 7.4.8 for a description on adverse event impact on HRQL.

In the renal sub-model, aspect of the disease to consider that might impact quality of life is:

- The development of CKD and the impact of CKD stages 1 to 5 on HRQL.
  - Considering the impact only from CKD on a patient's HRQL and not from their level of hepatic graft rejection, patients with no CKD are not expected to have their HRQL impacted. However, progression through the stages of CKD will affect HRQL negatively (Liem *et al.*, 2008[133], Neri *et al.*, 2012[134], Wyld *et al.*, 2012[135]).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Some evidence suggests a patient's HRQL improves over time post-transplant (Longworth *et al.*, 2003[132], Ratcliffe *et al.*, 2002[136]). This may be for one of three reasons:

- As acute rejections are most common in the immediate weeks/months post-transplant, the highest incidence of rejection falls over time. However, it should be noted that acute rejection episodes are

considered asymptomatic and not to impact a patient's HRQL (as described in section 7.4.1) so the correlation between a lower incidence of acute rejection and an improvement in HRQL may be difficult to make. However, severe chronic rejections do impact HRQL, and patients who reach a state of chronic rejection are assumed to have reached this through persistent acute rejection. Thus, if the incidence of acute rejection falls then the subsequent incidence of chronic rejection falls which may explain improving HRQL profiles over time.

- The first few months post-transplant may incur surgical recovery complications such as wound pain, or simply being confined to a hospital ward. As time moves on from surgery and these patients no longer suffer any negative impacts on HRQL caused by surgery, their HRQL profiles may improve.
- The coping mechanisms of patients are very likely playing a part in improving trends (Dolan *et al.*, 2008[137]). This phenomenon can be applied to any disease area in many diseases and is best described as patients becoming accustomed to poor health and becoming used to the impact on their HRQL. Consequently, patients will begin to perceive their poorer health as 'normal' and thus report more normal HRQL scores.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQL data was not collected in the H2304 clinical trial (de Simone *et al.*, 2012[7], Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]).

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No HRQL data was not collected in the H2304 clinical trial therefore a mapping exercise could not be conducted (de Simone *et al.*, 2012[7], Hexham *et al.*, 2011[39], Lopez *et al.*, 2013[42]).

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic literature review was conducted in order to identify relevant *Health State Utility Values* (HSUVs) for the *de novo* cost-effectiveness model. The systematic review for HSUVs was informed by a scoping stage drawing from the decision support unit technical support document on the identification, review and synthesis of HSUV from the literature (Papaioannou *et al.*, 2010[138]). The NICE DSU 9 guidance document (DSU9) recommends not limiting the review by the conventional PICOS for clinical effects but instead considering the health states, HSUVs and study design criteria.

Scoping stage

A scoping stage was undertaken to select relevant databases, align with the specific health states required by the model and assess the available HSUV in line with NICE requirements. The NICE Decision Support Unit 9 document states that: “A brief scoping search can be undertaken to locate published reviews. This can be limited to a few key electronic databases and searching using terms for each health state combined with terms for the EQ-5D” (Papaioannou *et al.*, 2010[138]). The scoping search involved not only identifying the existing published reviews but conducting a search with terms including a combination of adult post-liver transplantation as outlined in Section 6 and a search filter with extensive terms for HSUVs (Centre for Reviews and Dissemination, 2009[18]).

Databases searched:

Computerised bibliographic databases recommended by the CRD (Centre for Reviews and Dissemination, 2009[18]) were searched, including MEDLINE, MEDLINE In-Process, EMBASE, EconLit, the NHS Economic Evaluation Database (NHS EED), and the National Institute for Health Research in Health Technology Assessment (NIHR HTA). The databases were searched on 3rd July 2014.

Health States Required in the Model:

The health states required for the disease stage in the core cost-effectiveness model were for adult post liver transplantation patients including:

- Stable post-transplant
- Acute rejection
- Acute steroid resistant rejection
- Mild chronic rejection
- Severe chronic rejection (leading to graft loss)

The time since transplantation was also considered as acute rejection was most likely to occur within 3 months (Wiesner *et al.*, 2001[139]):

- 3 months
- post 3 months

HSUVs required:

The initial search was performed using the health state terms and any HSUV. The NICE reference case states that: "The EQ-5D is the preferred measure of health-related quality of life in adults." (NICE, 2013[116]) The initial search identified a number of studies using EQ-5D and therefore the eligibility criteria were narrowed to EQ-5D for the next stage of the HSUV review.

Following the scoping search a full search strategy including the same health state and HSUV search filter terms were used (see Appendix 12 for the full search strategy). The search strategy was limited to human studies and restricted to post-1990 publications in line with the cost-effectiveness search (section 7.1). Search terms were not restricted by study design, language or geographical scope.

Study selection

The search identified 3,946 records and the study flow diagram is provided in Figure 11. The scoping search formed the first stage of the study selection process which had been on the basis of the titles and abstracts 'dual' screened by two independent reviewers against only the health state and using any HSUV instrument. The first stage identified 521 records (using any

HSUV instrument). The scoping search also identified three published reviews (Tome *et al.*, 2008[129], Lim *et al.*, 2012[130], McLernon *et al.*, 2008[140]).

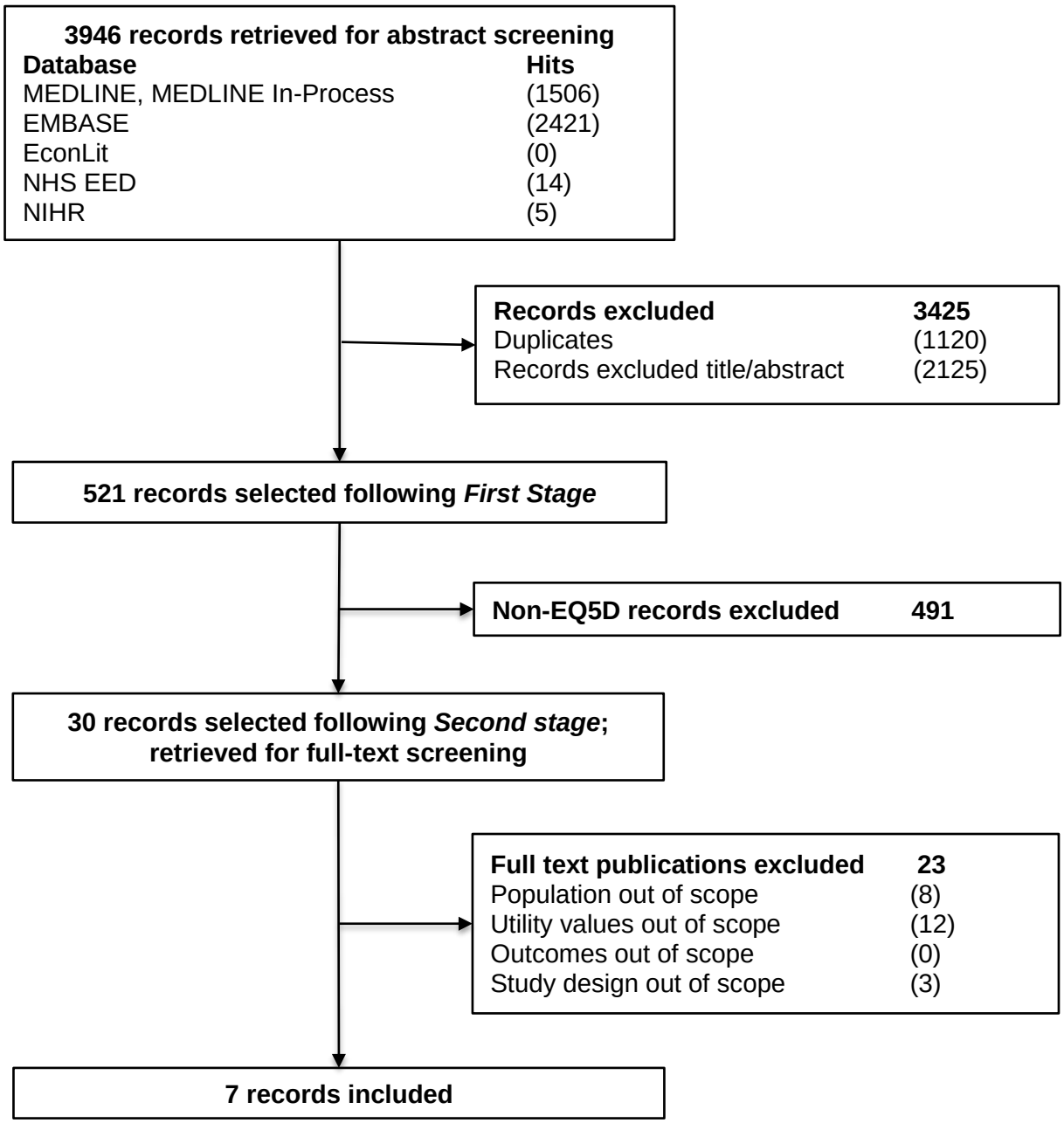
The second stage was to review the first stage scoping records for those records using the EQ-5D HSUV and this was checked by another reviewer. This second stage resulted in 30 potentially relevant records of which these represented 30 studies for which the full texts were retrieved.

The third stage was to review the full text studies against the study eligibility criteria which were designed to identify relevant HSUV for the cost-effectiveness model. This was performed by one reviewer and checked by a second. The criteria for the selection of the EQ-5D articles identified at the stage are detailed in Table 56. Upon disagreement on the relevance of a decision between the two reviewers, a third reviewer would assist in the attainment of a consensus decision for the screening and full text review. Following a review of the full-texts, seven records were selected for data extraction.

Table 56: Eligibility criteria for the review of HRQL data

Criteria	Inclusion	Exclusion
Health State	Adult post liver transplantation patients including: • Stable post-transplant. • Acute rejection. • Acute steroid resistant rejection. • Mild chronic rejection. • Severe chronic rejection (leading to graft loss). The time since transplantation: • 3 months. • post 3 months.	• Publications whose data was not pertinent to health states post-transplant.
Health State Utility Values	• EQ-5D including quantitative value. • Results must be elicited using the EQ-5D questionnaire.	• Studies without EQ-5D results. • Studies with only qualitative questionnaire results. • Studies without HSUV data, or without utility scores.
Study design	• RCTs that record HRQL data. • Observational studies. • HRQL studies. • Cost-utility analyses (containing primary EQ-5D elicited data)	• None.

Figure 11: Flow diagram for the selection of HRQL studies



7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Table 57 provides an overview of the seven studies included in the review. Five of the seven studies were studies eliciting EQ-5D in a UK population. These UK studies used the transplant centres across the UK (excluding the centre in Edinburgh) to recruit patients on the waiting list and at several time points post-transplantation. Two of the studies used the dataset obtained by (Ratcliffe *et al.*, 2002[136]), and one of these was for a subset of transplanted patients (subset defined by original diagnosis (Longworth *et al.*, 2003[132]).

All of the studies provided data for patients post-transplant, but none of the studies provided utility data specific to either acute or mild rejection, nor did they report disutility data specific to adverse events. Several studies also administered the SF-36 instrument to patients alongside the EQ-5D, although only EQ-5D results is reported in Table 57 (Bryan *et al.*, 1998[128], Longworth *et al.*, 2003[132], Ratcliffe *et al.*, 2002[136], Perez-San-Gregorio *et al.*, 2010[141], Russell *et al.*, 2009[142], Longworth *et al.*, 2003[143]).

Table 57: Results of the HRQL search

Study, Country	Population	Recruitment Info	No. of Respondents	Assessment Tools	Response Rate %	Health States and Time Period	Utility Values	**SD and CIs** (for mean values), **IQR** (for median values)	Appropriateness for CEA
(Russell *et al.*, 2009[142]) USA	• Mainly male • Mainly caucasian. • Most prevalent indication for transplantation was non-cholestatic (HBV, HCV, or alcoholic) cirrhosis)	• Piggy back on another study. • Data collection occurred at specific time points (every 6 months on waiting list, then 1 month, 3 months, 6 months, and yearly post-transplant). • A rolling enrolment system allowed for anytime participation	218	EQ-5D	76%	Pre-transplant	0.746 *mean* 0.778 *median*	CI, 0.712 to 0.780 IQR 0.689, 0.843	• Non-UK population • No longitudinal data collected
						Early post-transplant period (12 months)	0.765 *mean* 0.779 *median*	CI, 0.725 to 0.804 IQR 0.708, 0.843	
						Intermediate post-transplant period (13-36 months)	0.832 *mean* 0.816 *median*	CI, 0.797 to 0.866 IQR 0.778, 0.918	
						Late post-transplant period (36 months	0.817 *mean* 0.827 *median*	CI, 0.781 to 0.858 IQR 0.778, 1.0	
(Longworth *et al.*, 2003[143]) UK	• Adult cadaveric liver transplant patients in England and Wales.	• Recruited by questionnaire from centres in UK. • Patients listed for multiorgan transplantation were excluded • Data collected from patients before transplantation then timepoints after.	524	EQ-5D *(and SF-36, but data not reported here)*	90%	At start of waiting list for a transplant	0.517 mean	CI, 0.469–0.566	• UK data for all transplant patients in one year • Only has one timepoint • Uses dataset from Ratcliffe 2002
						12 months post-transplantation	0.608 mean	CI, 0.556–0.651	
(Longworth *et al.*, 2003[132])	• 122 PBC, 155 ALD, and 70 PSC	• Consecutive cohorts of all patients 16 years and older who	298	EQ-5D	86%	At start of waiting list for a transplant	PBC 0.385 *mean* ALD 0.459 *mean* PSC 0.516 *mean*	PBC 0.304 to 0.462 ALD 0.395 to 0.528 PSC 0.434 to 0.600	• EQ5D study elicited in a UK population, as desired in the NICE

UK	patients assessed for a liver transplant • Numbers who underwent transplantation during the study were 81, 82, and 45 for PBC, ALD, and PSC respectively.	were listed for an isolated liver transplant at the 6 centres in England and Wales were recruited. • Recruitment took place over a 12-month period, the start of which was staggered across the centres between December 1995 and December 1996.				3 months on waiting list	PBC 0.393 *mean* ALD 0.314 *mean* PSC 0.492 *mean*	PBC 0.249 to 0.540 ALD 0.146 to 0.489 PSC 0.313 to 0.681	reference case • 3 patient diagnosis subgroups (PBC, PSC, ALD); not entire liver transplant population (the disease subgroups represent around half of patients) • Data is only presented in graphs (raw dataset not available)
						6 months on waiting list	PBC 0.497 *mean* ALD 0.345 *mean* PSC 0.492 *mean*	PBC 0.267 to 0.731 ALD -0.034 to 0.728 PSC 0.114 to 0.741	
						3 months post-transplantation	PBC 0.575 *mean* ALD 0.550 *mean* PSC 0.605 *mean*	PBC 0.509 to 0.644 ALD 0.482 to 0.622 PSC 0.526 to 0.682	
						6 months post-transplantation	PBC 0.578 *mean* ALD 0.560 *mean* PSC 0.659 *mean*	PBC 0.504 to 0.661 ALD 0.491 to 0.640 PSC 0.573 to 0.765	
						12 months post-transplantation	PBC 0.613 *mean* ALD 0.565 *mean* PSC 0.669 *mean*	PBC 0.545 to 0.686 ALD 0.491 to 0.640 PSC 0.573 to 0.765	
						24 months post-transplantation	PBC 0.615 *mean* ALD 0.524 *mean* PSC 0.669 *mean*	PBC 0.553 to 0.691 ALD 0.452 to 0.598 PSC 0.555 to 0.785	
(Perez-San-Gregorio *et al.*, 2010[141]) Spain	• Adult patients who received a liver transplant from a deceased donor at the Hospital Virgen del Rocío of Seville.	• Recruited from a hospital in Seville, patients who were >18 years old at time of transplant waiting-list, able to complete questionnaires, and were having de novo transplants.	27	EQ-5D *(and SF-36, but data not reported here)*	100%	At time of inclusion onto the waiting list	34.26 *mean*	*Not reported*	• Non-UK population • Data not in a 0 to 1 useable format • Average score across 3 domains of EQ-5D questionnaire was used, not patient specific utilities (*e.g.* the overall patient scored 1.6, 1.4, 2.2, 2.0, 1.9 which was then converted to a score)
						6 months post-transplantation	73.52 *mean*		
						12 months post-transplantation	67.78 *mean*		
						24 months post-transplantation	69.63 *mean*		

(Bryan *et al.*, 1998[128]) UK	• Patients who had received a liver transplant at either the Queen Elizabeth Hospital or Royal Free Hospital in past 8 years.	• Postal questionnaire to patients over the age of 16 years at the time of transplant • Recruited from 2 centres in London. • Only patients with a permanent address in either the UK or Ireland were included.	121	EQ-5D *(and SF-36, but data not reported here)*	80%	No specific states - only point in time post-transplant that patient received questionnaire	Mean 0.75 Median 0.78	Mean CI, 0.71 to 0.79 Median IQR 0.69–0.85	• EQ-5D study elicited in a UK population • Subset of patients from only 2 of the 7 UK transplant centres • Results not specific to time post-transplant
(Ratcliffe *et al.*, 2002[136]) UK	• All individuals eligible to receive liver transplantation treatment from the NHS in one of 6 centres in UK.	• Postal questionnaire sent to all individuals eligible to receive transplant • Patients too ill to be asked to complete the questionnaire were not approached.	455	EQ-5D *(and SF-36, but data not reported here)*	84%	At start of waiting list	0.53	p-value .003	• EQ-5D study elicited in a UK population, as desired in the NICE reference case • No utility data for rejection states • Insignificant p-value suggesting no change in HRQL over time post-transplant
						3 months post-transplantation	0.57	Data adjusted for informative dropout p-value 0.55	
						6 months post-transplantation	0.60		
						12 month post-transplantation	0.59		
						24 month post-transplantation	0.56		
(Ratcliffe *et al.*, 2005[144]) UK	• All adults who were listed to receive liver transplants as NHS centres in England and Wales.	• Questionnaire sent out to all undergoing transplants. • Patients who, in the opinion of a clinical research nurse based at the centre, were too severely ill to be approached were not sent a questionnaire.	387	EQ-5D	97%	After 3 months on waiting list	0.365 *mean*	CI, 0.274 to 0.456	• UK data for all transplant patients in one year • Uses data from Ratcliffe 2002
						3 months post-transplantation	0.636 *mean*	CI, 0.605 to 0.667	
						6 months post-transplantation	0.689 *mean*	CI, 0.657 to 0.721	
						12 month post-transplantation	0.717 *mean*	CI, 0.687 to 0.747	
						24 month post-transplantation	0.725 *mean*	CI, 0.688 to 0.762	

Abbreviations: ALD: Alcoholic Liver Disease; CI: Confidence Interval; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IQR: Interquartile range; PBC: Primary biliary cirrhosis; PSC: Primary Sclerosing Cholangitis; UK: United Kingdom; USA: United States of America.

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

No comparison can be made as HRQL data was not collected in the H2304 clinical trial (Lopez *et al.*, 2013[42]).

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Treatment-related adverse events from immunosuppressive treatment regimens such as diabetes hypertension, herpes, tremor, insomnia, CMV and infections negatively impact quality of life by increasing morbidity (Machnicki *et al.*, 2006[145], Sullivan *et al.*, 2011[146]).

A key treatment-related event for consideration is renal dysfunction due to CNI nephrotoxicity. Renal dysfunction presents in the form of CKD which is an irreversible disease. As the stage of CKD worsens, symptoms and loss of normal functions increase in patients (see descriptions in Table 48, section 7.4.9). In addition, the waiting list for a renal transplant (considered for those in CKD stage 5 / end-stage renal disease) is between two to three years in the UK (Organ Donation, 2014[122]) as demand severely outweighs supply.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Following a lack of published studies in the systematic literature review reflective of each of our respective core cost-effectiveness (hepatic rejection) model health states, some assumptions were made with regard to acute rejection states and mild chronic rejection. After discussions with clinical experts who stated that these states are largely asymptomatic, utility was assumed to be the same as stable post-transplant state. The utility score calculated for patients immediately pre-transplant (in a state of liver failure) was applied in the model to patients in a state of graft loss (severe chronic rejection) as these patients would also be in a state of liver failure. Full details of the calculations are provided in section 7.4.15.

Utility scores for the renal sub-model were taken from a study of a UK population using the EQ-5D instrument to elicit scores (Neri *et al.*, 2012[134]). These scores were directly linked to our model's health states so no calculations were necessary.

Utility correlation between the main model and sub model

The clinical experts confirmed that the states in the core and sub-models could be considered independent, thus the HRQL between models was not correlated. However, when considering two detrimental impacts to HRQL (one from hepatic rejection and one from renal dysfunction) there are more than one way in which overall utility can be calculated. Although studies for single health states or disease conditions have been developed in many diseases, an off-the-shelf list is lacking for utilities for joint states (Fu, 2009[147]). The NICE DSU Technical Support Document 12 (Ara *et al.*, 2011[148]) highlights three conventional methods for calculating the overall probability of joint utilities:

- Multiplicative method ($U_{i,j} = U_i \times U_j$)

  e.g. Utility for CKD stage 5 is 0.4 and utility for acute rejection is 0.7. The joint state utility for those with both CKD stage 5 and acute rejection is 0.28 (=0.4 × 0.7).

- Minimum method [$U_{i,j} = \mathrm{Min}(U_i, U_j)$]

  e.g. Utility for CKD stage 5 is 0.4 and utility for acute rejection is 0.7. The joint state utility for those with both CKD stage 5 and acute rejection is 0.4.

- Additive method [$U_{i,j} = 1 – (U_i + U_j)$]

  e.g. Utility for CKD stage 5 is 0.4 and utility for acute rejection is 0.7. The joint state utility for those with both CKD stage 5 and acute rejection is -0.1 (=1 – [0.7 + 0.4]).

One Canadian study (Flanagan *et al.*, 2006[149]) using Health Utility Index Mark 3 scores supported the use of the multiplicative method, however with an extra step of rescaling. On the other hand, two more recent studies in the United States concluded the minimum model was the preferred choice and suggest the multiplicative method having larger bias and less efficiency than the minimum method (Dale *et al.*, 2008[150], Fu *et al.*, 2008[151]). The NICE DSU 12 (Ara *et al.*, 2011[148]) report concludes that there is currently no consensus on the most appropriate technique. For this economic model, a minimum method is used to calculate overall utility from the two models. Table 58 summarises the utility and disutility estimates used in the model.

Table 58: Summary of quality of life values for the cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Utility scores for health states in the main (hepatic rejection) model				
Stable post-transplant state	0.60	0.59 – 0.61	(Ratcliffe *et al.*, 2002[136])	Utility data was best fit of EQ-5D data in UK adult population.
Acute rejection	0.60	0.59 – 0.61	(Ratcliffe *et al.*, 2002[136])	Equalled to *Stable post-transplant state* as clinical expert assumption is that *Acute rejection* is asymptomatic, thus utility is same as in stable state.
Acute steroid resistant rejection	0.60	0.59 – 0.61	(Ratcliffe *et al.*, 2002[136])	Equalled to *Stable post-transplant state* as clinical expert assumption is that *Acute rejection* is asymptomatic, thus utility is same as in stable state.
Mild chronic rejection	0.60	0.59 – 0.61	(Ratcliffe *et al.*, 2002[136])	Equalled to *Stable post-transplant state* as clinical expert assumption is that *Acute rejection* is asymptomatic, thus utility is same as in stable state.
Graft loss (severe chronic rejection)	0.43	0.40 – 0.45	(Ratcliffe *et al.*, 2002[136])	Utility data was best fit of EQ-5D data in UK adult population.
Stable PT via liver re-transplant	0.58	0.55 – 0.60	(Ratcliffe *et al.*, 2002[136])	Utility data was best fit of EQ-5D data in UK adult population.
Death	0	0	(EuroQol, 2009[152])	EQ-5D user manual states the utility of death is zero.
Utility scores for health states in the sub (renal sparing) model				
No CKD	0.83	0.83 – 0.85	Assumption	No impact on health beyond the that incurred in the liver transplant is assumed if the patient has no CKD.
CKD stages 1 to 2	0.64	0.51 - 0.77	(Neri *et al.*, 2012[134]) No range stated, CI +/- 20%	EQ-5D study in a UK adult population.
CKD stage 3	0.58	0.46 – 0.70	(Neri *et al.*, 2012[134]) No range stated, CI +/- 20%	EQ-5D study in a UK adult population.
CKD stage 4	0.49	0.39 – 0.59	(Neri *et al.*, 2012[134]) No range stated, CI +/- 20%	EQ-5D study in a UK adult population.
CKD stage 5	0.28	0.22 – 0.34	(Neri *et al.*, 2012[134]) No range stated, CI +/- 20%	EQ-5D study in a UK adult population.

No CKD following renal transplant	0.81	0.65 – 0.97	(Liem *et al.*, 2008[133])	EQ-5D study in a UK adult population.
Death	0	0	(EuroQol, 2009[152])	EQ-5D user manual states the utility of death is zero.
Disutility scores for treatment related adverse events				
Hypertension	-0.04	-0.116 – -0,041	(Sullivan *et al.*, 2011[146])	No specific data on hypertension in post-liver transplant patients was identified ; general disutility associated with hypertension was used (098 Essential Hypertension).
New onset diabetes	-0.06	-0.180 – -0.061	(Sullivan *et al.*, 2011[146])	No specific data on new onset diabetes in post-liver transplant patients was identified ; general disutility associated with diabetes was used (049 Diabetes mellitus without complications).
Infection	-0.01	-0.029 – -0.0096	*Assumption*	No data relating to infection disutility was identified.
Herpes	-0.001	-0.0026 – 0.0000	(Sullivan *et al.*, 2011[146])	No specific data on herpes in post-liver transplant patients was identified ; general disutility associated with herpes was used (200 other skin disorders).
Tremor	-0.003	-0.0032 – 0.0000	(Sullivan *et al.*, 2011[146])	No specific data on tremor in post-liver transplant patients was identified ; general disutility associated with alcohol related disorders was used (alcohol-related disorders).
Insomnia	-0.04	-0.115 – 0.003	(Sullivan *et al.*, 2011[146])	No specific data on insomnia in post-liver transplant patients was identified ; general disutility associated with sleep disorders was used.
CMV	-0.01	-0.029 – -0.0096	*Assumption*	No data on CMV disutility was identified; assumed the same as infection.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

As described in section 7.3.5, three clinical experts were consulted. In the meeting, the experts were asked questions on the following topics related to HRQL (with their answers sub-bulleted):

- Hepatic rejection:
  - Patients are unlikely to have any health-related quality of life impact from acute rejection episodes (as they are usually asymptomatic).
  - There is a difference between mild chronic rejection and severe chronic rejection as mild chronic rejection bears similar health-related quality of life to those with steroid resistant acute rejection.
  - Severe chronic rejection could be grouped in the model with the state graft loss in terms of costs and health-related quality of life.
- Renal dysfunction:
  - The movement of a patient through the sub (renal sparing) model is independent of the patient's position in the main (hepatic

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

rejection) model (assumption from this point: the utility scores for both models can be assumed non-correlated and independent).

As the experts were in the same telephone meeting together (in separate locations), no iteration was used to collate the feedback as they discussed topics with one another in real time.

Besides the above assumptions, the experts did not assess the final utility scores for validity.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

In each health state of both models, a patient would experience a decrease in their HRQL if they have an adverse event. Table 59 gives a summary of what a patient may experience in each health state in terms of HRQL. Patients in the core model are assumed to have a stable HRQL over time, with most states assuming an asymptomatic state. Only in the more severe states (severe chronic rejection) would patients experience a decrease in HRQL (relative to the other states). In the renal sub-model, patients' HRQL will decrease as they progress and their symptoms worsen until renal transplant.

Table 59: Description of HRQL in each health state (excluding death)

Description of the HRQL in health states in the main (hepatic rejection) model	
Stable post-transplant state	The goal of transplant is to return to a 'normal' HRQL. However, patients have to take daily immunosuppressant's which is associated with a lower utility than average healthy patients (Longworth *et al.*, 2003[132], Ratcliffe *et al.*, 2002[136])
Acute rejection	Acute rejection episodes are assumed to be asymptomatic therefore HRQL is not impacted. However, patients may be hospitalised to treat these episodes.
Acute steroid resistant rejection	Assumed to be asymptomatic. Again, hospitalisation may occur for therapy.
Mild chronic rejection	Assumed asymptomatic, although patients with mild chronic rejection may present with jaundice.
Graft loss (severe chronic rejection)	HRQL is negatively impacted once a patient reaches this state. Original disease (e.g. HCC or HCV) may have recurred whilst ductopenia is common. Jaundice, swelling and bleeding may also present.
Description of the HRQL in health states in the sub (renal sparing) model	
No CKD	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease. Often asymptomatic, therefore no impact on HRQL and usually picked up in testing for other diseases.
CKD stages 1/2	Mildly reduced kidney function, many patients only realising they have CKD at this stage. Symptoms may include elevated blood pressure.
CKD stage 3	Moderately reduced kidney function and complications start to present such as hypertension, anaemia, kidney pain and early bone disease.
CKD stage 4	Severely reduced kidney function with waste product build up in the blood (uraemia). Hypertension, anaemia, cardiovascular problems, nausea, insomnia and concentration problems are all common.
CKD stage 5	Very severe, or end-stage kidney failure with patients feeling severely ill through the build-up of toxins in the blood. Symptoms from stage 4 are probable, along with swelling and muscle cramps. Dialysis is required.
No CKD following renal transplant	Patients return to a reasonably normal HRQL, but maintain immunosuppression. Similar HRQL to the *Stable Post-Transplant State* in the main (hepatic rejection) model.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The incremental cost-effectiveness ratio (ICER) is a measure used to determine the relative cost-effectiveness between two treatment regimens. Hence, items that were deemed to not be influenced by the choice of immunosuppressive regimen and thus have no relative difference on the ICER were not considered. These included:

- Hyperacute rejection (occurs within 24 hours post-transplant and the incidence is not influenced by the immunosuppressive regimen).
- Incidence post-transplant of HCV (justified using clinical expert opinion, please section 7.2.5 and section 6.7).
- Incidence post-transplant of HCC (justified using clinical expert opinion, please section 7.2.5 and section 6.7).

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline time point was immediately (one day) post-transplant. These patients entered in the model state *Stable Post-Transplant*. Thus, the baseline HRQL score was equalled to the score in the first cycle. However, disutility was applied upon entry if the patient experienced an adverse event upon entering the model.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

An examination of the studies identified in the systematic search for HRQL showed inconsistencies across studies with regards to whether HRQL improves over time. From the five studies that recorded data from more than one time-point post-transplantation, two studies showed no increase (Ratcliffe *et al.*, 2002[136], Perez-San-Gregorio *et al.*, 2010[141]) but three studies showed HRQL improving over time (Longworth *et al.*, 2003[132], Ratcliffe *et al.*, 2002[136], Russell *et al.*, 2009[142]). However, the level of graft rejection and graft functioning of the patients in the studies is not reported so it is difficult to establish why some patients may improve over time and some may not. As the model considers stages of rejection separate to no rejection, it would be incorrect to assume an improving trend is applicable to all patients, regardless of their state of rejection in the model due as the published utility trend data is likely derived from a mixed cohort of patients including both rejecters and none rejecters.

Consequently, changing HRQL scores over time were not applied in the model. Fixed scores were applied to each health state, but the consecutive time a patient spends in their health state was assumed not to change their HRQL. Only as patients transit through states over time (driven by transition probabilities in Section 7.3.2) would their HRQL change over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values used in the core cost-effectiveness (hepatic rejection) model were the weighted average scores from the post-transplant data in (Ratcliffe *et al.*, 2002[136]), with scores used that were adjusted for informative dropout. Table 60 displays the values taken from the study, and the calculated weighted average dependent on sample sizes. The p-value associated with these 4 values is 0.55 showing a non-significant difference over time.

Table 60: Weighted average of utility scores over different time points

Timepoint	Utility score adjusted for informative dropout	Sample size	Weighted average
3 months post-transplantation	0.57	309	0.5804
6 months post-transplantation	0.60	301	
12 months post-transplantation	0.59	329	
24 months post-transplantation	0.56	289	

Source: (Ratcliffe *et al.*, 2002[136])

It should be noted that the pre-transplant utility score elicited using the EQ-5D tariff was not adjusted for informative dropout (as this was a value taken at the start of the study so there were no dropouts). The pre-transplant utility score informed the *Graft Loss* health state (as it was assumed that on the waiting list pre-transplant patients have had liver failure).

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Adult patients eligible for everolimus in combination with reduced dose tacrolimus with corticosteroids must have undergone a liver transplantation. Clinical management of post-transplant patients is performed through check-ups post-transplant with the patient's liver specialist, but also through urinary testing (to monitor eGFR), liver function tests and a liver biopsy to determine occurrence of acute rejection. Check-ups with liver specialists are not explicitly stated in the National Schedule of Reference Costs (Department of Health, 2013[153], Curtis, 2013[154]) in the model and this cost was collected directly from liver transplant centres. Neither does the National Schedule of Reference Costs contain data for urinary tests nor liver function tests, however a cost for biopsies of £515 was identified (HRG tariff FZ61Z: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over).

The UK HRG tariff for "Hepatobiliary Transplant, 18 years and over" is GA01C (Department of Health, 2013[153]). The costs for this procedure are displayed in Table 61. This cost is applied in the model to those patients who have entered a state of graft loss and undergo a re-transplantation.

Table 61: Costs for hepatobiliary transplant (HRG tariff GA01C)

Category	Annual activity	Unit cost	Total cost
Total	426	£20,359	£8,672,765
Elective Inpatient	103	£15,630	£1,609,844
Elective Inpatient Excess Bed Days	123	£193	£23,736
Non-Elective Inpatient (Long Stay)	298	£20,422	£6,085,838
Non-Elective Inpatient (Long Stay) Excess Bed Days	743	£884	£656,815
Non-Elective Inpatient (Short Stay)	24	£12,344	£296,256
Day Cases	1	£276	£276

Source: (Department of Health, 2013[153])

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised

As treatment with everolimus plus reduced dose tacrolimus or one of the comparators will have direct cost impact on the NHS, the model utilised NHS reference costs or costs from the PSSRU to populate the model. These were considered to be appropriate as they represented the most up to date national source for costs to the NHS (Department of Health, 2013[153]). The following reference costs were considered appropriate for the intervention being appraised:

- GP visit (from PSSRU's Unit Costs of Health and Social Care).
- HRG tariff FZ61Z (Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over).
- HRG tariff GA01C (Hepatobiliary Transplant, 18 years and over).
- HRG tariff LA01A (19 years and over from cadaver non-heart-beating donor).

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic literature review was conducted in order to identify resource use studies. Patient population and disease terms from the search strings outlined in Section 6 were used in conjunction with a search filter for resource use in the UK (please see Appendix 13 for the full search strategy). The search string was not restricted by any intervention terms as it aimed to also pick up non-intervention specific data pertinent to the health states in the model. Searches were restricted to UK data, but not by language.

Computerised bibliographic databases advised by the CRD (Centre for Reviews and Dissemination, 2009[18]) were searched, including MEDLINE, MEDLINE In-Process, EMBASE, EconLit, the NHS Economic Evaluation Database (NHS EED), and the National Institute for Health Research in Health Technology Assessment (NIHR HTA). The databases were searched on 6th August 2014 and 193 records were retrieved.

Study selection

Records were screened by a primary reviewer and checked by a second reviewer in accordance with the following criteria:

- Population: the study must have data pertaining to UK adult patients who have undergone liver transplantation.
- Outcomes: the study must contain either resource use or unit cost data pertinent to the population of interest.

Full texts were retrieved and checked against the study eligibility criteria. From the 193 records retrieved, 183 were excluded based on title and abstract. Full-texts were retrieved for the remaining 10 studies, from which 3 were selected for data extraction. Figure 12 illustrates the study selection process.

Figure 12: Study selection process of the resource use systematic search

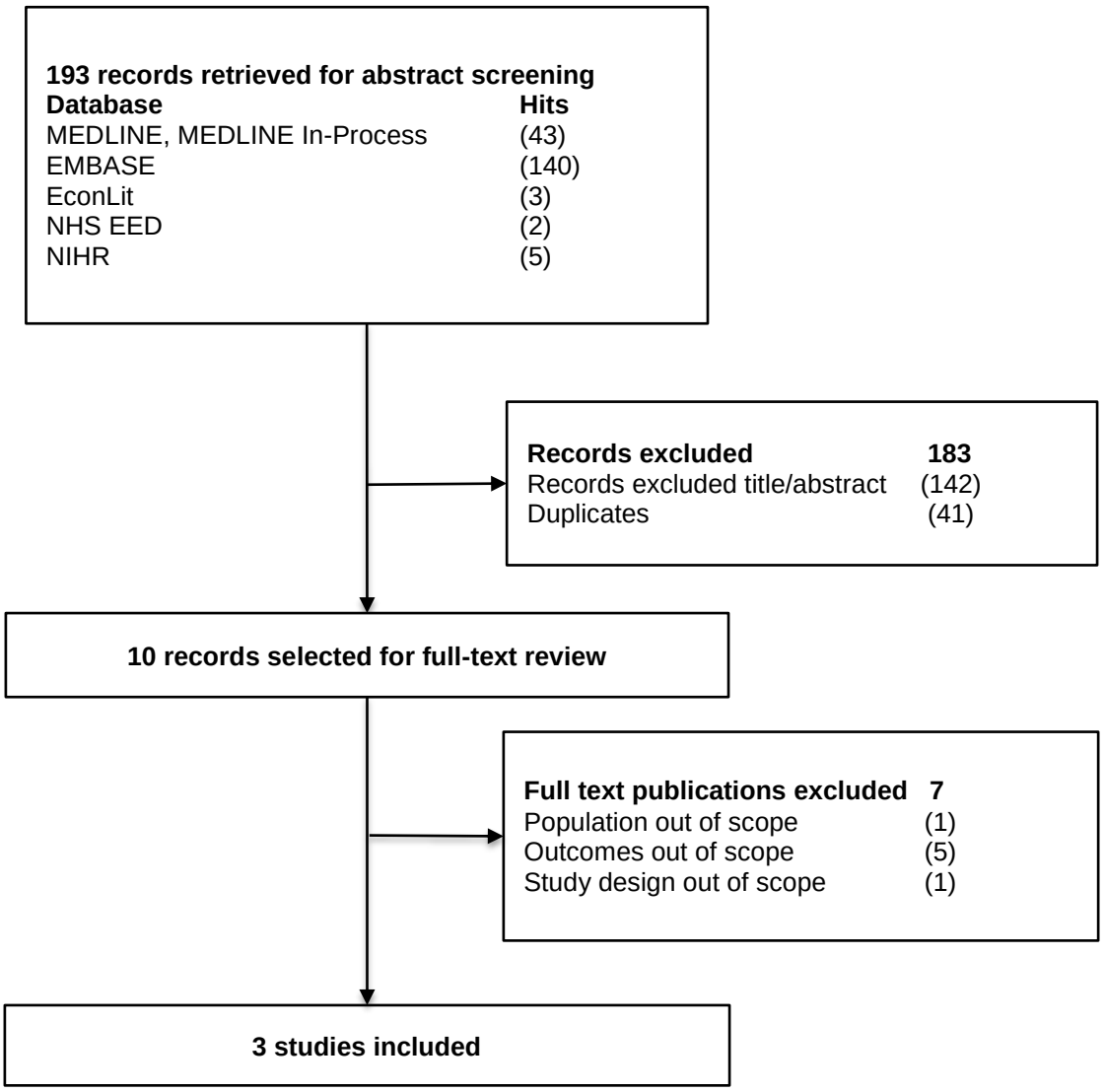


Table 62 displays the extracted data from the 3 final studies. One study focussed on CMV in liver transplant patients, an adverse event of interest to our analysis and included in the model (Annemans *et al.*, 2002[155]). A collated cost for a 14 day treatment of the event was presented (UK data, but presented in Euros), which was based around an intravenously administered Ganciclovir regimen. However, the key drawback of the study is the data is now 13 years old. A study from 1992 (Burroughs *et al.*, 1992[156]) investigated the hospital costs associated with liver transplantation patients. The key drawback of this study was that it was now over 20 years old and it is likely that clinical practice has changed. Finally, one study examined the cost of hospital stay, however this data is provided in the National Schedule of Reference Costs (Department of Health, 2013[153]), so the data from the study was not used in the model (Foxton *et al.*, 2010[157]).

Table 62: Results of the resource use search

Study, Country	Date of study	Applicability to UK clinical practice	Cost valuations in study	Technology costs	Costs for use in economic analysis
(Foxton *et al.*, 2010[157])	January 2000 to December 2003	Data taken from UK liver centre (King's College Hospital, London)	Median hospital stay post-transplantation: • MELD score <11 – ICU stay 2 days (IQR 1-4) – Total hospital stay 18 days – Cost £3600 (IQR £1800-£5400) • MELD score <11-18 – ICU stay 2 days (IQR 1-5) – Total hospital stay 20 days – Cost £3600 (IQR £1800-£7200) • MELD score <19-24 – ICU stay 3 days (IQR 1-8) – Total hospital stay 23.5 days – Cost £5400 (IQR £1800-£14400) • MELD score >24 – ICU stay 8 days (IQR 2-20) – Total hospital stay 23.5 days – Cost £12024 (IQR £4050-£51570)	None reported	As PbR data for hospital stay is available, and our analysis does not segment patients by MELD score, none of the costs are to be used in the model.
(Anneman s *et al.*, 2002[155])	2001	Data taken from the Public Health Laboratory Service and Royal Free London NHS trust	• Cost of treatment strategy for CMV in the UK: €8,490 to €9,180 • This cost includes drug treatment (Ganciclovir IV), testing, imaging, and possible increase in hospital stay	None reported	CMV is an adverse event. For the treatment cost to be considered for use in the model, the range must be converted into pounds at the 2002 exchange rate (= £5408 to £5847). The values must then be inflated to 2013 (= £10,921 to £11,808).

(Burroughs *et al.*, 1992[156])	1989 - 1990	Data taken from Royal Free London NHS trust	• Marginal costs per patient undergoing a liver transplant – initial admission (£11654), outpatients (£205), re-admission within 6 months (£317) • Marginal costs per patient with complications of cirrhosis – initial admission (£2195), outpatients (£280), re-admission within 6 months (£1180) • Fully absorbed costs per patient undergoing a liver transplant – initial admission (£22080), outpatients (£820), re-admission within 6 months (£1144) • Fully absorbed costs per patient with complications of cirrhosis – initial admission (£4978), outpatients (£1118), re-admission within 6 months (£2677)	None reported	Prices are in pounds sterling at 1989 -1990 prices, and would therefore need to inflated to 2014 value (multiple amounts by 2.34).

Resource use data for the core model was derived from contacting a leading liver transplant hospital (University Hospitals Birmingham Foundation Trust, 2013[158]) and assumptions validated by clinical expert opinion. For the renal sub-model, resource use data was taken from NICE clinical guidelines (NICE, 2014[100]) and the literature (Kerr *et al.*, 2012[159]). Table 63 summarises the resource use data by health state.

Table 63: Resource use by health state

States	Items	Resource use	Reference / assumption
Hepatic health states			
Stable post-transplant	GP Visit	1 visit	*Assumption*
	Liver function test	1 test	(UHBFT, 2012[160])
	Full blood count	1 test	(UHBFT, 2012[160])
	Urine and electrolytes	1 test	(UHBFT, 2012[160])
Acute rejection	Hospital inpatient stay	3 days	*Assumption*
	Hospital outpatient visits	1 days	*Assumption*
	GP visit	3 visits	*Assumption*
	Liver function test	3 tests	(UHBFT, 2012[160])
	Full blood count	3 tests	(UHBFT, 2012[160])
	Urine and electrolytes	3 tests	(UHBFT, 2012[160])
	High dose steroid therapy (methylprednisolone)	Average 1.14 courses/patient	*Clinical expert recommendation – 3 courses taken with 86.3% probability of success*
	Liver biopsy	1 test	*Assumption required to confirm rejection*
Acute steroid resistant rejection	Hospital inpatient stay	14 days	*Assumption*
	Hospital outpatient visits	1 days	*Assumption*
	GP visit	6 visits	*Assumption*
	Liver function test	5 tests	(UHBFT, 2012[160])
	Full blood count	5 tests	(UHBFT, 2012[160])
	Urine and electrolytes	5 tests	(UHBFT, 2012[160])
	Antilymphocyte therapy	14 days	*Clinical expert recommendation*
	Liver biopsy	1 test	*Assumption required to confirm rejection*
Mild chronic rejection	Hospital outpatient visits	3 days	*Assumption*
	GP visit	3 visits	*Assumption*

	Liver function test	3 tests	(UHBFT, 2012[160])
	Full blood count	3 tests	(UHBFT, 2012[160])
	Urine and electrolytes	3 tests	(UHBFT, 2012[160])
Acute steroid resistant rejection	Hospital inpatient stay	3 days	*Assumption*
	Hospital outpatient visits	14 days	*Assumption*
	GP visit	3 visits	*Assumption*
	Liver function test	6 tests	(UHBFT, 2012[160])
	Full blood count	6 tests	(UHBFT, 2012[160])
	Urine and electrolytes	6 tests	(UHBFT, 2012[160])
Stable post-transplant (first cycle after re-transplant)	GP visit	1 visit	*Assumption*
	Liver function test	1 test	(UHBFT, 2012[160])
	Full blood count	1 test	(UHBFT, 2012[160])
	Urine and electrolytes	1 test	(UHBFT, 2012[160])
	Liver transplant	1 transplant	*Assumption*
Renal health states			
CKD stages 1 to 2	GP visit	0.5 visits	(Kerr *et al.*, 2012[159])
	eGFR test	0.25 tests	(NICE, 2014[100])
CKD stage 3	GP visit	0.5 visits	(Kerr *et al.*, 2012[159])
	eGFR test	0.50 tests	(NICE, 2014[100])
CKD stage 4	Hospital outpatient visits	0.25 days	(NICE, 2014[100])
	eGFR test	1 test	(NICE, 2014[100])
	Renal ultrasound	0.25 tests	(NICE, 2014[100])
CKD stage 5	Hospital outpatient visits	0.25 days	(NICE, 2014[100])
	GP visit	0.5 visits	(Kerr *et al.*, 2012[159])
	eGFR test	1.0 tests	(NICE, 2014[100])
	Haemodialysis	0.25 of annual course	(NICE, 2014[100])
	Peritoneal dialysis	0.25 of annual course	(NICE, 2014[100])
	Waiting list clinic attendances	0.25 of annual cost	(Kerr et al. 2012)
Post renal	Renal transplant	1 transplant	*Assumption*

transplant	Post-transplant on going care costs	0.25 of annual cost	(Kerr et al. 2012)

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Three experts were consulted, two external to the manufacturer and one internally. Details for these experts (including conflicts of interest, method of interviews, and presentation of background materials) are described in Section 7.3.5. The clinical experts were used to determine the following:

- High dose methylprednisolone therapy is the first line therapy for patients suffering from acute rejection.
- Antilymphocyte therapy is the second line therapy for patients with acute steroid resistant rejection.
- No therapy can be assumed to be administered for patients with mild chronic rejection.

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Three components were considered for intervention and comparator costs:

- The list price of the individual technologies in the regimen.
- Costs relating to the administration of the regimens.
- Costs related to the monitoring of patients on the regimens.

The price of individual technologies in the regimens was taken from the British National Formulary (BNF, 2014[127]) and the Commercial Medicines Unit (Commercial Medicines Unit, 2014[161]) websites (searched July 2014) apart from the cost of everolimus (list price provided by the manufacturer) With respect to administration costs, therapies are taken orally. The only exception is intravenous MMF which is administered in the first 2 weeks post-transplant. The MHRA states that tacrolimus is to be prescribed by brand, and therefore we have used the Prograf brand price in the model. It is assumed a patient is still in hospital recovering from their transplant in this time and hence no additional administration costs need to be considered as the patient is already incurring in-patient stay costs. No on-going monitoring costs were included as it was assumed that that these were included in the consultations costs to avoid double-counting.

Table 64 shows the cost per milligram for each technology within each regimen, the daily dose (as of the first day the technology is administered before it may be titrated), and the expected annual cost of the regimen which takes into account the average body weight (73.9kg) of a patient for the doses that are determined by kilogram of body weight.

Table 64: Unit costs of medication in the economic model

Regimen/drug	Cost per mg	Reference in submission	Cost per patient per day (starting dose)	Annual cost in Year 1 post-transplant
Everolimus regimen cost per cycle				**£9,084.89 per year**
Everolimus	£9.90	Manufacturer internal	£19.80 /day	£6,624.75 per year
Tacrolimus	£1.61	Prograf® (BNF, 2014[127])	£5.04 /day	£2,438.13 per year
Corticosteroid	£0.01	Prednisolone (Commercial Medicines Unit, 2014[161])	£0.00 /day	£22.01 per year
Azathioprine regimen cost per cycle				**£3,967.22 per year**
Azathioprine	£0.001	non-proprietary (Commercial Medicines Unit, 2014[161])	£0.08 /day	£28.00 per year
Tacrolimus	£1.61	Prograf® (BNF, 2014[127])	£8.51 /day	£3917.22 per year
Corticosteroid	£0.01	Prednisolone (Commercial Medicines Unit, 2014[161])	£0.00 /day	£22.01 per year
MMF regimen cost per cycle				**£4,654.56 per year**
MMF intravenous	£0.02	CellCept® (BNF, 2014[127])	£0.00 /day	£512.12 per year
MMF oral	£0.0004	non-proprietary (Commercial Medicines Unit, 2014[161])	£1.16 /day	£203.21 per year
Tacrolimus	£1.61	Prograf® (BNF, 2014[127])	£8.51 /day	£3917.22 per year
Corticosteroid	£0.01	Prednisolone (Commercial Medicines Unit, 2014[161])	£0.00 /day	£22.01 per year

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Table 65 lists all the health states in both the core cost-effectiveness (hepatic rejection) model and the renal sub-model. The costs used in the model were sourced from NHS reference costs, PSSRU unit costs for health and social care, TA 252, and from the University Hospital Birmingham NHS Foundation Trust. Total cost per health state was calculated by multiplying the unit costs in Table 65 by the costs in Table 63 in section 7.5.3. These costs were chosen as they are representative of English clinical practice costs as they are sourced from national or local sources.

Table 65: Summary of non-medication related costs by health state

States	Items	Value	Reference in submission
Hepatic health states			
Stable post-transplant	GP Visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013**
	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	Total*	**£72.19**	
Acute rejection	Hospital inpatient stay	£337.94 per day	(Department of Health, 2013[153]) (GC01D) Liver Failure Disorders with single intervention gastroenterology
	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	GP visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43 per test	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013**
	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	High dose steroid therapy (methylprednisolone)	£32.16 per course	(Commercial Medicines Unit, 2014[161])
	Liver biopsy	£514.63	(Department of Health, 2013[153]) (FZ61Z)
	Total	**£1,922.32**	
Acute steroid-resisitant rejection	Hospital inpatient stay	£337.94 per day	(Department of Health, 2013[153]) (GC01D)
	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	GP visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43 per test	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013**
	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	Antilymphocyte therapy	£703.99 per 14 day course	(Commercial Medicines Unit, 2014[161])
	Liver biopsy	£514.63	(Department of Health, 2013[153]) (FZ61Z)
	Total	**£6,506.47**	
Mild chronic rejection	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	GP visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43 per test	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013*8

	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	Total	**£638.77**	
Acute steroid resistant rejection	Hospital inpatient stay	£337.94 per day	(Department of Health, 2013[153]) (GC01D)
	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	GP visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43 per test	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013**
	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	Total	**£2,126.36**	
Stable post-transplant (first cycle after re-transplant)	GP visit	£55.00	(Curtis, 2013[154])
	Liver function test	£5.43 per test	(NICE, 2012[162]), inflated to 2013**
	Full blood count	£3.32 per test	(NICE, 2012[162]), inflated to 2013**
	Urine and electrolytes	£8.44 per test	(NICE, 2012[162]), inflated to 2013**
	Liver transplant	£20,358.60	(Department of Health, 2013[153]) (GA01C)
	Total	**£20,430.80**	
Renal health states			
No CKD	*No costs*		
CKD stages 1 to 2	GP visit	£55.00	(Curtis, 2013[154])
	eGFR test	£150.00 per test	(NICE, 2014[163]). eGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. NICE diagnostics guidance 9.
	Total	**£66.35**	
CKD stage 3	GP visit	£55.00	(Curtis, 2013[154])
	eGFR test	£150.00 per test	(NICE, 2014[163])
	Total	**£107.39**	
CKD stage 4	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	eGFR test	£150.00 per test	(NICE, 2014[163])
	Renal ultrasound	£52.00 per scan	(Department of Health, 2013[153]) Ultrasound Scan, less than 20 minutes – (RA23Z)
	Total	**£126.62**	
CKD stage 5	Hospital outpatient visits	£140.73	(University Hospitals Birmingham Foundation Trust, 2013[158])
	GP visit	£55.00	(Curtis, 2013[154])
	eGFR test	£150.00 per test	(NICE, 2014[163])

	Haemodialysis	£30,020.01 per year	(Kerr *et al.*, 2012[159]) Inflated to 2013 prices from 2009
	Peritoneal dialysis	£25,069.32 per year	(Kerr *et al.*, 2012[159]) Inflated to 2013 prices from 2009
	Waiting list clinic attendances	£3,709.58 per patient year	(Kerr *et al.*, 2012[159]) Inflated to 2013 prices from 2009
	Total	**£17,282.90**	
Post renal transplant	Renal transplant	£17,266.00 per transplant	(Department of Health, 2013[153]) (LA01A)
	Post-transplant on going care costs	£9,137.23 per patient year	(Kerr *et al.*, 2012[159]) Inflated to 2013 prices from 2009
	Total	**£2,562.73 (plus one-off cost of renal transplant)**	

* Totals represent the cost per cycle **The source in the submission is not stated.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costs associated with treating adverse events are listed in Table 66. The expected cost per treatment regimen is calculated in the model by applying the cost of treating events with the probability of incurring the events. The probability of events can be found in Section 7.3 (Table 54).

Table 66: Adverse event costs used in the economic model

Adverse event	Items	Treatment cost	Reference in submission
Hypertension	Single treatment cost	£769.00	(Department of Health, 2013[153]) EB047)
New onset diabetes	Single treatment cost	£1,840.00	(Davidson *et al.*, 2003[164])*
Infection	Single treatment cost	£649.00	(Department of Health, 2013[153]) (PA18B) Minor Infections with CC Score 0
Herpes	GP visit	£55.00	(Curtis, 2013[154])
Tremor	GP visit	£55.00	(Curtis, 2013[154])
Insomnia	GP visit	£55.00	(Curtis, 2013[154])
CMV	Single cost includes IV Ganciclovir IV, testing, imaging, hospital stay (14 days)	£11,365.00	(Annemans *et al.*, 2002[155])*

*inflated to 2013 prices.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No other additional costs.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the core cost-effectiveness model is based upon patients transiting between health states over time dependent on a set of treatment arm-specific or general underlying transition probabilities. As there is uncertainty around this, four structural analyses / scenarios were tested to examine their influence on the ICER:

1. In the core cost-effectiveness model (hepatic), the state of *Mild Chronic Rejection* was removed.
   - This was performed as it is assumed that a patient who enters this state does not do so on account of their immunosuppressive regimen but rather it has a non-treatment specific underlying cause.

2. The opportunity for future transplantation was removed (in both the hepatic and renal models).
   - When a patient reaches a state of *Severe Chronic Rejection Leading to Graft Loss* in the main (hepatic rejection) model, the patient is placed on the waiting list for a new liver transplant.
   - When a patient progresses through the stages of CKD in the sub (renal sparing) model, they will persist in a state of *CKD Stage 5* whilst on dialysis until the point of a renal transplant.
   - It was expected that by removing these options for future transplants, patients would persist longer in the end states in both models and, because these states carry a high mortality rate, it was expected that the life years lived and the QALYs in each treatment arm would fall.
3. The core cost-effectiveness model (hepatic rejection) was run without the renal sub-model.
   - Everolimus with reduced dose tacrolimus and corticosteroids offers value as it is a renal sparing regimen that dampens the extent of renal dysfunction compared with standard dose tacrolimus regimens. The high success rates of therapy for acute rejections makes graft rejection a manageable process in today's world, so the true focus of benefit is on renal functioning.
   - By running the main (hepatic rejection) model only, it is expected to show minimal difference in life years lived and QALYs gained between treatment arms due to the good management of rejection. Such a result validates the hypothesis that the real value of this exercise is the renal sparing affect that everolimus with reduced dose tacrolimus and corticosteroids offers.
4. The change in baseline eGFR from 81 mL/ min per 1.73 m^2 (Lopez *et al.*, 2013[42]) to 60mL/min per 1.73 m^2.
   - One difference highlighted in section 6.10 between the H2304 trial and UK clinical practice was that the trial contained non-UK patients, dominated by US patients.
   - A discussion with a clinical expert revealed the profile of UK candidates for immunosuppressive treatment is usually a CKD stage lower than the US and the baseliner range would be more realistically around 55-65 mL/min per 1.73 m^2 post-transplant.
   - It is expected that lowering the eGFR used at the model's start will speed up the transitions to *CKD Stage 5* and consequential renal transplantation following this.

The results of the above four scenario and structural sensitivity analyses are presented in section 7.7.9.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The DSU guidance for patient level simulations in cost-effectiveness models (Davis *et al.*, 2014[103]) states that probabilistic sensitivity analysis is preferred to a deterministic sensitivity analysis. As running a full one-way sensitivity analysis on all variables would not be practicable given the necessary run time, only probabilistic sensitivity analysis is shown.

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis was run using 1,000 probabilistic simulations using 5,000 patients in the cohort for each simulation. These numbers were chosen to balance the model stability with a practical run time (current run time for PSA is 3.5 days). The lists of parameters included in the PSA are set out in Table 67 with the standard errors, the interval ranges and the distributions selected for the parameters. The key efficacy parameters that drove both the main and sub models were considered as well as all health state costs and all health state utilities.

Table 67: Parameters included in the PSA

Variable	Deterministic point estimate	Standard error	Lower interval	Upper interval	Distribution
Utility scores by health state					
Stable post-transplant state	0.58	0.01	0.56	0.60	Beta
Acute rejection	0.58	0.01	0.56	0.60	Beta
Acute steroid resistant rejection	0.58	0.01	0.56	0.60	Beta
Mild chronic rejection	0.58	0.01	0.56	0.60	Beta
Graft loss (severe chronic rejection)	0.53	0.01	0.50	0.56	Beta
Stable PT via liver re-transplant	0.58	0.01	0.56	0.60	Beta
No CKD	0.83	0.01	0.83	0.85	Beta
CKD stages 1 to 2	0.64	0.07	0.51	0.77	Beta
CKD stage 3	0.58	0.06	0.46	0.70	Beta
CKD stage 4	0.49	0.05	0.39	0.59	Beta
CKD stage 5	0.28	0.03	0.22	0.34	Beta
No CKD post renal transplant	0.81	0.08	0.65	0.97	Beta
Unit costs					
Hospital inpatient stay per day	£337.94	33.97	240.50	373.65	Gamma
Hospital outpatient visit	£140.73	14.36	112.58	168.88	Gamma
GP visit	£55.00	5.61	44.00	66.00	Gamma
Liver function test	£5.43	0.55	4.35	6.52	Gamma
Full blood count (FBC)	£3.32	0.34	2.66	3.99	Gamma
Urine and Electrolytes	£8.44	0.86	6.75	10.13	Gamma
High dose methylprednisolone	£32.16	3.28	25.73	38.59	Gamma

therapy					
Antilymphocyte therapy	£703.99	71.84	563.19	844.78	Gamma
Therapy for mild chronic rejection	£0.00	0.00	0.00	0.00	Gamma
Liver biopsy	£514.63	117.16	285.00	744.25	Gamma
Liver transplant	£20,358.60	3574.23	12437.00	26448.00	Gamma
eGFR Test	£140.73	14.36	112.58	168.88	Gamma
Renal ultrasound	£55.00	5.61	44.00	66.00	Gamma
Haemodialysis	£150.00	15.31	120.00	180.00	Gamma
Peritoneal dialysis	£52.00	9.69	31.00	69.00	Gamma
Waiting list clinic attendances	£30,020.01	3063.27	24016.01	36024.01	Gamma
On-going care costs post-renal transplant	£25,069.32	2558.09	20055.46	30083.19	Gamma
Renal transplant	£3,709.58	378.53	2967.66	4451.50	Gamma
Efficacy data for the everolimus with reduced dose tacrolimus and corticosteroids					
Probability of survival at 12 months	87.1%	0.09	0.72	0.95	Beta
Probability of survival at 24 months	85.3%	0.09	0.73	0.93	Beta
Hepatic graft survival at 12 months	80.4%	0.08	0.63	0.91	Beta
Hepatic graft survival at 24 months	79.7%	0.08	0.67	0.88	Beta
BPAR free at 3 months	98.1%	0.10	0.94	1.00	Beta
BPAR free at 6 months	94.4%	0.09	0.89	0.98	Beta
BPAR free at 12 months	89.5%	0.09	0.82	0.94	Beta
eGFR decrease at 12 months	23.1	2.783	27.4	18.7	Log-normal
Efficacy data for the azathioprine with standard dose tacrolimus and corticosteroids					
Probability of survival at 12 months	92.8%	0.09	0.88	0.96	Beta
Probability of	85.8%	0.09	0.77	0.92	Beta

survival at 24 months					
Hepatic graft survival at 12 months	89.5%	0.09	0.84	0.93	Beta
Hepatic graft survival at 24 months	80.8%	0.08	0.71	0.88	Beta
BPAR free at 3 months	86.2%	0.09	0.80	0.91	Beta
BPAR free at 6 months	78.7%	0.08	0.34	0.96	Beta
BPAR free at 12 months	75.6%	0.08	0.65	0.84	Beta
eGFR decrease at 12 months	31.6	3.142	32.30	30.90	Log-normal
Efficacy data for the MMF with standard dose tacrolimus and corticosteroids					
Probability of survival at 12 months	92.8%	0.09	0.88	0.96	Beta
Probability of survival at 24 months	85.8%	0.09	0.77	0.92	Beta
Hepatic graft survival at 12 months	89.5%	0.09	0.84	0.93	Beta
Hepatic graft survival at 24 months	80.8%	0.08	0.71	0.88	Beta
BPAR free at 3 months	86.2%	0.09	0.80	0.91	Beta
BPAR free at 6 months	78.7%	0.08	0.34	0.96	Beta
BPAR free at 12 months	75.6%	0.08	0.65	0.84	Beta
eGFR decrease at 12 months	31.6	3.142	32.30	30.90	Log-normal
Underlying CKD disease progression data					
No CKD to CKD stage 1/2	7.0%	0.01	0.06	0.08	Beta
CKD stages 1/2 to CKD stage 3	34.0%	0.03	0.27	0.41	Beta
CKD stage 3 to CKD stage 4	56.0%	0.06	0.45	0.67	Beta
CKD stage 4	3.0%	0.00	0.02	0.04	Beta

to CKD stage 5					
Adverse Events – Everolimus with reduced tacrolimus					
Hypertension	40.3%	0.06	29.1%	52.4%	Beta
New onset diabetes	15.7%	0.04	9.7%	24.0%	Beta
Infection	65.7%	0.05	56.4%	74.1%	Beta
Herpes	0.4%	0.0002	0.4%	0.4%	Beta
Tremor	10.2%	0.01	9.2%	11.2%	Beta
Insomnia	6.9%	0.004	6.2%	7.6%	Beta
CMV	4.1%	0.002	3.7%	4.5%	Beta
Adverse Events – Azathioprine with standard tacrolimus					
Hypertension	57.8%	0.14	28.7%	83.2%	Beta
New onset diabetes	18.3%	0.07	7.8%	36.1%	Beta
Infection	60.3%	0.07	45.9%	73.8%	Beta
Herpes	5.9%	0.003	5.3%	6.5%	Beta
Tremor	35.5%	0.02	32.0%	39.1%	Beta
Insomnia	47.0%	0.02	42.3%	51.7%	Beta
CMV	8.0%	0.004	7.2%	8.8%	Beta
Adverse Events – MMF with standard tacrolimus					
Hypertension	23.9%	0.06	14.2%	37.0%	Beta
New onset diabetes	11.6%	0.02	7.6%	16.7%	Beta
Infection	62.6%	0.07	48.8%	74.6%	Beta
Herpes	10.1%	0.01	9.1%	11.1%	Beta
Tremor	33.9%	0.02	30.5%	37.3%	Beta
Insomnia	52.3%	0.03	47.1%	57.5%	Beta

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The model is not structured to provide time to event analysis and as the clinical trial endpoints involved time to event outcome measures, this table cannot be provided. As stated in Section 5, graft function, graft fibrosis, and time to recurrence of hepatocellular carcinoma were not included in this model and therefore cannot be compared. The decision to exclude these items was based upon clinical expert opinion. HRQL was not measured in the trial and therefore this comparison is not made. However, time spent in each health state for a cohort of 10,000 patients is presented in Table 68.

Table 68: Average number of cycles spent in state by the cohort

Cycles in state	EVR + reduced TAC	AZA + standard TAC	MMF + standard TAC
Stable post-transplant	33.012	31.735	31.327
Acute Rejection	0.785	0.771	0.363
Steroid resistant acute rejection	0.014	0.015	0.006
Mild chronic rejection	6.777	6.571	6.974
Severe rejection	0.005	0.004	0.002
Stable post re-transplant	0.002	0.002	0.001
No CKD	0.000*	0.000	0.000
CKD1to2	5.278	4.848	4.753
CKD3	4.453	4.332	4.000
CKD4	14.421	14.328	14.129
CKD5	2.729	3.164	3.128
No CKD post transplant	4.271	4.868	4.799

*zero does not necessarily mean that no time was spent in state, but only that a small amount of time was spent in this state in the cohort. Patients would only spend 1 cycle in severe rejection, therefore the total time in this state on average is virtually zero. Similarly, most patients would already start the model in CKD1to2 and therefore the number of patients spending any time in No CKD is very small.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

As this is a patient simulation model, a Markov trace for each patient is not possible. However, Table 68 provides an indication of the average time spent in each health state by comparator.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

A patient level simulation approach is used in the model with a matrix grid tracking a patient's health states over time. Table 69 gives an example of how a patient moves through the model with costs and utilities accrued each cycle (this simplified example does not show non-health state costs and utilities such as drug costs and adverse event disutilities).

Once a patient exits the model from mortality, (their total costs, total life years lived, and total utility accrued is determined. To adjust for the cycle length of three months, total utilities are summed and divided by four to get the expected utility gain over a lifetime.

The patient level simulation simulates 10,000 patients in the base case analysis and the mean results of all these patients can be calculated to provide a single cost and QALY score per treatment arm.

Table 69: Example of tracking a single patient's accrued costs and utility as they move through the patient level simulation model over time

Cycle	State X	State Y	State Z	Costs in state	Utility in state
1 (Months 1-3)	*Patient starts in state X*			£ x	U_x
2 (Months 4-6)	*Patient in state X*			£ x	U_x
3 (Months 7-9)		*Patient moved to state Y*		£ y	U_y
4 (Months 10-12)		*Patient in state Y*		£ y	U_y
5 (Months 13-15)			*Patient moved to state Z*	£ z	U_z
6 (Months 16-18)			*Patient in state Z*	£ z	U_z
etc…					

It should be noted that discounting was applied every cycle before total lifetime utilities (and costs) were summed. This is opposed to summing utilities and then applying a discount rate afterwards.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

It is not possible to provide QALYs accrued for each clinical outcome as the clinical outcomes in section 6 are time to event outcomes. In the core cost-effectiveness (hepatic rejection) model and in the renal sub-model, quality adjusted life years are evaluated for each patient based on their health state, which is detailed in section 7.7.5.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 70 gives the undiscounted QALY results disaggregated by health state when comparing EVR + reduced TAC with MMF + standard TAC. Table 71 gives the undiscounted QALY results by health state when comparing EVR + reduced TAC with AZA + standard TAC. As the model does not track the time a patient has spent in each state, it is not possible to give disaggregated, discounted utilities. Patients in the cohort gained the majority of their QALYs in the *Stable Post Transplant State*. In the renal sub-model patients gained the most QALYs while in the CKD4 stage. This is reflective of the time spent in these states as seen in Table 68.

Table 70: Summary of undiscounted QALY gain by health state for EVR vs. MMF

Health state	QALY EVR + reduced TAC	QALY MMF + standard TAC	Increment	Absolute increment	% absolute increment
Stable post-transplant	19.160	18.182	0.978	0.978	73%
Acute rejection	0.456	0.211	0.245	0.245	18%
Acute steroid resistant rejection	0.008	0.004	0.004	0.004	0%
Mild Chronic rejection	3.934	4.048	-0.114	0.114	9%
Severe Chronic Rejection	0.002	0.001	0.002	0.002	0%
Stable post-rejection (post re-transplant)	0.001	0.000	0.001	0.001	0%
Total Hepatic Model	23.561	22.446	1.116	1.116	100%
No CKD	0.000	0.000	0.000	0.000	0%
CKD 1 to 2	3.378	3.042	0.336	0.336	30%
CKD 3	2.583	2.498	0.085	0.085	8%
CKD 4	7.066	6.923	0.143	0.143	13%
CKD 5	0.764	0.876	-0.112	0.112	10%
No CKD (post transplant)	3.460	3.887	-0.428	0.428	39%
Total Renal sub-model	17.251	17.226	0.025	1.103	100%

QALY, Quality-Adjusted Life Year
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 71: Summary of undiscounted QALY gain by health state for EVR vs. AZA

Health state	QALY EVR + reduced TAC	QALY AZA + standard TAC	Increment	Absolute increment	% absolute increment
Stable post-transplant	19.160	18.419	0.741	0.741	85%
Acute rejection	0.456	0.448	0.008	0.008	1%
Acute steroid resistant rejection	0.008	0.008	0.000	0.000	0%
Mild Chronic Rejection	3.934	3.814	0.120	0.120	14%
Severe Chronic Rejection	0.002	0.002	0.000	0.000	0%
Stable post-rejection (post re-transplant)	0.001	0.001	0.000	0.000	0%
Total hepatic model	23.561	22.692	0.869	0.869	100%
No CKD	0.000	0.000	0.000	0.000	0%
CKD 1 to 2	3.378	3.103	0.275	0.275	28%
CKD 3	2.583	2.513	0.070	0.070	7%
CKD 4	7.066	7.021	0.045	0.045	5%
CKD 5	0.764	0.886	-0.122	0.122	12%
No CKD (post transplant)	3.460	3.943	-0.483	0.483	49%
Total renal model	17.251	17.465	-0.215	0.996	100%

QALY, Quality-Adjusted Life Year
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

It is not possible to derive the resource use by cost group, as each health state had different components of resource use. As the model calculated costs for each health state by multiplying the associated resource use by the cost of that resource via the sum product function in Excel, a back calculation cannot be performed.

Table 72 presents a summary of the average health state costs for the core cost-effectiveness model, the renal sub-model, and adverse event costs for the comparison of EVR + reduced dose tacrolimus and MMF + standard dose tacrolimus. The cost difference between these comparators was largely driven by a difference in patients in CKD5. Table 73 presents the incremental costs when EVR + reduced TAC is compared to AZA + standard TAC.

Table 72: Summary of costs by health state for EVR + reduced TAC and MMF + standard TAC

Health state	Cost EVR + reduced TAC	Cost MMF + standard TAC	Increment	Absolute increment	% absolute increment
Stable post-transplant	2,383.24	2,261.62	121.62	121.62	11%
Acute Rejection	1,509.02	697.23	811.80	811.80	71%
Steroid resistant acute rejection	90.44	40.99	49.45	49.45	4%
Mild Chronic Rejection	4,329.13	4,454.91	-125.77	125.77	11%
Severe rejection	9.78	3.19	6.59	6.59	1%
Stable post-retransplant	46.99	12.26	34.73	34.73	3%
Total cost hepatic model	8,368.61	7,470.20	898.41	1,149.96	100%
No CKD	0.00	0.00	0.00	0.00	0%
CKD1to2	343.10	308.96	34.14	34.14	0%
CKD3	456.39	410.00	46.39	46.39	1%
CKD4	1,776.39	1,740.43	35.96	35.96	0%
CKD5	40,697.46	46,646.02	-5,948.56	5,948.56	82%
No CKD post transplant	9,756.51	10,962.85	-1,206.34	1,206.34	17%
Total cost renal sub-model	53,029.84	60,068.26	-7,038.42	7,271.39	100%

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 73: Summary of costs by health state for EVR + reduced TAC and AZA + reduced TAC

Health state	Cost EVR + reduced TAC	Cost AZA + standard TAC	Increment	Absolute increment	% absolute increment
Stable post-transplant	2,383.24	2,291.06	92.18	92.18	34%
Acute Rejection	1,509.02	1,482.49	26.53	26.53	10%
Steroid resistant acute rejection	90.44	94.99	-4.55	4.55	2%
Mild Chronic Rejection	4,329.13	4,197.35	131.78	131.78	49%
Severe rejection	9.78	8.08	1.70	1.70	1%
Stable post-retransplant	46.99	34.73	12.26	12.26	5%
Total cost hepatic model	8,368.61	8,108.71	259.89	269.00	100%
No CKD	0.00	0.00	0.00	0.00	0%
CKD1to2	343.10	315.13	27.96	27.96	0%
CKD3	456.39	444.04	12.35	12.35	0%
CKD4	1,776.39	1,765.01	11.38	11.38	0%
CKD5	40,697.46	47,188.83	-6,491.37	6,491.37	82%
No CKD post transplant	9,756.51	11,119.32	-1,362.82	1,362.82	17%
Total cost renal sub-model	53,029.84	60,832.34	-7,802.49	7,905.89	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

A decision was made on the basis of UK market share data (see Section 10) that the MMF regimen would be used as the standard of care as it is currently the most commonly prescribed therapy for immunosuppressive therapy in liver transplant patients. The results of the modelling presented in Table 74 indicate that it is also the least costly and least effective, which also supports this decision.

Figure 13 presents the cost-effectiveness frontier with MMF + standard TAC as the baseline therapy (point at zero). EVR + reduced TAC compared to MMF + standard TAC is more costly and more effective (£110,797 per QALY gained). The incremental analysis indicates that when compared to AZA + standard TAC, EVR + reduced TAC is more costly and more effective (£187,842 per QALY gained).

Figure 13: Cost-effectiveness frontier

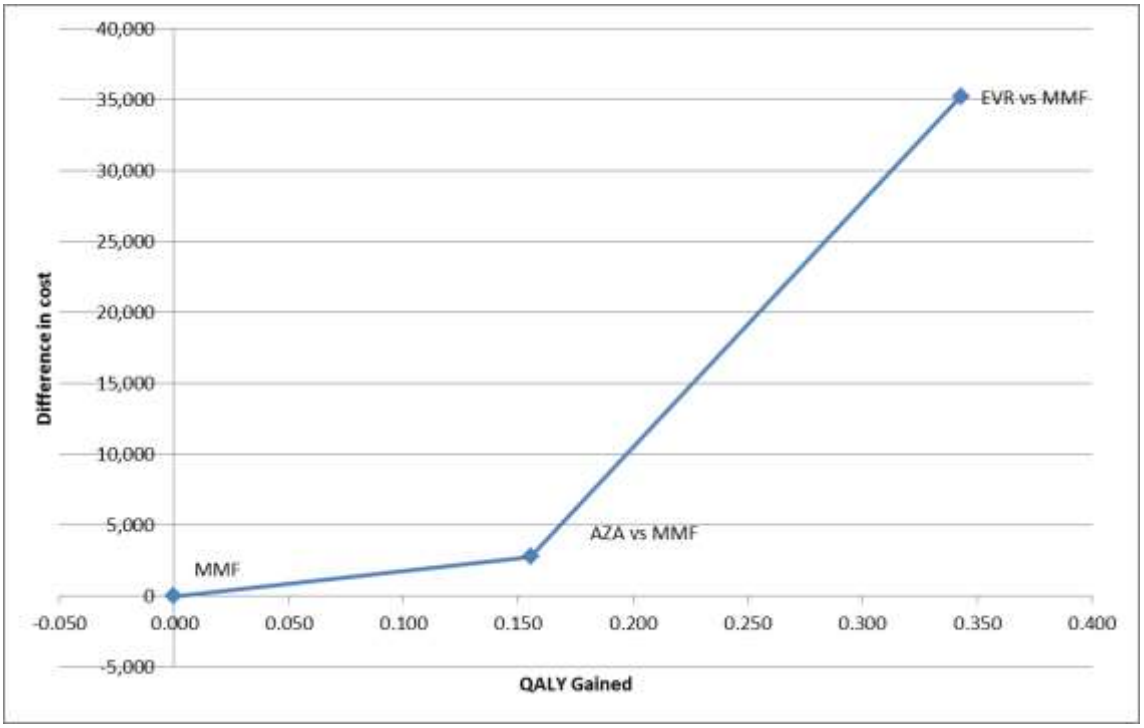


Table 74: Deterministic base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incrementa (EVR vs AZA)l (QALYs)
MMF + standard TAC*	102,746	9.691	3.867					
AZA + standard TAC	105,529	9.796	4.022	2,783	0.106	0.156	17,895	
EVR + reduced TAC	140,750	10.171	4.210	38,004	0.480	0.343	110,797	187,842

*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

No deterministic sensitivity analyses were conducted.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

A PSA was run using 1,000 simulations by 1,000 patients to balance the model stability with a practical run time. The results indicate a stable pattern of results at this level of simulation. A test of 2,000 by 5,000 patients (which increased model run time from 26 hours to 84 hours) gave similar results. The results of this analysis indicate an ICER similar to that of the base case deterministic patient simulation.

- The results for EVR + reduced TAC versus MMF+ standard TAC showed an incremental cost per LY gained of £152,521, and an incremental cost per QALY gained of £105,526 (Table 75).
- The results for EVR + reduced TAC versus AZA + standard TAC showed an incremental cost per LY gained of £141,537, and an incremental cost per QALY gained of £184,714 (Table 75).
- The results for AZA + standard TAC versus MMF + standard TAC showed that MMF + standard TAC dominated AZA + standard TAC when comparing life years gained, but an incremental cost per QALY gained of £13,762 (Table 75).

Table 75: PSA results with MMF as the baseline therapy

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incrementa (EVR vs AZA)l (QALYs)
MMF + standard TAC*	104,240	9.925	4.945					
AZA + standard TAC	106,384	9.922	5.101	2,145	-0.003	0.156	13,762	
EVR + reduced TAC	139,746	10.157	5.281	35,506	0.233	0.336	105,526	184,714

*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 14 shows the scatterplot for the comparison of EVR + reduced TAC and MMF + standard TAC. As indicated by the graph, all simulations indicate that the ICER is higher than a cost-effectiveness threshold of £30,000 per QALY (>99% above the threshold). The scatterplot indicates a similar comparison with EVR + reduced TAC and AZA + standard TAC, with the majority of points above the £30,000 per QALY threshold (>99% above the threshold). The scatterplot also indicate that there is little to differentiate MMF and AZA, as these estimates cross through all four quadrants.

Figure 14: Scatterplot for EVR + reduced TAC versus MMF + standard TAC and AZA + standard TAC

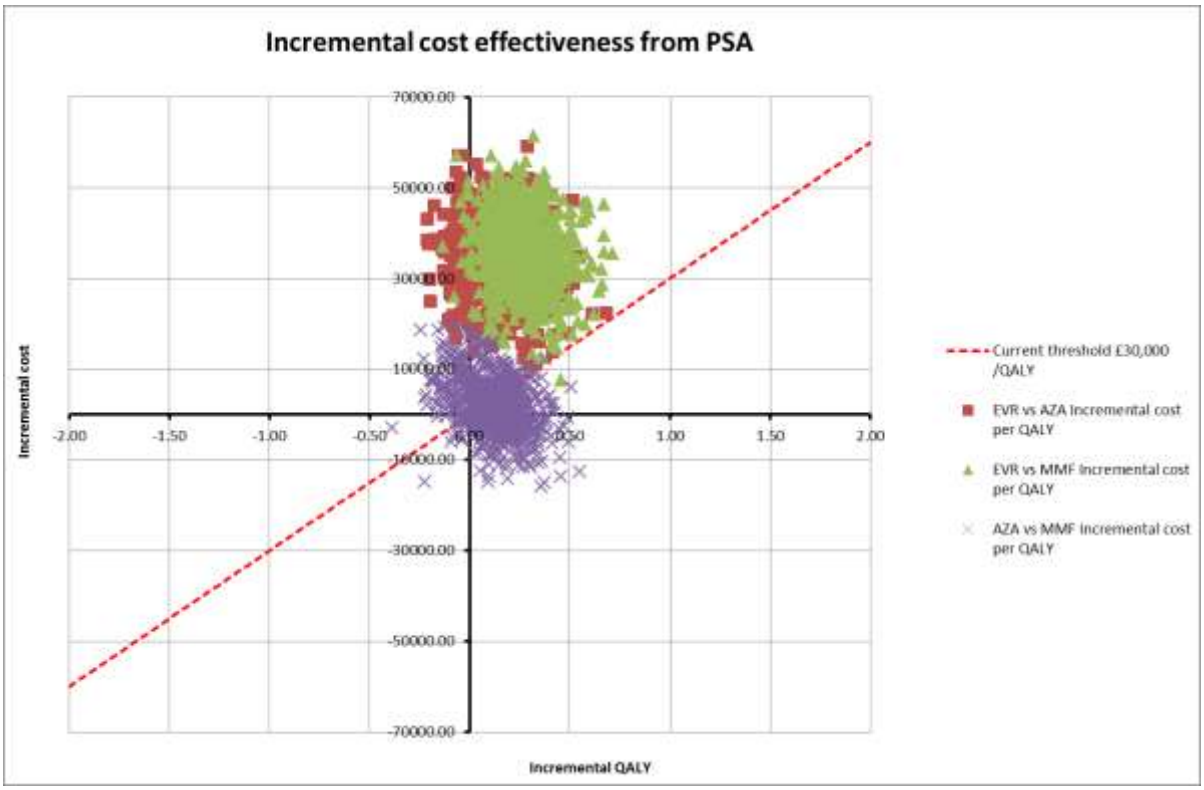
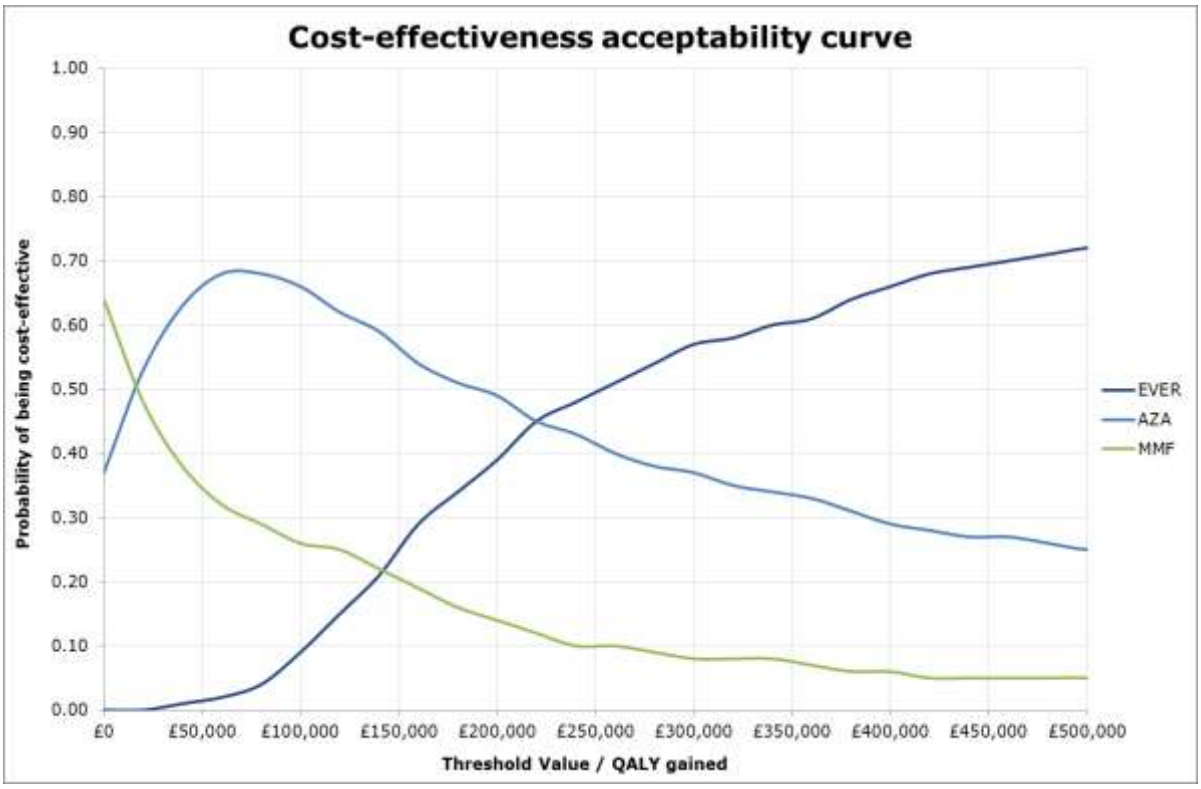


Figure 15 shows the cost-effectiveness acceptability curve (CEAC) for EVR + reduced TAC versus the other comparators. This indicates that EVR + reduced TAC is likely to be the most cost-effective therapy at thresholds over £200,000 per QALY gained.

Figure 15: Cost-effectiveness acceptability curves for EVR + reduced TAC versus MMF + standard TAC and AZA + standard TAC



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Section 7.6.1 presents the four proposed scenario and structural sensitivity analyses:

1. Removing the state of *Mild Chronic Rejection* state
2. Removing the possibility of future transplants (in both models)
3. The removal of the renal sub-model
4. Changing the baseline eGFR from 81ml/min per 1.73m^2 to 60 ml/min per 1.73m^2

Scenario 1:

In this scenario, AZA + reduced TAC is dominated by MMF + standard TAC. The removal of the *Mild Chronic Rejection* state changed the ICER to £227,528 per QALY gained when comparing EVR + reduced TAC and MMF + standard TAC. Table 76 presents the results of this analysis.

Table 76: Deterministic results when removing the *Mild Chronic Rejection* state

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
MMF + standard TAC*	102,856	10.16	4.09					
AZA + standard TAC	104,907	10.06	4.05	2,051	-0.10	-0.04	Dominated	
EVR + reduced TAC	140,189	10.47	4.25	37,333	0.31	0.16	227,528	-
*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Scenario 2:

The removal of the opportunity for re-transplant changed the ICER to £121,972 per QALY gained when comparing EVR + reduced TAC and MMF + standard TAC. Comparing EVR + reduced TAC to AZA + standard TAC gives an ICER of £117,285 per QALY gained. MMF + standard TAC shows extended dominance over AZA + standard TAC in this scenario Table 77 presents the results of the analysis.

Table 77: Deterministic results for the removal of future re-transplantation opportunity

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
MMF + standard TAC	119,924	8.61	3.45					
AZA + standard TAC	122,468	8.66	3.46	2,544	0.04	0.01	Extendedly dominated	
EVR + reduced TAC	149,418	9.07	3.69	29,494	0.45	0.24	121,972	117,285
*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Scenario 3:

The removal of the renal sub-model changed the ICER to £312,279 per QALY gained when comparing EVR + reduced TAC and MMF + standard TAC. When comparing EVR + reduced TAC to AZA + standard TAC, the ICER is 374,832 per QALY gained. Table 78 presents the results of the analysis.

Table 78: Deterministic results for the removal of the renal sub-model

Technology	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
MMF + standard TAC	43,666	9.01	4.10					
AZA + standard TAC	45,679	9.12	4.13	2,103	0.11	0.03	73,175	
EVR + reduced TAC	85,095	9.29	4.24	41,429	0.28	0.13	312,279	374,832
*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Scenario 4:

The reduction of baseline eGFR from 81ml/min per 1.73m^2 to 60 ml/min per 1.73m^2 changed the ICER to £184,372 per QALY gained when comparing EVR + reduced TAC and MMF + standard TAC. EVR + reduced TAC compared to AZA + standard TAC results in an ICER of £179,427 per QALY gained. Table 79 presents the results of the analysis.

Table 79: Deterministic results for the reduction of starting eGFR

Technologies	Total costs (£)	Total LYG	Total QALYs	Incre-mental costs (£)	Incre-mental LYG	Incre-mental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incre-mental (QALYs)
MMF + standard TAC	129,448	9.08	3.62					
AZA + standard TAC	131,392	9.09	3.63	1,943	0.02	0.01	Extendedly dominated	
EVR + reduced TAC	160,845	9.40	3.79	31,396	0.31	0.17	184,327	179,427

*Baseline is MMF + standard TAC; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

7.7.10 What were the main findings of each of the sensitivity analyses?

The sensitivity/scenario analysis findings were:

- The structural change of the removal of the mild chronic rejection state from the hepatic core model indicated sensitivity of the model to transitions to this state as the AZA + standard TAC regimen was dominated in the deterministic analysis. This may be driven by the apparent overlap in benefits between the treatment options modelled, making outcomes sensitive to relatively small changes
- A larger effect on ICER estimates was apparent from the removal of the hepatic and renal re-transplantation options from the model structures, as noted by the higher ICER in the comparison between EVR + reduced TAC and MMF + standard TAC. In this scenario, AZA + standard TAC is extendedly dominated
- Similar sensitivity was noted in the removal of the renal sub-model, with the ICER estimates being higher in all comparisons.
- Scenario 4 examined the impact of a lower baseline eGFR and indicated that the model was sensitive to this parameter, with the ICER increasing in the comparison between EVR + reduced TAC and MMF + standard TAC. The AZA + standard TAC option was again extendedly dominated

The results of the PSA indicated a wide spread across different quadrants of the cost-effectiveness plane for the comparisons with MMF + standard TAC. However, the comparison between EVR + reduced TAC and AZA + standard TAC is predominantly in the north-east quadrant as it was improved benefit, but higher incremental costs. This is further confirmed by the fact that in all of the scenario analyses undertaken, the EVR + reduced TAC always result in the highest benefits as measured by both mean life years and mean QALYs. The CEACs indicate that EVR + reduced TAC is more likely to become the preferred therapy at a cost-effectiveness threshold of over £200,000 per QALY gained.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of cost-effectiveness results are time to BPAR as the risk of acute rejection determines whether or not a patient then becomes at risk of developing chronic rejection and potential loss of the graft. Alongside this, the complications of immunosuppressive treatment as modelled in the renal sub-model have a large impact on results. The magnitude of the decline in renal function in year 1 followed by the progression of CKD appear to have a large

impact on the cost-effectiveness analysis. It should be noted again, that even when this aspect of the model is discounted or amended (e.g. removal of the renal sub-model, removal of the re-transplant option), EVR + reduced TAC offers the highest mean benefit in both life year and QALY terms.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Processes of both internal validation and external validation were carried out on the economic model.

Internal validation consisted of:

- Every formula and programming string was checked by a second modeller who did not construct that part of the model.
- Data inputs were checked by a second reviewer.
- Recommendations for improvements in programming and model were provided in a full quality check performed by a senior independent modeller.

External validation consisted of:

- A modelling team from another consultancy not involved in the preparation of the model independently scrutinised and reviewed the model for construct, programming and reliability of the model.
- Existing cost-effectiveness publications were unable to be cross-checked as there were none identified for the intervention of interest (see section 7.1).

Feedback from all parties and areas mentioned above was integrated into the model by the original modelling construct team and the results were re-run.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroups were analysed in the cost-effectiveness analysis. Potential subgroups of interest from the NICE scope were those with renal dysfunction, those with HCV and those with HCC.

- An analysis of renal dysfunction was incorporated into the evaluation via the sub (renal sparing) model, although this subgroup of patients was not specifically analysed.
- Consultations with key opinion leaders revealed that clinical consensus is that the choice of immunosuppression does not influence the probability of either HCV or HCC recurrence post-transplant.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

No subgroups were analysed in the cost-effectiveness analysis.

7.9.3 Please describe how the statistical analysis was undertaken.

No subgroups were analysed in the cost-effectiveness analysis.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

No subgroups were analysed in the cost-effectiveness analysis.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

No subgroups were analysed in the cost-effectiveness analysis.

7.10 Interpretation of economic evidence

There were no existing cost-effectiveness publications identified in the systematic literature review for the intervention of interest (see section 7.1). The results of the *de novo* cost-effectiveness analysis are presented in section 7.7. There is a notable difference in renal costs for everolimus plus reduced dose tacrolimus of £49,299 in comparison to MMF plus standard dose tacrolimus of £56,926 and £57,475 for azathioprine plus standard dose tacrolimus. This can be explained by the prevention of downstream costs associated with end stage renal dysfunction in the everolimus combination.

In the base case analysis, treatment with everolimus plus reduced dose tacrolimus instead of MMF plus standard dose tacrolimus increased costs by £38,004 and QALYs by 0.343 per patient, giving an ICER of £110,797 per additional QALY.

The probabilistic sensitivity analysis results demonstrated that everolimus + reduced dose tacrolimus versus MMF plus standard dose tacrolimus is predominantly in the north-east quadrant as it had improved benefit, but higher incremental costs. The CEACs indicate everolimus plus reduced dose tacrolimus more likely to become the preferred therapy at a cost-effectiveness threshold of over £200,000 per QALY gained.

The results of the scenario analyses which are preferred technique for assessing the parameter uncertainty and structural uncertainty in the patient level simulation model. The results demonstrated that the model was sensitive to changes in the reduction in eGFR decline in the model and baseline eGFR changes. The removal of the renal model in the second scenario had a large impact on the analysis results. This was anticipated because of the benefit that everolimus plus reduced dose tacrolimus provides for patients through renal sparing. The third scenario to remove re-transplantation for hepatic and renal patients reduced the ICER of everolimus plus reduced dose tacrolimus. The removal of the *Mild Chronic Rejection State* to assess the model structure had some impact on the results.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

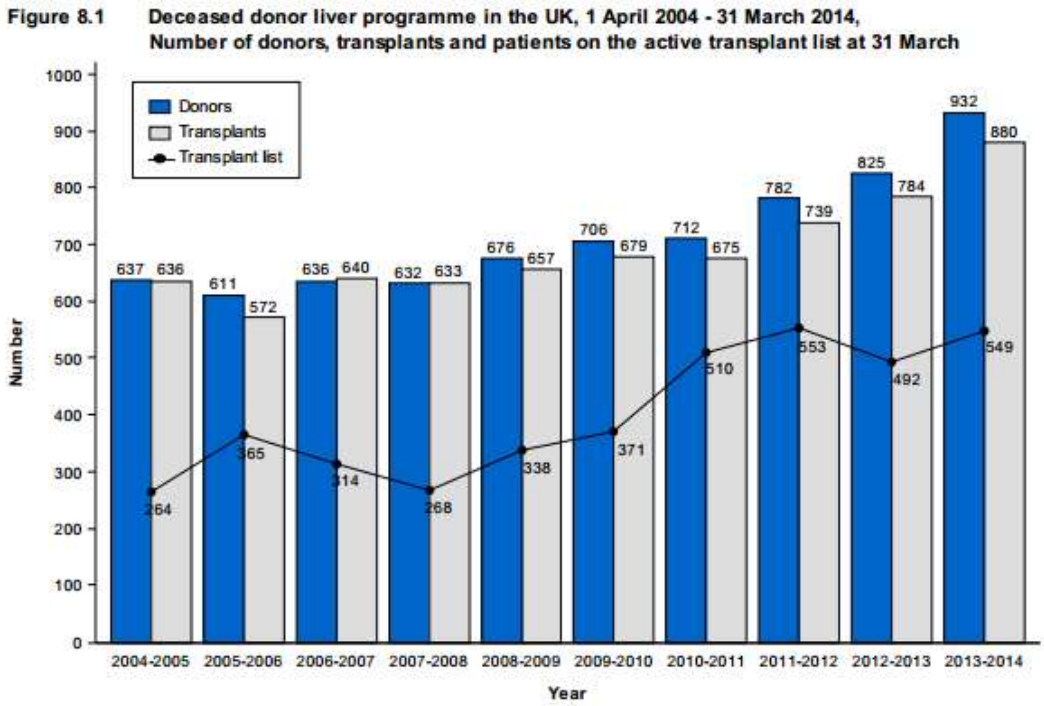
The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

It is anticipated that the vast majority of patients eligible for immunosuppressive treatment with everolimus in combination with reduced dose tacrolimus will be de novo liver transplant patients or patients undergoing a second (or subsequent) liver transplant. It is feasible for patients to 'switch' to everolimus from other immunosuppressive combinations but this is likely to occur only in patients that are unstable on their existing treatment. There is limited data to inform the size of this patient population, so eligibility estimates are based on the de novo transplant population as outlined above.

The number of liver transplants performed in the UK in the 12 month period from 2013 to 2014 was 880 (Organ Donation, 2014[15]). It should be noted that these statistics are for the whole of the UK, not only England and Wales. A clinical expert highlighted that statistics for solely England and Wales are not publically available, so data was weighted by population size. Hence, it is estimated that 781 transplants (88.8%) were conducted in England and Wales in 2013 to 2014.

Figure 16: Number of liver transplants in the UK, 2004 to 2014



Source: (OrganDonation, 2014[115])

Figure 16 illustrates an increasing trend in the number of transplants. Over the last 5 years, the number of transplants has increased 29.6% (679 to 880), averaging 5.9% annually. Using this 5.9% annual average growth rate over the last 5 years, the projected numbers of new liver transplant recipients are displayed in Table 80. The expected number of new transplant recipients eligible for everolimus plus reduced dose tacrolimus and corticosteroid treatment in 2015 following the launch of everolimus is 828.

Table 80: Expected number of liver transplants in England and Wales in the next 5 years

Year	Estimated number of new transplant recipients	Total number of new patients since 2014
2015	828	828
2016	877	1,668
2017	928	2,523
2018	983	3,395
2019	1,041	4,287

The data in the third column of Table 80 also takes into account an expected annual mortality rate of 4.4% per patient. This mortality rate is not used in the model in Section 7 as the 4.4% rate considers other causes of death besides hepatic rejection and renal dysfunction. The other causes of death are not dependent on the choice of immunosuppressive regimen and thus were not relevant to our decision problem[7].

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Data on file from Novartis provided details on treatment usage in current clinical practice from 4 of the 6 liver centres in England and Wales (Kings College London, Royal Free London, Birmingham and Leeds). The data retrieved from sites is displayed in Table 81.

Table 81: Treatment usage in current UK clinical practice

Regimen	Clinical practice usage	Excluding ciclosporin and sirolimus
MMF in combination with tacrolimus	[redacted]	[redacted]
Tacrolimus monotherapy	[redacted]	[redacted]
Azathioprine in combination with tacrolimus	[redacted]	[redacted]
Other regimens containing ciclosporin or sirolimus (no longer given to new UK patients)	[redacted]	[redacted]

Table 82 shows that tacrolimus monotherapy (this may be in combination with corticosteroids) is used in [redacted] of regimens. It was decided that this was significant enough a market share to be included in the *Implementation* (budget impact) analysis along with the comparator regimens stated in the

[7] Such causes of death may include primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), hepatitis-C virus (HCV), hepatocellular carcinoma (HCC) or alcoholic liver disease (ATOH)

NICE scope (MMF + standard TAC and AZA + standard TAC). As this data is cross-sectional, it includes those patients currently on tacrolimus monotherapy who commenced treatment on MMF or azathioprine in combination with tacrolimus, but then discontinued these therapies when beginning tacrolimus monotherapy. Clinical experts advised that regimens containing ciclosporin or sirolimus are no longer used in UK clinical practice in new patients, hence the *Implementation* analysis will not include these regimens as the analysis is for new patients only. Consequently, market share data will be used in the analysis to cover the following four regimens (all in combination with corticosteroids):

1. Everolimus in combination with reduced dose tacrolimus
2. MMF in combination with standard dose tacrolimus
3. Azathioprine in combination with standard dose tacrolimus
4. Tacrolimus monotherapy

8.3 What assumption(s) were made about market share (when relevant)?

Market share data for the '*Reference Scenario'* is presented in Table 82.

Table 82: Reference scenario market share over the next 5 years

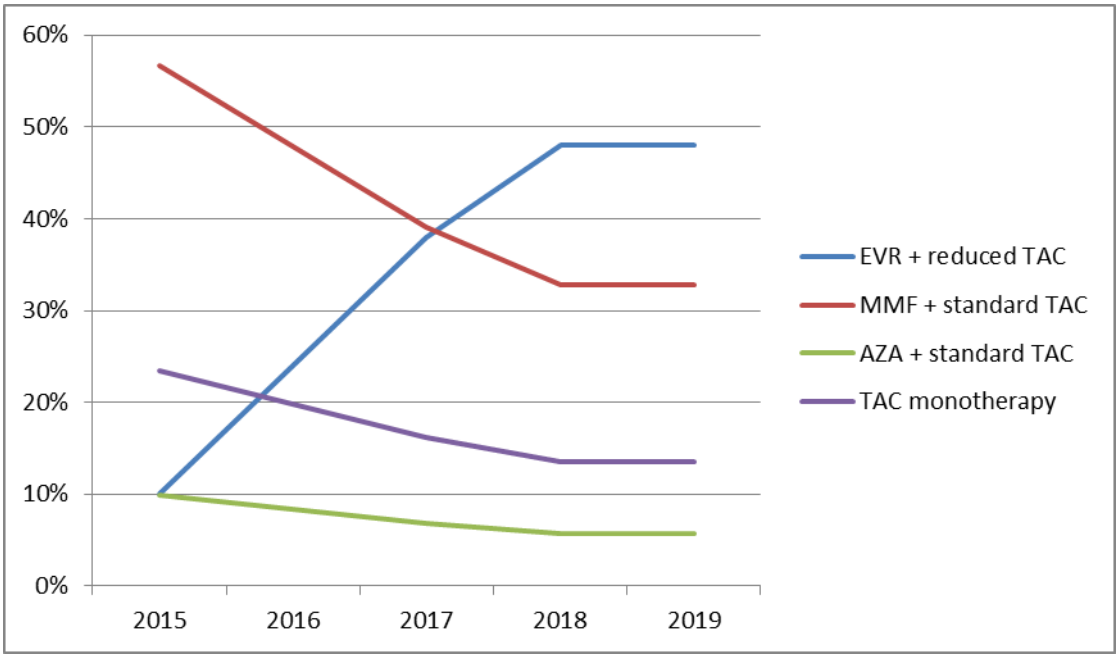
Regimen	2015	2016	2017	2018	2019
EVR + reduced TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMF + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It was assumed that the uptake of everolimus in combination with reduced dose tacrolimus (with corticosteroids) would be at an initial market impact of 10%, increasing to 48% over four years, and then remain static. in 2018. It was assumed that market share is taken equally for all comparators. The result of this scenario is shown in Table 83 ('*Anticipated Scenario'*, and graphically displayed in Figure 17).

Table 83: Anticipated scenario market share over the next 5 years

Regimen	2015	2016	2017	2018	2019
EVR + reduced TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMF + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 17: Anticipated scenario market share over the next 5 years



8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Two cost categories were incorporated into the *Implementation* analysis that may be of interest to commissioners:

1. **Titrated drug costs** – the doses of the technologies change over time and this affects cost. Just as was considered in the cost-effectiveness model in Section 7, the regimen cost from year 2 post-transplantation onwards is different to the regimen cost in year 1 post-transplantation. Furthermore, everolimus + reduced TAC is not administered until day

30 post-transplant, so the cost of everolimus + reduced TAC is only considered for 11 months during the first year.

2. **Serious adverse events costs** are considered in the analysis as the adverse events associated with immunosuppressive treatment can have significant impact on the NHS budget. Data used in the model (Lopez *et al.*, 2013[42], FDA, 1998[125]) indicated that there may be substantial differences in the incidence of AEs between treatments.

While administration costs and monitoring costs for immunosuppressive therapies occur as part of routine clinical practice, it was assumed that there was no difference in these costs between treatments and the addition of everolimus + reduced TAC would not incur further costs. Therefore, these costs are not included in the implementation analysis.

Adverse event costs are taken into account by multiplying the unit cost of the event (see Table 85) by the chance of a patient having an event (see Table 54). The annual adverse event costs per patient can be seen in Table 86.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for the four categories mentioned in Section 8.4 were considered in line with those in the cost-effectiveness model. Drug cost data is displayed in Table 84, and serious adverse events costs data in Table 85. No administration or monitoring costs are assumed (see Section 8.4).

Table 84: Unit costs of technologies

Drug	Brand	Pack/vial	Dose in pack/vial	Cost per pack/vial	Cost per mg	Source
Everolimus	Certican®	60 tabs	0.75mg	£445.50	£9.90	Data on file
Tacrolimus	Prograf®	100 caps	1 mg	£160.54	£1.61	(BNF, 2014[127])
Corticosteroid	Prednisolone	28 tabs	5mg	£1.31	£0.01	(Commercial Medicines Unit, 2014[161])
Azathioprine	non-proprietary	56 tabs	50 mg	£3.42	£0.001	(Commercial Medicines Unit, 2014[161])
MMF intravenous	CellCept®	1 vial	500 mg	£9.12	£0.02	(BNF, 2014[127])
MMF oral	non-proprietary	50 tabs	500 mg	£11.82	£0.0004	(Commercial Medicines Unit,

						2014[161])

Table 85: Serious adverse events costs by regimen

Adverse event (AE)	Cost to treat event	Reference
Hypertension	£769	(Department of Health, 2013[153])- EB047
New onset diabetes	£1,840	(Davidson *et al.*, 2003[164])
Infection	£649	(Department of Health, 2013[153]) - PA18B Minor Infections with CC Score 0
Herpes	£55	(Curtis, 2013[154]) - GP visit
Tremor	£55	(Curtis, 2013[154]) - GP visit
Insomnia	£55	(Curtis, 2013[154]) - GP visit
CMV	£11,365	(Annemans *et al.*, 2002[155])

Table 86: Annual costs of adverse events considered in the budget impact model

Adverse event (AE)	EVR + reduced TAC Annual cost	MMF + standard TAC annual cost	AZA + standard TAC annual cost	TAC monotherapy annual cost
Hypertension	£309.91	£183.79	£444.48	£183.79
New onset diabetes	£288.88	£213.44	£336.72	£213.44
Infection	£426.39	£406.27	£391.35	£391.35
Herpes	£0.22	£5.56	£3.25	£3.25
Tremor	£5.61	£18.65	£19.53	£18.65
Insomnia	£3.80	£28.77	£25.85	£25.85
CMV	£465.97	£31.86	£909.20	£31.86

8.6 Were there any estimates of resource savings? If so, what were they?

There were no resource savings with the introduction of everolimus. It should be noted that cost savings from a more favourable CKD profile using everolimus are not taken into account in the implementation analysis; this is discussed further in Section 8.8.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The reference scenario budget impact without everolimus is shown in Table 87. Table 88 shows the total budget impact of the anticipated scenario where everolimus uptake occurs. Figure 18 illustrates the differences between the two scenarios.

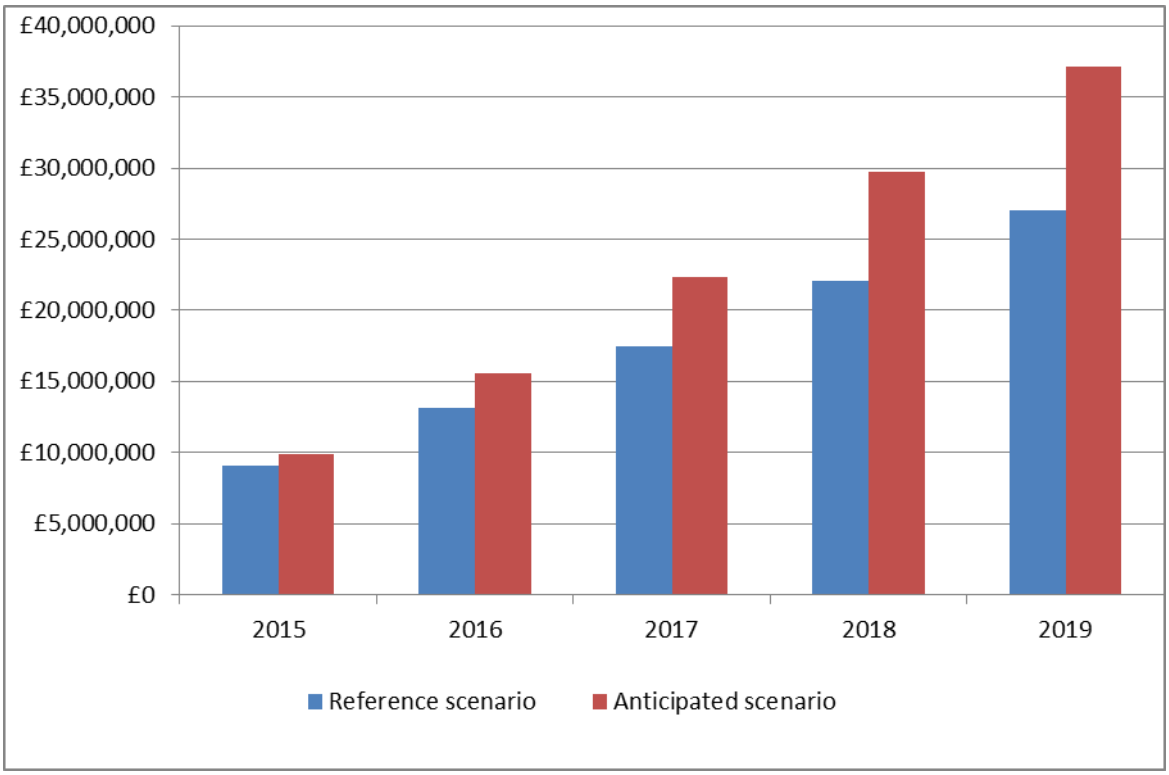
Table 87: Total NHS budget impact of *Reference Scenario*

Treatment regimen	**2015**	**2016**	**2017**	**2018**	**2019**
EVR + reduced TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMF + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget outlay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 88: Total NHS budget impact of *Anticipated Scenario*

Treatment regimen	**2015**	**2016**	**2017**	**2018**	**2019**
EVR + reduced TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AZA + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMF + standard TAC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TAC monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget outlay	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 18: NHS budget impact difference between the *Reference Scenario* and the *Anticipated Scenario*



8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

It should be noted that potential cost savings from a more favourable CKD profile using EVR + reduced TAC are not taken into account in the *Implementation* analysis. The cost-effectiveness renal sub-model indicated the potential for cost-savings from the slower decline in renal function when using EVR + reduced TAC. However, as the impact of therapy on renal function is dependent on a patient's starting eGFR, this could not be implemented in the budget impact model.

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