NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Rituximab (MabThera®) for the treatment of ANCA associated vasculitis

20th March 2013

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Executive summary

Approved Name	Rituximab
Brand Name	MabThera®
Marketing Status	Rituximab has had European marketing authorisation since the 2nd of June 1998.
Mechanism of action	Rituximab (RTX) is a chimeric murine/human monoclonal antibody that binds specifically to the CD20 antigen expressed on the surface of B cells; it does not bind to hematopoietic stem or CD20-negative precursor cells. RTX depletes peripheral B cells by several potential mechanisms, including complement-mediated lysis, antibody dependent cellular cytotoxicity (ADCC)-mediated killing, and apoptosis.
Proposed Indication	RTX, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).
Current Indications	**Non-Hodgkin's Lymphoma** RTX is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. RTX maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy. RTX monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. RTX is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (CYC,doxorubicin, vinristine, prednisolone) chemotherapy. **Chronic Lymphocytic Leukaemia** RTX in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including RTX or patients refractory to previous RTX plus chemotherapy. **Rheumatoid Arthritis** RTX in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies. RTX has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with methotrexate.
Formulation	RTX is administered as an intravenous injection.
Pack Sizes	10ml (100mg) 50ml (500mg)
Acquisition Cost	£174.63 - 10ml (100mg) £873.15 - 50ml (500mg)
Treatment regimen	For ANCA-associated vasculitis: dose 375mg/m^2 body surface area once weekly for 4 weeks.

Background on disease, current treatment standard and rituximab

AAV is progressive if untreated and severe disease can be fatal

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multisystem autoimmune disease characterised by ANCA production and small vessel inflammation. Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis, WG), and microscopic polyangiitis (MPA) are the two major forms of systemic vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) which have comparable clinical features and treatment responses. Because of this association, these two conditions are collectively referred to as AAV.

If untreated, AAV progresses in most cases from limited disease processes (e.g., inflammation in the upper respiratory tract or lung) to a generalised phase characterised by multiple complications of small-vessel vasculitis (e.g., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar haemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis). The outcome of untreated severe disease is death.

Treatment involves induction, maintenance, and relapse/flare management

Management involves three phases; remission induction, remission maintenance and treatment of relapse. Treatment is tailored according to severity of a patient's disease.

Cyclophosphamide and steroids are used to induce remission in standard care

The British Society for Rheumatology (BSR) and the European Vasculitis Study Group (EUVAS) produce guidelines for the management of adults with AAV [Lapraik et al. 2007; Mukhtyar et al. 2008]. The latest guidelines were developed before the emergence of recent data on the use of RTX in AAV and are based around the use of cyclophosphamide in severe disease.

Cyclophosphamide (CYC) is the standard remission induction agent, given as either a daily oral or IV pulse treatment, usually for 3-6 months and dose-adjusted for age, body weight and renal function. CYC is usually given with concomitant oral or IV corticosteroids such as prednisolone or methylprednisolone. For aggressive disease, plasmapheresis can be used in addition. In the induction setting, CYC therapy may be continued for up to 6 months, along with tapered doses of prednisolone.

Azathioprine may be used to maintain remission

Azathioprine (AZA) or methotrexate may be substituted for CYC after successful remission of disease. Mycophenolate mofetil or leflunomide may be used as alternatives for intolerance or lack of efficacy of AZA or methotrexate.

Rituximab's mode of action is relevant to AAV

In AAV, the presence of activated B-cells correlates with disease activity and autoantigen specific B-cells are present at sites of inflammation. The regulation of T-lymphocytes is dependent on B-cell function. B-cell depletion using RTX has therefore been developed as a therapeutic strategy for AAV [Arthritis Research UK].

Current UK Clinical Practice

In the UK, RTX has routinely been used off licence in the treatment of AAV and has significant clinical support. In December 2013 the NHS Commissioning Board recommended the use of RTX in the treatment of induction, relapse and maintenance for patients with AAV (NHSCB/A3C/1a, December 2012). This guidance will come into effect from April 2014.

Clinical evidence

The pivotal RAVE study has direct relevance to this STA

The clinical evidence base for RTX in the treatment of AAV, within the scope of this NICE appraisal, is restricted to one randomised control trial. The RTX in ANCA-associated Vasculitis (RAVE) study was a head to head randomised control trial evaluating the effectiveness of CYC compared to RTX (RTX). The primary objective was to demonstrate non-inferiority of RTX compared with conventional therapy (CYC/AZA) and to determine the efficacy of RTX (375 mg/m^2, four weekly infusions) and glucocorticoids in the induction of complete remission and cessation of steroids.

The RAVE study found that RTX was non-inferior to CYC at inducing complete remission

The primary endpoint for the RAVE study was the percentage of patients who achieved complete remission at Month 6, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) score of 0 with successful completion of the glucocorticoid taper at Month 6 (i.e., glucocorticoid dose = 0 mg at month 6) and is summarised in Table 1.

Table 1: RAVE primary endpoint clinical results

	RTX N=99 n (%)	CYC N=98 n(%)	Difference in Rate %	95% CI of Difference
N	99	98		
Complete Remission	63 (64)	52 (53)	10.6	-3.2, 24.3[a]
95% CI for proportion	54.1, 73.2	43.1, 63.0		

a, non-inferiority was demonstrated since the lower bound for the 95% confidence interval was higher than the pre-determined non-inferiority margin (-20%).

The secondary endpoint, evaluating the superiority of RTX to CYC at inducing complete remission, was not met. Patients in the RTX had numerically higher rates of remission than in the CYC arm, but the result was not statistically significant (p=0.18 in chi-square test).

Analysing disease score remission alone, RTX had superior efficacy to CYC

An exploratory analysis determined the rate of remission (BVAS/WG = 0) regardless of prednisone use (Table 2). Using worst-case imputation for missing data, 80 patients (80.8%) in the RTX arm achieved a BVAS/WG of 0 compared with 65 (66.3%) patients in the CYC arm, resulting in a treatment difference of 14.5 (95% CI: 2.3, 26.6), p=0.021.

Table 2: BVAS/WG remission at 6 Months (ITT Population)

	RTX N=99 n (%)	CYC N=98 n(%)	Difference in Rate %	95% CI of Difference[b]
Remission[a] n (%)	80 (81)	65 (66)	(14.5)	0.021
95% CI for proportion	73.1, 88.6	60.0, 75.7	2.3, 26.6	

a, the proportion of patients who achieved a BVAS/WG of 0; b p-value is from a chi-square test.

Cost-effectiveness

The cost-effectiveness model simulates attainment of remission, based on outcomes from RAVE

Our cost-effectiveness analysis employs a Markov model involving four health states: non-remission, complete remission, uncontrolled disease and death.

The *de novo* analysis was designed to reflect clinical practice in the UK for treating AAV patients who are not in clinical remission. We limited the scope of the analysis to the induction of remission only, not the treatment of flares or maintenance.

The structure is simple and largely reflective of the RAVE study [Stone et al 2010] with 'non-remission' and a 'complete remission' health states directly linked to the study's primary endpoint.

Clinical experts advised us that a sequence of treatments is usually tried in the induction setting; we have tried to model this

We have modelled a sequence of treatments to reflect real life clinical practice. Expert clinical opinion suggests that RTX will be used as an alternative induction agent rather than replacing CYC induction therapy.

In the standard of care arm we have assumed that patients receive a maximum of two induction courses of CYC. In the intervention arm, patients receive one course of RTX followed by a second course only for those patients who failed to attain remission on the first course. Following RTX, we assume that non-responding patients will also be offered one course of CYC induction therapy.

An 'uncontrolled disease' health state was created to reflect the relapsing nature of AAV. Once patients have transitioned through all the induction courses in their arm and subsequently relapsed, they are assumed to enter the uncontrolled disease health state where no further induction therapy is administered. Patients in the uncontrolled disease health state are assumed to receive best supportive care and, as a result of the relatively poor control this affords over AAV flares and progressive effects are assumed to have a lower average quality of life.

Our base case analysis produces an ICER of about £11k/QALY

A summary of the total costs, outcomes (QALYs gained) and incremental cost effectiveness ratio (ICER) for our base case analysis is given in Table 3

Table 3: Base-case cost-effectiveness results

	RTX arm	CYC arm
Technology acquisition cost	£13,521	£6,594
Administration costs	£2,067	£2,435
Other costs	£443	£776
Health Sector costs	£84,843	£89,282
Total costs	£100,874	£99,087
Incremental costs		**£1,787**
Life years	11.82	11.78
Incremental life years		0.0422
QALYs	8.18	8.02
Incremental QALYs		0.1640
ICER		£10,898

Figures are rounded for clarity of presentation so some minor discrepancies may appear.

The ICER estimated is within the range normally considered cost-effective by NICE. Our sensitivity analysis suggests that the results are reasonably robust to clinical and cost parameter uncertainty. The sequence of treatments modelled understandably has a more substantial impact on the ICER.

A subgroup analysis of 'CYC intolerant' patients was also run – here RTX was dominant

The scope of the appraisal identifies a small subgroup of patients who are considered to be "intolerant to CYC". It is well known that while highly effective, CYC is associated with significant side effects including but not limited to bladder cancer and infertility. Although we have limited clinical data for this group, we used the available data from RAVE to simulate the expected cost-effectiveness in CYC-intolerant patients. We have assumed that the subgroup of patients with newly diagnosed disease who have yet to receive induction therapy best represent those patients intolerant to CYC.

The results of the subgroup analysis are presented in the table below.

Table 4: Subgroup analysis patients intolerant to CYC

	Totals			Incremental results			
	Costs	Life Years	QALYs	Costs	Life Years	QALYs	ICER
RTX	£100.0k	11.8	8.0				
CYC	£102.7k	11.6	7.5	-£2.6k	0.139	0.543	RTX dominates

For the subgroup of patients intolerant to CYC, there is a high unmet need for an effective induction agent. The results indicate that for patients unable to receive CYC, the use of RTX will significantly improve the clinical outcomes of patients while avoiding significant health care costs in the future.

Conclusion

RTX is as effective as CYC with fewer side effects

RTX has demonstrated in RCTs and clinical practice to be an effective agent in the treatment of AAV. The addition of RTX to the current treatment pathway will greatly improve the long term outcomes of patients with AAV, who will inevitably relapse following treatment with CYC. RTX will provide patients with another valuable line of therapy, where currently the number of induction regimens is limited due to the associated toxicity of continued CYC therapy.

We have demonstrated that RTX is an effective alternative induction agent in the treatment of severe AAV. The initial costs associated with RTX are largely offset by longer term cost savings associated with better disease control. RTX therefore represents a cost-effective use of NHS resources.

We strongly believe that patients with ANCA-associated vasculitis need an effective alternative induction therapy to the current standard of care. Our clinical results indicate that RTX is as effective as current therapy and would greatly improve the long term outcomes of patients with this relapsing remitting disease.

Section A – Decision problem

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.

RTX (MabThera®), therapeutic class: monoclonal antibodies / antineoplastic agents

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

RTX (hereafter RTX) is a chimeric murine/human monoclonal antibody that binds specifically to the CD20 antigen expressed on the surface of B cells; it does not bind to hematopoietic stem or CD20-negative precursor cells. RTX depletes peripheral B cells by several potential mechanisms, including complement-mediated lysis, antibody dependent cellular cytotoxicity (ADCC)-mediated killing, and apoptosis.

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).

The variation for RTX in granulomatosis with polyangiitis (GPA) and Microscopic Polyangiitis (MPA) is on-going. Positive Opinion is expected at the March 2013 CHMP meeting. It is anticipated that the Commission Decision will be received (final approval) by the end of May 2013.

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 main points of discussion with the Regulators:

Dose justification; 1,000mg day 1 and 15 (one course) RTX is widely used off-label for AAV and gives less exposure compared with 375mg/m^2 once weekly for 4 weeks as used in the clinical trial. Likely outcome: dose of 375mg/m^2 once weekly for 4 weeks.

The place of RTX in the current treatment algorithm was unclear. In the US, the label is very broad ("treatment of adult patients"), whereas in Europe it is likely to be limited to induction of remission:

The need for maintenance therapy with RTX required further evaluation. Roche was requested to develop guidance on maintenance therapy for prescribers

The Co-rapporteur commented: it should be discussed whether the place of RTX should be in first or second line treatment, or whether the place should not be specified as treatment is individualised and under expert care

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

Anticipated indication:

Granulomatosis with polyangiitis and Microscopic polyangiitis

RTX, in combination with glucocorticoids, is indicated for the induction of remission in adult patients with severe, active Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA).

Current therapeutic indications:

Non-Hodgkin's Lymphoma

RTX is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy. RTX maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

RTX monotherapy is indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. RTX is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (CYC,doxorubicin, vincristine, prednisolone) chemotherapy.

Chronic Lymphocytic Leukaemia

RTX in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including RTX or patients refractory to previous RTX plus chemotherapy.

Rheumatoid Arthritis

RTX in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

RTX has been shown to reduce the rate of progression of joint damage as measured by x-ray and to improve physical function, when given in combination with methotrexate.

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.

There are two studies known to Roche which may provide more data on the use of RTX in AAV. However, they are unlikely to provide data within the 12 month timeframe specified (see Table below):

Name	Identifier	Data to be collected	Start date	Stop date	Sponsor
RAVELOS	NCT01586858	RAVE long-term follow-up (safety)	May 2012	May 2016	Johns Hopkins University
RITAZAREM	NCT01697267	RTX vs AZA for maintenance of remission	Dec 2012	Dec 2016	Cambridge University Hospitals NHS Foundation Trust

We are also aware of one further study which may report findings in the next 12 months. The study evaluates the use of RTX as a maintenance therapy which currently falls outside the scope of this appraisal.

Name	Identifier	Data to be collected	Start date	Stop date	Sponsor
MAINRITSAN	NCT00748644	Open-label RTX vs AZA for maintenance (non-standard dose, 500mg at Day 1 and 15, 6 monthly)	Oct 2008	Dec 2013	Assistance Publique - Hôpitaux de Paris

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

RTX has been available in Europe since 1998 for various oncology indications and since 2006 for RA. The current proposed variation for RTX in Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) is ongoing. It is anticipated that the Commission Decision will be received (final approval) by the end of May 2013 with launch shortly afterwards.

As discussed at the scoping workshop, RTX is currently widely used within the treatment of vasculitis in the United Kingdom.

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

RTX has been licensed and is marketed for both oncology and RA in over 100 countries including the US, all EU member states, New Zealand, Norway, Iceland, Japan, Australia, Canada and Switzerland. The variation for RTX in Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) was granted in the US in April 2011.

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 are currently engaging with the Scottish Medicines Consortium (SMC) on a possible date to submit following CHMP approval. Providing we can submit evidence in May 2013, we expect the SMC to publish guidance on their website in September 2013.

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 5: Unit costs of technology being appraised

Pharmaceutical formulation	RTX is supplied as a sterile solution for intravenous (IV) administration
Acquisition cost (excluding VAT)	500mg RTX = £873.15 (excl. VAT) 100mg RTX = £174.63 (excl VAT)
Method of administration	IV infusion
Doses	375mg/m^2 body surface area (BSA)

Dosing frequency	Once weekly for 4 weeks
Average length of a course of treatment	One course = 4 weeks
Average cost of a course of treatment	Based on body surface area of 1.79m^2 and no vial sharing: £4,889.64
Anticipated average interval between courses of treatments	Unknown
Anticipated number of repeat courses of treatments	Unknown
Dose adjustments	None

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.

N/A

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

No additional tests over and above those needed to diagnose AAV are needed to be able to prescribe RTX for this condition. RTX infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available. See 1.14 for other administration requirements.

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

There are no additional tests or investigations needed (other than those required in usual clinical practice for infusion of a biologic) prior to initiation of RTX.

RTX infusions should be administered under the close supervision of an experienced physician, and in an environment where full resuscitation facilities are immediately available.

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?

Based on the *proposed* SmPC: Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an anti-histaminic drug (e.g. diphenhydramine) should always be administered before each RTX infusion.

Methylprednisolone given intravenously for 1 to 3 days at a dose of 1,000 mg per day is recommended prior to the first infusion of RTX (the last dose of methylprednisolone may be given on the same day as the first infusion of RTX). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80mg/day, and tapered as rapidly as possible based on clinical need) during and after RTX treatment.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with Granulomatosis with polyangiitis or Microscopic polyangiitis during and following RTX treatment, as appropriate.

2 Context

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.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a multisystem autoimmune disease characterized by ANCA production and small vessel inflammation. Granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis [WG]), and microscopic polyangiitis (MPA) are the two major forms of systemic vasculitis associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCAs) which have comparable clinical features and treatment responses. Because of this association, these two conditions are collectively referred to as AAV.

If untreated, AAV progresses in most cases from limited disease processes (e.g., inflammation in the upper respiratory tract or lung) to a generalised phase characterised by multiple complications of small-vessel vasculitis (e.g., leukocytoclastic vasculitis of the skin, mononeuritis multiplex, alveolar haemorrhage, rapidly progressive glomerulonephritis, and mesenteric vasculitis). The outcome of untreated severe disease is death.

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.

We estimate that up to 1,660 patients could be eligible for RTX annually based on the proposed license restricting to patients with severe GPA or MPA as an induction therapy only.

We have estimated the total MPA and GPA population to be 13,000 patients annually, based on prevalence data from a 2012 epidemiology study [Watts et al, 2012]. We note however, that the licence for RTX is more restrictive, and can only be administered to patients with severe active disease and as an induction therapy only.

While we have evidence from market research indicating that approximately 5,000 patients per annum are treated with induction therapy, the breakdown

based on severity of disease is particularly difficult. Our evidence suggests only one third are defined as severe, but as explained in section 2.6 (Severity of Disease), there are many reasons why clinicians would consider deviating from the guidelines when defining severe disease.

The current market authorisation for RTX covers an eligible patient population in the United Kingdom of approximately 39,000 patients annually.

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.

The natural history of untreated AAV is of a rapidly progressive, usually fatal disease and not everyone responds to treatment; early studies observed a mean survival of 5 months, with 82% of patients dying within 1 year and more than 90% dying within 2 years in patients with GPA [Walton, 1958].

The introduction of CYC (CYC) combined with prednisolone resulted in a significant improvement in mortality of GPA with a 5-yr survival rate of 82%, although there remains considerable morbidity associated with both disease and treatment; 20% of these survivors will have significant renal disease [Lapraik et al. 2007].

Disease onset usually occurs at 65-74 years, although it can occur at any age [Watts et al. 2000]. Increasing age and renal involvement at diagnosis are poor prognostic factors. The likelihood of relapse varies according to disease but is highest in GPA; up to 50% of patients will relapse within 5 years, even with maintenance immunosuppression. Each relapse carries a risk of subsequent critical organ damage [Lapraik et al, 2007; Walton, 1958].

Unfortunately, therapies used to treat AAV are themselves also associated with substantial toxicities that frequently result in severe and permanent patient morbidity and mortality [Jayne et al, 2003].

In particular, treating AAV with CYC can lead to opportunistic infections, bone-marrow suppression, hemorrhagic cystitis, infertility, and cancer—particularly hematopoietic and bladder malignancies [Reza et al, 1975; Guillevin et al, 1997].

Cumulative exposure to immunosuppressive therapy is also a significant risk factor for adverse events; cumulative CYC doses were found to be associated with mortality. Infection rates also appeared to be higher in patients exposed to a greater amount of CYC [Little et al, 2009].

There are also substantial morbidities associated with a repeated and prolonged course of glucocorticoids. Infections are a well-known complication of glucocorticoids, especially in the treatment of vasculitis [Hoffman et al, 1992]. Other known complications of steroid therapy include new-onset diabetes, osteoporosis, avascular necrosis, peptic ulcers and cataracts [Little et al, 2009].

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 NICE guidance on AAV available. There are however a number of NHS local protocols available for the use of RTX in AAV, using both the proposed AAV dose of RTX (375mg/m^2) and the licensed RA dose (1g on day 1 and 15), for example, Salford Royal NHS Foundation Trust protocol (375mg/m^2 or 1g every 6 months for two years), Bristol, North Somerset and South Gloucestershire (1 g day 1 and 15, to be repeated at a minimum of 6 monthly intervals for 2 years).

Perhaps more significantly, the NHS Commissioning Board in their draft document [NHSCB/A3C/1a, December 2012], have said they intend to commission RTX for AAV, for patients with relapsing disease, with primary treatment failure or with adverse reactions or contra-indications to CYC. In brief, the document describes the four different situations where RTX would be routinely prescribed for AAV:

- Initial remission induction agent in newly diagnosed patients where avoiding CYC is desirable
- As a remission induction agent when CYC has not been effective
- As a remission induction agent at time of first relapse

- As a remission maintenance agent

We anticipate the final guidance will be issued in April 2013.

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.

The British Society for Rheumatology (BSR) and the European Vasculitis Study Group (EUVAS) have produced guidelines for the management of adults with AAV [Lapraik et al. 2007; Mukhtyar et al. 2008]. They were developed before the emergence of recent data on the use of RTX in AAV and are based around the use of CYC in severe disease.

Management involves three phases; remission induction, remission maintenance and treatment of relapse. Treatment is tailored according to severity and extent of disease and the level of immunosuppression reflects the severity of the vasculitis.

CYC (CYC) is the standard remission induction agent, given as either a daily oral or IV pulse and is usually given for 3-6 months, adjusted for age, body weight and renal function. CYC is usually given with oral or IV corticosteroids such as prednisolone or methylprednisolone. For aggressive disease, plasmapheresis can be used in addition to standard therapy.

To maintain remission, CYC therapy may be continued for up to 6 months, along with tapered doses of prednisolone. AZA (AZA) or methotrexate may be substituted for CYC after successful remission of disease. Mycophenolate or leflunomide may be used as alternatives for intolerance or lack of efficacy of AZA or methotrexate.

Patients may continue maintenance therapy/immunosuppression for up to 5 years.

Relapses have been classified as minor or major, according to the absence or presence of threatened vital organ function. Minor relapse is treated with an

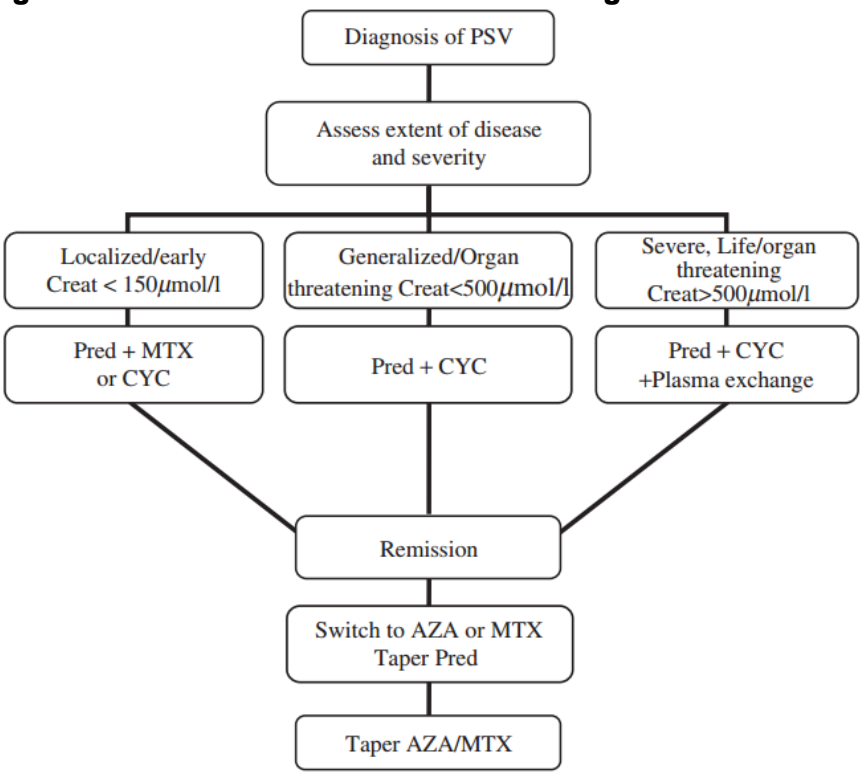
increase in prednisolone dose to 30 mg/day then gradual taper and optimisation of the concurrent immunosuppressive dose.

Major relapse is treated with CYC as in remission induction and an increase in prednisolone to 30 mg/day; intravenous methyl prednisolone or plasma exchange may be considered.

Disease refractory to full dose CYC and prednisolone is rare. More commonly, optimal doses are not tolerated or a prolonged relapsing disease course with high cumulative exposure to CYC and prednisolone are the indications for alternative agents. For relapses on AZA or methotrexate a switch to mycophenolate or leflunomide may be considered.

The diagram below (from BSR Guidelines, Lapraik et al, 2007) may help to clarify the current standard of care:

Figure 1: BSR ANCA-associated vasculitis guidelines



The place of RTX

The proposed license for RTX suggests that, in combination with glucocorticoids, it may be used for the induction of remission in adult patients with severe, active GPA and MPA. This may include:

Initial remission induction agent in newly diagnosed patients where avoiding use of CYC is desirable (because of toxicity and especially with regard to long-term use)

- As a remission induction agent when CYC has not been effective
- As a remission induction agent at time of first relapse

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

One of the critical issues relating to current clinical practice is the toxicity of standard therapies.

Conventional therapies for AAV are associated with significant toxicity, treatment failures, and disease relapses, frequently resulting in severe, permanent morbidity and mortality. Preventing fatal outcomes in severe AAV requires immunosuppressive therapy with glucocorticoids and cytotoxic agents, usually CYC. Although many patients achieve remission with expert care, they usually experience disease flares when therapy is tapered or discontinued.

CYC in particular has significant side effects including gonadal toxicity, bone marrow depression, haemorrhagic cystitis and an increased risk of future development of bladder cancer. There are therefore specific situations where the avoidance of CYC is desirable:

- Females who have not yet completed their family and who are at risk of CYC-induced premature menopause
- Where there has been a previous uroepithelial malignancy
- Where there is intolerance of CYC due to side-effects or cytopenia

- Where there is a high risk of infection

In addition, clinical trial data have demonstrated that during the first year of therapy, adverse events and not the active vasculitis contribute the most to mortality.

Severity of disease

The BSR guidelines suggest that treatment of AAV is tailored according to severity and extent of disease. The level of immunosuppression should reflect the severity of vasculitis.

However, the definition of “severe” it not clear and not defined in clinical practice. It is therefore important not to exclude patients from effective treatment based on a simple definition.

AAV is by definition a severe (organ- and/or life -threatening) disease. The definition of “severity” was introduced to try to limit the use of CYC. In clinical studies e.g. RAVE; patients must have severe disease to enter the study. Here it is defined as one or more of the major BVAS/WG items or disease severe enough to require treatment with CYC. BVAS/WG minor items with a significant risk of morbidity may also be classified as severe.

The BSR guidelines definition of severity implies that localised disease is not severe and therefore can be treated conservatively, without CYC. However, localised disease may also have severe consequences e.g. retro-orbital disease or localized vasculitis of the eye, and such patients require effective therapies such as CYC (or RTX). Indeed, 'mild/moderate" disease, which is designated “limited disease” on the BVAS/WG, can progress rapidly to a fatal outcome.

Dosage of RTX

The 1,000mg dose of RTX (effectively the RA dose, given on day 1 and 15) is widely used off-label for AAV and gives less exposure compared with 375mg/m^2 once weekly for 4 weeks schedule, which has been used in the RAVE clinical trial and is likely to be stipulated in the license

Judging by market research findings, we believe that the 2 x 1,000mg dose has widespread use across the UK, with some variation according to the speciality treating AAV; 80% of rheumatologists are likely to prescribe 2 x 1,000mg RTX for induction of remission, but this number is 40% for nephrologists. This also varies with stage of treatment (induction, maintenance, flare).

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

CYC is the main comparator; as shown in previous sections, it is the current standard of care for induction of remission as well as treatment of relapse in AAV patients.

A small proportion of patients intolerant or contraindicated to CYC may receive alternative treatments in the induction of remission, namely AZA, methotrexate, and mycophenolate.

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

The main adverse reactions following RTX infusions are infusion-related reactions (IRRs) and infections. Most of the data come from the use of RTX in RA, but IRRs for patients with GPA and MPA were similar to those seen for rheumatoid arthritis patients in clinical trials (proposed SmPC).

As a result of these IRRs, which may be related to release of cytokines and/or other chemical mediators, premedication consisting of an analgesic/anti-pyretic drug and an anti-histaminic drug, should always be administered before each infusion of RTX.

Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of RTX.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis or microscopic polyangiitis during and following RTX treatment, as appropriate.

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.

RTX is delivered through an intravenous infusion, in an outpatient setting. The cost of administering and monitoring RTX is captured in the fixed tariff of £171.33 [Barton et al 2004, inflated from £124]. We note that RTX is currently funded for use in AAV in a number of centres across the UK, and therefore do not expect positive NICE guidance to be associated with significant additional resource allocation.

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

RTX is given in hospital as a day case procedure for both rheumatology and oncology indications. The infrastructure is already in place widely across the UK for RTX use in these settings; there are no additional requirements for use in vasculitis.

3 Equality

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.

N/A

3.1.2 How has the analysis addressed these issues?

N/A

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.**

RTX is the first monoclonal antibody to be successfully studied in the treatment of vasculitis. The approval of RTX will hopefully encourage additional innovative medicines to be studied in vasculitis patients providing a step change in the management of the disease.

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.**

It is well documented that CYC reduces the fertility in both males and females. As a consequence, patients considering having children have a difficult decision to make in the treatment of their disease. Currently the alternative induction agents are considered less effective compared to CYC, with RTX it is proven to be as effective as CYC while maintaining fertility in patients.

The benefit to patients of treating the disease effectively while maintaining fertility cannot be captured in the QALY currently.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with anti-neutrophil cytoplasmic antibody associated vasculitis	People with severe ANCA-associated vasculitis (GPA or MPA)	In line with the proposed license for RTX
Intervention	RTX in combination with corticosteroids	RTX in combination with corticosteroids for induction treatment only.	In line with the proposed license for RTX.
Comparators	Treatment strategies without RTX, including CYC, AZA, methotrexate, and mycophenolate (in combination with corticosteroids)	CYC (in combination with corticosteroids) for induction of remission. Patients intolerant to CYC may receive alternative induction treatments including AZA, methotrexate, and mycophenolate (in combination with corticosteroids)	Clinical opinion has informed us that with the exception of patients intolerant to CYC, CYC is the standard of care in the induction of remission, with the use of other agents usually reserved for less severe forms of AAV. The RAVE study compared RTX with CYC. We have no evidence of RTX directly compared to other induction agents in the target population.
Outcomes	The outcome measures to be considered include: mortality remission rate and duration of remission number and severity of relapses change in renal function cumulative dose of immunosuppressants adverse effects of treatment health-related quality of life.	We have explored the following outcome measures based on the evidence available: mortality remission rate and duration of remission relapse rates cumulative dose of immunosuppressants adverse effects of treatment health-related quality of life	Not all the outcomes outlined in the final scope could be included due to limitations in the evidence base. The RAVE clinical study has provided information related to relapse rates, however, we have not been able to model the severity of individual relapses due to limitations in the data.
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	Same as the scope	-

	time horizon for estimating clinical and cost effectiveness should be sufficiently long to 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 for whom CYC is contraindicated	We have considered the following subgroups Patients with de novo disease Patients with prior exposure to CYC Patients for whom CYC is contraindicated	The RAVE study included patients with either newly diagnosed or relapsing disease. The study reported significantly different outcomes based on prior exposure to CYC. Due to the limitations in the available evidence we have undertaken scenario analyses for patients who are considered intolerant to CYC and are receiving alternative induction agents (AZA, methotrexate, and mycophenolate)
Special considerations, including issues related to equity or equality		CYC is known to reduce the fertility of both males and females. RTX offers an effective alternative to patients looking at preserving their fertility without compromising on the effectiveness of their treatment.	

Section B – Clinical and cost effectiveness

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)

6 Clinical evidence

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 9.2, appendix 2.**

The following databases were used to identify relevant studies (no date limits were set):

- Embase, Embase Alerts, Medline and Medline In-Process (via ProQuest) on 11 March 2013
- PubMed on 28 Jan 2013

The Cochrane Library, accessed via Wiley Interscience at www3.interscience.wiley.com. The Cochrane Library was be searched with unrestricted dates, searched on 08 March, 2013

Searches used index and text words which included RTX (or RTX) and vasculitis, ANCA, AAV, Wegener's, Granulomatosis with polyangiitis (GPA), Microscopic polyangiitis (MPA), as major descriptors. The search was restricted to include only documents relating to humans and clinical trials and in the English language. The search was further restricted manually according to inclusion/exclusion criteria.

RCTs (including head-to-head) data were the preferred data source, however, in the absence of valid RCT evidence, evidence from other study designs was considered, with reference to the inherent limitation inferred by the study design, including good-quality observational studies to supplement RCT data.

6.2 Study selection

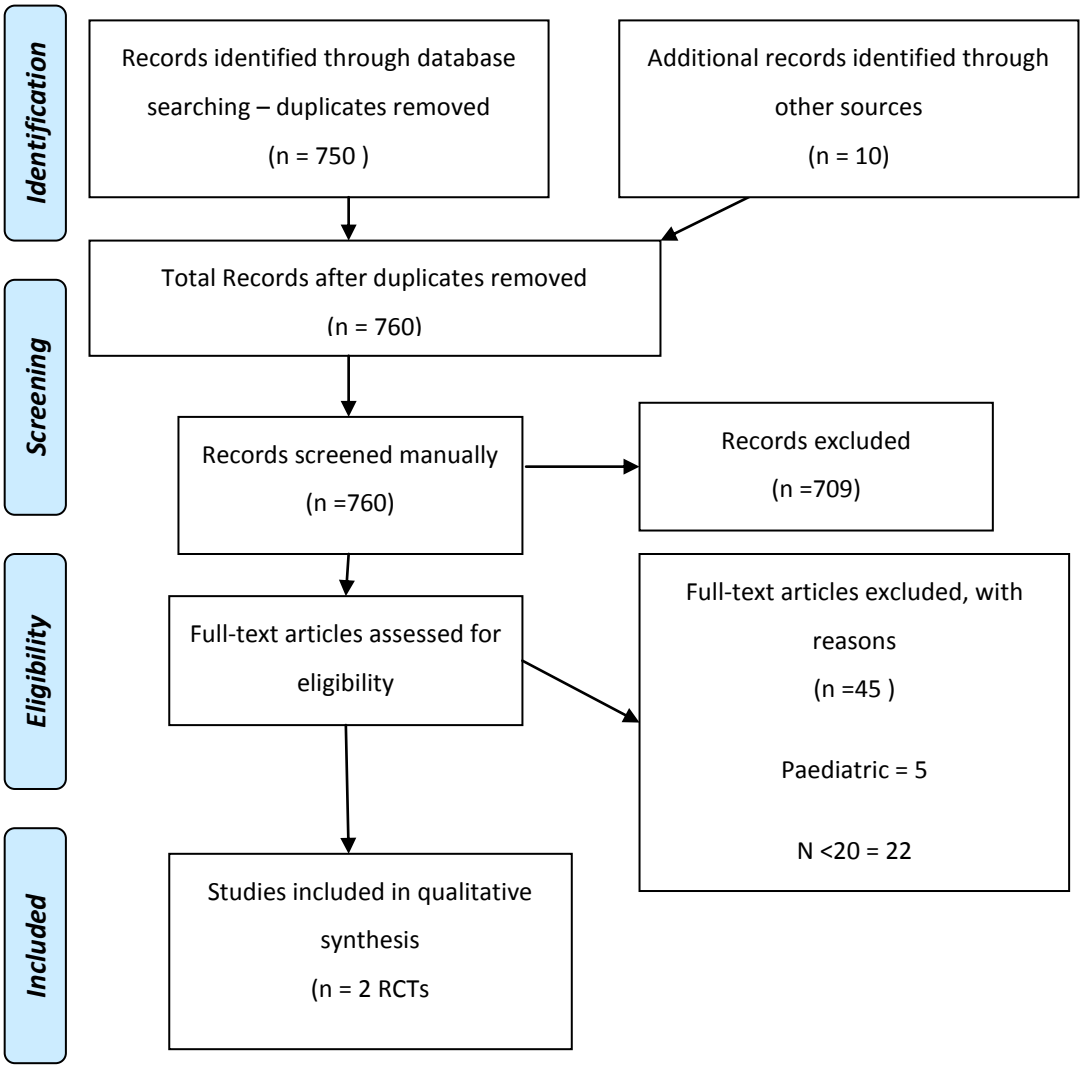
6.2.1 **Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.**

Table 6: Eligibility criteria used in search strategy

Inclusion criteria	Published papers or abstracts which evaluated the following were included: • RTX had to be the major focus of the paper, in order to eliminate papers which mentioned RTX as part of a discussion of treatments for rheumatoid arthritis • AAV had to be a major focus of the paper, in order to eliminate papers covering the use of RTX in other autoimmune diseases • Patient population should consist of those patients who were receiving RTX for induction of remission (or treatment of flare), i.e. not maintenance data, to be consistent with the proposed RTX licence • Correct dosage of RTX 375mg/m2 body surface area once weekly for 4 weeks • Clinical trial data • Documents relating to humans
Exclusion criteria	Published papers or abstracts which evaluated the following were excluded: • Any papers providing a review, update or commentary on data published elsewhere were excluded • Any papers which only mentioned RTX within a discussion of treatments for AAV or other auto-immune diseases were excluded • Papers covering the use of RTX Churg-Strauss syndrome were excluded • Animal studies or in vitro research • Case reports • Studies where there were data for fewer than 20 patients • Paediatric studies • Incorrect dosage • Maintenance of remission only • Posthoc subgroup analyses • Animal data

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 5.2.4.**

Figure 1: Prisma flow diagram for clinical literature search



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.

From the above flow diagram, it can be seen that a number of full-text articles were excluded from the discussion. Five studies were excluded because they were abstracts containing preliminary data that were subsequently published more fully.

Three further papers were excluded because they were abstracts of data from post-hoc analyses of RAVE. One was a post-hoc analysis of long-term outcomes of patients who had renal involvement at baseline in RAVE. The

second abstract contained post-hoc data exploring reasons for primary endpoint failure in RAVE. The third abstract explored levels of markers of inflammation and platelet activation in RAVE to determine whether levels of markers predict future complete remission in AAV.

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.**

Table 7: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
RAVE	RTX 375mg/m^2 x 4 weeks	CYC (2 mg per kg per day)	AAV; GPA/MPA patients with active disease	Stone et al., N Engl J Med 2010;363:221-32
RITUXVAS	RTX 375mg/m^2 x 4 weeks + 2 CYC IV pulses	IV CYC followed by AZA	AAV; GPA/MPA patients and renal involvement	Jones et al., N Engl J Med 2010;363:211-20

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.**

Both studies above compare the intervention (RTX) directly with the appropriate comparator (CYC), however, RITUXVAS also includes 2 pulses of CYC together with RTX at the beginning of the study. RAVE recruited both newly diagnosed and relapsing patients, whereas RITUXVAS recruited newly diagnosed patients with renal involvement. RAVE is included as the main pivotal study for the decision problem, with RITUXVAS included as supporting data.

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.**

Both the RAVE and RITUXVAS studies have been assessed in the appraisal.

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 5.8 and key details should be presented in a table; the following is a suggested format.**

Table 8: List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Fixed interval RTX re-treatment. Retrospective data collection	RTX 375mg/m^2 x4 or 2x1g (induction and relapse)	Patients with refractory or relapsing AAV	Reduction of relapse rates with fixed interval RTX retreatment	Smith et al. Arth Rheum 2012	Large number of AAV patients (n=91) with 2 different doses of RTX for induction)
RTX survey, Retrospective data collection	RTX for refractory AAV in UK, 375mg/m^2 x4 or 2x1g	Patients with refractory or relapsing AAV	Efficacy and safety of RTX in a large, multicentre cohort. Comparison of dosing regimens	Jones et al., Arth Rheum 2009; 60: 2156-2168	N=65. Two different doses of RTX for induction (licensed dose and commonly used dose)
Protocolised RTX treatment	RTX 2x1g every 6 months for 2 years vs RTX PRN	Patients with refractory AAV	Comparing protocolised vs PRN treatment with RTX	Jones et al., Arth Rheum 2010, 62; Suppl. Abstract	N=72. May help to inform retreatment
Wegener's granulomatosis cohort study. Retrospective case note review	RTX 375mg/m^2 x4 or 2x1g	WG of the head and neck	Review of efficacy of RTX for refractory head and neck manifestations of WG	Del Pero et al., Clin Otolaryngol 2009; 34: 328-335	N=34. Two different doses of RTX
RTX for remission induction and maintenance in WG - single centre observational 10 year experience	RTX 375mg/m^2 x4 or 2x1g	WG (GPA) with refractory disease	Efficacy and safety of repeated B cell depletion for long-term remission maintenance in WG	Cartin-Ceba et al., Arth Rheum 2012.	N=53. Two different doses of RTX
RTX efficacy and safety in granulomatous vs vasculitic GPA. Retrospective data collection	RTX 375mg/m^2 x4	Refractory WG/GPA	RTX efficacy and safety in in tertiary referral centre	Holle et al., Ann Rheum Dis 2012; 71: 327 – 333	N=59, licensed dose
GRAID (German Registry)	RTX 375mg/m^2 x4 or 2x1g	AAV, refractory to standard treatment	Efficacy and safety in a German Registry	Roll et al., J Rheumatol 2012; 39: 2153-2156	"Real-life" data

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**.**

Two studies were identified that adequately addressed the decision problem, RAVE and RITUXVAS. This section describes those studies in detail, as they relate to the decision problem.

RAVE: Stone et al 2010

The RAVE study investigators aimed to use RTX in patients with AAV to eliminate potentially pathogenic B cells and disease-amplifying ANCAs. This therapy was expected to result in disease remission.

The primary objective was to demonstrate non-inferiority of RTX compared with conventional therapy (CYC/AZA) and to determine the efficacy of RTX (375 mg/m^2, four weekly infusions) and glucocorticoids in the induction of complete remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0 when off glucocorticoid therapy in patients with severe ANCA-associated vasculitis.

RITUXVAS: Jones et al 2010

While the focus in this STA is on efficacy data from the 6-month induction phase in RAVE, these data are complemented with published efficacy data from a controlled, open-label, randomised study (RITUXVAS) in 44 patients with newly diagnosed AAV that provides important data supporting the efficacy of RTX in the treatment of severe AAV.

The purpose of RITUXVAS was to assess the treatment response and rates of associated severe adverse events with a RTX-based regimen, as

compared with a CYC-based regimen, as induction therapy in patients with recently diagnosed, severe ANCA-associated vasculitis with glomerulonephritis.

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.

Location

RAVE Nine centres in the United States and the Netherlands

RITUXVAS Eight centres in Europe and Australia

Design

RAVE Randomised, multicentre, double-blinded, double-dummy, placebo-controlled, international study of RTX (375 mg/m^2) in patients with severe AAV, designed to demonstrate non-inferiority to conventional therapy (CYC/AZA) and superiority to a historical control

RITUXVAS Phase II, open-label, randomised, controlled, prospective study comparing a RTX- based (375 mg/m^2) regimen with a standard CYC/ AZA regimen, as induction therapy in patients with recently diagnosed, severe AAV

Duration of study

RAVE The study consisted of two phases:

- 6-month remission induction phase, followed by
- 12-month remission maintenance phase

All patients were to be followed until 18 months after enrolment of the last patient

RITUXVAS 3 years: 6 months recruitment, two year follow-up per patient and 6 month analyses

Method of randomisation

RAVE Participants enrolled and assigned a unique participant number (sequentially according to a randomisation schedule provided to the site pharmacist). Patients were randomised at a ratio of 1:1 to the two treatment arms just prior to receiving investigational treatment at the baseline visit. Randomisation was stratified by clinical study centre and type of ANCA (PR3 or MPO)

RITUXVAS Randomisation was performed with a computer minimization algorithm to maintain concealment of study-group assignments from the investigators. The algorithm was stratified according to the patients' age, diagnosis, and baseline renal function. A 3:1 ratio for random assignment was used

Method of blinding (care provider, patient and outcome assessor)

RAVE Study centres were provided with blinded generic oral medication kits and RTX/RTX placebo vials (without patient identifiers). Blinded kits/vials containing the opposite study therapy regimen were provided if a blinded crossover was needed. To minimize bias due to reactions from RTX infusion and adverse events associated with conventional therapy, the following measures were taken:

- Patients in both study arms received concomitant glucocorticoids to reduce possible systemic reactions associated with RTX infusions
- To conceal thinning hair associated with CYC, patients wore hats to their study visits

- Each patient was evaluated by two physicians: a safety officer and an investigator
- Any potential difference in the time required to achieve remission was minimized by not switching any patient to the maintenance therapy before Month 3 unless they developed hemorrhagic cystitis
- Patients considered treatment failures before the Month 6 Visit could be crossed over to the opposite treatment arm in a blinded fashion. Patients who experienced early treatment failure were not unblinded and were treated according to BMJ
- The study drug packaging, labeling, correspondence, and preparation procedures were designed to maintain the study blind
- If a serious or life-threatening adverse event occurred and knowledge of drug administration was required, the NIAID Medical Monitor was notified before the patient's treatment assignment was unblinded. This was then discussed promptly with the Protocol Chairs and ITN Clinical Trial Physician. For all other events requiring the unblinding, the Medical Monitor was contacted before unblinding occurred. In all cases, the NIAID Medical Monitor was to notify the Protocol Chairs and the ITN Clinical Trial Physician. Any unblinding event was to be reported immediately to the DSMB

RITUXVAS Open-label

Intervention(s) and comparator(s)

RAVE Two hundred patients were to be randomised in a 1:1 ratio to the experimental or control arm. Patients in both arms received 1 g of intravenous (IV) pulse methylprednisolone (or an equivalent IV dose of another glucocorticoid preparation), followed by a protocol-mandated oral prednisone taper (dose starting at 1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by the Month 6 Visit to meet the definition of complete remission.

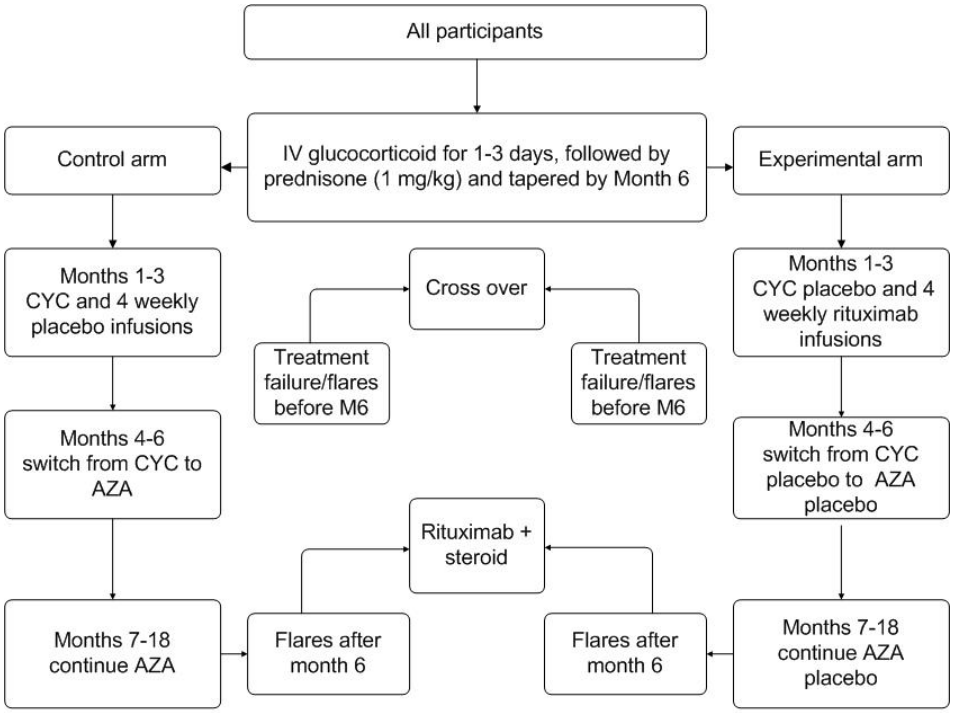


Figure 2: RAVE study design

The study consisted of two phases:

- 6-month remission induction phase followed by
- 2-month remission maintenance phase

During the remission induction phase, patients in the control arm (conventional treatment) received oral prednisone daily, RTX placebo infusions once weekly for 4 weeks, and oral CYC daily (2 mg/kg/day) for 3 to 6 months. Patients in the experimental arm (RTX and glucocorticoids) received oral prednisone daily, RTX (375 mg/m^2) infusions once weekly for 4 weeks, and CYC placebo daily for 3 to 6 months.

During the remission maintenance phase, patients in the control arm discontinued CYC and started oral AZA (AZA) (2 mg/kg/day), and patients in the experimental arm discontinued CYC placebo and started oral daily AZA placebo. Both arms continued oral AZA/AZA placebo daily up to Month 18.

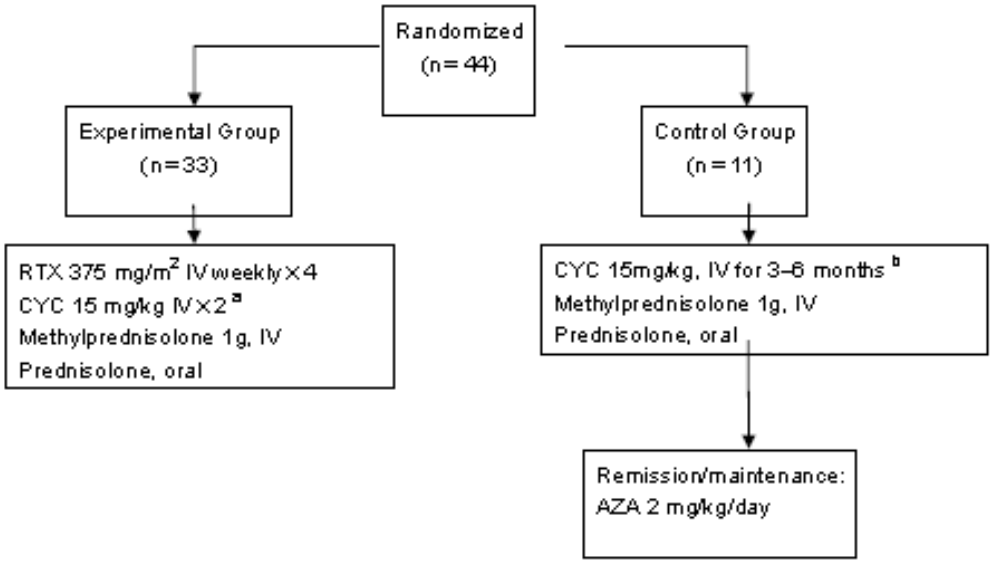
Patients who experienced severe disease flares or treatment failure between Visit V5 and Visit V8 (Month 6 Visit) were crossed over to the opposite treatment arm.

Patients in either group who achieved remission, defined as a BVAS/WG of 0 before completing 6 months of therapy, could switch from CYC/CYC placebo to AZA/AZA placebo. No patient in either group was allowed to switch from CYC or CYC placebo before completing 3 months of CYC or CYC placebo therapy.

Note that, upon achievement of remission in the RTX group, no additional maintenance therapy was to be provided to these patients

RITUXVAS The patient flow is shown in the following figure:

Figure 3: RITUXVAS study design



[a] Given with the first and third RTX infusion.
[b] The first three cycles of CYC given at 2-week intervals; following doses given at 3-week intervals. CYC continued until remission was achieved (BVAS of 0 for 2 months).

RTX regimen: RTX, 375mg/m^2 IV once a week for 4 weeks (i.e. 4 doses total), with 2 doses of CYC 15mg/kg, 2 weeks apart given with the 1st and 3rd RTX dose

Control (CYC/ AZA) regimen: CYC 15mg/kg for 3-6 months (6-10 doses total) to be given IV for remission induction. CYC should be converted to AZA for remission maintenance

Steroids: All patients received 1g IV methylprednisolone, then the same daily oral corticosteroid regimen.

Plasma exchange or IV methylprednisolone was allowed according to local practice for patients with organ threatening disease. NB randomisation should not occur until completion of plasma exchange to avoid loss of RTX during plasma exchange. The first dose of CYC could be given prior to completion of plasma exchange.

In the case of progressive disease; additional treatment was allowed:

i) RTX arm: 3rd dose of CYC (15mg/kg)

ii) CYC arm: Plasma exchange or IV methylprednisolone (according to local practice)

In the case of relapse, the following treatments were allowed:

i) RTX arm: RTX with steroid was used for major and minor relapse. Additional CYC also used for major relapse

ii) CYC arm: increased AZA and steroid for minor relapse and CYC and steroid for major relapse

	Primary outcomes (including scoring methods and timings of assessments)
RAVE	Percentage of patients who achieved complete remission at 6 months, as defined by a BVAS/WG of 0 and successful completion of the glucocorticoid taper at 6 months after randomisation (glucocorticoid dose of 0 at Month 6)
RITUXVAS	Percentage of patients achieving sustained remission at 12 months. Remission was defined as an absence of clinical disease activity, measured as a BVAS of 0 maintained for 2 months. Sustained remission was an absence of disease activity, maintained for at least 6 months.

Secondary outcomes (including scoring methods and timings of assessments)

RAVE Secondary efficacy endpoint:

Superiority of RTX to CYC for the percentage of patients who had a BVAS/WG of 0 and successfully completed the glucocorticoid taper by 6 months after randomisation. (secondary analysis of the primary efficacy endpoint.)

Tertiary efficacy endpoints:

- Cumulative BVAS/WG area under the curve (AUC) during the 6 months after randomisation
- Percentage of patients who achieved and maintained partial remission as defined by BVAS ≤ 2 and off glucocorticoids at Month 6
- Percentage of patients who achieved a BVAS/WG of 0 on prednisone< 10 mg/day at 6 months
- Cumulative glucocorticoid dose at 6 months
- Number of severe flares (i.e., increase in BVAS/WG to ≥ 3 or experiencing one major BVAS/WG item requiring treatment with CYC) at 6 months
- Number of limited flares (new occurrence or worsening of one or more minor BVAS/WG items) at 6 months
- Quality of life using SF-36 PCS and MCS scores
- The endpoints for the assessment of long-term efficacy, assessed out to 18 months, included the duration of complete remission, and the time to limited and/or severe flare after complete remission in the two treatment groups.

RITUXVAS Major Secondary and Tertiary Endpoints:

- Time to remission (BVAS = 0)
- BVAS area under the curve
- Change in glomerular filtration rate (GFR)
- Prednisolone dose
- Quality of life and disease damage (assessed through the Short Form 36 [SF-36] questionnaire and Vasculitis Damage Index [VDI] between 0 and 12 months).

Duration of follow-up

RAVE All patients were to be followed until 18 months after enrolment of the last patient

RITUXVAS 12 months

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 is more than one RCT. Highlight any differences between the trials.**

Table 9: Eligibility criteria of RAVE and RITUXVAS

Trial	Inclusion criteria	Exclusion criteria
RAVE	1. Age: 15 years of age or older 2. Weight: at least 40 kg 3. Diagnosis type: diagnosis of WG or MPA according to the definitions of the Chapel Hill Consensus Conference. The maximum number of patients with a diagnosis of MPA was not to exceed 50% of all patients 4. Screening diagnosis: newly diagnosed disease or must have had a disease flare fulfilling Inclusion Criteria 5, 6, and 7 5. Disease activity: active disease with a BVAS/WG≥3 that would normally have required treatment with CYC 6. Disease severity: severe disease (i.e., one or more major BVAS/WG items, or disease severe enough to require treatment with CYC 7. ANCA status: positive for either proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA at the Screening Visit 8. Competence: willing and able to provide informed consent	1. Churg Strauss syndrome as defined by the Chapel Hill Consensus Conference 2. Disease severity: • Limited disease that would not normally be treated with CYC • Severe disease: required mechanical ventilation because of alveolar haemorrhage 3. Co-morbidities: • history of severe allergic reactions to human or chimeric monoclonal antibodies or murine protein • active systemic infection • history of documented anti-glomerular basement membrane disease • active malignancy or a history of malignancy in the last 5 years 4. Diagnostics: • White blood cell count <4,000/µL • Platelet count <120,000/µL • ALT or AST level >2.5x the upper limit of normal, which could not be attributed to underlying AAV disease • Serum creatinine level >4.0 mg/dL attributed to renal failure from a current flare • Human antichimeric antibodies (HACA) 5. Treatments: • Intolerant to CYC • Used CYC, oral or IV, within the past 4 months, unless

		started oral CYC not more than 1 week prior to enrolment • any previous treatment with RTX or Campath-1H • received treatment with plasma exchange within 3 months preceding the Screening Visit
RITUXVAS	(all four inclusion criteria must be present) 1. A new diagnosis of WG, MP or renal-limited vasculitis (RLV) 2. Renal involvement attributable to active WG, MP or RLV with at least one of the following: • Biopsy demonstrating necrotizing glomerulonephritis. • Red cell casts on urine microscopy or ≥ ++ haematuria 3. ANCA positivity 4. Written informed consent	1. Previous CYC (greater than 2 weeks of an oral or IV pulse CYC regimen) 2. Co-existence of another multisystem autoimmune disease, e.g. SLE, Churg Strauss Syndrome, Henoch Schonlein Purpura, rheumatoid vasculitis, essential mixed cryoglobulinaemia, anti-glomerular basement membrane antibody positivity 3. Hepatitis B e antigen positive or Hepatitis C antibody positive 4. Known HIV positive 5. Previous malignancy 6. Pregnancy, breast feeding or inadequate contraception if female 7. Allergy to a study medication 8. Live vaccine within last 4 weeks

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.

As the number of baseline characteristics described in the two studies were different, it has not been possible to combine them into one table. Both studies' baseline characteristics are thus described separately below.

RAVE

Table 10: RAVE baseline demographics (ITT population)

	RTX n = 99	CYC n = 98	All patients n = 197
Age at screening, years			
Mean (SD)	54.0 (16.76)	51.5 (14.07)	52.8 (15.49)
Gender (%)			
Male	46.5	54.1	50.3
Female	53.5	45.9	49.7
Primary Race (%)			
White	91.9	94.9	93.4
Black or African-American	3.0	3.1	3.0
Asian	1.0	0.0	0.5
Other	4.0	2.0	3.0
Ethnicity (%)			
Not Hispanic or Latino	91.9	94.9	93.4
Hispanic or Latino	6.1	3.1	4.6
Unknown	2.0	2.0	2.0

The demographic characteristics were similar between the treatment arms in terms of age at disease onset, gender, primary race, and ethnicity (Table 10). The median age of patients was 52.0 years with a range of 15 to 92 years, and most of the patients (93.4%) were white.

The majority of patients (147, 74.6%) had a diagnosis of GPA (WG), and 48 (24.4%) had a diagnosis of MPA (Table 11). Ninety-six (48.7%) patients were newly diagnosed at the time of screening, including the majority of patients with MPA (39 of 48 patients). By BVAS/WG assessment at Baseline, the

majority of patients in each arm had renal, pulmonary, systemic, or ear/nose/throat involvement. Baseline disease characteristics were generally balanced between the two treatment arms with the exception of estimated creatinine clearance. Mean (SD) creatinine clearance was 76.51 (46.27) and 91.40 (49.24) ml/min for the RTX and CYC arms, respectively. The median values were also lower in the RTX arm compared with the CYC arm (67.61 vs. 87.47 ml/min, respectively).

Approximately two-thirds of the patients in each arm were positive for C-ANCA by immunofluorescence and the remaining one-third was positive for P-ANCA (Table 12). Similarly, approximately two-thirds of the patients were positive for PR3-specific antibodies, and one-third were positive for MPO-specific antibodies.

Table 11: RAVE baseline disease characteristics (ITT population)

	Rituximab N=99	Cyclophosphamide N=98	All Patients N=197
ANCA-associated vasculitis type (%)			
Wegener's granulomatosis	73.7	75.5	74.6
Microscopic polyangiitis	24.2	24.5	24.4
Indeterminate	1.0	0	0.5
Missing	1.0	0	0.5
Newly diagnosed at enrollment (%)	48.5	49.0	48.7
BVAS/WG score[a] (mean [SD])	8.1 (2.82)	8.0 (3.41)	8.0 (3.12)
Creatinine clearance (mean [SD]) mL/min	76.5 (46.27)	91.4 (49.24)	83.9 (48.23)
Organ involvement (%)[b]			
Renal	65.7	66.3	66.0
Hematuria	28.3	28.6	28.4
Red blood cell casts	37.4	35.7	36.5
Rise in creatinine >30% or fall in creatinine clearance >25%	34.3	36.7	35.5
Pulmonary	52.5	54.1	53.3
Alveolar hemorrhage	27.3	23.5	25.4
Endobronchial involvement	4.0	9.2	6.6
Nodules or cavities	18.2	27.6	22.8
Other lung infiltrate	25.3	21.4	23.4
Pleurisy	8.1	9.2	8.6
Respiratory failure	2.0	0	1.0
Systemic[c]	55.6	66.3	60.9
Ear/nose/throat	60.6	56.1	58.4
Mucous membranes/eyes	27.3	25.5	26.4
Nervous system	25.3	15.3	20.3
Cutaneous	20.2	16.3	18.3
Gastrointestinal	2.0	0	1.0
Mesenteric ischemia	2.0	0	1.0
Cardiovascular	0	1.0	0.5
Pericarditis	0	1.0	0.5

ANCA=anti-neutrophil cytoplasmic antibody; BVAS/WG=Birmingham Vasculitis Activity Score for Wegener's granulomatosis; ITT=Intent-to-Treat; SF-36=Short Form-36 v.2™ Survey

[a] Scores for new/worse disease range from 0 to 67 (higher scores=more active disease) N=77 for rituximab arm and N=67 for CYC arm.

[b] Tabulation includes new/worse disease and not persistent.

[c] Systemic signs of disease, especially signs of either arthritis/arthralgias or fever.

Table 12: RAVE Baseline ANCA status (ITT population)

	Rituximab N=99 n (%)	Cyclophosphamide N=98 n (%)	All Patients N=197 n (%)
Positive immunofluorescence assay ANCA results[a]	97 (100)	94 (100)	191 (100)
C-ANCA	65 (67.0)	61 (64.9)	126 (66.0)
P-ANCA	33 (34.0)	33 (35.1)	66 (34.6)
Positive ELISA results for ANCA[a,b]	97 (98.0)	98 (100)	195 (99.0)
PR3	66 (68.0)	65 (66.3)	131 (67.2)
MPO	32 (33.0)	33 (33.7)	65 (33.3)

ANCA=anti-neutrophil cytoplasmic antibody; C-ANCA=cytoplasmic ANCA;
CRF=case report form; ELISA=enzyme-linked immunosorbent assay; ITT=Intent-to-Treat;
MPO=myeloperoxidase; P-ANCA=perinuclear ANCA; PR3=proteinase 3

[a] Percentage is based on number of subjects with non-missing values.

[b] One patient in the rituximab group had a CRF page without a check mark for positive immunofluorescence or ELISA results; however, results were entered for the specific ANCA pattern/antigen on the CRF.

RITUXVAS

Baseline characteristics of the RITUXVAS patients are shown in Table 13. No major imbalances at baseline were seen between the two groups, with the exception of a greater proportion of renal-limited vasculitis patients in the CYC group and a greater proportion of patients requiring dialysis in the RTX + low-dose CYC group. The use of plasma exchange was balanced between groups. Overall, as expected for this population, renal function was generally poor in both groups at study entry.

Table 13: RITUXVAS baseline characteristics (ITT Population)

	RTX n=33	**CYC n=11**
Age (yrs), median (min-max)	68 (20-85)	67 (51-83)
Sex (male, %)	17 (52%)	6 (55%)
No. diagnosed:		
WG	18 (55%)	4(36%)
MPA	12 (36%)	4 (36%)
Renal-limited vasculitis	3 (9%)	3 (27%)
No. diagnosed:		
c-ANCA positive	20 (61%)	5 (45%)
p-ANCA positive	13 (39%)	6 (55%)

GFR in ml/min/1.73m² (median (min-max)	20 (0-74)	12 (0-48)
CRP in mg/ml, median (min-max)	28 (2-297)	25 (1-157)
BVAS, median (min-max)	19 (9-42)	18 (12-33)
required dialysis	8 (24%)	1 (9%)
Received plasma exchange	8 (24%)	3 (27%)

ANCA = anti-neutrophil cytoplasmic antibodies; BVAS = Birmingham Vasculitis Activity Score; C-ANCA = cytoplasmic ANCA; CRP = C-reactive protein; GFR = glomerular filtration rate; MPA = microscopic polyangiitis; p-ANCA = perinuclear ANCA; WG = Wegener's granulomatosis.

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.**

We believe the nature of the outcomes in the two studies is best described as a narrative, rather than in a table.

RAVE: outcomes

Primary efficacy endpoint:

The percentage of patients who achieved complete remission at 6 months, as defined by a BVAS/WG of 0 and successful completion of the glucocorticoid taper at 6 months after randomisation (glucocorticoid dose of 0 at Month 6). Since long-term glucocorticoid use is associated with significant side effects, the glucocorticoid taper is an important additional goal of treatment and supports the clinical relevance and interpretation of the primary endpoint.

Secondary Endpoints:

The secondary efficacy objective for RAVE was the superiority of RTX to CYC for the percentage of patients who had a BVAS/WG of 0 and successfully completed the glucocorticoid taper by 6 months after randomisation. (This was a secondary analysis of the primary efficacy endpoint.)

The tertiary efficacy endpoints for RAVE were:

- The cumulative BVAS/WG area under the curve (AUC) during the 6 months after randomisation
- Percentage of patients who achieved and maintained partial remission as defined by having BVAS ≤ 2 and off glucocorticoids at Month 6
- Percentage of patients who achieved a BVAS/WG of 0 on prednisone< 10 mg/day at 6 months
- Cumulative glucocorticoid dose at 6 months
- Number of severe flares (i.e., increase in BVAS/WG to ≥ 3 or experiencing one major BVAS/WG item requiring treatment with CYC) at 6 months
- Number of limited flares (new occurrence or worsening of one or more minor BVAS/WG items) at 6 months
- Quality of life using SF-36 PCS and MCS scores

The endpoints for the assessment of long-term efficacy, assessed out to 18 months, included the duration of complete remission, and the time to limited and/or severe flare after complete remission in the two treatment groups.

Disease Activity Measures used in RAVE

Birmingham Vasculitis Activity Score (BVAS) and BVAS for Wegener's Granulomatosis (BVAS/WG)

The BVAS is a validated instrument for the assessment of disease activity and response to treatment in AAV, and is a clinically relevant measure of disease activity experienced by the participant over time. The BVAS has been adopted and used by most research groups involved in international clinical trials in vasculitis. The BVAS form, which provides a numerical score, is divided into nine organ-based systems with each section including symptoms/signs that characterize particular organ involvement in systemic vasculitis. The clinician only scores features believed to be present and due to active vasculitis (as opposed to pre-existing irreversible damage).

The BVAS and its versions assign a score of 0 if no clinical activity is present, thus aiding a comparison of remission (BVAS or BVAS/WG = 0) across studies.

The BVAS has also been revised and validated as an index of WG activity. The maximum score for BVAS is 63. The maximum score for BVAS/WG is 68. The BVAS/WG is supplemented by a visual analogue scale of the physician's global assessment of disease activity and an opportunity to assign patients to a specific disease state of remission, minor flare or major flare. While the instrument was initially validated in WG patients, it has been used in clinical trials enrolling both WG and MPA patients. RAVE employed the BVAS/WG form.

Quality of life

The health status instrument used in the study was the SF-36 v.2™ Health Survey, provided by the Medical Outcomes Trust, (Boston, MA). This standard consists of 36 questions that refer to eight domains of physical functioning: physical role limitations, bodily pain, social functioning, mental health, emotional role limitations, vitality, and general health. It is a generic health-related quality of life instrument that has been widely tested for its psychometric properties and widely used in clinical and epidemiological studies. The questionnaire was provided in the local languages of the sites participating in the study.

RITUXVAS: outcomes

Primary Efficacy Endpoints

Percentage of patients achieving sustained remission at 12 months. Remission was defined as an absence of clinical disease activity, measured as a BVAS of 0 maintained for 2 months.

Sustained remission was an absence of disease activity, maintained for at least 6 months.

Major Secondary and Tertiary Endpoints

- Time to remission (BVAS = 0)
- BVAS area under the curve
- Change in glomerular filtration rate (GFR)
- Prednisolone dose
- Quality of life and disease damage (assessed through the Short Form 36 [SF-36] questionnaire and Vasculitis Damage Index [VDI] between 0 and 12 months).

The VDI scale measures the presence or absence of vasculitis damage related items across multiple organ systems wherein 1 point is assigned per item with a maximum score of 64. Damage items may be related to prior disease activity or complications of therapy.

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.**

We believe the nature of the analyses in the two studies is best described as a narrative, rather than in a table.

RAVE: analyses

Hypothesis

This trial tested the hypothesis that RTX is not inferior to conventional therapy in its ability to induce disease remission in AAV at 6 months. The primary efficacy outcome of the study was the ability of RTX to induce complete remission during the first 6 months after randomisation.

Sample size

Untreated AAV is essentially fatal within 6–12 months; therefore, it can be assumed that 0% of participants with severe disease who do not receive active treatment, will enter remission within 6 months. A recently completed trial in Wegener's granulomatosis on 180 participants (WGET trial, WGET Res Group, 2005 NEJM), indicated that approximately 70% of participants who receive CYC as induction regimen, will have a BVAS/WG of 0 by month 6.

Based on these data, the sample size was calculated assuming that 70% of the participants who receive CYC and RTX will attain complete remission during the first 6 months after randomisation and that there will be a non-inferiority limit of 20% on the difference in the complete remission percentage between RTX and CYC. If it is also assumed there is a 10% dropout rate that is equally distributed between treatment groups, a sample size of 100 participants per arm will yield 83% power to conclude non-inferiority using a one-sided, 0.025 level test.

The non-inferiority limit of 20% was chosen based on the assumption that 0% of untreated participants would attain remission and that, with this bound, RTX would still be considered an effective treatment.

Thus, if the lower limit of the two-sided 95% CI for the difference between the RTX and CYC groups in complete remission at 6 months was greater than −20, it would be concluded that RTX was statistically significantly non-inferior to

CYC/AZA with respect to the primary endpoint. The confidence level of 95% (as opposed to 95%) was chosen for consistency with the significance level, α = 0.049, for the test of superiority versus CYC/AZA (the secondary objective).

In addition, if the observed complete remission rate of the RTX group was lower than that of the CYC/AZA group, the latter was required to be greater than 40% to conclude non-inferiority of RTX to conventional therapy. This provision was mandated because an observed CYC/AZA remission rate less than 40% at 6 months would be inconsistent with expected remission rates, suggesting that the population enrolled was refractory to conventional therapy.

An additional test for the efficacy of RTX with respect to historical placebo was also pre-specified; in order to conclude that RTX was efficacious in RAVE, superiority to the expected survival rates from untreated patients, in addition to non-inferiority to the active control at the pre-specified non-inferiority margin, would have to be demonstrated. In the absence of current data on complete remission rates in untreated patients at 6 months, RTX outcomes were to be compared with the survival rate generated from Walton et al., 1958, describing a cohort of 56 largely untreated patients with WG (Table 14). Under a “best-case scenario” for untreated patients, assuming that all patients who survived would have achieved the definition of complete remission at 6 months, a maximum of 38% of the untreated patients (95% CI: 24.9%, 51.5%) would have met this endpoint.

Because the percentage of patients in complete remission could be no greater than the percentage of survivors, the actual number of untreated patients in remission was likely much lower than 38%.

Based on the upper limit of this 95% CI, to conclude efficacy for RTX in RAVE, the lower limit of the 95% CI of the complete remission rate at 6 months in the RTX group was required to be > 50%.

Table 14: Outcome of GPA patients [Walton et al., 1958]

Timepoint	% of patients who died	% of surviving patients*	95% CI of the surviving patients**
6 months	63	38	24.9, 51.5
9 months	75	25	14.4, 38.4
12 months	82	18	8.9, 30.4

*The percentage of patients in complete remission is no greater than the percentage of survivors; **tThe upper confidence limit is the 'best case scenario' for the percentage of patients in complete remission.

Statistical analysis

Continuous data (e.g., age, body weight) was summarized using descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum). For categorical data (e.g., race and gender), the number and percentage of participants in each category is presented. Descriptive statistics and two-sided 95% confidence intervals were calculated to assist the interpretation of secondary efficacy outcomes and comparison between study arms.

Analysis Populations

This study used the ITT, Per Protocol (PP), and Safety Analysis populations.

ITT Analysis Population

The ITT analysis population included all randomised and treated patients. The ITT analysis population was used in the analysis of efficacy endpoints according to the treatment assigned and not the treatment actually received, if different.

PP Analysis Population

The PP analysis population was a subset of the ITT analysis population that excluded the following patients:

- Patients without any BVAS/WG observation post randomisation
- Patients with less than 75% of total 375 mg/m^2 × 4 RTX/placebo infusions

- Patients with major protocol deviations, which were determined by blinded Sponsor review prior to database lock

- Patients excluded from the PP analysis population were identified prior to study unblinding. Analysis of the PP analysis population was used as a supporting analysis to the ITT analysis.

Sensitivity Analyses

As a sensitivity analysis, the primary endpoint was also determined using worst-case imputation for ITT patients who discontinued permanently from study treatment or withdrew from study before Month 6, without having already been classified as treatment failures (i.e., patients with missing primary endpoint at Month 6). In the worst-case imputation, these patients were considered to have experienced treatment failure at 6 months.

Secondary Efficacy Endpoints

The main secondary efficacy objective was to demonstrate superiority of RTX to CYC in achieving complete remission at 6 months. If the lower limit of the CI for the difference in complete remission rates was greater than 0 and the lower limit of two-sided 95% CI of the complete remission rate for the RTX group was greater than or equal to 50%, it would be concluded that RTX was superior to CYC/AZA. A p-value for a test of superiority of RTX vs. CYC/AZA for achievement of complete remission at 6 months was calculated using a X^2 test, and statistical significance was judged at the $\alpha = 0.049$ level. Other secondary efficacy endpoints included analyses for duration of remission, time to remission, and time to complete remission.

Safety Analysis Population

The Safety Analysis population included all patients who received at least one dose of any study drug (RTX/RTX placebo, CYC/CYC placebo, or AZA/AZA placebo). The Safety Analysis population was used for all safety analyses. Patients in the Safety Analysis population were analysed according to the actual treatments initially received, unless otherwise indicated.

Long term efficacy analyses

Efficacy data (BVAS/WG, flares, corticosteroid dose, etc.) collected beyond the 6-month remission induction period, after the point of switching therapy (crossover, open-label RTX, or treatment under BMJ) were considered missing after the point of treatment switch. For binary endpoints (complete remission, remission, remission on prednisone < 10 mg/day), two types of analyses were performed; observed-case analysis and worst-case analysis.

The observed-case analysis excluded patients with missing efficacy measures; therefore, the number of patients included in this analysis varied by timepoint and endpoint. The worst-case analysis imputed missing efficacy measures as treatment failures, and all patients were included in the analysis at all timepoints and for all endpoints.

A data review committee at the Statistical and Data Coordination Centre who managed the RAVE study identified a number of anomalies in the clinical data after the original unblinding and reporting of the study results. At their recommendation, changes were made to the analysis datasets to correct the anomalies of most concern. This resulted in minor numerical changes to some long-term efficacy endpoints at the 12- and 18-month time points. The differences did not alter the data interpretation or overall conclusions. The 6-month results were not affected.

RITUXVAS: analyses

A total of 30 patients were scheduled to receive RTX. The expected sustained remission rate for RTX is 86%, based on the results of former studies. The 95% confidence interval for a sustained remission rate of 86% is 70.3%-94.7% when the sample size is 30.

The expected response rate of 86% is considered clinically significant as patients with active newly diagnosed generalised AAV without 3-6 months of CYC are conventionally expected to experience disease progression (worsening of clinical signs and symptoms). The expected sustained remission rate in the control group is 75%.

Analyses on the 40 patients were considered exploratory.

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.

No subgroup analyses were described for RITUXVAS.

RAVE: Stone et al 2010

The effects of various baseline characteristics were explored in relation to the primary endpoint. Exploratory analyses were performed in the following subgroups of patients:

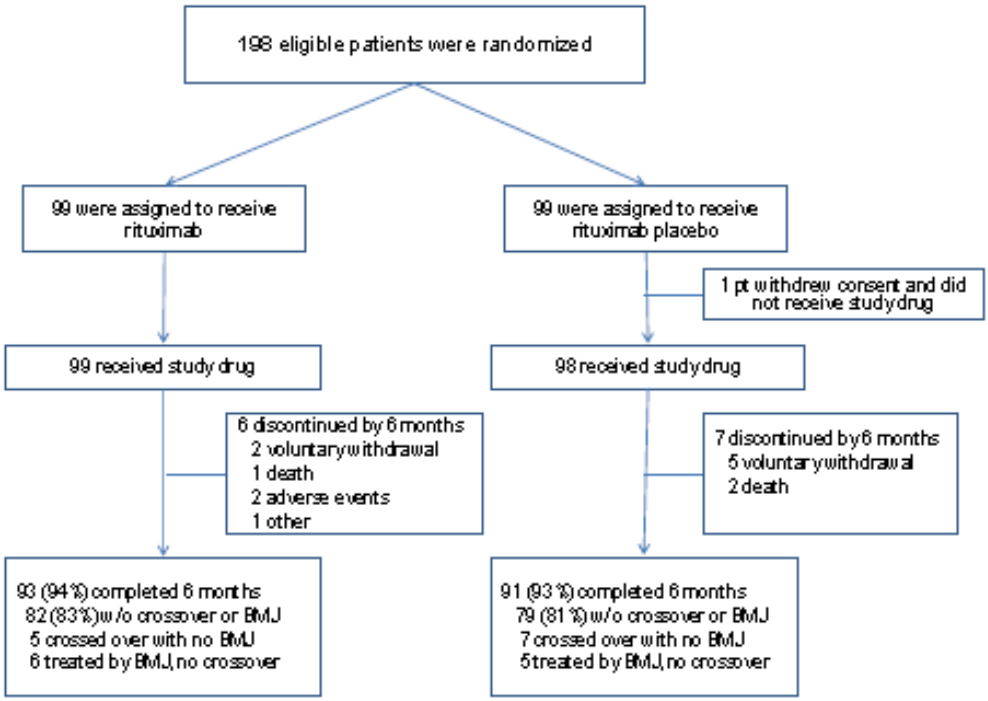
- Age (<52, ≥ 52; <65, ≥ 65)
- Gender (Male, Female)
- Disease status at baseline (new vs. relapsing)
- Organ involvement at baseline: renal involvement (no BVAS/WG major renal item, major renal item)
- Organ involvement at baseline: alveolar hemorrhage (yes/no)
- Organ involvement at baseline: systemic disease (yes/no)
- Baseline creatinine clearance (< 60, ≥ 60)
- Baseline serum creatinine (< 1.2, ≥ 1.2)

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.**

RAVE: patient disposition

Figure 4 shows the patient disposition for patients in RAVE during the 6-month remission induction phase. Eighty-two (83%) patients in the RTX group and 79 (81%) patients in the CYC group completed 6 months of the study without crossover or change to BMJ. During the maintenance phase of the study, patients in RAVE were followed up to a common closeout (CCO) date, corresponding to the last patient's 18-month visit. In total, 123 completed 18 months on their randomised treatment (61 of 99 [62%] on RTX and 62 of 98 [63%] on CYC).

Figure 4: RAVE patient disposition



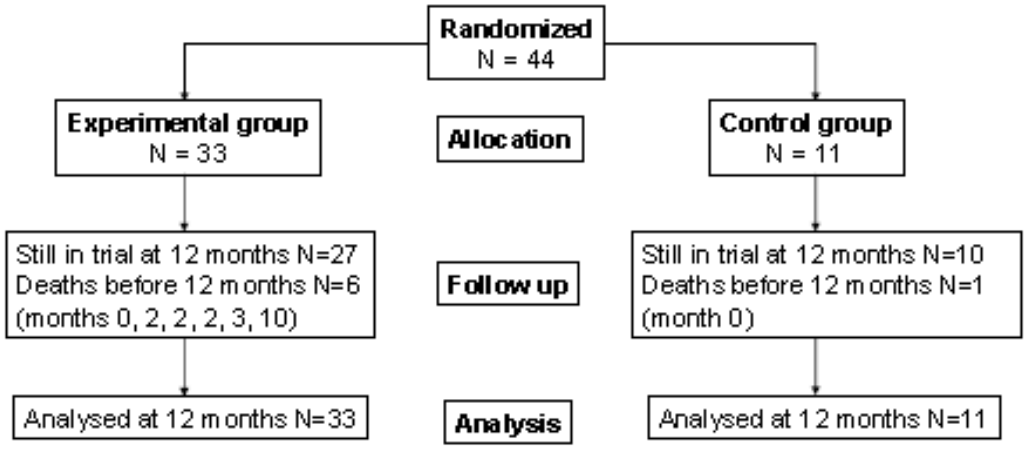
BMJ = best medical judgment. One patient randomised to CYC withdrew consent and discontinued the study prior to the first treatment.

RITUXVAS: patient disposition

No patients were lost to follow-up in RITUXVAS (see

Figure 5). Six patients (18%) in the RTX + low-dose CYC group and 1 patient (9%) in the CYC group had died by 12 months. One other patient in the CYC group died at 19 months (a total of 18% of patients died in the CYC group). Two patients from the RTX + low-dose CYC group received a third CYC dose (i.e., a protocol violation): one was classified as a treatment failure, and the other had responded to the RTX regimen. This patient was classified as a treatment success.

Figure 5: RITUXVAS patient disposition



Note: The experimental group was RTX + low-dose CYC at Weeks 1 and 3; the control group was CYC.

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.**

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.**

Please refer to Appendix 10.3 for quality assessments of the RAVE and RITUXVAS studies.

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.**

Please refer to Appendix 10.3 for quality assessments of the RAVE and RITUXVAS studies.

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.

RAVE: results

Table 15 provides a summary of the efficacy outcomes in RAVE (ITT Population). Individual results are described in more detail in the section 6.5.

Table 15: RAVE clinical results

	RTX (n=99)	CYC (n=98)	Absolute Difference (95% CI)	p-value [a]
Primary endpoint				
n analysed [b]	98	95		
% in complete remission [c] (95% CI)	64.3 (54.8, 73.8)	54.7 (44.7, 64.8)	9.5 (-4.3, 23.4) [d]	0.177
Secondary and tertiary endpoints				
n analysed	99	98		
% in complete remission [c] (95% CI)	63.6 (54.1, 73.2)	53.1 (43.1, 63.0)	10.6 (-3.2, 24.3)	0.132
% in remission on < 10 mg/day of prednisone (95% CI)	70.7 (61.7, 79.7)	62.2 (52.6, 71.8)	8.5 (-4.7, 21.6)	0.208
% with severe flare	5.1	10.2		
Rate of severe flares per patient-month	0.011	0.019		0.293
% with limited flare	12.1	14.3		
Rate of limited flares per patient-month	0.026	0.026		0.98
Mean (SD) BVAS/WG AUC over first 6 months	1.29 (1.33)	1.25 (1.03)		
Median cumulative prednisone dose (1,000mgs) (95% CI)	3.3 (1.0, 6.9)	3.5 (0.7, 8.3)		0.055
Mean change from baseline in ESR (95% CI)	-14.4 (-18.7, -10.1)	-9.3 (-15.6, -3.0)	7.6 (2.2, 13.1) [e]	0.006
Mean change from baseline in CRP (95% CI)	-2.69 (-5.44, 0.06)	-2.84 (-7.07, 1.40)	0.61 (-0.5, 1.73) [e]	0.278
Exploratory endpoints				
Patients (%) in remission (BVAS/WG = 0) (95% CI)	80.8 (73.0, 88.6)	66.3 (60.0, 75.7)	14.5 (2.3, 26.7)	.021
% of newly diagnosed pts in complete remission	60.4	64.6	-4.2 (-23.6, 15.3)	0.673

% of relapsing pts in complete remission	66.7	42.0	24.7 (5.8, 43.6)	0.013

AUC = area under the curve; BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WG = Wegener's granulomatosis; WCI = worst case imputation; a, p-value is from a chi-square test of superiority; b, Patients with non-missing results for complete remission at 6 months after randomisation; c, Defined as BVAS/WG = 0 with successful completion of glucocorticoid taper at Month 6; d, The lower limit of the 95% CI for the absolute difference, -4.3%, was greater than -20% and thus met the protocol-specified non-inferiority criterion; e, the differences in ESR and CRP are adjusted by ANCA status, site, and baseline value.

Primary Efficacy Results

The primary endpoint for this study was the percentage of patients who achieved complete remission at Month 6, defined as a BVAS/WG score of 0 with successful completion of the glucocorticoid taper at Month 6 (i.e., glucocorticoid dose = 0 mg) and is summarized in Table 16. Patients who discontinued the study prior to 6 months without having met the treatment-failure criteria were excluded from the primary analysis.

Sixty-three (64.3%) of the 98 patients in the RTX arm achieved complete remission at 6 months compared with 52 (54.7%) of 95 patients in the CYC arm. The treatment difference in rate of remission was 9.5% with a two-sided 95% CI of -4.30% and 23.40%, which demonstrated the non-inferiority of RTX to CYC treatment in the induction of complete remission.

Table 16: Complete remission at month 6 (ITT Population)

	RTX N (%)	CYC N (%)	Difference in rate %	95.1% CI of difference
n analysed	98	95		
Complete Remission	63 (64.3)	52 (54.7)	9.5	-4.3, 23.4 [a]
95% CI for proportion	54.8, 73.8	44.7, 64.8		

CI, confidence interval; ITT, Intent-to-Treat.

Note: Percentages are based on the number of patients with non-missing results for complete remission at the Month 6 cut-off. The calculation of the primary endpoint used the "as defined" approach; [a] Non-inferiority was demonstrated since the lower bound (-4.30%) was higher than the pre-determined non-inferiority margin (-20%).

After imputation of missing month 6 complete remission status by worst case imputation (WOCF), 63.6% patients in the RTX arm achieved complete remission at 6 months compared with 53.1% patients in the CYC arm, with a treatment difference of 10.6% (95% CI: - 3.18% and 24.33%),Table 17.

Table 17: Complete remission at month 6, worst-case Imputation (ITT Population)

	RTX N (%)	CYC N (%)	Difference in rate %	95.1% CI of difference
n analysed	99	98		
Complete Remission	63 (63.6)	52 (53.1)	10.6	-3.2, 24.3[a]
95% CI for proportion	54.1, 73.1	43.1, 63.0		

CI, confidence interval; ITT, Intent-to-Treat. a Non-inferiority was demonstrated since the lower bound (-3.18%) was higher than the pre-determined non-inferiority margin (-20%).

In order to study the robustness of the non-inferiority conclusion and the influence of individual study centres on the overall treatment difference, an exploratory analysis of the primary endpoint results by study centre was performed using WOCF. After sorting the centres by number of patients enrolled, smaller study centres were grouped together to form a total of at least 30 patients per .'aggregate' study centre. This resulted in 5 subsets of patients corresponding to single Centres 002, 006, and 001, Centres 004 and 009 combined, and Centres 003, 005, 007, and 008 combined.

Complete remission rates at 6 months tended to increase with the study centre size in both treatment groups, with a CYC complete remission rate of approximately 55-61% at the top 3 largest centres, compared to 41-43% at the lowest enrolling aggregate centres. The complete remission rates at 6

months in the RTX group varied from as high as 82-92% at 2 of the top 3 largest enrolling centres, to 29% at the lowest enrolling aggregate centre.

The largest treatment difference was 8 patients (33% [11.8%, 54.3%]) and was achieved at the top-enrolling centre (n = 53 patients). The robustness of the non-inferiority conclusion is supported by the observation that, even after excluding the results recorded at this centre, the treatment difference remains positive in favour of the experimental arm, with a point estimate of 2.7%, and a lower bound of the 95.1% CI of - 13.7%, which exceeded the - 20% non-inferiority margin, despite the lower sample size.

Table 18: Complete remission at 6 months after randomisation by study centre (ITT population)

Centre number	RTX n/N (%)	CYC n/N (%)	Difference (%)	95% CI of difference
002	24/26 (92.3)	16/27 (59.3)	33.0	11.8, 54.3
006	11/21 (52.4)	12/22 (54.5)	- 2.2	- 32.1, 27.8
001	14/17 (82.4)	11/18 (61.1)	21.2	- 7.8, 50.3
004 and 009	9/18 (50.0)	7/17 (41.2)	8.8	- 24.2, 41.8
003, 005, 007, and 008	5/17 (29.4)	6/14 (42.9)	- 13.4	- 47.4, 20.5
All centres except 002	39/73 (53.4)	36/71 (50.7)	2.7	- 13.7, 19.1

CI = confidence interval; ITT = Intent-to-Treat. Note: Results reflect worst case imputation for missing Month 6 complete remission status.

Secondary Efficacy Results

Assessment of Superiority of RTX

A secondary efficacy objective for RAVE was to assess the superiority of RTX compared with CYC/AZA in terms of the percentage of patients who achieved complete remission at 6 months after randomisation.

The proportion of patients in the RTX arm that achieved complete remission was numerically higher than in the CYC arm; however, the result was not statistically significant (95% CI for the difference: - 4.30%, 23.40%; p = 0.177, chi-square test). The outcome was similar using the worst case imputation (95% CI for the difference: -3.2%, 24.3%; p =0.132).

While the RTX remission rate at 6 months was not statistically significantly superior to CYC at 6 months, the lower limit of the 95% CI of the remission rate at 6 months in the RTX group exceeded 50%, which was based on the upper bound of the 95% CI of the survival rate of the Walton cohort at 6

months. This finding confirms that RTX is superior to historical placebo, thus demonstrating efficacy.

As previously noted, this represents a conservative estimate for the historical control; because the percentage of patients in complete remission can be no greater than the percentage of survivors, the actual number of untreated patients in complete remission is likely much lower (i.e. <5%) and the superiority of RTX to placebo control greater.

Cumulative BVAS/WG AUC during the first 6 Months

Using worst case imputation, the mean (SD) BVAS/WG AUC/month over the first 6 months was 1.29 (1.331) points for the RTX group and 1.25 (1.030) points for the CYC group. No significant difference was observed between the treatment arms.

Remission on < 10 mg/day prednisone at 6 months

Using worst case imputation, 70 patients (70.7%) in the RTX group achieved a BVAS/WG of 0 at 6 months while on < 10 mg prednisone per day. Fewer patients (61, 62.2%) in the CYC group achieved this outcome; however, the resulting treatment difference (8.5%) was not statistically significant (Table 19).

Table 19: Remission on < 10 mg/day prednisone at 6 months, worst-case imputation (ITT population)

	RTX	CYC	Difference (%)	p-value [a]
Remission n (%)	70 (70.7%)	61 (62.2%)	8.5	0.208
95% CI for proportion	61.7, 79.7	52.65, 71.84	- 4.67, 21.6	

a P-value is from a chi-square test of superiority.

Partial Remission

Using worst-case imputation, 70 (70.7%) patients in the RTX arm achieved a BVAS/WG ≤2 while off glucocorticoids at 6 months after randomisation. Fewer patients (61, 62.2%) in the CYC arm achieved this outcome; however, the resulting treatment difference (8.5%) was not significant (95%CI: - 4.67%, 21.60%, p = 0.208).

Ad-Hoc Exploratory Analysis - Remission

An exploratory analysis was conducted to determine the rate of remission (BVAS\WG = 0) regardless of prednisone use (Table 20). Using worst-case imputation, 80 patients (80.8%) in the RTX arm achieved a BVAS/WG of 0 compared with 65 (66.3%) patients in the CYC arm, resulting in a treatment difference of 14.5 (95% CI: 2.3, 26.6), p = 0.021.

Table 20: Remission at 6 months, worst case imputation (ITT Population)

	RTX	CYC	Difference (%)	p-value [b]
Remission [a]	80 (80.8%)	65 (66.3%)	14.5	0.021
95% CI for proportion	73.05, 88.57	59.97, 75.68	2.33, 26.64	

a, the proportion of patients who achieved a BVAS/WG of 0; b, p-value is from a chi-square test.

Severe and Limited Flares

In the first 6 months after randomisation, no significant difference in rates of severe or limited flares was observed between the two treatment arms (Table 21). In this analysis, flares that occurred during crossover were excluded. Five (5.1%) patients in the RTX arm and 10 (10.2%) patients in the CYC arm experienced severe flares. These events translated to a severe flare rate of 0.011 and 0.019 severe flares per patient-month, respectively (p = 0.293). The rate of limited flares was the same between the treatment arms with a rate of 0.026 limited flares per patient-month (p = 0.975).

Table 21: Severe and limited flares during the first 6 months (ITT Population)

	RTX	CYC	p-value[a]
Severe flares			
Total number	6	10	
Patients with ≥ 1 event	5 (5.1%)	10 (10.2%)	
Sum of patient-months	533.4	531.8	
Rate per person-year	0.011	0.019	0.293
Limited flares			
Total number	14	14	
Patients with ≥ 1 event	12 (12.1%)	14 (14.3%)	
Sum of patient-months experiencing flare	533.4	531.8	
Rate per person-year	0.026	0.026	0.980

Note: Flare assessments for patients during crossover were excluded from this analysis; a, p-value for the treatment effect was derived from the Poisson regression model and adjusted for clinical study centre and the type of anti-neutrophil cytoplasmic antibody.

Cumulative Glucocorticoid Dose

This analysis includes the following three study periods: from 2 weeks prior to randomisation to randomisation, from randomisation through 6 months after randomisation, and from 2 weeks prior to randomisation through 6 months after randomisation.

During the 2 weeks prior to randomisation, the median cumulative dose of methylprednisolone was 0 mg in both treatment arms; however, the maximum value was 4000 mg and 6000 mg in the RTX and CYC arms, respectively (Table 22). The median cumulative dose of prednisone was 240.0 mg in the RTX arm and 270.0 mg in the CYC arm.

Table 22: Cumulative glucocorticoid dose during 2 weeks prior to randomisation (ITT Population)

	RTX	CYC
Methylprednisolone IV (1,000mgs)		
N assessed	89	91
Mean (SD)	0.82 (1.2)	0.80 (1.2)
Median	0	0
Min, Max	0, 4	0, 6
Prednisone oral (1,000mgs)		
N assessed	88	90
Mean (SD)	0.3 (0.26)	346.2 (305.51)
Median	0.24	0.27
Min, Max	0, 1.45	0, 1.80

Note: Glucocorticoid dosage over 99 mg daily was classified as IV administration and dosage ≤99 mg was classified as oral administration; a, p-value from Wilcoxon rank sum test.

From randomisation through 6 months post-randomisation, intravenous administration of methylprednisolone was similar across treatment arms, with a median dose of 1,000 mg for both arms. The median cumulative dose of prednisone from randomisation to 6 months was lower in the RTX arm (3310.0 mg) compared with the CYC arm (3450.0 mg, $p = 0.055$) (

Table 23).

Table 23: Cumulative prednisone dose from randomisation through 6 months post randomisation (ITT population)

	RTX	CYC	p-value
Dose in 1,000mgs			
Mean (SD)	3.3 (0.98)	3.7 (1.2)	
Median	3.3	3.5	0.055
Min, Max	1.03, 6.88	0.66, 8.31	

a, p-value from Wilcoxon rank sum test

These results suggest that the efficacy results seen in the RTX group were not due to increased prednisone exposure compared with the control group. The demonstration of numerically higher remission with associated lower prednisone exposure is clinically meaningful, since prednisone use is associated with damage, including osteoporosis, cataracts, diabetes, avascular necrosis, and other conditions.

Subgroup Analyses

The effects of various baseline characteristics were explored in relation to outcome with either treatment. Results for the as-defined analysis of the primary endpoint, using the WOCF imputation, are presented.

Relapsing Disease at Baseline

Fifty-one (51.5%) patients in the RTX arm and 50 (51.0%) patients in the CYC arm had relapsing disease at Baseline (

Table 24). Of patients with relapsing disease, a higher proportion in the RTX arm achieved complete remission at 6 months compared with the CYC arm (66.7% vs. 42.0%, $p = 0.013$). The complete remission rates in patients with new disease were similar between the RTX and CYC arms.

Table 24: Complete remission at 6 months for patients with new or relapsing disease at baseline (ITT population)

	RTX n/N (%)	CYC n/N (%)	Difference (95% CI)	p-value[a]
New disease at baseline	29/48 (60.4)	31/48 (64.6)	-4.2 -23.6, 15.3	0.673
Relapsing disease at baseline	34/51 (66.7)	21/50 (42.0)	24.7 5.8, 43.6	0.013

Note: Results shown used worst observation carried forward imputation; a, p-value is from chi-square test.

Renal Disease at Baseline

Using the BVAS/WG assessment, a major renal item includes new or worsening events of the following two symptoms: RBC casts and a rise in creatinine >30% or a fall in creatinine clearance >25%. The complete remission rates in patients who had at least one major renal disease item on the BVAS/WG at Baseline were similar between the RTX and CYC arms (60.8% vs. 62.7%, Table 25).

Patients without a major renal disease item were more likely to achieve complete remission in the RTX arm compared to the CYC arm (66.7% vs. 42.6%).

Table 25: Complete remission at 6 months for patients either with or without one major renal item on BVAS/WG at baseline (ITT population)

Patient group	RTX n/N (%)	CYC n/N (%)	Difference (%) 95% CI	p-value[a]
One major renal item on BVAS/WG	31/51 (60.8)	32/51 (62.7)	- 2.0 - 20.9, 17.0	0.839
No major renal item on BVAS/WG	32/48 (66.7)	20/47 (42.6)	24.1 4.69, 43.6	0.018

Results shown used worst observation carried forward imputation; a, p-value comes from a chi-square test.

Outcome was also analysed on the basis of creatinine clearance values at baseline (

Table 26). Complete remission rates at 6 months were slightly higher in the CYC arm for those patients whose creatinine clearance values at Baseline were <60 ml/min, with a treatment difference of -8.7% (95% CI of -31.76%,

14.30%). For those patients with creatinine clearance values at Baseline of ≥60 ml/min, the complete remission rates were higher in the RTX arm, with a treatment difference of 21.8% (95% CI of 4.83%, 38.77%; p =0.015).

Table 26: Complete remission at 6 months for patients with creatinine clearance values <60 ml/min or ≥60 ml/min at baseline (ITT population)

	RTX n/N (%)	CYC n/N (%)	Difference (%) 95% CI	p-value[a]
CCl < 60 ml/min	25/45 (55.6)	18/28 (64.3)	- 8.7 - 31.8, 14.3	0.461
CCl ≥ 60 ml/min	38/54 (70.4)	34/70 (48.6)	21.8 4.8, 38.8	0.015

CCl, creatinine clearance; results shown used worst observation carried forward imputation; a, p-value comes from chi-square test.

Outcome was also analysed on the basis of creatinine values at Baseline (Table 27). For those patients with a creatinine level ≤ 1.2 mg/dL at Baseline, complete remission rates at 6 months were higher in the RTX arm, with a treatment difference of 29.6% (95% CI of 11.34%, 47.88%). For those patients with creatinine values at Baseline of > 1.2 mg/dL, the complete remission rates were higher in the CYC arm, with a treatment difference of -11.4% (95% CI of -31.09%, 8.21%).

Table 27: Complete remission at 6 months for patients with creatinine ≤ or > 1.2 mg/dl (ITT population)

	RTX n/N (%)	CYC n/N (%)	Difference (%) 95% CI	p-value[a]
Creatinine ≤ 1.2 mg/dLb	36/52 (69.2)	21/53 (39.6)	29.6 11.3, 47.9	0.002
Creatinine > 1.2 mg/dLb	27/47 (57.4)	31/45 (68.9)	- 11.4 - 31.0, 8.2	0.256

Results shown used worst observation carried forward imputation; a, p-value comes from chi-square test; b, the median serum creatinine value at baseline was 1.2 mg/dL.

Alveolar haemorrhage at baseline

Twenty-seven and 23 patients in the RTX and CYC arms, respectively, had an alveolar haemorrhage at Baseline. The complete remission rates at 6 months were numerically higher in the RTX arm compared with the CYC arm,

regardless of the presence of alveolar haemorrhage at Baseline. For those patients with an alveolar haemorrhage, the treatment difference was 11.4% (Table 28).

Table 28: complete remission at 6 months for patients either with or without alveolar haemorrhage at baseline (ITT population)

	RTX n/N (%)	CYC n/N (%)	Difference (%) 95% CI	p-value[a]
With haemorrhage	16/27 (59.3)	11/23 (47.8)	11.4 -16.3, 39.1	0.419
Without haemorrhage	47/72 (65.3)	41/75 (54.7)	10.6 -5.2, 26.4	0.190

Results shown used worst observation carried forward imputation; a, p-value comes from chi-square test.

ANCA type at baseline

Outcome was also analysed on the basis of ANCA type at Baseline (Table 29).

Using worst-case, complete remission rates at 6 months were similar in both treatment groups for those patients with MPO antibodies, with a treatment difference of –3.0% (95% CI of –26.53%, 20.47%). For those patients with PR3 antibodies at Baseline, the complete remission rates were higher in the RTX arm, with a treatment difference of 17.5% (95% CI of 0.66%, 34.25%).

Table 29: Complete remission at 6 months for patients with either MPO or pr3 antibodies at baseline (ITT Population)

	RTX n/N (%)	CYC n/N (%)	Difference (%) 95% CI	p-value[a]
MPO+ at Baseline	20/33 (60.6)	21/33 (63.6)	- 3.0 - 26.5, 20.5	0.800
PR3+ at Baseline	43/66 (65.2)	31/65 (47.7)	17.5 0.7, 34.3	0.044

Results shown used worst observation carried forward imputation; a, p-value comes from chi-square test; MPO = myeloperoxidase; PR3 = proteinase 3

Other Baseline Characteristics

Each of the following baseline characteristics was analysed by treatment group for its impact on the primary efficacy outcome: gender, age (< 52 vs. ≥52), presence of systemic disease, and AAV disease type. None of the variables led to a significant difference in complete remission at 6 months.

Change in ANCA Status

In addition to the hospital determination of baseline ANCA status, blood samples were collected at Screening and various time points after remission induction and sent to the Mayo Clinic lab for analysis of seroconversion. A total of 166 patients had a sample collected for the lab assay at Screening and a subsequent time point, and the Screening samples tested positive for either PR3 or MPO antibodies (Table 30). Of the 166 patients, the proportion of patients who became negative for ANCA was higher in the RTX arm compared with the CYC arm ($p = 0.050$). The greatest effect on becoming seronegative was observed for patients who were PR3+ and were treated with RTX ($p = 0.013$). The ability to induce seronegative results in MPO+ patients was similar between treatments.

Table 30: Change in ANCA status by treatment arm (ITT population)

	RTX n/N (%)	CYC n/N (%)	p-value[a]
ANCA* at Baseline [a]	88 (88.9)	78 (79.6)	
ANCA* to ANCA	39/88 (44.3)	23/78 (29.0)	0.050
MPO* at Baseline	28 (28.3)	22 (22.4)	
MPO* to MPO	11/28 (39.3)	9/22 (40.9)	0.907
PR3* at Baseline	61 (61.6)	56 (57.1)	
PR3* to PR3*	29/61 (47.5)	14/56 (25.0)	0.013

MPO, myeloperoxidase; PR3, proteinase 3; analysis was restricted to patients with valid ANCA status at both baseline and 6 months; a, one subject in the RTX arm tested positive for both MPO and PR3.

Vasculitis damage and quality of life

Scores on the Vasculitis Damage Index increased by 1.3 points from baseline to 6 months in the RTX group and by 1.5 points in the control group (P = 0.62).

Quality-of-life scores improved in both groups. In the RTX group, SF-36 physical and mental health component summary scores (range 0-100) improved by 5.9 (SD=10.4) and 7.9 (12.6) points, respectively. These same summary scores improved by 6.0 (10.4) and 5.3 (12.9) points in the CYC group. There was no significant difference between treatment groups in the change from baseline to month 6 in the quality-of-life scores or their rate of change over this period.

RITUXVAS: results

Primary Outcome

The primary efficacy endpoint for RITUXVAS was sustained remission, defined as a BVAS score of 0 that was maintained for at least 6 months.

Sustained remission occurred in 25 of 33 patients (76%) in the RTX + low-dose CYC group and in 9 out of 11 patients (82%) in the CYC group (Table 31). The absolute difference in sustained remission with RTX compared with CYC was - 6% (95% CI: - 33, 21).

Among patients who reached 12 months, 93% of patients in the RTX + low-dose CYC group and 90% of patients in the CYC group achieved sustained remission.

Reasons for not achieving sustained remission at 12 months included death (18% in the RTX + low-dose CYC group and 9% in the CYC group), re-treatment for incomplete remission (1 patient in the RTX + low-dose CYC group; subsequently led to full remission), and relapse within 6 months after achieving remission (1 patient from each treatment group).

Nine patients were dialysis dependent at entry, 8 in the RTX + low-dose CYC group and 1 in the CYC group. Of these, 6 out of 8 patients from the RTX + low-dose CYC group had a sustained remission, with 5 patients becoming dialysis independent. The one patient from the CYC group who was dialysis dependent at the start of the study, died shortly after study entry.

Table 31: RITUXVAS: primary efficacy results (ITT population)

	RTX + low dose CYC n (%)	CYC n (%)
Achieved sustained remission at 12 months	25 (76)	9 (82)
Reasons for non-response		
Death	6 (18)	1 (9)*
Relapse within 6 months after remission	1 (4)	1 (9)
Re-treated for incomplete remission	1 (4)	0

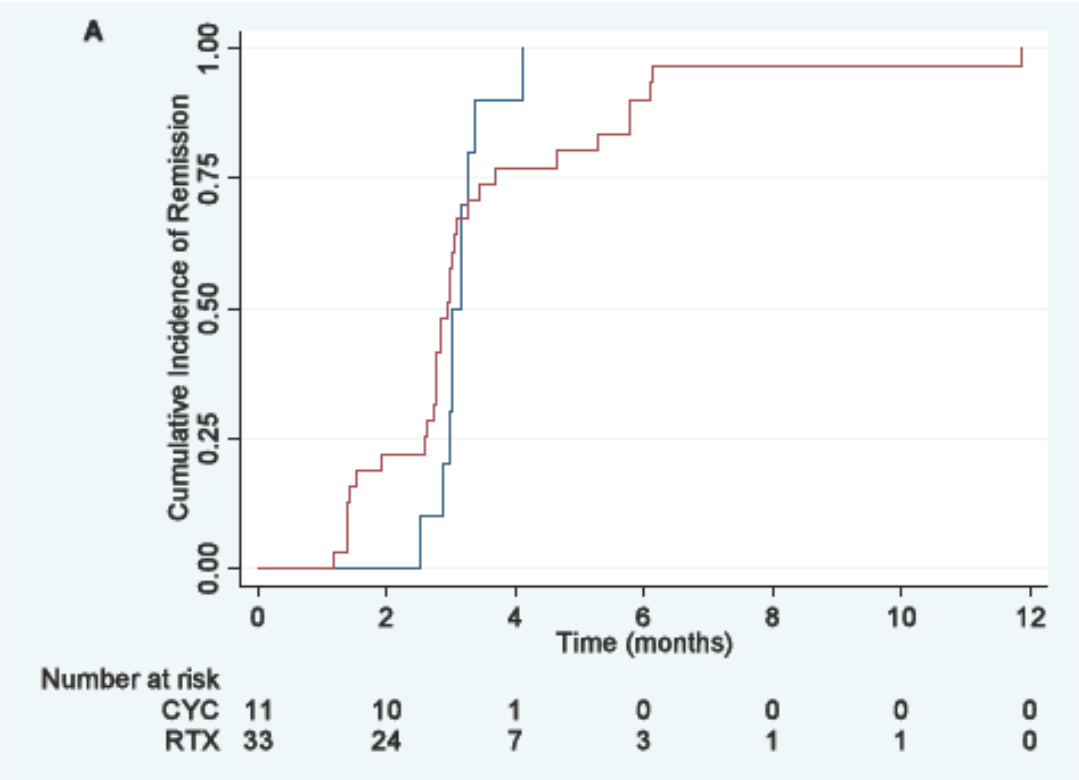
* Another patient died at 19 months, for a total of 2/11 (18%) deaths in the control arm

Secondary Outcomes

Time to Remission

Remission (defined in this study as a BVAS 2003 score of 0 for 2 months) occurred in 30 out of 33 patients (91%) in the RTX + low-dose CYC group and 10 of the 11 patients (91%) in the CYC group. The median time to remission was 90 days (IQR, 79-112 days) in the RTX + low-dose CYC group and 94 days (IQR, 91-100 days) in the CYC group (Figure 6).

Figure 6: RITUXVAS: Kaplan-Meier plot of time to remission



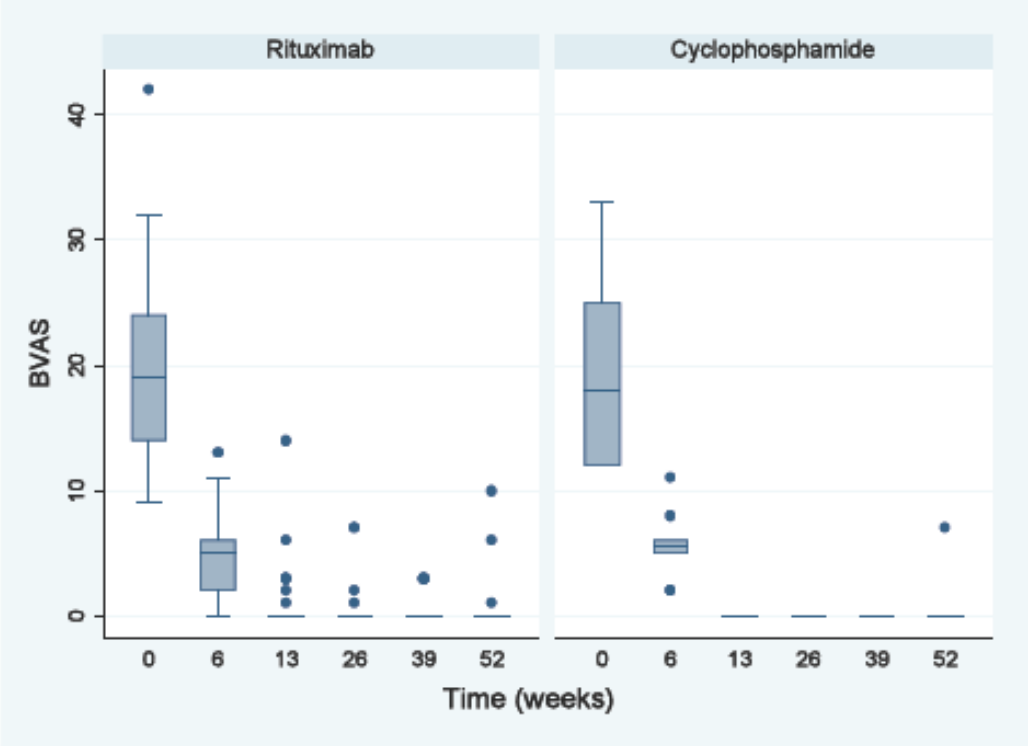
Blue line, CYC group; red line, RTX + low-dose CYC group; lines censored for deaths.

BVAS

In RITUXVAS, median BVAS fell from 19 (IQR, 14-24) at entry to 0 (IQR, 0-1.5) at 3 months in the RTX + low-dose CYC group and 18 (IQR, 12-25) at entry to 0 (IQR, 0-0) at 3 months in the CYC group (

Figure 7).

Figure 7: RITUXVAS BVAS score distribution



Change in Glomerular Filtration Rate

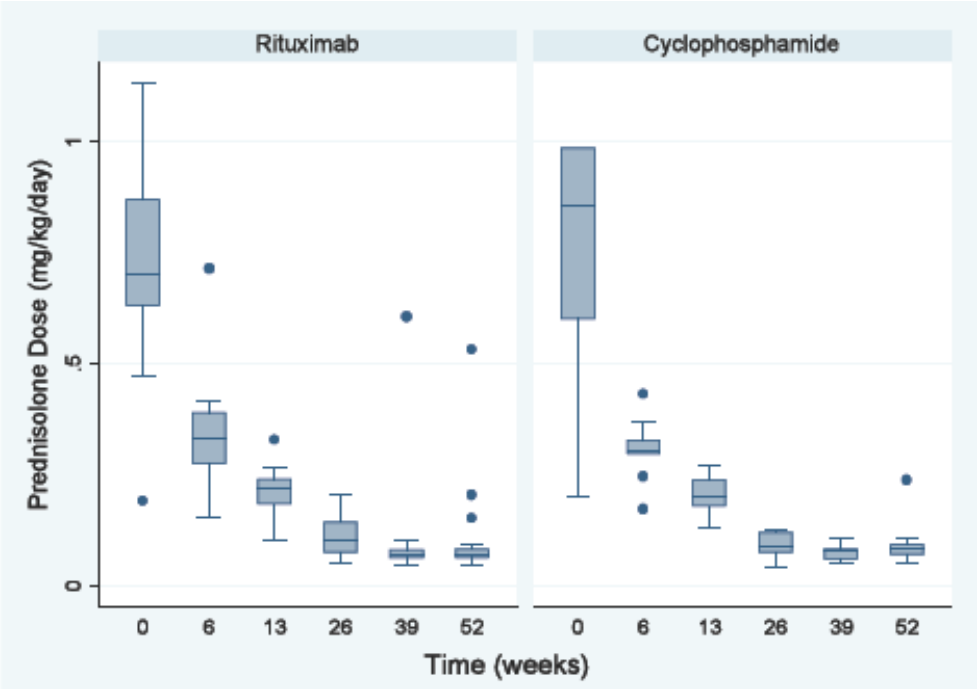
The median estimated GFR (eGFR; ml/min/1.73 m2) levels in the RTX + low-dose CYC group increased from 20 (IQR, 5-44) at entry to 39 (IQR, 20-45) at 12 months. In the CYC group, the median eGFR increased from 12 (IQR, 9-33) at entry to 27 (IQR, 12-47) at 12 months.

Prednisolone Dose

Prednisolone doses were reduced in both groups in accordance with the protocol, with 96% from the RTX + low-dose CYC group and 89% from the CYC group receiving 5 mg/day by 9 months. At 12 months, median weight-adjusted prednisolone doses (mg/kg/day) were 0.071 (IQR, 0.062-0.082) for the RTX + low dose CYC group and 0.082 (IQR, 0.071-0.093) for the control group (

Figure 8).

Figure 8: RITUXVAS weight-adjusted prednisolone doses



Quality of Life and Disease Damage

The median change in the VDI in the RTX + low-dose CYC group was 2 (IQR, 0-3) and was not significantly different from the CYC group's change of 1 (IQR, 0-2) (p = 0.38). Similarly, the treatment groups did not differ with respect to the change in the physical composite score of the SF-36 (p = 0.36).

The CYC group had an improved mental composite SF-36 score in comparison with the RTX + low-dose CYC group (p = 0.04); this difference was largely accounted for by 2 patients' scores in the RTX + low-dose CYC group. Exclusion of these 2 patients' data led to a p = 0.32.

6.6 Meta-analysis

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).**

Please see 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.**

No meta-analysis was undertaken as part of the appraisal. Whilst we have provided an overview of the RITUXVAS study for context, the way in which RTX was given in these two trials is fundamentally different, and only the RAVE study reflects the license and scope of this appraisal. Therefore the economic evaluation has been based on the results of RAVE alone.

6.6.3 **If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

Not applicable.

6.7 Indirect and mixed treatment comparisons

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 9.4, appendix 4.**

No indirect comparisons were undertaken.

6.8 Non-RCT evidence

6.8.1 **If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 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' (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 9.6 and 9.7, appendices 6 and 7.**

Seven non-RCTs were identified as part of the systematic literature search. Although they fulfilled the inclusion criteria for the search, they were found not to have sufficient data to be useful to the decision problem. They are described below.

Table 32: Summary of supporting non-RCTs

Author	Description
Smith et al 2012	**Objective**: The aim of this study was to reduce relapse rates using a fixed-interval RTX re-treatment protocol. **Methods:** Twenty eight patients initially received RTX, either 375mg/m^2/week x4 or 1g chi-square (two week interval) and only received further RTX at the time of clinical relapse (Group A). Forty five patients followed the routine repeat RTX re-treatment regimen consisting of RTX, 1g chi-square (two week interval) followed by a single 1g dose every six months for two years (6g total over 24 months), following which routine administration of RTX was discontinued (Group B). **Results:** Response (complete/partial remission) occurred in 26 of the 28 patients (93%) in group A, 43 of the 45 patients (96%) in group B, and 18 of the 19 patients (95%) in group C. At 2 years, relapses had occurred in 19 of 26 patients (73%) in group A, 5 of 43 (12%) in group B (P < 0.001), and 2 of 18 (11%) in group C (P < 0.001). At the last follow up (median of 44 months), relapses had occurred in 85% of those in group A (22 of 26), 26% of those in group B (11 of 43; P < 0.001), and 56% of those in group C (10 of 18; P = 0.001). Glucocorticoid dosages were decreased and immunosuppression therapy was withdrawn in the majority of patients. Routine RTX re-treatment was well tolerated, and no new safety issues were identified. **Conclusion**: Two-year, fixed-interval RTX re-treatment was associated with a reduction in relapse rates during the re-treatment period and a more prolonged period of remission during subsequent follow up.
Jones et al 2009	**Objective:** The aim of this study was to determine the efficacy and safety of RTX for ANCA-associated vasculitis in a larger multicentre cohort. **Methods:** Retrospective, standardized data collection from 65 sequential patients receiving RTX for refractory ANCA-associated vasculitis at 4 centers in the UK was used. **Results:** Complete remission occurred in 49 of the 65 patients (75%), partial remission in 15 (23%), and no response in 1 (2%). The prednisolone dosage was reduced from 12.5 mg/day (median) to 9.0 mg/day at 6 months (P = 0.0006). Immunosuppressive therapy was withdrawn in 37 of 60 patients (62%). Twenty-eight of 49 patients who achieved full remission (57%) experienced relapse

	(median 11.5 months). B cell return preceded relapse in 14 of 27 patients (52%). Although ANCA levels fell after RTX therapy, relapse was not associated with ANCA positivity or a rise in ANCA levels. Neither the initial RTX regimen (4 infusions of 375 mg/m2 each given 1 week apart or 2 infusions of 1 gm each given 2 weeks apart) nor withdrawal of immunosuppressive therapy (37 of 60 patients [62%]) influenced the timing of relapse. Thirty-eight patients received ≥2 courses of RTX, and complete remission was induced or maintained in 32 of them (84%). IgM levels fell, although IgG levels remained stable. Forty-six serious adverse events occurred, including 2 episodes of late-onset neutropenia, which were attributed to RTX. **Conclusions:** RTX was effective remission induction therapy for refractory ANCA-associated vasculitis in this study. There was no difference in efficacy between the 2 main treatment regimens. Continuing immunosuppression did not reduce relapses. Relapses occurred, but re-treatment was effective and safe. There was no clear influence of RTX on the frequency of serious adverse events. ANCA and B cell levels lacked sufficient sensitivity to guide the timing of re-treatment.
Jones et al 2010	**Objective:** Single centre cohort study comparing six monthly, protocolised RTX re-treatment and non-protocolised RTX re-treatment according to clinical need for refractory ANCA-associated vasculitis. **Methods:** 72 patients received a protocolised RTX regimen; 1g ×2 followed by 1g ×1 every 6 months for 2 years (5g total) with early immunosuppression and corticosteroid withdrawal. 34 received non-protocolised RTX; either 1g×2 or 375mg/m2×4 only repeated if relapse occurred. Overall 75% patients had Wegener's granulomatosis. At first RTX course, median disease duration was 55 months: prior CYC exposure was 14g. RTX indication was relapsing disease in 82% of protocol and 83% of non-protocol patients; the remainder had grumbling disease whilst receiving continuous high dose corticosteroids or immunosuppression. Median follow-up was 31 (4–56) months, protocol patients versus 22 (6–84) months, non-protocol patients. **Results:** Response to RTX occurred in 70/72 (97%) protocol patients (93% full remission, 4% partial), and 33/34 (97%) non-protocol patients (82% full remission, 15% partial). In protocol patients only 4/72 (6%) were still receiving immunosuppression at 6 months and by 24 months 26% had withdrawn from prednisolone (4.75mg/day median). At 2 years relapse had occurred in 16/72 (22%) protocol patients versus 24/34 (71%) non-protocol patients and by the end of follow-up 21/72 (29%) protocol patients, 26/34 (76%) non-protocol patients ($p<0.01$). **Conclusions:** Six monthly protocolised RTX re-treatment was effective for relapse prevention, allowing immunosuppression withdrawal in refractory ANCA-associated vasculitis.
Cartin-Ceba et al 2012	**Objective:** This study was conducted to evaluate the efficacy and safety of repeated and prolonged B-cell depletion with RTX (RTX) for long-term remission maintenance in patients with chronically relapsing granulomatosis with polyangiitis (Wegener's) (GPA). **Methods:** We conducted a single-center observational study of all patients with chronic relapsing GPA treated with at least 2 courses of RTX between January 1, 2000 and May 31, 2010. Participants in the RTX in ANCA-Associated Vasculitis (RAVE) trial were excluded from this analysis. Data were abstracted from electronic medical records. **Results:** Fifty-three patients with refractory GPA (median age 46 years [interquartile range (IQR) 30-61 years]; 53% women) received at least 2 courses of RTX to treat GPA relapses or to maintain remission. All but 1 patient had antineutrophil cytoplasmic antibodies (ANCA) against proteinase 3 (PR3). These patients received a median of 4 courses of RTX (IQR 3-5); all had depletion of B cells, and the median time to return of B cells was 8.5 months (IQR 6-11 months). All observed relapses occurred after reconstitution of B cells and were accompanied or preceded by an increase in ANCA levels, except for the 1 ANCA-

	negative patient. Infusion-related adverse events occurred in 16 patients. During the period of B cell depletion, 30 infections requiring antimicrobial therapy were recorded. **Conclusions:** RTX appeared to be effective and safe for the induction and maintenance of remission in patients with chronic relapsing GPA. Repeated depletion of B lymphocytes seems to be associated with a low risk of infections. Pre-emptive re-treatment decisions can be individualized based on serial B lymphocyte and PR3 ANCA monitoring. The use of RTX for the maintenance of long-term remission merits further formal investigation**.**
Holle et al 2011	**Objective:** To investigate the overall efficacy and safety of RTX (RTX) in refractory Granulomatosis with polyangiitis (GPA) in a tertiary referral centre: to compare the efficacy of RTX in granulomatous and vasculitic manifestations in GPA. **Methods:** This study comprised a retrospective, standardised data collection from all patients who received RTX for refractory Wegener's granulomatosis from 2002 to 2010. Patients were assessed by a standardised interdisciplinary diagnostic procedure (including ear, nose and throat and ophthalmology assessment, MRI, immunodiagnostics, B-cell levels and Birmingham Vasculitis Activity Score) and were treated by standardised therapeutic regimens according to available evidence. **Results**: 59 patients received 75 cycles of RTX. 9.3% achieved complete remission. A response was documented in 61.3% (improvement in 52%, unchanged disease activity in 9.3%), 26.7% had refractory disease. Birmingham Vasculitis Activity Score, disease extent index, erythrocyte sedimentation rate, C-reactive protein and prednisolone demand decreased significantly. All patients achieved B-cell depletion. Granulomatous manifestations such as orbital granuloma and pachymeningitis were more frequently refractory to RTX than vasculitis or other granulomatous manifestations. Thus, for example, complete remission/improvement was found in 89.2% of patients with renal disease and in only 44.4% of those with orbital masses (p=0.003). The relapse rate was 44.4% after a median period of 13.5 months. Adverse events occurred in 29%, pneumonia in 15% and death in 3%. **Conclusions:** The overall response rate of refractory GPA to RTX was high (61.3% complete remission or improvement). Response rates of vasculitic manifestations were excellent; failure of response/progress was mostly due to granulomatous manifestations, especially orbital masses. Relapse rates were high (40%) despite maintenance treatment.
Roll et al, 2012	**Objective**: RTX (RTX) therapy is a treatment option in patients with refractory antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). We investigated the tolerability and clinical efficacy of RTX in a cohort of patients with refractory AAV. **Methods**: Clinical and safety data of patients with AAV treated with RTX were retrospectively assessed from the data of a German national registry. **Results**: In total, 58 patients were included in this analysis (50/58 with granulomatosis with polyangiitis; 8/58 with microscopic polyangiitis who received at least 1 cycle, 17 patients who received 2 cycles, and 3 patients who received 3 cycles of RTX). Response was classified as complete and partial in 22 (40%) and in 29 cases (52.7%), respectively. Four patients (7.3%) were classified as nonresponders. **Conclusions**: RTX was well tolerated with good clinical efficacy in patients with refractory AAV
Pullerits et al 2012	**Objective**: To evaluate long-term clinical and immunological effects of Rituximab (RTX) in patients with AAV refractory to conventional immunosuppressive treatment. **Methods**: RTX was added to on-going immunosuppressive treatment in 29 patients with refractory AAV. Disease activity was measured using BVAS/WG and

clinical laboratory variables were recorded.

Results: Median BVAS/WG score before treatment was 6 (IQR 3–8), and 28 patients (97%) had disease flare classified either severe (62%) or limited (34%). Six of 29 patients (21%) achieved a complete remission, and 12 (41%) had a treatment response with ≥50% decrease in BVAS/WG score at 6 months. Fourteen patients (64%) with kidney involvement achieved remission, in seven patients (50%), no flare was seen during the follow-up period. Three patients had renal flare and were successfully re-treated with RTX. Seventeen patients had disease symptoms from airways and eyes at RTX initiation, whereas only 29% displayed ≥50% treatment response.

Conclusions: RTX is a potent therapeutic option for AAV refractory to conventional treatment. Best response may be expected in patients with vasculitic manifestations

6.9 Adverse events

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 5.1 to 5.5 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 9.8 and 9.9, appendices 8 and 9.**

The following section describes the safety profile of RTX (RTX) in the treatment of adults with severe AAV as presented in the Summary of Clinical Safety (SCS) provided to the EMA to support the licence application for RTX in AAV. The rationale for including this summary is that these data have been extracted, reviewed and effectively summarised to satisfy all regulatory requirements. The SCS focuses on data collected up to 18 months from RAVE, a pivotal Phase II/III, multicentre, randomised, active-controlled, double-dummy, double-blind, parallel group, international trial in 197 randomised and treated patients with severe AAV.

Additional safety information is provided from a published, open-label, randomised-controlled study in 44 patients with newly diagnosed severe AAV (RITUXVAS), as well as from published information from a number of smaller investigator-initiated studies in which a total of 162 patients have been treated

with RTX. As data from these studies are from the published literature, information is limited.

This group of studies comprised uncontrolled case series of patients who had failed or were intolerant of standard therapy or who had relapsing disease. Patient populations were variable across these studies. While the dose of RTX administered was generally consistent (375 mg/m^2 weekly ≥ 4), therapies given concomitantly with RTX varied (Table 1). The duration of follow up for safety, as well as the type and amount of safety data reported, also differed across studies. Published information included the incidence of serious and/or severe adverse events, deaths, malignancies, and serious and/or severe infections.

This submission summarises exposure to RTX in a total 99 AAV patients who were followed for 18 months as part of the RAVE study long-term follow-up. In addition, 33 patients in RITUXVAS were followed for up to 24 months, and 162 patients in other investigator-initiated studies were followed for variable amounts of time ranging from 3 to 55 months.

Overall, safety data from RITUXVAS and other investigator-initiated studies were limited but consistent with RAVE. Table 33 includes an overview of further studies containing safety observations about RTX.

Table 33: Studies of RTX in AAV with safety data

Study type and publication	No. of Patients	Patient Description	Dose of RTX	Concomitant Therapies in RTX Group
Randomised, controlled study (RAVE)	99 RTX [a] 98 CYC/AZA [a]	Severe WG or MPA Newly diagnosed or relapsing	375 mg/m^2 weekly × 4	GC tapered down, with goal to discontinue by Month 6
Randomised, controlled study (RITUXVAS)	33 RTX 11 CYC/AZA	WG, MPA, or renal-limited vasculitis	375 mg/m^2 weekly × 4	GC and IV CYC (15 mg/kg with 1st and 3rd RTX doses)
Uncontrolled studies/case series:				
Aries et al. 2006	8	WG with granulomatous manifestations Refractory to therapy	375 mg/m^2 every 4 weeks × 4	CYC, MMF, MTX, GC
Brihaye et al. 2007	8	8 WG Refractory/contraindications to CYC + GC or relapsing	375 mg/m^2 weekly × 4	CYC, GC
Eriksson 2005	9	WG and MPA Refractory to therapy or frequently relapsing	500 mg weekly × 4 (n = 6) or 500 mg every other week × 2 (n = 3)	MMF, AZA, CYC, GC
Jones et al. 2009	65	WG, MPA, CSS Refractory to or intolerant of standard therapies or relapsing	1 g × 2 (n = 32) 375 mg/m^2 weekly × 4 (n = 26)	Anti-TNF, IVIG, AZA, MTX, MMF, CYC
Keogh et al. 2005	11	Severe AAV Refractory/contraindications to CYC + GC	375 mg/m^2 weekly × 4	Plasma exchange for nephritis, GC
Keogh et al. 2006	10	Severe WG or MPA Refractory or relapsing with contraindications to CYC + GC	375 mg/m^2 weekly × 4	GC
Lovric et al. 2009	15	WG, MPA, or CSS Refractory to therapy or relapsing	375 mg/m^2 weekly × 4	AZA, MMF, CYC, CsA, MTX, IFX, GC
Omdal et al. 2005	3	WG Refractory to therapy	375 mg/m^2 weekly × 4	Not reported

Sanchez-Cano et al. 2008	4	WG with granulomatous manifestations Refractory to therapy	375 mg/m^2 weekly × 4	CYC, GC, MTX
Seo et al. 2008	8	Limited WG Refractory to or intolerant of standard therapies	375 mg/m^2 weekly × 4	CYC, GC
Smith et al. 2006	11	Severe MPA, WG, CSS Refractory to therapy	375 mg/m^2 weekly × 4	CYC, MMF, AZA, GC
Stasi et al. 2006	10	WG or MPA Refractory to standard therapy or ≥ 2 relapses	375 mg/m^2 weekly × 4	GC

anti-TNF, anti-tumor necrosis factor biologicals; CsA, cyclosporine A; CSS, Churg-Strauss syndrome; GC, glucocorticoids; MMF, mycophenolate mofetil; NIAID, National Institute of Allergy and Infectious Diseases; IFX, infliximab; IV, intravenous; IVIG, intravenous immunoglobulin; MTX, methotrexate; WG, Wegener's granulomatosis; a, Initial treatment groups as randomised and treated. Some patients crossed over treatment arms and may have been exposed to additional therapies

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.**

Overview of Key Safety Findings

The data presented in this submission suggest that RTX is generally well tolerated in patients with AAV, with no new safety signals identified. In the randomised, controlled studies, the overall safety of RTX appeared to be comparable with that seen with CYC treatment and remained consistent out to 18 months. The key observations are listed in the sections below.

Adverse Events

At 6 months and 18 months overall safety was comparable between the RTX and CYC groups in RAVE; including the incidences and rates per patient-year of any adverse event, selected adverse events, Grade ≥ 3 adverse events, serious adverse events, and serious infections

In RAVE, common adverse events with an absolute increase of ≥ 5% in incidence in the RTX group over the CYC group were diarrhea (24.2% vs.17.3%), peripheral edema (20.2% vs. 12.2%), urinary tract infection (UTI) (16.2% vs. 6.1%), and cough (28.3% vs. 18.4%)

Common adverse events with an increased incidence (≥ 5%) in the CYC group compared with the RTX group in RAVE were leukopenia (26.5% vs 10.1%), nausea, increased ALT and AST, rash, alopecia, RBC sedimentation rate, increased, hematuria, hematocrit decreased, vomiting, pyrexia, and fatigue

While the data are limited, safety in the other published studies was, overall, consistent with that reported in RAVE. The most common type of adverse

event reported in these studies was infection (most frequently, respiratory infection).

Deaths

In RAVE, at 18 months and at the CCO date, deaths were balanced in the RTX and CYC groups: In total, there were 2 deaths in the CYC group both due to infections. There were also 2 deaths in the RTX group (1 due to multi-organ failure and 1 due to pulmonary alveolar hemorrhage [PAH])

The overall death rates and causes of death in RAVE and RITUXVAS were similar between RTX and CYC groups

The most common cause of death was infection (9 of 18 total deaths in all patients included in RAVE, RITUXVAS, and other investigator-initiated studies), followed by cardiovascular disease and complications of end-stage renal disease

The death rates from RAVE and RITUXVAS and the causes of death across all studies discussed in this submission are consistent with those expected in AAV

<u>Other Serious Adverse Events</u>

Overall, the incidences and rates of serious adverse events were comparable between the RTX and CYC groups in RAVE at 6 months (33.3% vs 33.7%) and 18 months (46.5% vs. 41.8%), and in RITUXVAS at 12 months (42% [0.94 events/patient] vs. 36% [1.1 events/patient]) and at 2 years (61% [1.52 events/patient] vs 36% [1.36 events/patient],

The most commonly reported type of serious adverse event in all studies was infection, with similar incidences between RTX and CYC groups in the controlled studies. In RAVE at 18 months infection frequencies and rates were 15.2% and 0.13/patient-year in the RTX group vs. 15.3% and 0.16/patient-year in the CYC group

In RAVE, serious events of deep vein thrombosis (DVT) were more common with CYC than with RTX treatment at both 6 and 18 months (8.2% vs. 1.0% at 18 months for CYC and RTX groups, respectively). Otherwise, there was no clear imbalance in individual serious adverse event terms between treatments

In the analyses to the CCO date in RAVE, the cumulative incidence of serious adverse events was higher in RTX-treated patients (60.6%) than in the CYC-treated patients (48.0%). This difference in percent incidence may be partly due to a longer period of follow-up for the RTX group (299 patient-years in the RTX group vs. 275 patient-years in the CYC group), as well as to numerically higher proportions of patients reporting events within the gastrointestinal, injury, and respiratory/mediastinal/thoracic system organ classes (SOCs). Importantly, the overall rates of serious adverse events per patient-year were comparable between the RTX (0.41/patient-year) and CYC (0.36/ patient-year) groups at the CCO date.

Adverse Events Leading to Study Withdrawal or Treatment Discontinuation

In RAVE, more patients in the CYC group compared with the RTX group reported adverse events that led to a permanent discontinuation of study drug by 6 months (13.3% vs 8.1%) and by 18 months (25.5% vs 16.2%)

In RAVE, at 6 months, the most frequently reported adverse events that led to a permanent discontinuation of study drug were leukopenia (in CYC group only) and (drug) hypersensitivity and renal failure (both adverse events were balanced across the RTX and CYC groups). Other events leading to treatment discontinuation included a mixture of events, with no clear imbalance across treatment arms. By 18 months, the profile of adverse events leading to treatment discontinuation was consistent with that reported by 6 months, with the addition of more study drug discontinuations due to infection and to AAV-related respiratory symptoms in both groups

In RAVE, no IRR occurring within 24 hours of an infusion led to study drug discontinuation. One event of hypersensitivity, reported as an IRR but

occurring 2 days after the third RTX infusion, led to discontinuation of study drug.

Selected Adverse Events in RAVE

The overall rates of selected adverse events were balanced across treatment arms at 6 months and remained balanced at 18 months:

At 6 months, the proportion of patients experiencing the pre-specified selected adverse events in RAVE was lower in the RTX group (22.2%) than in the CYC group (34.7%). However, as patients may have experienced multiple types of selected events, the rate of these events per patient-year was similar in each group (0.78 vs. 0.94, respectively; p = 0.294)

By 18 months, the proportion of patients experiencing any of the pre-specified selected adverse events in RAVE was 33.3% in the RTX group and 42.9% in the CYC group. The rate of these events per patient-year was similar in the two treatment groups (0.47 per patient-year in the RTX group vs. 0.48 per patient-year in the CYC group)

Leukopenia was more frequent in the CYC group compared with the RTX group at 6 and 18 months. Contrary to published literature in AAV, leukopaenic events were not associated with a higher rate of infection in RAVE, a finding that may be explained by the close monitoring and prompt dose modification (temporary or permanent study drug discontinuation) stipulated in the RAVE protocol

The subset of hospitalizations associated with AAV or study drug per the investigator's opinion remained more frequent in the RTX group at 6 months and remained so at 18 months. The majority of hospitalizations associated with AAV or study drug per the investigator's opinion were due to infections in both groups. Importantly, hospitalizations are a subset of serious adverse events, and the per cent incidences and rates of serious adverse events and serious infections were balanced across treatment groups

At both the 6- and 18-month time points, the incidences and rates of severe (Grade ≥3) infections were balanced across treatment arms

Infusion-Related Reactions(IRRs)

During the initial course (first four infusions) of RTX, no serious IRRs were reported

The incidence of IRRs was the highest during the first infusion and decreased with subsequent infusions. In the RTX group, the proportion of patients experiencing an IRR was 12.1%, 5.1%, 4.1%, and 1.1% following the first, second, third, and fourth infusions, respectively

All the IRRs were mild or moderate (NCI CTCAE Grade 1 or 2). One event of hypersensitivity considered infusion related by the investigator led to discontinuation of study drug, but the event occurred 2 days after the infusion and thus was outside of the pre-defined time window to meet the criteria for an IRR

Sixteen patients in the RTX group received a second course of open-label RTX and 20 patients in the CYC group subsequently received RTX (resulting from crossover and/or open-label RTX). Two of these 36 patients reported IRRs.

Infectious Adverse Events

Overall, the infection profile observed in RTX-treated AAV patients was similar to the known safety profile of RTX and the disease under study:

At 6 months in RAVE, the proportion of patients experiencing any infectious adverse event and the rate of infectious adverse events per patient-year were numerically greater in the RTX group (61.6%, 2.10 per patient-year) than in the CYC group (46.9%, 1.47 per patient-year)

At 18 months in RAVE, the proportion of patients who experienced any infectious adverse event remained numerically higher in the RTX (79.8%) versus the CYC group (70.4%). However, the overall rates of infections were comparable between both groups (RTX group, 1.41 events per patient-year; CYC group, 1.24 events per patient-year). A similar pattern was seen through the CCO date

At 6 months and 18 months in RAVE, the incidences and rates of serious or severe (Grade ≥ 3) infectious adverse events were similar between the RTX and CYC groups (11.1% vs 10.2% and 15.2% vs. 15.3% at 6 and 18 months, respectively, for serious infection and 10.1% vs 10.2% and 13.1% vs. 13.3% at 6 and 18 months, respectively, for severe infections). A similar pattern was seen for the analysis through the CCO date

The types of serious or severe (Grade ≥ 3) infections reported in RTX-treated patients were consistent with those observed with CYC treatment

The overall frequency of opportunistic infections was low across both treatment groups in RAVE. There was one serious opportunistic infection (pneumocystis jiroveci pneumonia) in the CYC group and no serious opportunistic infections in the RTX group. No opportunistic infections were reported in RITUXVAS or in the other investigator-initiated studies

One patient treated with RTX and AZA reported a hepatitis B reactivation in an investigator-initiated study. This case and one additional published case of hepatitis B reactivation in an AAV patient treated with RTX have been reported in the Global Safety Database as of 31 August 2011

No confirmed cases of progressive multifocal leukoencephalopathy (PML) have been reported in RAVE up to the CCO date. Also, there have been no confirmed cases of PML in AAV patients reported in association with RTX in the Global Safety Database drug up to 31 August 2011 or in the literature

The contribution of RTX or CYC versus high dose GC treatment to the infections observed is unclear

Cardiac and Vascular Events

The overall incidence of any cardiac events at 18 months was higher in the RTX group (18.2%) than in the CYC group (12.2%), whereas the difference in incidence at 6 months was less pronounced (12.1% in the RTX group vs. 8.2% in the CYC group). The imbalance at 18 months was mainly attributable to Grade 1 or 2 tachycardia and atrial fibrillation events. The incidence of serious cardiac events remained similar between RTX and CYC treatments (2.0% in each group) at 18 months. Findings up to the CCO date were overall consistent with the 18-month analysis

There were no serious cardiac ischemic events (e.g., myocardial infarction [MI]) reported in the RTX group and one serious cardiac ischemic event (MI) in the CYC group up to the CCO date

The interpretation of the numerical imbalances in nonserious cardiac events was limited by the small number of events, the underlying cardiovascular risks associated with AAV, and differences in baseline age, renal function, and medication use, which may impact likelihood of cardiac events

At both 6 months and 18 months, the overall incidence of venous thromboembolic events (a pre-defined selected adverse event) was higher in patients treated with CYC (9.2% in the CYC group vs. 5.1% in the RTX group at 18 months) and included three events of deep vein thrombosis (DVT) and two of pulmonary embolism (PE) in the RTX group and eight events of DVT and two of PE in the CYC group. Most of these events were serious (3 of 5 and 10 of 10 in the RTX and CYC groups, respectively). Findings up to the CCO date were consistent with the 18-month analysis

Malignancies

The total cancers reported in RAVE from randomisation up to the CCO were six confirmed malignancies in 5 patients randomised to and treated with RTX and two confirmed malignancies in 2 patients randomised to and treated with CYC. There was no particular pattern in the type of malignancies. Two cases

in the RTX group had previously received CYC. Also, two cases of prostate cancer (one in each treatment group) were diagnosed within 3 months of trial entry and were, therefore, likely prevalent cases. Given the small event rate and these confounders, the contribution of RTX, if any, is unclear

On the basis of the current duration of observation up to the CCO date, the rates (95% CI) of malignancy in the RTX and CYC groups were 2.00 (0.90-4.46) and 0.73 (0.18-2.91) per 100 patient-years, respectively

The standardized incidence ratio (SIR) for malignancy based on incidence in an age- and sex-matched general U.S. population according to 2000 to 2007 data from the Surveillance Epidemiology and End Results (SEER) database were 2.02 (95% CI, 0.74-4.39) and 1.02 (95% CI, 0.11-3.70) in patients randomised to and treated with RTX and in those randomised to and treated with CYC, respectively. The SIR in the RTX arm falls within the range of the reported 1.6-to 6-fold increase in the risk of overall malignancy among patients with AAV - treated with, (where reported) conventional therapy (CYC/AZA/MTX/glucocorticoids) – compared with the general population. The SIR for the CYC arm was below the range observed in the literaturebelow the range observed in the literature.

Overall evidence from AAV and experience with RTX in other indications do not suggest an effect of RTX on malignancy risk.

Information from the other small investigator initiated studies supports the safety of RTX treatment in AAV. These trials typically enrolled patients with severe disease, refractory to, intolerant of, or relapsing after CYC. The results of these studies were consistent with those from RAVE, with no additional safety concerns identified.

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

The data presented in this STA suggest that RTX is generally well tolerated in patients with AAV, with no new safety signals identified. In the randomised, controlled studies, the overall safety of RTX appeared to be comparable with that seen with CYC treatment and remained consistent out to 18 months.

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.

The goals of therapy in AAV are the rapid reduction of inflammation, limitation of therapy-induced toxicity, and prevention of damage. While mortality due to AAV has significantly improved through the use of CYC, there continue to be major unmet needs, such as improved remission rates, more effective therapy, prevention of flares, and reduction of toxicities associated with current therapy.

The introduction of oral CYC in the 1970s revolutionized the care of these severely ill patients and enabled survival, when previously patients would predictably have suffered from progressive inflammation leading to organ failure and death. A historical case series described in the 1950s and 1960s [Walton 1958; Hollander and Manning 1967]. clarified this natural history of untreated or minimally treated patients, and the introduction of CYC shifted equipoise significantly such that placebo-controlled trials were no longer possible.

These data and subsequent studies of the efficacy and safety of CYC in patients with severe AAV enabled the planning of the non-inferiority RAVE trial. The published, cumulative toxicities of CYC include infertility, increased malignancy risk, bone-marrow suppression, and infection. CYC-treated patients have a high rate of relapse, further increasing the likelihood of repeated exposure to a drug with cumulative toxicities. Thus, there is a major unmet medical need for new effective therapies with improved safety profiles. The role of B cells and their products (ANCAs) were characterized in surviving AAV patients, and this knowledge led to the introduction of RTX as an alternative therapy in AAV patients.

RAVE is a well-conducted, multicentre study that has demonstrated non-inferiority of RTX compared with oral CYC in terms of complete remission at 6 months. Complete remission results were numerically higher in the RTX group than in the CYC group, although not statistically superior, and comparable efficacy was demonstrated when investigating the occurrence of limited or

severe flares, remission by AAV type, or remission by organ involvement at 6 months. Pre-specified subgroup exploratory analyses indicated that RTX was superior to CYC in severely active relapsing patients ($p < 0.05$), despite the fact that the RTX group had a lower baseline creatinine clearance than the CYC group. The complete remission rate observed with RTX was associated with lower mean cumulative prednisone doses at 6 months. Furthermore, data from the maintenance phase of the study suggest that similar proportions of patients maintained their remission out to 12 and 18 months in both treatment arms, despite no maintenance with AZA and a numerically lower GC dose in the RTX arm.

Overall safety was comparable between the RTX and CYC groups over 6 months and 18 months in RAVE, although frequency of certain specific adverse events varied across groups. Similar proportions of patients in the two treatment groups experienced adverse events, severe adverse events, deaths, and serious infections. Certain adverse events, such as leukopenia and serious vascular events, were more common in the CYC group, while overall infections and hospitalizations occurred more frequently in the RTX group. Although the proportion of patients experiencing any infection was higher in the RTX group, this difference was largely due to Grade 1 and 2 infections, and only two infections in each treatment group led to permanent discontinuation of study drug up to 18 months. Patients in the RTX group had overall worse renal function, which has been associated with increased risk of infection. Importantly, proportions of patients experiencing severe and serious infections were balanced across groups. In terms of hospitalizations associated with underlying disease or study drug per the investigator's opinion, the RTX group had a higher proportion of patients ≥ 65 years old and a greater proportion of hospitalizations occurring in older patients compared with the CYC group, which may in part explain the difference in the number of these hospitalizations between treatment groups. Due to the manner in which hospitalization data were collected in this study, it is unknown whether there was a numeric imbalance in overall hospitalizations. However, as hospitalizations are a subset of serious adverse events, it is important to note that the rates of serious adverse events were balanced across the two

treatment groups. Given the well-documented longer-term risks associated with CYC, including malignancy and infertility, which are not suggested by the overall evidence from RTX in AAV and other indications, RTX is an important therapeutic option for the treatment of severe AAV.

The results from RAVE have demonstrated that severely active AAV patients can achieve complete remission with an acceptable safety profile in the absence of CYC. This finding, in patients with a potentially fatal and orphan-designated illness without any approved therapies, represents a major advance in patient care. The positive benefit–risk assessment is further strengthened with the longer-term data out to 18 months.

RTX, therefore, represents a new therapeutic option for severely ill AAV patients for whom CYC was previously the only option.

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

RAVE was an adequate and well-controlled study which had a valid comparison against current standard of care (CYC). The measures used to assess the patients' responses were well-defined and reliable; BVAS/WG is a validated instrument for assessing disease activity for AAV patients. The definition of remission for the primary endpoint required the absence of BVAS/WG items, together with the elimination of prednisone use, representing a major efficacy response.

The main limitation of the data provided in this STA is the fact that there is only 1 RCT to provide the bulk of the evidence. Supporting data came from an open-label study which also included CYC in the RTX arm (plus limited safety data from a series of very small studies).

The RAVE trial itself had certain limitations. Only patients with severe ANCA-associated vasculitis who were ANCA-positive were enrolled. Thus, it is not clear whether the treatment effects extend to patients with *limited* Wegener's granulomatosis or those who are ANCA-negative. Patients with alveolar haemorrhage severe enough to require ventilator support and those with

advanced renal dysfunction were also excluded. Thus, the comparative efficacy of these two regimens is uncertain in such patients.

The study focused exclusively on remission induction but did not address the question of retreatment with RTX. RTX was not re-administered after the return of peripheral-blood B cells (anticipated by 9 to 12 months). This question is being addressed currently in a new clinical trial (RITAZAREM).

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.**

The evidence base is directly linked to the decision problem in terms of population, interventions, comparators and outcomes. Although only a single RCT was submitted as the main evidence, it was directly related to the decision problem: RAVE randomised patients with severe AAV to receive either RTX or CYC as their induction therapy. The main efficacy measure, complete remission (defined as a zero score on BVAS/WG as well as successful taper of glucocorticoids), is a clinically meaningful outcome in this disease, since the goal of induction therapy is not just to prevent mortality and morbidity caused by the illness, but also to spare the patient from exposure to steroids, which are essential in managing the disease but whose long-term toxicity is serious and well-established. Not all the outcomes outlined in the final scope could be included due to limitations in the evidence base, but we feel that the economic model provides a useful and conservative starting point.

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?**

The RTX licence is likely to cover the induction of remission. However, one of the main unanswered questions in what to do with patients who relapse on

RTX. Although it is outside of the proposed licence and scope of this appraisal, physicians treating AAV with RTX do currently use protocols both for maintenance of remission and treating flares. This is not addressed in this submission, but is likely to be an important discussion point amongst treating physicians.

The dose used in both RAVE and RITUXVAS is the dose submitted for licensing (i.e. 375mg/m^2 body surface area once weekly for 4 weeks). However, some of the supporting studies also describe the RA dose (1,000mg on day 1 and 15).

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 9.10, appendix 10.**

A systematic review was conducted on 5th February 2013 for literature addressing the cost effectiveness of one or more interventions for patients with either granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Medline, Medline In-Process, Embase, Embase Alerts, Econlit and NHS EED were searched using the database provider. The internal company database PubCenter was also searched for any cost effectiveness literature.

Articles were excluded if they were not related to humans, not written in the English language, or the patient population was inappropriate (≤18 years old). Articles were also excluded if they reported on the cost effectiveness of treating co-morbidities potentially associated with MPA or GPA. There was no restriction in the search strategy on intervention and comparators.

Articles were included if they reported a measure relevant to cost-effectiveness, for example:

- incremental cost per QALY gained
- cost of being in remission/not being in remission
- cost of disease relapse compared with not having a relapse
- direct and indirect costs of treating GPA or MPA in any currency and at any geographical location.

Articles were also included if they used a decision model to estimate the cost effectiveness of any intervention for MPA or GPA.

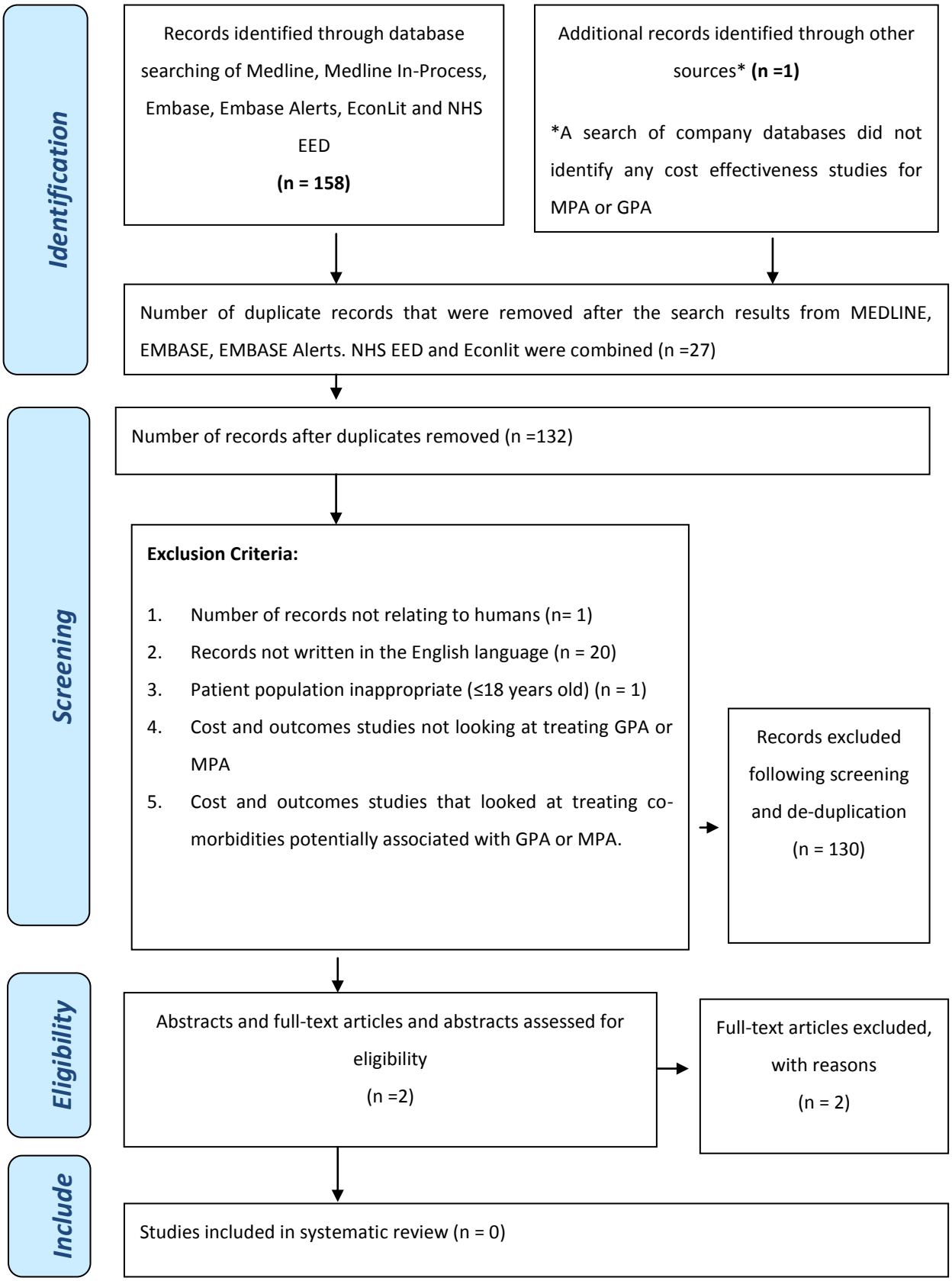
A total of 159 records were identified. There were 27 duplicates which were removed. The 132 remaining records were screened using the specified inclusion/exclusion criteria. A total of 130 records were excluded at screening and 2 articles were eligible for further assessment. These 2 articles were subsequently excluded because they did not report on a cost effectiveness evaluation.

Thus, the systematic review did not identify any studies that reported on the cost effectiveness of treatment for MPA or GPA.

Figure 9 shows the Prisma 2009[1] flow diagram that was used to identify appropriate articles. Further detail on the search strategy is available in Appendix 10.7.

[1] Moher D, Libterati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for systematic Reviews and Meta-Analysis: The PRISMA Statement. PLoS

Figure 9: Prisma Flow Diagram for cost-effectiveness studies



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 following two articles were eligible for further assessment according to the exclusion/inclusion criteria. Following a review, the papers were deemed unsuitable and excluded from the systematic literature review.

Table 34:Summary list of other cost-effectiveness evaluations

Citation	Reason why this article was excluded
Hoffman GS et al. Wegener's Granulomatosis. Arthritis and Rheumatism 1998; 41 (12): 2258-2262	The article reported on a self-administered questionnaire developed by the authors for 100 patients with GPA. Questions were related to the medical, financial and social impact of the disease. Patients included in the sample matched the American College of Rheumatology proposed criteria for GPA 1990, and were recorded on a GPA registry at the Cleveland Clinic Foundation. This article is not a cost effectiveness evaluation and provides only a description of direct and indirect costs and potential outcomes for patients with GPA at a single centre.
Ndir A et al. A budget impact model of RTX introduction in Wegener Granulomatosis Therapies. Value in Health 2011; 14 (7): A411	A budget impact model for RTX compared with CYC in France. The six month induction cost was evaluated for treating a hypothetical cohort of patients consisting of newly diagnosed and relapsing patients. Even though the budget impact model estimates the cost of GPA, costs are not linked to clinical outcomes. This is not a cost effectiveness analysis and was therefore excluded from the systematic review.

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 9.11, appendix 11.

No cost-effectiveness studies were identified.

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 1.4 and 5.3.3, 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.**

The economic analysis population is based on the RAVE study selection criteria, which in turn form the criteria for the proposed marketing authorisation. Patients in RAVE had positive serum assays for proteinase 3-ANCA or myeloperoxidase-ANCA, manifestations of severe disease and a Birmingham Vasculitis Activity Score for GPA of 3 or more. Patients with either newly diagnosed or relapsing disease were eligible for enrolment.

The NICE scoping workshop identified a small subgroup of patients (<10%) who cannot tolerate CYC (CYC) or in whom continued use of CYC would be inappropriate. Whilst this population is covered by the licence they were not represented in the pivotal RAVE study and therefore are not accounted for in the base case economic evaluation.

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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.

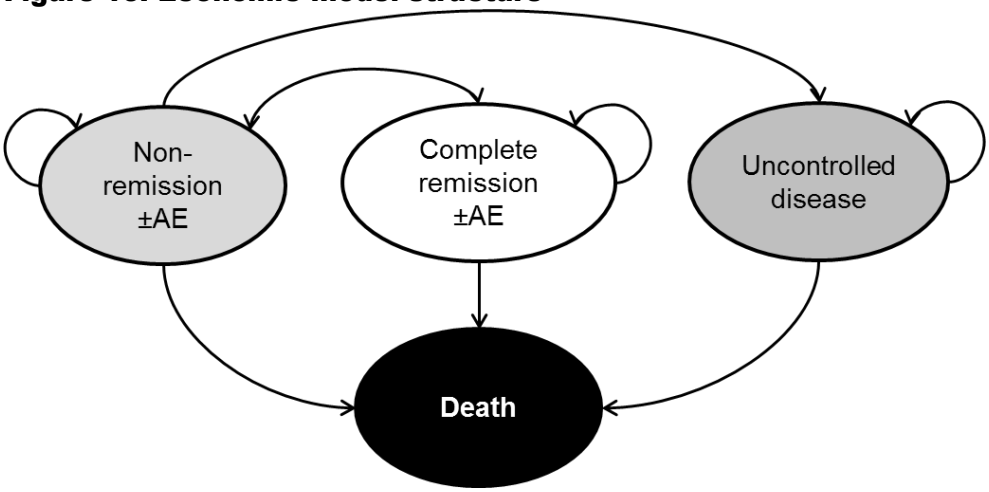
We have undertaken a separate subgroup analysis to estimate the cost-effectiveness of RTX in AAV patients where CYC is not considered the standard of care. Evidence was sourced from the subgroup of patients in the RAVE study who were newly diagnosed and had not received induction therapy.

Model structure

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

Our economic model health states include ‘complete remission’, a state reflecting treatment success as assessed in the RAVE study; ‘non-remission’, a state reflecting non-attainment of remission; and ‘uncontrolled disease’, a state of worse health which patients enter once their simulated treatment options have been exhausted. Death is also included.

Figure 10: Economic model structure



7.2.3 **Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.**

The de novo analysis has been designed to reflect clinical practice in the UK for treating ANCA-associated vasculitis (AAV) patients. Under the proposed licence, the scope of the analysis is restricted to the induction of remission only and not the treatment of flares or maintenance therapy.

The cost-effectiveness analysis employs a Markov model consisting of four different health states: non- remission, complete remission, uncontrolled disease and death (see Figure 10).

The structure is simple, and largely reflective of the RAVE study [Stone et al 2010] with a non-remission and a complete remission health state. Patients enter the model in the non-remission health state where they go on to receive induction therapy. Based on the probability of achieving remission patients can then transition to the complete remission health state or if they did not achieve remission they will remain in the non-remission health state.

Our base case analysis is designed to compare two 'arms', each of which contains a sequence of treatments. Moving from one treatment to the next in each arm's sequence is triggered either by the patient eventually relapsing, or by failing to attain complete remission. This design is similar to that used in our previous NICE submission for tocilizumab in rheumatoid arthritis [NICE TA 247, 2012].

In the 'standard of care' arm we have assumed that patients receive induction therapy with CYC. We also anticipated that patients in this arm would be re-challenged with CYC in the event that they do not attain remission or relapse. However, we also recognize that the number of repeat doses is likely to be restricted. CYC is highly effective in the treatment of AAV, but has known side effects including infertility, cytopenias, infections, bladder injury, and cancer, and concomitant glucocorticoids are major causes of long-term disease and death in their own right [Stone et al 2010]. So we have sought to limit the number of repeat CYC courses in the model to a realistic number.

The Hoffman study of CYC in AAV [Hoffman et al 1992] observed diminishing returns from repeat induction courses with CYC. Clinical expert advice considered that in standard clinical practice a maximum of two courses of CYC would be administered.

In the intervention arm of the model we have assumed RTX can be administered as an alternative induction agent. We know that within clinical practice the treatment sequence for RTX may differ based on a number of

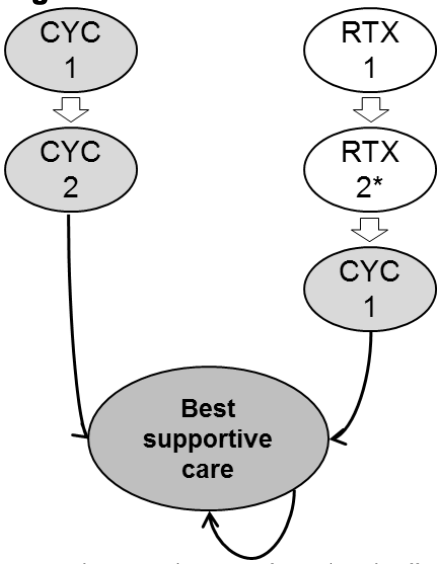
factors including prior treatment, previous experience with RTX and tolerance to CYC.

In the base case we assume patients receive RTX as a first line induction therapy. Patients who fail to achieve complete remission in line with the definition in the RAVE study are assumed to receive one further course of RTX. This assumption has been made on the basis on expert opinion. The RAVE study did not investigate the effects of retreatment with RTX. Patients who respond to RTX are not eligible for retreatment upon relapse as this is outside the scope of the licence.

Following relapse in the intervention arm, and after exhausting two cycles on RTX, patients are assumed to receive one course of CYC treatment as a last attempt to induce remission. We have explored the impact of assuming two courses of CYC in the intervention arm in the sensitivity arm (see 7.7.7).

Patients who achieve remission following CYC therapy switch to AZA therapy while in remission. Patients who achieve remission following RTX do not receive any further treatment until relapse. The patient treatment flow is outlined in Figure 11.

Figure 11: AAV economic model treatment sequences (base case)



Note: * the second course of RTX is only offered to patients who did not respond at all to the first course. Moreover, its efficacy is assumed to be lower.

Once patients have transitioned through all available induction treatments, they are assumed to enter the ‘uncontrolled disease’ health state where no further induction therapy is administered. Patients in the uncontrolled disease health state are assumed to receive best supportive care. Because this implies worse disease control compared to that attainable on RTX or CYC, this state is assumed to have a worse quality of life (refer to 7.4).

We know that in the UK, current standard of care for a number of centres includes off label use of RTX for induction therapy, treatment of relapse and maintenance treatment. This has not been considered within the economic analysis.

A lifetime model has been chosen to capture all relevant costs and benefits related to the treatment of AAV.

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

Patients enter the model in the non-remission health state with active disease defined as a BVAS/WG score of 3 or more in line with the RAVE study. In the base case analysis, patients entering the model may either have newly diagnosed disease or relapsing disease following prior induction therapy. Patients with active disease are at risk of serious morbidity and premature mortality without effective therapy to prevent disease progression [Reinhold-Keller et al, 2000].

The complete remission health state is defined in accordance with the RAVE study. Patients in the complete remission health state were required to have a BVAS/WG score of 0 and completed a successful taper of prednisone at 6 months [Stone et al, 2010]. The health state captures those patients that have successfully responded to treatment and achieved remission. Patients with stable disease in the complete remission health state are assumed to have an improved quality of life based on the health related quality of life data sourced from the RAVE study and a reduced resource use. Based on UK registry data in patients with AAV, patients in complete remission are assumed to have a

reduced risk of mortality compared to those patients not in the complete remission health state.

The uncontrolled disease health state represents the proportion of patients who have received several courses of induction therapy and never achieved complete remission or have subsequently relapsed following complete remission. Patients in the uncontrolled disease health state are assumed to have a reduced quality of life and increased mortality risk compared to patients in either the non-remission health state or those in complete remission. Patients are assumed to have exhausted all induction therapy options and as a result only receive best supportive care.

Death represents the terminal health state for disease-related and all-cause mortality in 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.

AAV is associated with considerable morbidity in the long term, with up to 50% of patients relapsing within 5 years. Each relapse carries a risk of subsequent critical organ damage [Lapraik et al, 2007; Walton, 1958]. The model is designed to capture the improvements in quality of life and improved prognosis associated with a patient successfully being induced into remission.

We acknowledge that due to limitations in the evidence we are not able to produce a model that captures all of the main clinical aspects of the disease. We know that particular organs play a significantly bigger role in long term morbidity for patients, particular renal and respiratory involvement. Separating individual organ-involvement patients and performing a heterogeneity analysis to feed into a patient simulation model was not deemed appropriate due to the low number of patients within each group of organ comorbidity. Therefore, the analysis has not been able to model individual patients progression based on which particular organ was affected by the disease, nor does it capture the severity of relapses which will vary according to the particular organ involved.

These limitations we believe may lead to an underestimation of the true benefit of successful induction therapy.

We have undertaken subgroup analysis to capture the minority of patients who are intolerant to CYC. We have assumed the newly diagnosed patient data from RAVE best reflects those patients who are intolerant to CYC. The model has applied a number of assumptions to estimate what the actual underlying disease progression is in patients intolerant to CYC (see section 7.9).

The underlying disease progression for patients with severe AAV has been modelled on the CYC arm of the RAVE study. We know that for the majority of patients with severe AAV, CYC is regarded as the standard of care therapy for inducing remission.

Mortality data for the underlying AAV population was sourced from a retrospective study in the UK [Lane et al. 2005]. The Lane et al. study calculated standardised mortality ratios (SMRs) for AAV patients compared to the local population. The SMRs from the study are applied to a standard life table of the UK general population (Interim Life Tables in the UK [ONS, 2011]) to derive mortality risks for patients with AAV in our model.

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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.

Table 35: Key features of analysis

Factor	Chosen values	Justification
Time horizon	lifetime	NICE guides to methods
Cycle length	6 months	The primary outcome was reported at 6 months
Half-cycle correction	Yes	NICE guide to methods
Were health effects measured in QALYs; if not, what was used?	Yes	NICE guide to methods
Discount of 3.5% for utilities and costs	Yes	NICE guide to methods
Perspective (NHS/PSS)	Yes	NICE guide to methods

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?**

RTX is administered in the model in line with the proposed marketing authorisation as an induction therapy at the dose of 375 (mg/m^2) every week for 4 weeks. The proposed licence for RTX does not cover the treatment of relapse, nor maintenance therapy in AAV. The model has therefore assumed patients receive one course of RTX as per the RAVE study regimen. Based on the expert clinical advice, we have assumed in our base case that patients who do not respond to RTX are permitted to receive one further course of induction treatment. This practice is not ruled out by the license, and is designed to reflect UK clinical practice in which no more than two courses of RTX are likely to be administered.

RTX is currently used in a number of centres in the UK, and furthermore we know that the NHS Commissioning Board in their draft document [NHSCB/A3C/1a, December 2012] has endorsed the use of RTX in AAV. Within the UK there is also evolving research on the best treatment regimen under which to administer RTX. We know that currently a number of different treatment protocols in the UK NHS [Salford Royal NHS. Treatment Protocol, 2010, NHSCB/A3C/1a, December 2012] differ to that given in the RAVE study; notably a dose of 1,000mg on days 1 and 15 is preferred by some UK clinicians. We have not explored the effect of continued treatment with RTX, nor the efficacy of using the 1,000mg dose due to evidence limitations because we do not have efficacy data for these regimens.

Following successful induction therapy with RTX, we assume patients go on to receive no maintenance therapy. This is in line with the RAVE study protocol, expert clinical opinion and the anticipated licence.

CYC is regarded as the standard of care in the induction of remission in patients with severe disease. CYC can be administered either orally or as an IV infusion (pulse therapy). We know that within the United Kingdom the

majority of patients with severe AAV receive CYC pulse therapy. The model has included both oral therapy and IV pulse options based on market research of clinicians treating AAV in the UK.

Our economic model assumes that oral CYC is given at a dose of 2mg per kg daily [Stone et al, 2010], this is consistent with RAVE. The IV dose is assumed to be given at 15mg/kg [Mukhtyar et al, 2009], every three weeks with the first three doses administered two weeks apart. We have assumed patients receive CYC treatment for 6 months, equivalent to the length of a model cycle.

Patients attaining remission following induction therapy with CYC are assumed to receive AZA (AZA) as a maintenance therapy until they relapse. AZA is dosed at 2mg/kg on a daily basis in line with the protocol in the RAVE study [Stone et al, 2010].

In line with the BSR guidelines and the RAVE trial protocol, patients received methylprednisone and prednisone while undergoing induction therapy [Lapraik et al 2007, Stone et al 2010].

Patients receiving CYC will receive prophylaxis trimethoprim in order to prevent against Pneumocystis jiroveci (formally Pneumocstis carinii) as outlined by the BSR guidelines [Mukhtyar et al 2009].

We note that within the NICE Scope a number of alternative agents were described as alternatives to CYC induction therapy. To our knowledge there are no direct head to head studies comparing the effectiveness of myclophenolate or methotrexate with RTX. Having sought expert opinion on these we note that both alternative agents are considered inferior to CYC in inducing remission.

We have not compared the effectiveness of RTX to any of the alternative agents due to evidence limitations. In the subgroup analysis for patients who cannot tolerate CYC, we have compared RTX to best supportive care.

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.**

In line with the evidence from the RAVE study, patients receive one course of RTX (375mg/m2 once weekly for four weeks). We then assume that if a patient fails to respond to treatment with RTX, or eventually relapses, they will receive a second course of treatment in the second cycle. We do not have evidence about what proportion of patients who will receive a second course of treatment with RTX, but as the course is only delivered over a four week period, we have assumed all patients will receive another course if they did not respond. Clinical opinion suggests that patients who still fail to achieve remission subsequently will not be re-challenged with RTX.

As the proposed licence is restricted to induction therapy we have not specifically modelled the treatment of relapse, nor maintenance therapy using RTX. We know that within the UK NHS, a number of clinical protocols endorse the use of RTX as maintenance therapy in AAV [Salford Royal NHS. Treatment Protocol, 2010, NHSCB/A3C/1a, December 2012]. So whilst we have assumed a maximum of two courses to achieve a suitable balance between the license, NICE Scope and clinical practice, we also note that current clinical opinion is indicating increasing preference for the longer term use of RTX.

As described previously, we assume that patients in the CYC arm will receive no more than two 6-month courses of CYC induction therapy.

7.3 Clinical parameters and variables

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

The Markov model moves patients from the ‘non-remission’ health state into the ‘complete remission’ state based on the probability of achieving complete remission from the RAVE study. In the RAVE study ‘complete remission’ was defined as having BVAS/WG=0, and no glucocorticoid therapy.

Patients in the ‘complete remission’ health state have a constant probability of relapsing based on the RAVE study relapse rates – these rates have been extrapolated based on an exponential fit (see 7.3.7) throughout the lifetime of the model.

The model’s fourth health state, ‘uncontrolled disease’ was informed by clinical expert opinion. In this health state patients are assumed to have exhausted all available induction treatment options and their health may be subject to a mix of relapses, flares, stable disease, temporary remissions and critical episodes – however this complex disease activity is not modelled – instead a lower average utility is assigned to the whole state. Patients in ‘uncontrolled disease’ receive best supportive care only and do not transition to any other health state other than ‘death’.

The mortality rate applied in the model has been sourced from Lane et al 2005. A health state dependent risk of mortality has also been applied to each of the three alive health states in the economic model, based on standardised mortality ratios (please see 7.3.4). The use of a secondary source for mortality was necessary as the information could not be sourced from RAVE.

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 transition probabilities in the base case model are based on the primary endpoints from RAVE are outlined in the

Table 36. As we consider RTX as an alternative induction agent to the current standard of care for all patients we have used the ITT results from the RAVE study rather than the subgroup analysis for relapsing and newly diagnosed patient groups.

A constant rate of relapse has been applied in the economic model based on the risk of relapse observed in the RAVE study.

Table 36: Transition probabilities derived from RAVE

Transition Probabilities	Value	Source
1st course of treatment		
Non-remission to complete remission (CYC_1)	0.5306	Stone et al, 2010
Non-remission to complete remission (RTX_1)	0.6364	Stone et al, 2010
Relapse rates		
Constant Relapse rate (CYC)	0.1496	Stone et al, 2010
Constant Relapse rate (RTX)	0.1647	Stone et al, 2010

There is evidence of diminishing returns associated with subsequent cycles of CYC [Hoffman et al 1992]; we have therefore assumed that the second course of CYC is associated with a different probability of achieving remission to the first course of treatment.

The results of the subgroup analysis in the RAVE study for patients with relapsing disease was used to estimate the probability of achieving remission for the second course of CYC treatment (Table 37). The majority of patients in the relapsing patient subgroup in RAVE had previously used CYC (74% in the CYC treatment arm) and are therefore representative of relapsing CYC patients.

Table 37: RAVE subgroup transition probabilities

Transition Probabilities	Value	Source
Newly diagnosed Subgroup		
Complete remission (CYC)	0.6458	Stone et al, 2010
Complete remission (RTX)	0.6364	Stone et al, 2010
Relapsing Patients Subgroup		
Complete remission (CYC)	0.4200	Stone et al, 2010
Complete remission (RTX)	0.6042	Stone et al, 2010

The relapse rates from the subgroup analyses are stated below. These have been used in the sensitivity analysis (see 7.6.2).

Table 38: Subgroup analyses - relapse rates

Subgroup Relapse rates	CYC	RTX	Source
Newly diagnosed	0.0704	0.1199	RAVE
Relapsing patients	0.1668	0.3058	RAVE

Subsequent RTX cycles are also assumed to be associated with a reduced probability of achieving remission for those patients who failed to obtain remission with RTX. As RAVE did not investigate retreatment with RTX, we have assumed that the 2nd course of RTX has the same diminishing returns rate as observed between the CYC *newly diagnosed* and *relapsing* patient groups (Table 37). The probability of achieving remission with an additional course of RTX is assumed to reduce by a rate of 35%.

We have assumed the probability of obtaining remission with CYC is the same regardless of prior RTX therapy.

Table 39: Transition probabilities in the economic model

Transition Probabilities	Value	Source
2nd course of treatment		
Non-remission to complete remission (CYC_2)	0.4200	Stone et al, 2010
Non-remission to complete remission (RTX_2)	0.4138	Assumption
CYC following RTX		
Non-remission to complete remission (CYC_1)	0.5306	Stone et al, 2010

Adverse events transition probabilities

The model's safety analysis is based on data observed in the RAVE clinical trial.

Table 40 and Table 41 show the proportion of patients with the identified AEs.. Since it is possible for the same event to be classified under each category more than once for the same patient, the analysis incorporates the maximum number of patients across all the categories.

Table 40: Percentage of patients with AEs in CYC only treatment (6 months and >2%)

	Severity grades				Model
	3	4	5	Max	input
Leukopenia	3.5%	0.0%	0.0%	3.5%	3.5%
Anaemia	3.5%	0.0%	0.0%	3.5%	3.5%
Pneumonia	2.4%	0.0%	1.2%	2.4%	2.4%
Dyspnoea	2.4%	0.0%	0.0%	2.4%	1.2%*
DVT	5.9%	0.0%	0.0%	5.9%	1.2%

*Only 1.2% of DVT cases were considered related to CYC, therefore the model input is 1.2% not 5.9%.

Table 41: AEs observed in RTX only treatment (6 months and >2%)

	Severity grades				Model input
	3	4	5	Max	
Leukopenia	0.0%	2.3%	0.0%	2.3%	2.3%
Anaemia	3.5%	0.0%	0.0%	3.5%	3.5%
Diarrhoea	2.3%	0.0%	0.0%	2.3%	2.3%
Pneumonia	2.3%	1.2%	0.0%	2.3%	2.3%

The safety data on AZA treatment was not available from RAVE and therefore post-hoc analysis on the trial data was conducted in order to retrieve this information. The analysis was based on the same criteria, as mentioned above. The results showed 3 patients experienced leukopenia when receiving AZA treatment. The probability of leukopenia for AZA was assumed to be in the model 0.03.

Table 42: AEs observed in AZA only treatment (6 months and >2%)

	Model input
Leukopenia	3%

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.

We have assumed that the probability of achieving remission varies based on the line of treatment it is administered in. Please see 7.3.2 for further detail.

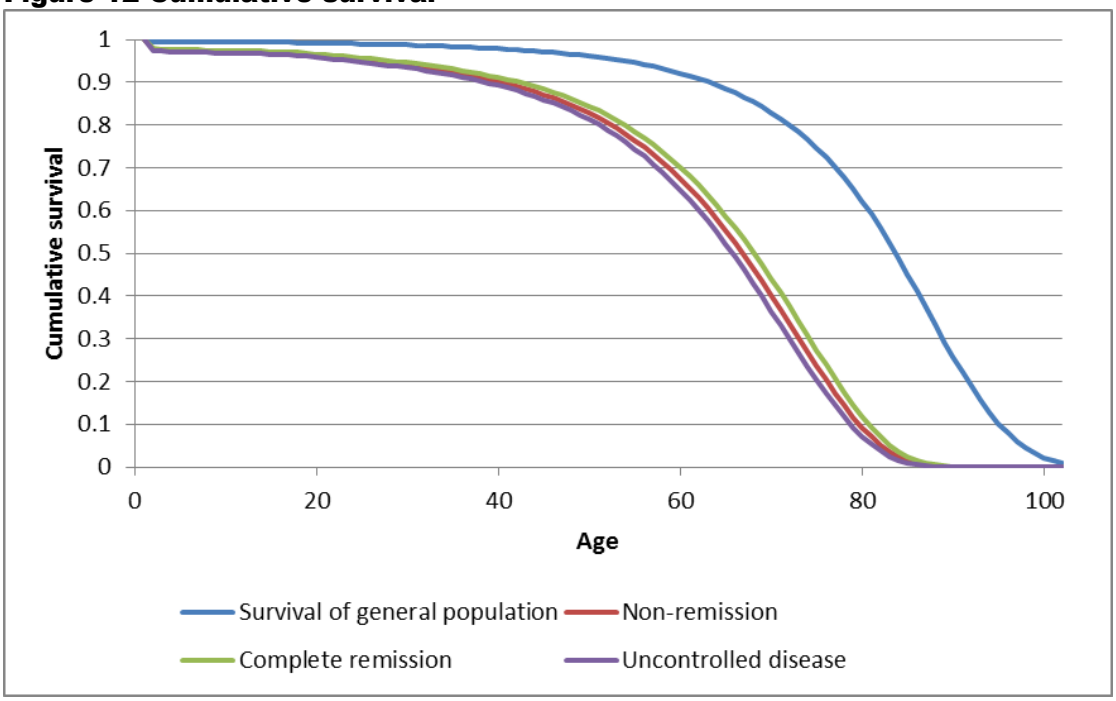
7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

In our model we have assumed that patients in complete remission have a lower risk of disease-related mortality. Patients in either of the two remaining non-remission health states are assumed to have an increased risk of disease-related mortality.

Disease-specific mortality risks in the economic model come from a retrospective study of an AAV cohort in the UK [Lane et al. 2005], where the authors calculated standardized mortality ratios (SMRs) comparing the local general population (Norwich, UK) with the AAV population. The estimated SMR for AAV patients is: 4.8 (95% CI 2.9-6.6).

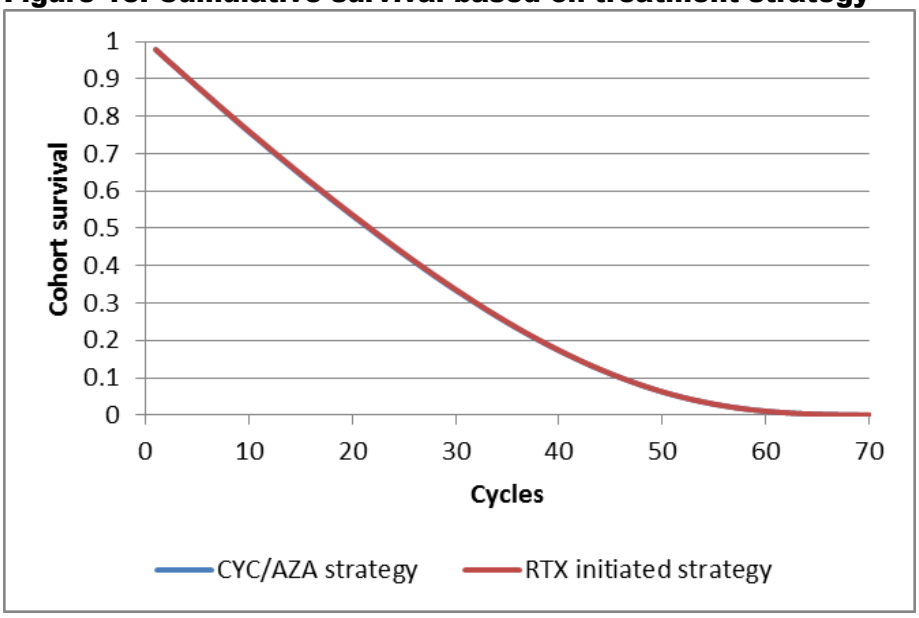
We do not have any mortality data based on the health state a patient is in. We have assumed the mean SMR represents patients who are not in remission, with an arbitrary ±10% applied to patients in the uncontrolled and complete remission health states. The SMR is applied to a standard life table of the UK general population (Interim Life Tables in the UK [ONS, 2011]), in order to estimate the mortality risk in the economic model (see Figure 12).

Figure 12 Cumulative survival



The cumulative survival estimates as modelled for the RTX or CYC treatment arms are presented below. However, due to the small difference in overall survival (0.0442 LY) the curves appear overlapping.

Figure 13: Cumulative survival based on treatment strategy



NOTE: blue and red lines are overlapping in this graphic

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

Our nominated expert for the technology appraisal of RTX in AAV has provided advice on request throughout the development of our evidence submission. The expert was identified as an international key opinion leader in the field of ANCA-associated vasculitis with significant experience in prescribing RTX for the treatment of AAV in the United Kingdom. We sought the expert's opinion through an advisory board meeting where we presented the economic model and its key assumptions. Additional contact was made via email following the advisory board meeting.

The clinical expert was asked to comment on the overall structure of the economic model, clinical inputs, current UK clinical pathway including relevant comparators, dosing regimens, quality of life measures, and long term clinical outcomes.

[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.

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.**

Table 43: Summary of variables applied in the economic model

Variable	Value	Std Error	Reference to section in submission
Basic characteristics			
Starting age	52 years	1.069	6.3.4
Gender: male	50.3%	-	6.3.4
Weight	67kg	-	7.3.8
Height	171.5cm	0.728	6.3.4
Body Surface Area	1.79	-	7.3.8
Remission rates			
RTX – All patients	0.6364		6.5.1
CYC – All patients	0.5306		6.5.1
RTX- Newly diagnosed	0.6042		6.5.1
CYC- Newly diagnosed	0.6667		6.5.1
Relapse rates			
RTX – All patients	0.1647		6.5.1
CYC – All patients	0.1496		6.5.1
RTX- Newly diagnosed	0.1199		6.5.1
CYC- Newly diagnosed	0.0704		6.5.1
Both treatments, health state utilities			
uRemission	0.84	0.02	7.4.9
uNonRemission	0.75	0.02	7.4.9
uUncontrolled Disease	0.67	-	7.4.9
Utilities of AEs			
uAnaemia	0.63	0.19	7.4.8
uLeukopenia	0.70	0.17	7.4.8
uDVT	0.69	0.17	7.4.8
uDyspnoea	0.82	-	7.4.8
uPneumonia	0.21	-	7.4.8
Unit costs			
Blood test	£3	0.2744	7.5.6
Liver function tests	£8.99	-	7.5.6
Consultant Rheumatologist	£125.68	0.1508	7.5.6
Consultant Nephrologist	£150.53	0.1239	7.5.6
Consultant Pulmonologist	£131.12	0.1514	7.5.6
Consultant Neurologist	£139.61	0.1670	7.5.6
Consultant Otolaryngologist	£72.99	0.1660	7.5.6
Consultant Ophthalmologist	£73.47	0.1161	7.5.6

Consultant Dermatologist	£86.37	0.1610	7.5.6
Imaging: chest x-ray or CT scan (for patients with pulmonary symptoms)	£29.08	0.1508	7.5.6
Costs of AE (cost per event)			
Anaemia	£363.66	0.2174	7.5.7
Leukopenia	£406.60	0.2115	7.5.7
DVT	£387.34	0.1902	7.5.7
Pneumonia	£1224.70	0.1363	7.5.7
Best supportive care (unit cost)	£254.06	0.3380	7.5.6

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.**

The probability of relapse from complete remission is based on the RAVE trial data. Figure 14 shows the probabilities of remaining in remission after achieving complete remission at 6 months. The time-to-relapse figure starts at 6 months after the beginning of the trial. An exponential distribution is fitted to estimate the relapse probability for each strategy:

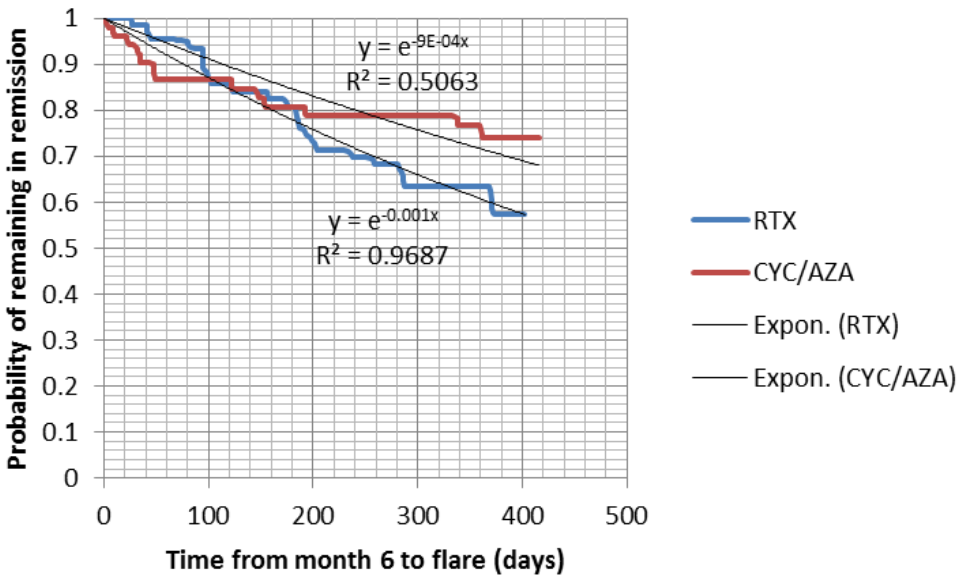
- RTX: exponential distribution: $y=e^{-0.001x}$; $R^2=0.9687$
- CYC/AZA: exponential distribution: $y=e^{-9E-04x}$; $R^2=0.5063$

Daily relapse rates of the RTX and CYC/AZA strategies are 0.001 and 0.0009, which is converted to 6-month probability of 16% and 15%, respectively (Table 44).

Table 44: Relapse probability of the two strategies

Strategy	Relapse	Source
RTX	16%	Stone et al 2010
CYC/AZA	15%	Stone et al 2010

Figure 14: Probability of remaining in remission



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

The modelled treatment arm for RTX is based on the RAVE study protocol as well as clinical expert opinion. We have assumed the following:

The dosing regimen is 375mg/m^2 given once a week for four consecutive weeks.

Patients in the RTX arm may receive a maximum of two courses of the drug, providing they did not respond to the first course of treatment

All patients who do not respond to the first course of RTX are assumed to receive a second.

Patients who respond to treatment with RTX and are in clinical remission are assumed to receive no maintenance therapy.

Patients who relapse following their courses of RTX are assumed to receive one further course of CYC.

In the standard of care arm patients can receive up to two courses of CYC. When patients achieve complete remission following CYC treatment patients

go on to receive maintenance therapy with AZA in line with the RAVE protocol.

The complete remission rates from RAVE have been used to estimate the transition probabilities for the first course of CYC and RTX.

We have assumed the probability of obtaining remission with the second course of CYC is equal to that of the CYC relapsing population in the RAVE study.

For patients treated with a second course of RTX we have assumed a reduced probability of obtaining remission. The estimate is based on the relative reduction seen between CYC newly diagnosed patients and relapsing patients in RAVE.

We have assumed the average body surface area for patients in the model to be 1.79m^2 based on an estimate for UK cancer patients [Sacco et al, 2010]. Patients in the RAVE study which recruited mainly in the USA as well as the Netherlands had an average BSA of 1.998m^2. This included an average weight of 87kg, which was not considered reflective of UK patients,

We have applied a time-dependent and increased risk of death for the three ‘alive’ health states. The SMR sourced from UK registry is assumed to represent those patients not in remission [Lane et al 2005]. An arbitrary ±10% has been applied to the SMR to estimate the risk of death in the uncontrolled and complete remission health state.

In the uncontrolled disease health state, patients have tried and failed all possible treatment options and are assumed to go on to receive best supportive care. We have based this assumption on the premise that as discussed above, it is unrealistic to receive unlimited cycles of CYC and therefore patients must run out of treatment alternatives. The health state is also assigned the lowest utility of the health states and has the highest risk of mortality.

7.4 Measurement and valuation of health effects

Patient experience

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

The signs and symptoms of vasculitis vary depending on which blood vessels and, as a result, which organ systems are affected. However, general signs and symptoms that many people with vasculitis experience include fever, fatigue, weight loss, skin lesions, blurred vision, hearing loss, muscle and joint pain and nerve problems.

With MPA, blood vessel swelling causes multiple tissues at the same time to be affected. It can be seen in the kidneys, skin, nerves, and lungs. In patients with GPA, granulomatous inflammation often affects the lung, sinuses, nose, eyes, or ears.

Most patients present with a constellation of organ manifestations when diagnosed with AAV that together may result in significantly impaired HRQL [Walsh et al, 2011].

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

AAV is a chronic condition with relapsing and remitting episodes and chronic sequelae that most patients live with for years [Carpenter et al, 2009]. Patients HRQL is likely to be strongly correlated with their disease activity as shown in the RAVE study which demonstrated an improved quality of life for patients when in remission.

HRQL data derived from clinical trials

7.4.3 **If HRQL data were collected in the clinical trials identified in section 5 (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.**

In the RAVE study HRQL data were collected using the 36-item Short Form health survey (SF-36). The SF-36 was administered at baseline and again at the 6 month assessment point.

Table 45: RAVE SF-36 scores at baseline, mean ± SE

Variable	RTX (n=99)	CYC (n=98)	P Value
Physical component	37.2±9.8	38.6±11.9	0.38
Mental component	41.7±13.2	44.0±11.4	0.20

Quality-of-life SF-36 scores improved from baseline in both groups (Table 46). In the RTX group, SF-36 physical and mental health component summary scores (range 0-100) improved by 5.9 (SD=10.4) and 7.9 (12.6) points, respectively. These same summary scores improved by 6.0 (10.4) and 5.3 (12.9) points in the CYC group. There was no significant difference between treatment groups in the change from baseline to month 6 in the quality-of-life scores or their rate of change over this period [Stone et al, 2010].

Table 46: RAVE SF-36 scores at week 24, mean ± SE

Variable	RTX (n=99)	CYC (n=98)
Physical component	43.1±10.4	44.6±10.4
Mental component	49.6±12.6	49.3±12.9

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.

The RAVE trial reports health related quality of life using SF-36. The SF-36 scores were converted from the non-remission and remission health states to the EQ-5D in a post-hoc analysis using a published model [Ara and Brazier 2008]. In addition to mapping we also applied disutility adjustments for adverse events (see section 7.4.9).

Table 47 shows the mapping model used in the economic analysis. Model 2 from Ara and Brazier was chosen to derive the default values for the economic analysis because it is reported to be more accurate when predicting incremental differences between study arms and changes over time [Ara and Brazier 2008]. Model 1 is reported to have the best fit when tested against external data [Ara and Brazier 2008] and is used in sensitivity analysis. Please see section 7.4.9 for more details.

Table 47: Mapping models from Ara and Brazier [2008]

	Model 1	Model 2
Intercept	0.03256	-0.18105
PF	0.00370	0.00781
SF	0.00111	0.00213
RP	-0.00024	
RE	0.00024	0.00022
MH	0.00256	0.00599
VT	-0.00063	
BP	0.00286	0.00472
GH	0.00052	0.00064

Table 48 shows the utility of each model health state (non-remission and complete remission) derived using both mapping equations. Results from model 2 were used in the base case analysis. A sensitivity analysis explores the effects of using mapping model 1.

Table 48: Utility in the economic model using mapping models from Ara and Brazier

	Model 1	Model 2
Complete remission	0.7865185	0.8366848
Non-remission	0.6988610	0.754041

The utility scores were adjusted for baseline utility, as is described in 7.4.9.

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 9.12, appendix 12.**

A systematic review was conducted on 4th February 2013 for studies that have measured Health Related Quality of Life (HRQL) in patient with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Medline, Medline In-Process, Embase, Embase Alerts, Econlit and NHS EED were searched using the database provider ProQuest. The internal company

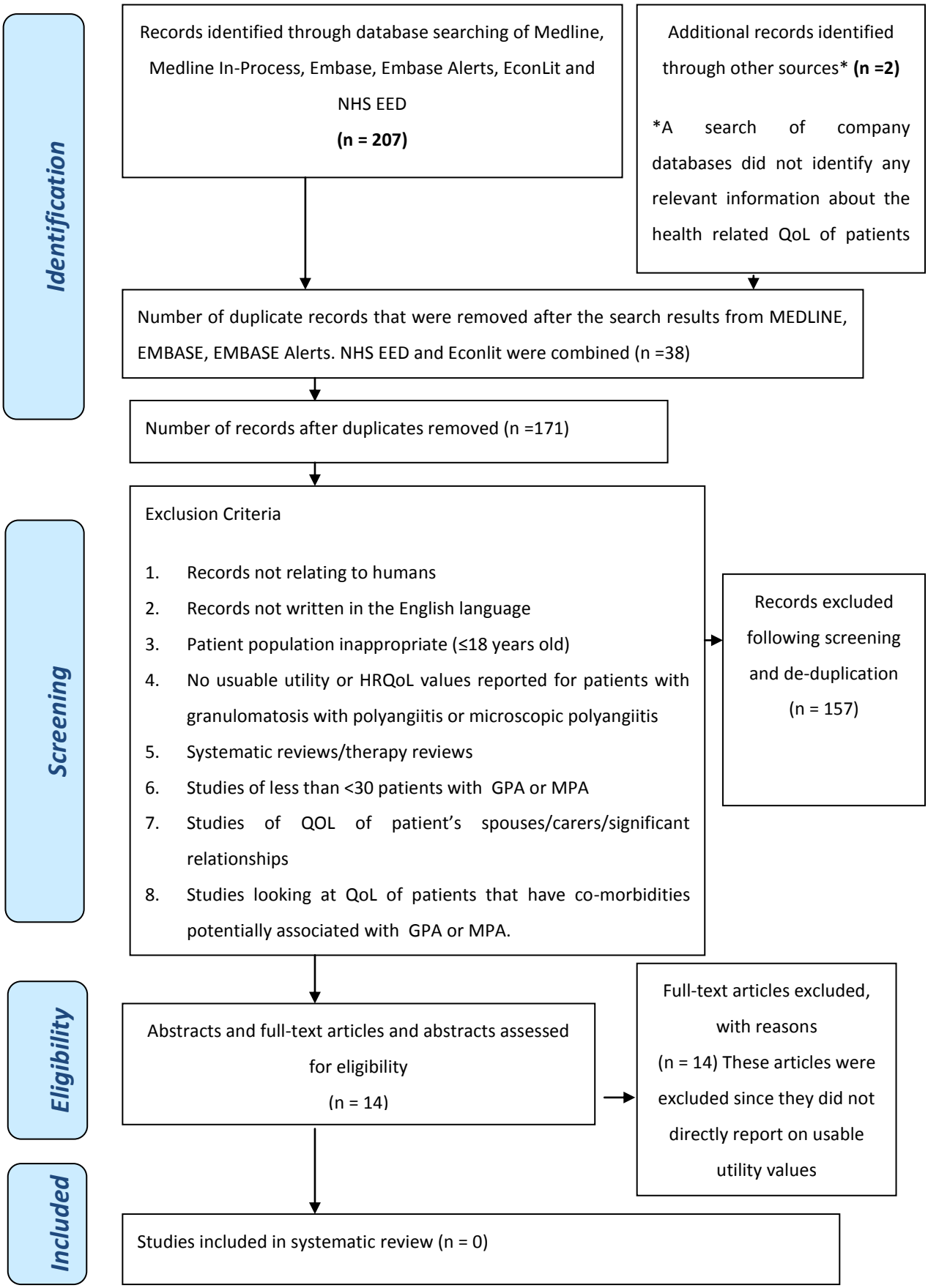
database PubCenter was also searched for any quality of life data, however no records were identified.

Inclusion criteria included any article in any geographical location were utility terms (HRQoL, utility values, utility scores) were reported in the abstract, including any articles where utilities are directly derived using the standard gamble or the time trade off approach or indirectly derived using generic preference instruments (including but not limited to EQ-5D, SF-36, SF-12) or disease specific preference instruments.

Articles were excluded if they were not related to humans, not written in the English language or the patient population was inappropriate (≤18 years old). Studies that included a patient population smaller than 30 subjects were excluded due to likely lack of generalizability and statistical uncertainty. Articles were excluded if they measured the quality of life of co-morbidities potentially associated with MPA or GPA. Systematic reviews were also excluded because any study they refer to will be reported in the original article. Additionally, any articles that reported on the quality of life of the patient's spouse/carer/significant other relationship were excluded. Articles were also excluded if they did not report any usable utility values.

The literature search identified 209 records. Following de-duplication, 171 underwent initial screening. A total of 157 articles were excluded at screening. A total of 14 were identified as being eligible for further assessment against the inclusion/exclusion criteria. These 14 articles were not included in the systematic review since they did not report usable utility values.

Figure 15: Prisma 2009 Flow Diagram for valuation of health effects.



7.4.6 Provide details of the studies in which HRQL is measured.

The systematic literature review did not identify any usable utility values related to patients with either GPA or MPA

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.

Not applicable.

Adverse events

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

In the model we have assumed that adverse events are associated with a disutility. This has been supported by secondary sources outlined in Table 49.

The utility scores of each AE were adjusted to control for baseline-utility of the population of each respective source (see details in 7.4.9).

Table 49: Source of utility data for AEs in the economic model

	Source
Anaemia	Borg et al. 2008 (TTO from [Wilson et al. 2007]) utility of moderate anaemia (HB-level 9-10) - assume age/male as in RAVE, assume score refers to annual utility
Leukopenia	Wang et al. 2008 (SF-36 from [Fortner et al. 2005]) utility of leukopenia, assumed range equals 95% CI, assume same as thrombocytopenia
DVT	Mathias et al 1999; utility of severe DVT sufferers
Dyspnoea	van den Boom et al. 2001 QALY (own health state) of placebo group at baseline, using the Maastricht Utility Measurement Questionnaire, an adapted Dutch translation of the Health Utility Index
Pneumonia	Sisk et al. 1997 QALY of bacteremia case -assume male as in RAVE, assume score reflects annual utility

7.4.9 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?

Evidence shows that using the baseline utility of perfect health (utility=1) to represent not having the health condition overestimates the QoL benefits associated with the disease. This ignores natural decline in mental/physical functions due to age and co-morbidities which also affect QoL. This also

assumes the detriment on QoL associated with a health condition is constant irrespective of age [Ara and Brazier 2010].

All utility scores in the model were adjusted and applied onto a baseline-utility of the general population.

The utility multiplier:

All scores extracted from RAVE and the literature were compared to the utility score of the general population and a multiplier was estimated reflecting the proportional decline in utility from that of the general population:

$$\Phi = UHS/UGP$$

Where φ is the utility multiplier, UHS is the utility score from RAVE or each other source, and UGP is the utility score of the general population from each respective source.

Baseline-utility score

The utility of the general population that applied in the economic model is based on a model developed by Ara and Brazier [2010], which takes in to account of the age and gender distribution of the population (see Equation 1).

Equation 1: General population utility

*General population utility = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * (age)2*

Combination of utility scores for health states and AEs

The multiplicative approach is used to combine the respective utility multipliers for health states and adverse events. The model assumes that patients who have repeated doses of treatment have the same risk of AE at every cycle. Patients who switch treatment have the corresponding AEs of the treatment to which they switch. For instance, if patients switch from RTX to CYC they will experience CYC related adverse events.

The utility per cycle is estimated as:

Equation 2: Utility per cycle

Utility per cycle=U∑(N=j)(Pj*φj)*

Where U is the baseline QoL, j is each adverse event associated with treatment, and P is the risk of each event.

Although in reality, patients can move from non-remission to remission at any time in a 6 month cycle, the model estimates utilities at the end of each cycle. The model similarly does not allow patients to relapse earlier than the end of the cycle.

7.4.10 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The utilities chosen for the economic analysis demonstrate an improved quality of life for patients with controlled disease compared with patients who are not controlled. The source for the quality of life data for the complete remission and non-remission health state are sourced directly from the pivotal study which collected SF-36 data. The utilities have then been mapped using a published model [Ara and Brazier 2008].

We do not have published data to inform the quality of life data for patients in the uncontrolled disease health state. As this health state is to reflect clinical practice where patients no longer receive treatment it is unlikely that HRQL data will be published in this setting. We have assumed a utility value which is worse than ‘non-remission’ by the same absolute amount that ‘non-remission’ is worse than ‘complete remission’.

Table 50: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Source
Complete Remission	0.8366848	Stone et al, 2010
Non-remission	0.754041	Stone et al, 2010
Uncontrolled disease	0.671	Assumption
Death	0	Assumption

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

Please refer to 7.3.5.

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

Due to the wide range of organs which can be involved, patient experiences will be significantly different due to the heterogeneity of the disease. Patients with active disease will be experiencing a range of symptoms (as outlined in 7.4.1). The entry criteria for the RAVE study required patients to have a BVAS/WG score of 3 or more, with a higher score indicating greater disease activity [Stone et al 2001]. In the RAVE study the BVAS/WG range was between 0 and 63, indicating that some patients had significant disease activity when they were recruited. In addition the definition of complete remission in the RAVE study was very strict and not only required a BVAS/WG score of 0 but also a complete taper of steroids. Some patients in the non-remission health state may have symptomatic control but as a result of the strict remission criteria would not be considered to be complete remitters. Due to the time that patients are likely to be in the health state it is likely the HRQL will remain constant.

When in complete remission the symptoms patients experience will have improved. The HRQL for patients in the complete remission health state is constant.

In the uncontrolled disease health state patients are assumed to receive only best supportive care. In this health state patients are assumed to have highly symptomatic disease that will continue to worsen. However, no quality of life

[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.

values are available for this health state and an assumption was made on the utility value.

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

Health effects related to AEs were excluded if they reflected very low incidence (≤2%), were unrelated to the study drug, or were not severe (<grade 3). Diarrhoea is of minimal disutility (utility value of 0.7604 for 7 days) and is excluded from the model [Tengs and Wallace 2000].

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

HRQL is assumed to be constant within each cycle, but varies through the course of the model based on age, health-state membership, and model arm (CYC or RTX).

7.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The adjustments to the utility scores are presented in 7.4.9. No other adjustments were made apart from reflecting:

- The baseline utility
- The combination of the health states and AEs associated with each treatment.

7.5 Resource identification, measurement and valuation

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.**

A systematic review of the literature yielded no data on the medical-resource use and costs of care for patients with ANCA-associated vasculitis.

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

NHS reference costs are more appropriate for costing the management and treatment of the condition. Cost data (excluding drug cost) were largely derived from National Reference Costs, which represent charges paid by those commissioning services to those providing services (hospitals).

Where available, all costs were based on the National Reference Costs for 2009/10.

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 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources.**

A systematic literature review was conducted on 5th February 2013 for data on resource utilization when treating patients with GPA or MPA in the UK.

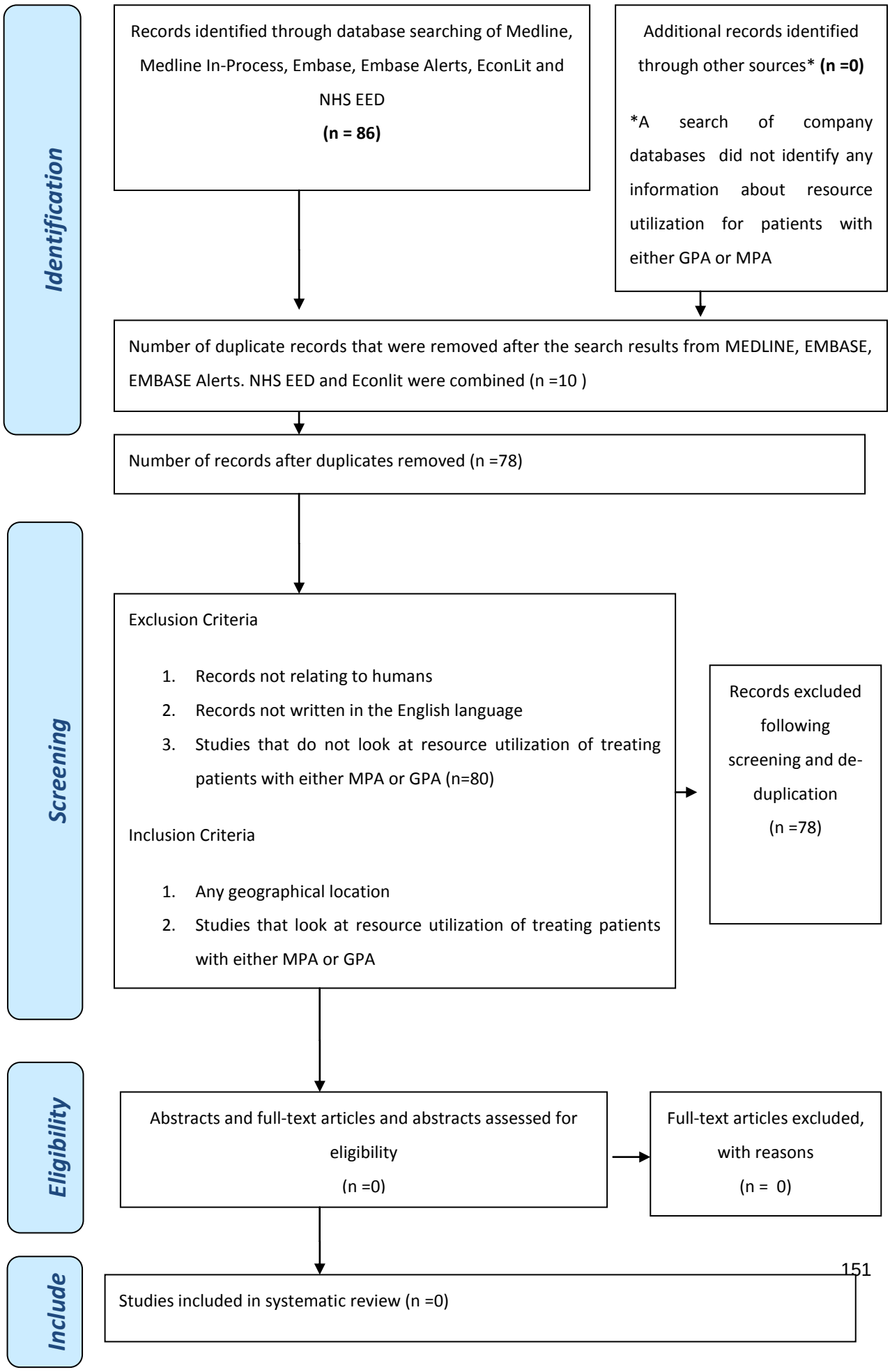
Medline, Medline InProcess, Embase, Embase Alerts, Econlit and NHS EED were searched using the database provider ProQuest.

Articles were excluded if they were not related to humans, not written in the English language, the patient population was inappropriate (less than ≤18 years old), the article did not refer to resource utilization for patients with GPA or MPA.

Inclusion criteria including any article reporting on resource utilization when treating patients with GPA or MPA in any geographical location.

A total of 86 records were retrieved, 10 records were removed following de-duplication. All remaining 78 records were removed during screening. Therefore, no articles were identified about resource utilization for patients receiving treatment for GPA or MPA in the UK or any other geographical location.

Figure 16: Prisma 2009 flow diagram used to identify resource studies



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

Clinical opinion was sought on the likely resource use associated with the management of the disease. The clinician was contacted by email and provided details on the frequency patients would likely receive clinical treatment related to their disease progression.

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 6.2.2.**

The model included the assessment drugs RTX, CYC, and AZA in the base case economic analysis. We have also summarised the treatment costs related to alternative induction therapies methotrexate, and myclophenolate.

Methylprednisone and prednisone are commonly prescribed as part of induction therapy and therefore have been included in the economic analysis as costs [Lapraik et al 2007, Stone et al 2010]. Patients receiving CYC will receive prophylaxis trimethoprim in order to prevent against Pneumocystis jiroveci (formally Pneumocstis carinii) as outlined by the BSR guidelines [Mukhtyar et al 2009].

The total acquisition cost, per cycle, was calculated by multiplying the drug unit cost [British National Formulary, 2011] by the total required dose (mg). Under this assumption no wastage for vial administrations is assumed, however this has been tested in the sensitivity analysis and in section 8.

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[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.

The treatment regimen for trimethoprim was sourced from the BSR guidelines. [Lapraik et al 2007].

Table 51: Unit costs associated with the technology in the economic model

Items	Units Provided	Total Cost	Cost per mg	Source
RTX	10ml (100mg)	£174.63	£1.73	BNF 64
	50ml (500mg)	£873.15	£1.73	BNF 64
CYC	50mg (100 tablets)	£20.20	£0.0040	BNF 64
	500-mg vial	£5.66	£0.0113	BNF 64
	1g vial	£10.66	£0.0107	BNF 64
AZA	25mg (28 tablets)	£6.02	£0.004	BNF 64
	25mg (56 tablets)	£5.04	£0.02	BNF 64
Methylprednisone	1g – vial	£17.3	£0.02	BNF 64
Prednisone	1mg (30 tablets)	£26.7	£0.89	BNF 64
Trimethoprim	200mg (14 tablets)	£0.82	£0.00029	BNF 64
Methotrexate	2.5mg (24 tablets)	£2.39	£0.0398	BNF 64
	2.5 (28 tablets)	£3.27	£0.0467	BNF 64
Mycophenolate Mofetil	500mg (50 tablets)	£31.50	£0.001	BNF 64

The BSA average used in the model has been sourced from Sacco et al. We noted that the BSA average from the RAVE study was 1.99, considerably bigger than previous estimates related to the UK population. The following calculations are based on the patient characteristics in 7.3.6.

Table 52: Mean drug cost per cycle

Items	Average drug cost per cycle	Dosing description	Reference
RTX	£4,689.78	375mg per sqm^2; once weekly for 4 weeks	Stone et al 2010
CYC			
(oral)	£99.15	2mg/kg per day	Mukhtyar et al 2009
(IV pulse)	£110.84	15mg/kg every 2 weeks for the first 3 pulses, followed by infusions every 3 weeks for the next 3-6 pulses.	Mukhtyar et al 2009
AZA	£149.70	2mg/kg per day	Mukhtyar et al 2009
Methylprednisone	£28.73*	1,000mg per infusion every 4 months	Jayne et al 2007

Prednisone	£3,120	RAVE study average	Stone et al 2010
Trimethoprim	£21.38	400mg per day	Mukhtyar et al 2009
Methotrexate	£25.32	22.5mg per week	Mukhtyar et al 2009
Mycophenolate mofetil	£459.90	2000 mg per day	Mukhtyar et al 2009

*The prednisone dose is based on the average from the RAVE study.

Administration Cost

As RTX is given intravenously (IV), the model applies a fixed tariff of £180.29 (£124 inflated to 2012 prices) for the cost per infusion [Barton et al 2004]. Based on the required dose of 4 infusions, the total administration cost per cycle is £685.31, as shown in Table 53.

We have assumed the cost of intravenously administering CYC pulse therapy through an infusion is equivalent to the infusion cost of RTX.

Table 53: Treatment administration cost

Treatment	Cost per infusion	Total cost per cycle
RTX	£180.29	£721.16
CYC	£180.29	£1,802.89

Since the cost of administering methylprednisone in the comparator arm is already included in the cost of infusing RTX, the model conservatively assumes zero cost for the administration of methylprednisone.

<u>Monitoring Cost</u>

The monitoring cost for RTX and IV CYC is assumed to be captured in the administration cost of £171.33 (see Table 53). Similarly to the administration cost, the monitoring cost for methylprednisone is assumed to be zero

The monitoring of oral CYC [Lapraik et al 2007] and AZA [Chakravarty et al 2008 and 2009] is assumed to involve 1-2 blood tests and 1-2 liver function tests (LFTs) a month. The cost of monitoring, per cycle, is shown in Table 54, where the cost per blood test is £3 (NHS reference cost 2009-2010 [DoH 2011] and the cost per LFT is £9 [Barton et al 2004].

Table 54: Treatment monitoring cost

Treatment	Cost per blood test	Cost per LFT	Frequency of blood test (per month)	Frequency of LFT (per month)	Total cost per cycle
CYC and AZA	£3	£9	1-2	1-2	£108

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 6.2.4.**

Outpatient visits

The model assumes patients will require additional treatment and management related to their condition. Based on clinical opinion, the resource use schedule is shown in Table 55.

Table 55: Health sector costs for the clinical management of patients

			Non-remission and uncontrolled disease health states		Remission health state	
Item	**Unit Cost**	**% of patients**	Frequency	Per-cycle cost	Frequency	Per-cycle cost
Outpatient visits						
Rheumatologist	£125.68	0.61	1.5 per wk	£1,331.43	every 3 mo.	£153.21
Nephrologist	£150.53	0.66	1.5 per wk	£1,726.80	every 3 mo.	£198.70
Pulmonologist	£131.12	0.53	1.5 per wk	£1,214.67	every 3 mo.	£139.77
Neurologist	£139.61	0.20	1.5 per wk	£492.59	every 3 mo.	£56.68
Otolaryngologist	£72.99	0.58	1.5 per wk	£740.24	every 3 mo.	£85.18
Ophthalmologist	£73.47	0.26	1.5 per wk	£337.12	every 3 mo.	£38.79
Dermatologist	£86.37	0.202	1.5 per wk	£273.98	every 3 mo.	£31.53
(other body system organ involvement)	£125.68	0.061	1.5 per wk	£133.25	every 3 mo.	£15.33
Labs						
Imaging: chest x-ray or CT scan (for patients with pulmonary symptoms	£27.63	0.53	1.5 per mo.	£58.91	every 1.5 mo.	£58.91
			TOTAL	**£6,309.01**		**£778.10**

The model assumes that the above outpatient cost schedule is not related to AEs – those costs are assumed to be separate.

The allocation of consultant time from each organ speciality was estimated based on the proportion of patients recorded with the corresponding organ involvement at baseline in RAVE. Only organ categories with a greater than 2% of patients were included in the model. For example, only 1 patient was recorded to have gastrointestinal organ involvement in the RAVE trial and therefore the model does not include the cost of a gastroenterologist. All specialists involved in health state management are in accordance with those listed on the RTX SPC.

As lab tests (i.e. blood test and LFTs) have been included in the monitoring cost, the model excludes them from health state resource schedule to avoid double counting.

Best supportive care

Patients with uncontrolled disease are assumed to receive best supportive care only. The cost of best supportive care, per patient, is estimated at £254.06 [SD04A, NHS reference cost 2009-2010] and the frequency of receiving best supportive care is assumed to be same as the non-remission consultant visit schedule i.e. 1.5 times weekly. The total per-cycle cost was calculated by multiplying the NHS reference cost for supportive care by the appropriate number of visits giving a total of £4,415.73. Note that this parameter was tested in a sensitivity analysis.

Table 56: Uncontrolled disease treatment cost

Uncontrolled disease treatment	Unit Cost	Frequency	Total cost (per cycle)
Best Supportive Care	£254.06	1.5 times per week in each 6-month cycle	£4,415.73

7.5.7 **Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. 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 6.2.2.**

The costs of AEs are given per event and are shown in Table 57. The adverse events are treatment-related and are therefore total AE costs vary between the CYC and RTX arms. The model assumes the cohort who has repeated courses of the same treatment has the same risk of AEs at every cycle.

The model assumes zero cost for the management of dyspnoea and diarrhoea as these conditions can be treated with over-the-counter medicines.

Table 57: List of adverse events and summary of costs included in the economic model

Adverse Event	AE probability RTX	AE probability CYC	AE probability AZA	Cost per event	Source
Anaemia	3.5%	3.5%	-	£363.66	NHS reference costs 2009-2010
Leukopenia	2.3%	3.5%	3%	£406.60	NHS reference costs 2009-2010
Pneumonia	2.3%	2.4%	-	£1,224.70	NHS reference costs 2009-2010
DVT	-	1.2%	-	£387.34	NHS reference costs 2009-2010

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.**

None

7.6 Sensitivity analysis

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.**

A list of parameters evaluated via both one-way, scenario and probabilistic sensitivity analysis is provided in this section.

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 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.**

In order to assess the robustness of the results and explore how sensitive the model is when underlying assumptions are changed, the following scenario analyses were carried out

<u>Clinical parameters and variables:</u>

1. Due to the non-inferiority design of the study, we have tested the effect of applying the same complete remission rate to both interventions (RTX & CYC courses of treatment).

2. The base case model has applied diminishing returns to subsequent induction regimens with CYC and RTX. We have tested the effect on ICERs of removing this assumption.

3. The model applies a mortality rate associated with the health state a patient is in, this indirectly applies a small survival benefit for patients in the RTX arm who proportionally spend slightly more time in complete remission. We tested the effect of applying the mean standardised mortality rate for AAV patients across all health states in the model, thereby removing any survival advantage in the model. We also varied the assumed mortality rates for the uncontrolled disease and complete remission health states.

Measurement and valuation of health effects:

4. Utility values for patients in the non-remission and complete remission health state were sourced directly from the clinical trial. An assumption on the utility of patients in the uncontrolled disease health state was made in the economic model. We tested the effect of the uncontrolled disease health state having a utility value of 0.75 and 0.58. I

Resource measurement and valuation:

5. In the base case the administration of RTX and CYC is not associated with wastage. We have tested the effect of assuming 100% wastage (i.e. no vial sharing).

6. The proportion of patients who receive their CYC as pulse IV therapy rather than oral treatment is set at 72% in the base case, based on our own market research. We have tested the model's sensitivity to this assumption by using alternative values of 100%, 50% and 33%.

7. The base case had assumed a BSA more reflective of the UK population based on UK cancer patients [Sacco et al 2010]. We have tested the effect of using the baseline characteristics of patients in the pivotal RAVE study.

8. Health state resource use was informed based on clinical opinion. We note that particularly the uncontrolled disease health state represents a significant proportion of health care spend in the model. We have tested the effect of increasing and decreasing the frequency of consultant visits by 50% across all health states.

9. We have explored the impact of RTX patients receiving the 1,000mg dose on day 1 and 15. We note that this course is associated with 2 less infusions and therefore a reduced administration cost.

Treatment pathway

We acknowledge that the greatest source of structural uncertainty in the model is the assumed treatment pathway. The model currently assumes that due to the cumulative toxicity effects of continued CYC, it is reasonable to apply a 'cap' on the number of courses of CYC – this assumption has been supported by expert clinical opinion.

We have therefore tested the following scenarios relating to the use of CYC in the model:

10. One course of CYC in the standard of care arm, with no additional courses of CYC in the intervention arm (i.e. just two RTX cycles then best supportive care).

11. Two courses of CYC in the standard of care arm, with no additional courses in the intervention arm.

12. Two courses of CYC in the intervention arm.

13. One course of CYC in both treatment arms.

Informed by clinical opinion we have assumed RTX will be administered for up to two courses of treatment. However, receiving a second course is restricted to patients who failed to achieve complete remission as defined in the RAVE study. We note this may not align with all clinical interpretations of which patients should receive treatment under the proposed licence of induction therapy, and therefore we have tested this assumption.

The following scenarios have been tested relating to the retreatment of RTX, the transition probabilities in the base case have been applied to the below scenarios:

14. No patients in the intervention arm receive a second course of RTX.

15. All patients receive a second course of RTX following relapse.

16. Only patients who relapse are eligible for a second course of RTX treatment.

Subgroup Analysis

We understand that some clinicians may consider rituximab as an alternative induction agent in the first line setting while some may reserve it for the treatment of relapsing patients where it is proven to be significantly better than CYC [Stone et al 2010]. We have undertaken subgroup analyses using the newly diagnosed and relapsing patient populations from RAVE to test the sensitivity to the different clinical inputs.

We note that while the subgroup analyses were pre-specified in the RAVE study, the patient numbers are very low in each arm (n≈50). We note one particular input the relapse rate for RTX patients in the relapsing subgroup is significantly higher. We are not aware of the clinical rational behind the higher relapse rate as patients have not been exposed to RTX.

The scenarios and the clinical inputs are outlined below. In addition to the subgroup analysis we have tested the number of CYC courses in the intervention arm.

Table 58: Subgroup (newly diagnosed patients) transition probabilities

Transition Probabilities	Value	Source
Newly diagnosed Subgroup		
Non-remission to complete remission (CYC_1)	0.6458	Stone et al 2010
Non-remission to complete remission (CYC_2)	0.4200	Stone et al 2010
Non-remission to complete remission (RTX_1)	0.6042	Stone et al 2010
Non-remission to complete remission (RTX_2)	0.3929	Assumption
Relapse rates		
Constant rate of relapse (CYC)	0.0704	Stone et al 2010
Constant rate of relapse (RTX)	0.1199	Stone et al 2010

Table 59: Subgroup (relapsing patients) transition probabilities

Transition Probabilities	Value	Source
Relapsed patient Subgroup		
Non-remission to complete remission (CYC_1)	0.4200	Stone et al 2010
Non-remission to complete remission (CYC_2)	0.3065	Hoffman et al 1992
Non-remission to complete remission (RTX_1)	0.6667	Stone et al 2010
Non-remission to complete remission (RTX_2)	0.4335	Assumption
Relapse rates		
Constant rate of relapse (CYC)	0.1668	Stone et al 2010
Constant rate of relapse (RTX)	0.3	Stone et al 2010

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 6.3.6, 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 probability sensitivity analysis was undertaken as part of the economic evaluation. An assumption of 1,000 samples was used. The table below summarizes the assumptions relating to distributions and ranges of each parameter included within the PSA analysis.

Beta distributions are applied around the following parameters to reflect parameter uncertainty in the model. (See Table 60).

Table 60: Probabilistic sensitivity analysis inputs

Variable	Value	Probabilistic	Distribution (range)
Remission rates			
RTX_1	0.6364	0.6496	Beta
CYC_1	0.5306	0.4312	Beta
RTX_2	0.4138	0.4779	Beta
CYC_2	0.4200	0.4815	Beta
Relapse rates			
RTX	0.1647	0.1410	Beta
CYC	0.1496	0.1202	Beta
Both treatments, health state utility: utilities			
uRemission	0.84	0.86	Beta
uNonRemission	0.75	0.77	Beta
uUncontrolled Disease	0.67	0.69	-
Utility whilst having an AEs			
uAnaemia	0.63	0.85	Beta
uLeukopenia	0.70	0.41	Beta
uDVT	0.69	0.86	Beta
uDyspnoea	0.82	0.84	Beta
uPneumonia	0.21	0.18	Beta
Test costs			
Blood test	3	4.65	Lognormal
Liver function tests	8.99	13.96	-
Consultant Rheumatologist	125.68	128.08	Lognormal
Consultant Nephrologist	150.53	156.59	Lognormal
Consultant Pulmonologist	131.12	144.27	Lognormal
Consultant Neurologist	139.61	163.40	Lognormal
Consultant Otolaryngologist	72.99	67.90	Lognormal
Consultant Ophthalmologist	73.47	69.56	Lognormal
Consultant Dermatologist	86.37	107.98	Lognormal
Imaging: CXR or chest CT (pts with pulmonary symptoms)	29.08	45.09	Lognormal
Costs of AE (cost per event)			
Anaemia	363.66	433.39	Lognormal
Leukopenia	406.60	423.52	Lognormal
DVT	387.34	327.41	Lognormal
Pneumonia	1224.70	1121.63	Lognormal
Cost of best supportive care (unit cost)	254.06	380.07	Lognormal

7.7 Results

Clinical outcomes from the model

7.7.1 **For the outcomes highlighted in the decision problem (see section 4), 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 has incorporated the key clinical inputs from the RAVE study including adverse events, HRQL data, remission rates, and relapse rates. Secondary sources were used to populate the mortality outcomes for the model as this was not possible from the low event rate in the RAVE study.

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.**

A Markov trace has not been tabled in the submission due to the large number of cycles in the model. This can be produced on request, but is already available within the economic model submitted alongside this submission.

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 Markov trace was used to calculate QALYs accrued in each health state.

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:**

Table 61: Model outputs for CYC

Outcome	LY	QALY	Cost (£)
Non-remission	0.93797	0.7036	£20,597.57
Complete Remission	2.51463	2.0664	£4,977.62
Uncontrolled disease	8.3286	5.2819	£73,511.78

Table 62: Model outputs for RTX

Outcome	LY	QALY	Cost (£)
Non-remission	1.0946	0.8202	£29,331.70
Complete Remission	3.25825	2.6752	£5,608.88
Uncontrolled disease	7.46577	4.7173	£65,933.60

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 63: Summary of QALY gain by health state

Health state	QALY intervention	QALY comparator	Increment	Absolute increment	% absolute increment
Non-remission	0.8202	0.7036	0.1166	0.1166	9%
Complete remission	2.6752	2.0664	0.6088	0.6088	47%
Uncontrolled disease	4.7173	5.2819	-0.5646	0.5646	44%
Adverse events	-0.0302	-0.0333	0.0031	0.0031	0%
Total	8.1826	8.0186	0.1639	1.2931	100%

Table 64: Summary of costs by health state

Health state	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Non-remission	£29,331.70	£20,597.57	£8,734.13	£8,734.13	52%
Complete remission	£5,608.88	£4,977.62	£631.26	£631.26	4%
Uncontrolled disease	£65,933.60	£73,511.78	-£7,578.18	£7,578.18	44%
Total	£100,874.18	£99,086.96	£1,787.22	£16,943.57	100%

Table 65: Summary of predicted resource use by category of cost

Item	Cost intervention	Cost comparator	Increment	Absolute increment	% absolute increment
Technology cost	£13,521.1	£6,594.49	£6,926.61	£6926.61	91%
Administration cost	£2,067.04	£2,435.13	-£368.09	£368.09	5%
Monitoring cost	£294.00	599.89	-£305.89	£305.89	4%
Adverse events	£149.42	£175.78	-£26.36	£26.36	0%
Total	£16,031.60	£9,805.29	£6,226.27	£7,626.95	100%

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 summary of the total costs, outcomes (QALYs gained) and incremental cost effectiveness ratio (ICER) for our base case analysis can be found in Table 66.

Table 66: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) incremental (QALYs)
RTX	£100,874	11.82	8.18				
CYC	£99,087	11.78	8.02	£1,787	0.042	0.1640	£10,898.24

The ICER estimated for RTX is well within the range normally considered cost-effective by NICE. We note the results are reasonably robust to clinical and cost parameter uncertainty.

We strongly believe that patients with ANCA-associated vasculitis need an effective alternative induction therapy to the current standard of care. Our clinical results indicate that RTX is as effective as current therapy and would greatly improve the long term outcomes of patients with this relapsing remitting disease.

Sensitivity analyses

7.7.7 **Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

Table 67: Deterministic sensitivity analysis results

Scenario/parameter		Base Case	Tested values	ICER
CYC complete remission rate is equal to RTX		0.5306	0.6364	£27,804.90
Removal of degradation rate for CYC and RTX		CYC_2 - 0.4200	CYC_2 - 0.5306	£14,856.55
		RTX – 0.4138	RTX_2- 0.6364	
Standardised mortality ratio – set equal in all health states	NR CR UD	4.8 4.32 5.28	4.8	£10,659.38
Standardised mortality ratio – improve in CR and worsen in UD	NR CR UD	4.8 4.32 5.28	4.8 3.36 6.24	£11,118.98
Uncontrolled disease utility		0.67	0.75	£18,506.02
			0.58	£7,451.87
IV wastage		None	100%	£11,098.45
% of IV pulse therapy		72%	33%	£15,076.86
			50%	£13,255.41
			100%	£7,898.20
Patient mean weight		67kg	87kg	£14,741.39
Number of RTX infusions		4	2	£7,945.66
Frequency of consultant visits (per cycle)		As per section 7.5.6	+50%	RTX dominates
			-50%	£24,773.12

NR, non-remitters; CR, complete-remission; UD, uncontrolled disease

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

In order to explore uncertainty around the model's key variables in the base case, probabilistic sensitivity analysis was performed (1,000 samples). Figure 17 and Figure 18 present the cost-effectiveness scatterplot and the cost-effectiveness acceptability curve (CEAC).

The probability of rituximab being cost-effective at the £20,000 and £30,000 threshold is estimated at 57.8% and 64.6% respectively. The CEAC's unusual shape is attributed to the relatively large number of PSA trials in which the RTX arm was estimated to be cost-saving and associated with superior QALY gain compared with the CYC arm.

Figure 17: PSA CEAC

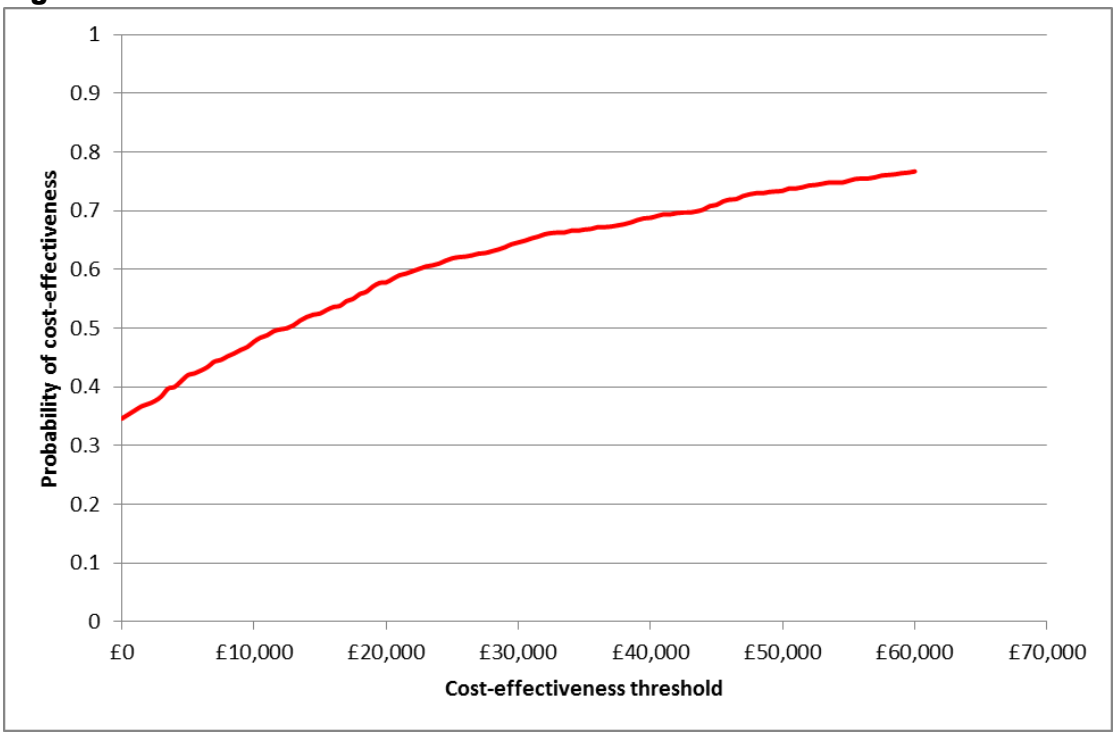
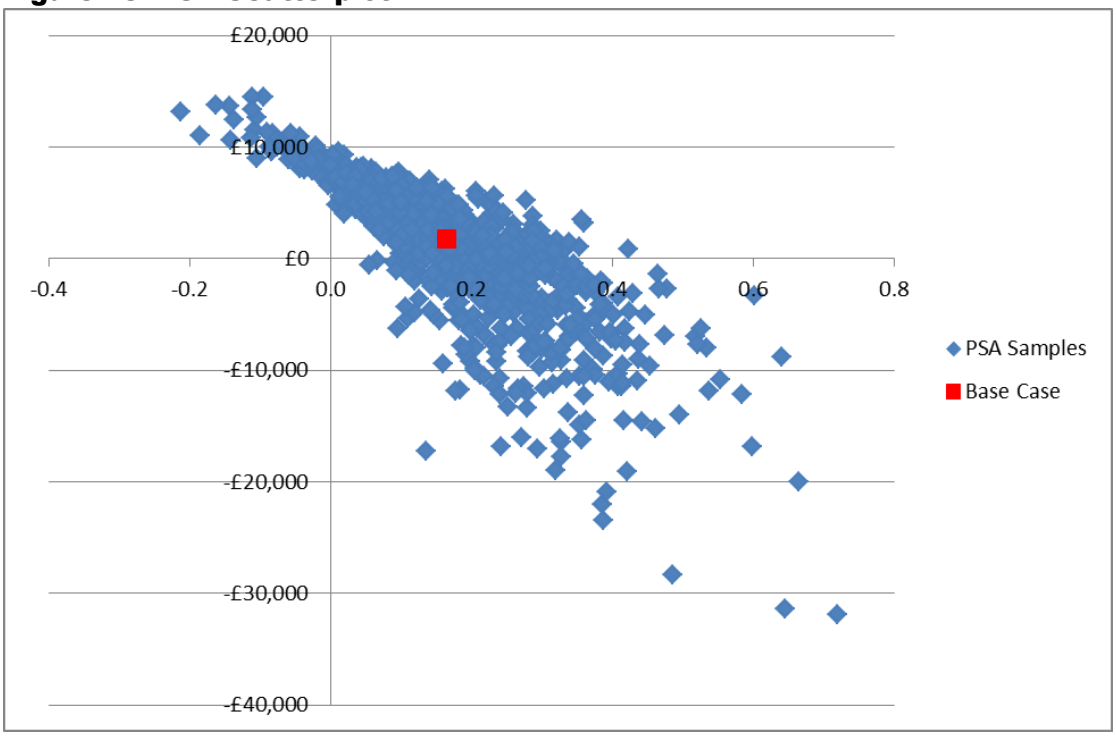


Figure 18: PSA Scatterplot



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The scenario analysis results are presented below. We note due to the small differences in costs and benefits the results are particularly sensitive to changes in the treatment sequence.

Table 68: Scenario analysis results

Parameter/attribute	Base Case	Tested values	ICER
Number of CYC courses	SoC – 2 Intervention – 1	SoC – 1 Intervention – 0	£26,990.81
		SoC – 2 Intervention – 0	RTX dominated
		SoC – 2 Intervention – 2	£3,822.90
		SoC – 1 Intervention – 1	£2,746.40
Which patients are offered a second course of RTX?	Non-remitters	No patients	£5,770.82
		Relapsing patients only	£12,659.60
		All patients	£13,792.84

Subgroup Analysis

Table 69: Subgroup analysis results

Subgroup	Number of CYC courses	ICER	Discussion
Newly diagnosed patients	SoC – 2 Intervention – 1	£60,435.44	Base case # of CYC cycles
	SoC – 2 Intervention – 2	£5,985.71	More plausible # of CYC cycles for this subgroup
Relapsing patients	SoC – 2 Intervention – 1	£47,408.51	Base case # of CYC cycles
	SoC – 0 Intervention – 0	£19,998.08	More plausible # of CYC cycles for this subgroup

7.7.10 What were the main findings of each of the sensitivity analyses?

Overall the economic model is robust to the main parameters in the model. Changes in the cost parameters including the health state costs, patient characteristics, and the proportion of patients who receive IV CYC compared to oral therapy have very little effect on the overall ICER.

As the RAVE study was a non-inferiority study, the impact of assuming equal efficacy was tested in the model. This is likely to be a conservative assumption as the results of the RAVE study did show the trend of improved remission rates in the RTX arm. However, even when the CYC remission rate was assumed equal to that of CYC the overall result remained cost-effective.

The assumed frequency of consultant visits does have an impact on the ICER. We note there is no published evidence to inform this assumption and that due to the large variation in organ involvement a number of clinicians could be involved in the management of a patient. When the frequency of consultation visits was tested over a range of ±50%, the ICER remained below the cost-effectiveness threshold.

When more CYC courses are assumed to be administered alongside RTX, the clinical outcomes for patients greatly improves, decreasing the ICER. In the base case we have conservatively assumed that patients will only receive one course of CYC in the RTX arm. We note that if clinical practice

recommended RTX to be administered only after the use of CYC, then the number of CYC courses should be considered equal across the treatment arms. Under this assumption RTX is a cost-effective use of NHS resources.

The uncertainty related to the second course of RTX did not have a noteworthy effect on the ICER.

We have presented additional analyses using the pre-specified subgroups from the RAVE study, however due to the low patient numbers in each arm (approximately 50 in each arm), the results should be interpreted with a degree of caution. Our results show that when using the base case set of assumptions (with respect to the expected number of cycles of CYC administered) neither the newly diagnosed or relapsing subgroup of patients appears cost-effective. We however believe that for the newly diagnosed patient group, it would be more reasonable to consider all patients would receive two courses of CYC. When this assumption is applied the ICER drops considerably, to £5,986. In the relapsing patient subgroup, when we applied the assumption that patients who have failed previous induction therapy have no further tolerance to additional CYC courses, the ICER was estimated at £19,998.

7.7.11 What are the key drivers of the cost-effectiveness results?

As discussed in the sensitivity analysis, due to the similar efficacy of RTX and CYC in inducing remission, the assumption surrounding the likely treatment sequence is a key driver in the outcome of the result. We have tested a number of scenarios replicating the likely treatment path. However, we acknowledge this is difficult in a disease where treatment strategies are evolving, notably in the treatment of flares or maintenance therapy. Our analysis suggests, however, for most reasonable treatment pathways explored in the base case, that the incremental health spend associated with RTX represents good value for money.

The other notable driver in the model is the assumed cost offsets in the future. We have made an assumption within the model to reflect clinical practice that patients will eventually exhaust all treatment options and go on to receive best

supportive care. The additional costs accrued in this health state offset some of the additional costs with administering RTX. However when testing the value of the supportive health care costs the model is not overly sensitive.

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.**

The economic model was validated by an independent reviewer not involved in the original development of the economic model. The model was reconstructed using TreeAge to compare the incremental costs and QALYs. Only modest differences were observed between the two models which was likely due to the differences in the how the software calculates half cycle correction.

7.9 Subgroup analysis

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 5.3.7.**

At the NICE scoping workshop there was support for a subgroup analyses on the small proportion of patients who are considered to be intolerant to CYC. This group has been identified due to the limited effective alternative induction agents for patients who cannot receive CYC. Clinical opinion has suggested that for patients who cannot tolerate CYC there is a high unmet need for a more effective alternative therapy.

As outlined in the innovation section 4.1.1, a proportion of patients will be unable to receive CYC due to the infertility side effects associated with continued treatment. This poses a difficult decision for patients looking at having children with such a serious disease.

7.9.2 **Please clearly define the characteristics of patients in the subgroup.**

The scope of the appraisal identified a small subgroup of patients who are considered to be intolerant to CYC. This group of patients has been considered based on UK clinical experience, and is thought to represent less than 10% of all eligible patients. It is well known that while highly effective, CYC is associated with significant side effects including but not limited to bladder cancer and infertility. This latter side effect in particular has a significant effect on a small proportion of patients who are considering having children.

We have undertaken a subgroup analysis in order to identify the cohort of patients that are most reflective of the subgroup of patients intolerant to CYC. The RAVE study included a pre-specified subgroup of patients, with newly diagnosed disease that had yet to receive induction therapy. Due to the limited data available for patients truly intolerant to CYC, we have assumed that those patients with newly diagnosed disease who are yet to receive induction therapy are most reflective of the patients intolerant to CYC. We recognise the limitation in this approach, however in lieu of any available evidence this was considered the best available assumption to inform this analysis.

In the intervention arm patients are assumed to receive RTX in line with the base case, but following relapse patients are assumed to transition straight to the uncontrolled disease health state after exhausting all treatment options to receive best supportive care. In the standard of care arm we have assumed that patients receive only best supportive care. This assumption has been made due to the paucity of data related to alternative induction agents.

7.9.3 Please describe how the statistical analysis was undertaken.

The subgroup of newly diagnosed patients was pre-specified in the RAVE study (refer to 6.3.7).

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Table 70: Cost-effectiveness results for newly-diagnosed patients subgroup

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER (£) incremental (QALYs)
RTX	£100,066	11.77	8.01				
CYC	£102,720	11.63	7.47	-£2,654	0.139	0.543	RTX dominates

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 4.**

In accordance with the proposed licence we have considered the cost-effectiveness of RTX as an alternative induction agent in severe ANCA-associated vasculitis. For this reason we did not present an analysis of the relapsing disease subgroup in the RAVE study.

As described in the clinical section, patients with relapsing disease had a significantly better response associated with RTX than with CYC. However we have presented the data using the ITT population from RAVE instead to demonstrate in line with the scope of the NICE appraisal that RTX is an effective treatment in comparison to CYC.

7.10 Interpretation of economic evidence

7.10.1 **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

Our systematic review did not identify any other health economic models for the treatment of severe ANCA-associated vasculitis. As outlined in 7.2, the results of our model can be considered as a de novo analysis.

7.10.2 **Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?**

Yes.

7.10.3 **What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

Strengths

The key clinical inputs to the model, the complete remission rates are directly sourced from the pivotal study evaluating the effectiveness of RTX in severe AAV.

Health related quality of life values are sourced from the RAVE study for two of the health states within the model. The utility values were mapped from SF-36 to EQ-5D using a published formula previously assessed within NICE appraisals.

All major model parameters are included within the PSA providing a robust illustration of the uncertainty surrounding the deterministic values of the ICER for RTX.

The model captures the effectiveness of RTX in addition to standard of care to reflect clinical practice, rather than assuming RTX would substitute for CYC.

Weaknesses

We have identified the uncontrolled disease health state based on dialogue with clinical experts and not from the RAVE study. We have therefore relied on assumptions regarding resource use and quality of life for this patient group.

There are evolving practices relating to the treatment of severe AAV. We know that different treatment regimens that fall outside the scope of the NICE appraisal are currently used in NHS clinical practice, we have not been able to evaluate the effectiveness of maintenance therapy RTX or the dosing regimen of 1,000mg of RTX in days 1 and 15.

No mortality data specific to the treatments in the disease could be sourced. Mortality rates in the model are based on a secondary source which estimates the mortality rate of all AAV patients against the whole population.

7.10.4 **There are only two RCTs that evaluate the effectiveness of RTX in severe AAV, only one of these studies relates to the the use of RTX as an alternative induction therapy rather than in addition to CYC therapy. What further analyses could be**

undertaken to enhance the robustness/completeness of the results?

We would suggest the following:

- A study which evaluated the effectiveness of maintenance therapy RTX compared to CYC.
- A long term study which evaluated the health and resource burden associated with the care of patients in AAV who are not in remission.
- An evaluation of the mortality risks associated with poor disease control.
- A real world estimate on the actual dose of CYC administered to AAV patients in the UK.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

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.

We expect that based on current epidemiology data that up to 1,473 patients would be eligible for treatment with RTX. This is based on the prevalence data reported in Watts et al 2012. We have assumed in line with clinical opinion that one third of patients would have severe disease in line with the definition used in RAVE.

Year	2014	2015	2016	2017	2018
Eligible patients	1,485	1,497	1,509	1,521	1,532

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

The market research undertaken has indicated that approximately 41% of ANCA-associated vasculitis patients will require induction therapy and of those patients approximately 92% will receive treatment.

8.3 What assumption(s) were made about market share (when relevant)?

We have limited evidence to inform the likely market share RTX will gain in the AAV market. We have therefore presented the most optimistic sales forecast assuming all eligible patients would receive treatment with RTX, in 8.7 we outline the reasons why this is likely to be an overestimate..

Table 71: RTX market share

Year	2014	2015	2016	2017	2018
RTX	25%	75%	100%	100%	100%

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).

RTX is administered through intravenous infusion and will therefore require resources associated with the delivery of the treatment.

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?

All unit costs are sourced from the British National Formulary. The annual cost for RTX is associated with wastage.

8.6 Were there any estimates of resource savings? If so, what were they?

No

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact presented below should be considered as the upper bound. We note there are several reasons why the actual impact would be lower than the estimate presented below:

- The market share of RTX is unlikely to be 100% of the market
- Biosimilar RTX is expected to launch in 2016 and will likely further reduce the market share of branded RTX (MabThera®).

Table 72. Estimated budget impact

2014	2015	2016	2017	2018
£2,380,700	£7,200,642	£9,677,472	£9,752,286	£9,826,231

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

The draft SPC is attached with the references.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.
-

Medline, Medline In-Process, Embase, Embase Alerts, were searched using the database provider ProQuest. Databases Medline and Medline In-Process have been amalgamated in ProQuest and therefore the user needs only to make one selection to search both databases. This differs to other database providers such as OVID where Medline and Medline In-Process are listed as two separate databases.

PubMed and The Cochrane Library were also searched.

10.2.2 The date on which the search was conducted.

ProQuest was searched on 11 March 2013, The Cochrane Library was searched on 08 March 2013, PubMed was searched on 18 January 2013

10.2.3 The date span of the search.

No date limiters were used in these search strategies.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 73: Strategy used to search The Cochrane Library

Set	Key Terms	Results
#1	MeSH descriptor: [Microscopic Polyangiitis] explode all trees	7
#2	MeSH descriptor: [Wegener Granulomatosis] 3 tree(s) exploded	40
#3	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] 2 tree(s) exploded	59
#4	(microscopic near/3 polyarteritis) or (microsopic near/3 polyangiitis)	9
#5	(wegener* near/3 granulomatosis) or (granulomatosis near/3 polyangiitis) or (wegener* near/3 disease)	90
#6	anca near/3 associated near/3 vascul*	46
#7	#1 or #2 or #3 or #4 or #5 or #6	136

Table 74: Strategy used to search Medline, Medline In-Process, Embase and Embase Alerts

Set#	Searched for	Databases	Results
S25	s24 AND (human(yes) AND la.exact("English"))	Embase®, Embase® Alert, MEDLINE®	750°
S24	s23	Embase®, Embase® Alert, MEDLINE®	950°
S23	s19 and s22	Embase®, Embase® Alert, MEDLINE®	1149
S22	s20 or s21	Embase®, Embase® Alert, MEDLINE®	43473
S21	RTX	Embase®, Embase® Alert, MEDLINE®	43473
S20	MJEMB.EXACT.EXPLODE("RTX")	Embase®, Embase® Alert, MEDLINE®	7874
S19	s18 or s12 or s6	Embase®, Embase® Alert, MEDLINE®	21104*
S18	s16 or s17	Embase®, Embase® Alert, MEDLINE®	2731°
S17	s14 or s15	Embase®, Embase® Alert, MEDLINE®	2688°
S16	s13 or s15	Embase®, Embase® Alert, MEDLINE®	2731°
S15	anca near/3 associated near/3 vascul*	Embase®, Embase® Alert, MEDLINE®	2688°
S14	MJEMB.EXACT.EXPLODE("ANCA associated vasculitis")	Embase®, Embase® Alert, MEDLINE®	881°
S13	MJMESH.EXACT("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis")	Embase®, Embase® Alert, MEDLINE®	287°
S12	s10 or s11	Embase®, Embase® Alert, MEDLINE®	912°
S11	s7 or s9	Embase®, Embase® Alert, MEDLINE®	627°
S10	s7 or s8	Embase®, Embase® Alert, MEDLINE®	862°
S9	MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.20.111.193.750") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.940.897.249.500") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.253.329.600") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.10.228.140.300.275.600")	Embase®, Embase® Alert, MEDLINE®	128°
S8	MJEMB.EXACT.EXPLODE("microscopic polyangiitis")	Embase®, Embase® Alert, MEDLINE®	387°
S7	(microscopic near/3 polyarteritis) OR (microsopic near/3 polyangiitis)	Embase®, Embase® Alert, MEDLINE®	501°
S6	s4 or s5	Embase®, Embase® Alert,	18151*

		MEDLINE®	
S5	s1 or s3	Embase®, Embase® Alert, MEDLINE®	18151*
S4	s1 or s2	Embase®, Embase® Alert, MEDLINE®	18151*
S3	MJEMB.EXACT.EXPLODE("Wegener granulomatosis")	Embase®, Embase® Alert, MEDLINE®	6083*
S2	MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.14.907.940.897.249.750") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.20.111.193.875") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.08.381.483.950")	Embase®, Embase® Alert, MEDLINE®	4230°
S1	(wegener* NEAR/3 granulomatosis) OR (granulomatosis NEAR/3 polyangiitis) OR (wegener* NEAR/3 disease)	Embase®, Embase® Alert, MEDLINE®	18151*

Table 75: Strategy used to Search PubMed

Set	Key Terms	Results
S1	RTX (or RTX) And (vasculitis) OR (anca associated vasculitis) OR (anca) OR (AAV) OR (Wegener) OR (Granulomatosis Polyangiitis) OR (Microscopic Polyangiitis) (MPA)	134

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

A search of Roche's internal literature database PubCenter on 28/01/2013 yielded no additional results. PubCenter contains publically available articles along with company presented posters and abstracts.

10.2.6 The inclusion and exclusion criteria.

Exclusion Criteria for the clinical searches

- Records not relating to humans
- Records not written in the English language

10.2.7 The data abstraction strategy.

Data were exported from ProQuest into an Acrobat PDF file.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

Table 76: Quality assessment results for RCTs

RAVE study

Study question	How is the question addressed in the study?	Grade
Was randomisation carried out appropriately?	Treatment assignment minimized bias to assure the comparability of treatment groups: Randomisation was stratified by clinical study centre and ANCA type (PR3 or MPO), and the two treatment groups were shown to be well balanced with respect to most baseline characteristics. Participants were assigned a unique participant number, sequentially according to a randomisation schedule provided to the site pharmacist	**yes**
Was the concealment of treatment allocation adequate?	Participants were assigned a unique participant number, sequentially according to a randomisation schedule provided to the site pharmacist	**yes**
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The method of patient selection adequately assured that the patients enrolled had the condition being studied (i.e., severe AAV). The demographic and disease characteristics were similar between the treatment arms in terms of age at disease onset, gender, primary race, and ethnicity, diagnosis of GPA (WG), and MPA. Baseline disease characteristics were generally balanced between the two treatment arms with the exception of estimated creatinine clearance.	**yes**
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)?	Patients, investigators, and Sponsor personnel were blinded to treatment assignment Certain study assessments and safety events reporting were performed by a safety officer at each site, different from the primary investigator, in order to minimize opportunities for unblinding Patients were required to wear hats during visits to conceal any signs of alopecia, an adverse drug reaction associated with CYC treatment.	**yes**
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Patient disposition was similar between the groups. Eighty-three percent of patients in the RTX arm and 81% of patients in the CYC arm completed 6 months of the study without crossover or change to BMJ. The two treatment arms were similar in the proportion of patients who discontinued by 6 months, crossed over, or were on BMJ by 6 months	**yes**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No evidence, however 18 month long-term follow-up has not yet been reported in full (abstract only)	**yes**

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The study objectives, non-inferiority margin, and method of analysis were prospectively defined in the protocol and the statistical analysis plan, and were described in the CSR Study used the ITT, Per Protocol (PP), and Safety analysis populations ITT analysis population included all randomised and treated patients, used in the analysis of efficacy endpoints according to the treatment assigned and not the treatment actually received, if different The PP analysis population was a subset of the ITT analysis population. Patients excluded from the PP analysis population were identified prior to study unblinding. Analysis of the PP analysis population was used as a supporting analysis to the ITT analysis The study design permitted a valid comparison with an active control (CYC) with a well-defined treatment effect	**yes**

RITUXVAS study

Study question	How is the question addressed in the study?	Grade
Was randomisation carried out appropriately?	Randomisation was performed with the use of a computer minimization algorithm to maintain concealment of study-group assignments from the investigators. This algorithm was stratified according to the patients' age, diagnosis, and baseline renal function. A 3:1 ratio for random assignment was used	**yes**
Was the concealment of treatment allocation adequate?	Randomisation was performed with the use of a computer minimization algorithm to maintain concealment of study-group assignments from the investigators	**yes**
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No major imbalances at baseline were seen between the two groups, with the exception of a greater proportion of renal-limited vasculitis patients in the CYC group and a greater proportion of patients requiring dialysis in the RTX + low-dose CYC group. The use of plasma exchange was balanced between groups. Overall, as expected for this population, renal function was generally poor in both groups at study entry. The use of plasma exchange was balanced between the groups	**yes**

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)?	Open-label study	**N/A**
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No patients were lost to follow-up in RITUXVAS. Six patients (18%) in the RTX + low-dose CYC group and 1 patient (9%) in the CYC group had died by 12 months. One other patient in the CYC group died at 19 months (a total of 18% of patients died in the CYC group)	**yes**
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	**yes**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Analyses were performed on an intention-to-treat basis. All analyses included 44 patients. Missing laboratory data (e.g., the GFR) for patients who died were imputed with the use of the last value-carried-forward method to provide a conservative estimate of effects	**yes**

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

10.4.1 The specific databases searched and the service provider used.

There were no indirect or mixed treatment comparisons.

10.5 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.5.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Both Randomised Controlled Trials (RCTs) and non-RCTs were included in the original searches in 10.2 (rather than separate searches for both categories)

10.6 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

10.6.2 The date on which the search was conducted.

The adverse events in the submission were based on the safety profile of rituximab (RTX) in the treatment of adults with severe anti-neutrophil cytoplasmic antibody (ANCA)−associated vasculitis (AAV) as presented in the Summary of Clinical Safety (SCS) provided to the EMA to support the licence application for RTX in AAV. The rationale is that these data were extracted, reviewed and effectively summarised to satisfy all regulatory requirements. Therefore no separate search was performed.

10.7 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.7.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Medline, Medline In-Process, Embase, Embase Alerts, were searched using the database provider ProQuest. Databases Medline and Medline In-Process have been amalgamated in ProQuest and therefore the user needs only to make one selection to search both databases. This differs to other database

providers such as OVID where Medline and Medline In-Process are listed as two separate databases.

Econlit was searched and is provided by the American Economic Association. NHS EED was also searched and is provided by the Centre for Reviews and Dissemination.

10.7.2 The date on which the search was conducted.

The systematic literature search was conducted on 05/02/2013.

10.7.3 The date span of the search.

No date limiter was used in any search strategy

10.7.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 77: Search strategy used to search Medline, Medline In-Process, Embase and Embase Alerts

Set#	Searched for	Databases	Results
S1	MJEMB.EXACT.EXPLODE("quality adjusted life year")	Embase®, Embase® Alert, MEDLINE®	762
S2	MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:L.01.280.975.475.700") OR MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:N.01.224.935.530.700") OR MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:E.05.318.740.100.500.700")	Embase®, Embase® Alert, MEDLINE®	1278
S3	s1 or s2	Embase®, Embase® Alert, MEDLINE®	1580
S4	quality near/5 adjusted near/5 life near/5 year*	Embase®, Embase® Alert, MEDLINE®	20745
S5	s3 or s4	Embase®, Embase® Alert, MEDLINE®	20745
S6	MJMESH.EXACT.EXPLODE("Economics, Pharmaceutical") OR MJMESH.EXACT.EXPLODE("Health Care Sector:N.03.219.650") OR MJMESH.EXACT.EXPLODE("Costs and Cost Analysis") OR (MJMESH.EXACT.EXPLODE("Models, Econometric:N.05.715.360.750.530.500.500") OR MJMESH.EXACT.EXPLODE("Models, Economic:N.06.850.520.830.500.600") OR MJMESH.EXACT.EXPLODE("Models, Economic:E.05.599.835.890") OR MJMESH.EXACT.EXPLODE("Models, Econometric:N.06.850.520.830.500.600.500") OR MJMESH.EXACT.EXPLODE("Models, Econometric:E.05.318.740.500.600.500") OR MJMESH.EXACT.EXPLODE("Models, Economic:E.05.318.740.500.600") OR MJMESH.EXACT.EXPLODE("Models, Economic:N.05.715.360.750.530.500") OR MJMESH.EXACT.EXPLODE("Models, Econometric:E.05.599.835.890.500"))	Embase®, Embase® Alert, MEDLINE®	47946
S7	MJEMB.EXACT.EXPLODE("drug utilization") OR (MJEMB.EXACT.EXPLODE("health economics") OR MJEMB.EXACT.EXPLODE("economic evaluation")) OR MJEMB.EXACT.EXPLODE("health care cost")	Embase®, Embase® Alert, MEDLINE®	185297
S8	(drug near/3 utili?ation) OR (cost near/5 effectiveness near/5 acceptability near/5 curve) OR (incremental near/5 cost near/5 effectiveness near/5 ratio) OR ti(ICER) OR (health NEAR/3 care NEAR/3 cost) OR (drug near/3 cost) OR (health near/3 care near/3 financing) OR (hospital near/3 cost) OR (nursing near/3 cost) OR cost	Embase®, Embase® Alert, MEDLINE®	975676
S9	(cost near/3 effectiveness near/3 analysis) OR (cost near/3 control) OR (cost near/3 benefit near/3 analysis) OR (cost near/3 minimi?ation near/3 analysis) OR (cost near/3 illness) OR (cost near/3 utility) OR (drug near/3	Embase®, Embase® Alert, MEDLINE®	365409

	utili?ation) OR markov OR (cost near/3 allocation) OR (direct near/3 service near/3 cost)		
S10	s8 or s9	Embase®, Embase® Alert, MEDLINE®	998381
S11	s6 or s7	Embase®, Embase® Alert, MEDLINE®	233243
S12	s10 or s11	Embase®, Embase® Alert, MEDLINE®	1088814
S13	s12 or s5	Embase®, Embase® Alert, MEDLINE®	1091690
S14	(wegener* NEAR/3 granulomatosis) OR (granulomatosis NEAR/3 polyangiitis) OR (wegener* NEAR/3 disease)	Embase®, Embase® Alert, MEDLINE®	18023
S15	MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.14.907.940.897.249.750") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.20.111.193.875") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.08.381.483.950")	Embase®, Embase® Alert, MEDLINE®	4267
S16	MJEMB.EXACT.EXPLODE("Wegener granulomatosis")	Embase®, Embase® Alert, MEDLINE®	6063
S17	s1 or s2	Embase®, Embase® Alert, MEDLINE®	18023
S18	s1 or s3	Embase®, Embase® Alert, MEDLINE®	18023
S19	s4 or s5	Embase®, Embase® Alert, MEDLINE®	18023
S20	(microscopic near/3 polyarteritis) OR (microsopic near/3 polyangiitis)	Embase®, Embase® Alert, MEDLINE®	447
S21	MJEMB.EXACT.EXPLODE("microscopic polyangiitis")	Embase®, Embase® Alert, MEDLINE®	382
S22	MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.20.111.193.750") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.940.897.249.500") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.253.329.600") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.10.228.140.300.275.600")	Embase®, Embase® Alert, MEDLINE®	124
S23	s7 or s8	Embase®, Embase® Alert, MEDLINE®	804
S24	s7 or s9	Embase®, Embase® Alert, MEDLINE®	570
S25	s10 or s11	Embase®, Embase® Alert, MEDLINE®	841
S26	MJMESH.EXACT("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis")	Embase®, Embase® Alert, MEDLINE®	286
S27	MJEMB.EXACT.EXPLODE("ANCA associated vasculitis")	Embase®, Embase® Alert, MEDLINE®	837

S28	anca near/3 associated near/3 vascul*	Embase®, Embase® Alert, MEDLINE®	2446
S29	s13 or s15	Embase®, Embase® Alert, MEDLINE®	2476
S30	s14 or s15	Embase®, Embase® Alert, MEDLINE®	2446
S31	s16 or s17	Embase®, Embase® Alert, MEDLINE®	2476
S32	s18 or s12 or s6	Embase®, Embase® Alert, MEDLINE®	20917
S33	s13 and s32	Embase®, Embase® Alert, MEDLINE®	121
S34	s33	Embase®, Embase® Alert, MEDLINE®	145
S35	s33 AND (human(yes) AND human(yes))	Embase®, Embase® Alert, MEDLINE®	120
S36	s33 AND la.exact("English")	Embase®, Embase® Alert, MEDLINE®	101
S37	s33 AND (human(yes) AND human(yes) AND la.exact("English"))	Embase®, Embase® Alert, MEDLINE®	100

Table 78: Search strategy NHS EED

Set	Key Terms	Results
S1	(granulomatosis polyangiitis) OR (microscopic polyangiitis) OR (Wegener) OR (anca associated vasculitis)	13

Three of the 13 records identified in NHS EED have also been identified in MEDLINE, MEDLINE In-Process, EMBASE and EMBASE-alerts.

Table 79: Search strategy EconLit

Set	Key Terms	Results
S1	microscopic polyangiitis	0
S2	wegener's disease	0
S3	granulomatosis polyangiitis	0
S4	anca associated vasculitis	0

10.7.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

A search of Roche's internal Publication database PubCenter on 05/02/2013 yielded no additional results. PubCenter contains publically available articles along with company presented posters and abstracts.

10.8 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

No cost effectiveness studies were identified; therefore a complete quality assessment was not undertaken.

10.9 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

10.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline, Medline In-Process, Embase, Embase Alerts, were searched using the database provider ProQuest. Databases Medline and Medline In-Process have been amalgamated in ProQuest and therefore the user needs only to make one selection to search both databases. This differs to other database providers such as OVID where Medline and Medline In-Process are listed as two separate databases.

Econlit was searched and is provided by the American Economic Association. NHS EED was also searched and is provided by the Centre for Reviews and Dissemination

10.9.2 The date on which the search was conducted.

The systematic literature search was conducted on 04/02/2013.

10.9.3 The date span of the search.

No date limiter was used in this search strategy

10.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Table 80: Search strategy used to search Medline, Medline In-Process, Embase and Embase Alerts

Set#	Searched	Databases	Results
S1	(wegener* NEAR/3 granulomatosis) OR (granulomatosis NEAR/3 polyangiitis) OR (wegener* NEAR/3 disease)	Embase®, Embase® Alert, MEDLINE®	18021
S2	MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.14.907.940.897.249.750") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.20.111.193.875") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.08.381.483.950")	Embase®, Embase® Alert, MEDLINE®	4267
S3	MJEMB.EXACT.EXPLODE("Wegener granulomatosis")	Embase®, Embase® Alert, MEDLINE®	6061
S4	s1 or s2	Embase®, Embase® Alert, MEDLINE®	18021
S6	s1 or s3	Embase®, Embase® Alert, MEDLINE®	18021
S7	s4 or s6	Embase®, Embase® Alert, MEDLINE®	18021
S8	(microscopic near/3 polyarteritis) OR (microsopic near/3 polyangiitis)	Embase®, Embase® Alert, MEDLINE®	447
S9	MJEMB.EXACT.EXPLODE("microscopic polyangiitis")	Embase®, Embase® Alert, MEDLINE®	381
S10	MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.20.111.193.750") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.940.897.249.500") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.253.329.600") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.10.228.140.300.275.600")	Embase®, Embase® Alert, MEDLINE®	124
S11	s8 or s9	Embase®, Embase® Alert, MEDLINE®	803
S12	s8 or s10	Embase®, Embase® Alert, MEDLINE®	570
S13	s11 or s12	Embase®, Embase® Alert, MEDLINE®	840
S14	MJMESH.EXACT("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis")	Embase®, Embase® Alert, MEDLINE®	286
S15	MJEMB.EXACT.EXPLODE("ANCA associated vasculitis")	Embase®, Embase® Alert, MEDLINE®	835
S16	anca near/3 associated near/3 vascul*	Embase®, Embase® Alert, MEDLINE®	2442
S17	s14 or s16	Embase®, Embase® Alert, MEDLINE®	2472
S18	s15 or s16	Embase®, Embase® Alert, MEDLINE®	2442
S19	s17 or s18	Embase®, Embase®	2472

		Alert, MEDLINE®	
S20	s19 or s13 or s7	Embase®, Embase® Alert, MEDLINE®	20911
S23	MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:N.01.224.935.530.700") OR MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:E.05.318.740.100.500.700") OR MJMESH.EXACT.EXPLODE("Life Tables:N.01.224.935.530") OR MJMESH.EXACT.EXPLODE("Life Tables:L.01.280.975.475") OR MJMESH.EXACT.EXPLODE("Life Tables:E.05.318.740.100.500") OR MJMESH.EXACT.EXPLODE("Quality-Adjusted Life Years:L.01.280.975.475.700")	Embase®, Embase® Alert, MEDLINE®	1993
S36	MJEMB.EXACT.EXPLODE("life table") OR MJEMB.EXACT.EXPLODE("quality of working life") OR (MJEMB.EXACT.EXPLODE("Short Form 12") OR MJEMB.EXACT.EXPLODE("quality of life index") OR MJEMB.EXACT.EXPLODE("quality adjusted life year") OR MJEMB.EXACT.EXPLODE("Short Form 8") OR MJEMB.EXACT.EXPLODE("Short Form 36") OR MJEMB.EXACT.EXPLODE("Short Form 20") OR MJEMB.EXACT.EXPLODE("quality of life"))	Embase®, Embase® Alert, MEDLINE®	51535
S37	(self NEAR/3 administered NEAR/3 questionnaire) OR SF?36* OR (short NEAR/3 form NEAR/3 36) OR (short NEAR/3 form NEAR/3 12) OR (rand NEAR/5 36 NEAR/5 item NEAR/5 health NEAR/5 survey) OR (rand NEAR/5 12 NEAR/5 item NEAR/5 health NEAR/5 survey) OR WHO?QOL?100 OR (WHO NEAR/3 QOL NEAR/3 100) OR EQ?5D* OR (euro NEAR/3 qol*)	Embase®, Embase® Alert, MEDLINE®	55635
S38	euroqol* OR (health NEAR/5 related NEAR/5 quality NEAR/5 life) OR (quality NEAR/3 life) OR (quality near/4 adjusted near/4 life near/4 year) OR (utility near/3 value*) OR (utility near/3 score*) OR (time near/3 trade near/3 off) OR (standard near/3 gamble) OR ti(TTO) OR ti(SG)	Embase®, Embase® Alert, MEDLINE®	455630
S49	MJEMB.EXACT.EXPLODE("cost utility analysis")	Embase®, Embase® Alert, MEDLINE®	738
S51	s23 or s37 or s38	Embase®, Embase® Alert, MEDLINE®	490064
S52	s36 or s37 or s38 or s49	Embase®, Embase® Alert, MEDLINE®	490661
S53	s51 or s52	Embase®, Embase® Alert, MEDLINE®	491368
S54	s20 and s53	Embase®, Embase® Alert, MEDLINE®	194
S55	s54	Embase®, Embase® Alert, MEDLINE®	158
S56	s54 AND (human(yes) AND human(yes))	Embase®, Embase® Alert, MEDLINE®	150

S57	s54 AND at.exact("Article" OR "Feature" OR "Patent" OR "Commentary" OR "Bibliography" OR "Technical Report" OR "Correction/Retraction" OR "Conference" OR "Correspondence" OR "Conference Proceeding" OR "Book" OR "Memoir/Personal Document" OR "Government & Official Document" OR "Dictionary/Glossary" OR "Interview" OR "Instructional Material/Guideline" OR "Directory" OR "Biography" OR "Reference Document" OR "Speech/Lecture" OR "Editorial" OR "Undefined" OR "Case Study" OR "News" OR "Conference Paper" OR "Report")	Embase®, Embase® Alert, MEDLINE®	109
S58	s54 AND la.exact("English")	Embase®, Embase® Alert, MEDLINE®	145
S59	s54 AND (human(yes) AND human(yes) AND at.exact("Article" OR "Feature" OR "Patent" OR "Commentary" OR "Bibliography" OR "Technical Report" OR "Correction/Retraction" OR "Conference" OR "Correspondence" OR "Conference Proceeding" OR "Book" OR "Memoir/Personal Document" OR "Government & Official Document" OR "Dictionary/Glossary" OR "Interview" OR "Instructional Material/Guideline" OR "Directory" OR "Biography" OR "Reference Document" OR "Speech/Lecture" OR "Editorial" OR "Undefined" OR "Case Study" OR "News" OR "Conference Paper" OR "Report") AND la.exact("English"))	Embase®, Embase® Alert, MEDLINE®	94

Table 81: Search strategy for EED

Set	Key Terms	Results
S1	(granulomatosis polyangiitis) OR (microscopic polyangiitis) OR (Wegener) OR (anca associated vasculitis)	13

Three of the 13 records identified in NHS EED have also been identified in MEDLINE, MEDLINE In-Process, EMBASE and EMBASE-alerts.

Table 82:Search strategy EconLit

Set	Key Terms	Results
S1	microscopic polyangiitis	0
S2	wegener's disease	0
S3	granulomatosis polyangiitis	0
S4	anca associated vasculitis	0

10.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

A search of Roche's internal Publication database PubCenter on 04/02/2013 yielded no additional results. Pubcenter contains publically available articles along with company presented posters and abstracts.

10.9.6 The inclusion and exclusion criteria.

Exclusion Criteria

- Records not relating to humans
- Records not written in the English language
- Patient population inappropriate (≤18 years old)
- No usable utility or HRQoL values reported for patients with GPA or MPA
- Systematic reviews/therapy reviews
- Studies of less than <30 patients with GPA or MPA
- Studies of QOL of patient's spouses/carers/significant relationship
- Studies that measured the quality of life of co-morbidities potentially associated with MPA or GPA

Inclusion Criteria

- Any geographical location
- Utility terms (HRQoL, utility values, utility scores) reported in the abstract, including any articles where utilities are directly derived using the standard gamble or the time trade off approach or indirectly derived using generic preference instruments (including but not limited to EQ-5D, SF-36, SF-12) or disease specific preference instruments.)
- Article must directly report usable utility values

- Measurement of HRQoL in patients receiving any intervention for the treatment of GPA or MPA

10.9.7 The data abstraction strategy.

Data were exported from ProQuest into a PDF.

10.10 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline, Medline In-Process, Embase, Embase Alerts, were searched using the database provider ProQuest. Databases Medline and Medline In-Process have been amalgamated in ProQuest and therefore the user needs only to make one selection to search both databases. This differs to other database providers such as OVID where Medline and Medline In-Process are listed as two separate databases.

Econlit was searched and is provided by the American Economic Association. NHS EED was also searched and is provided by the Centre for Reviews and Dissemination.

10.10.2 The date on which the search was conducted.

The systematic literature search was conducted on 05/02/2013.

10.10.3 The date span of the search.

No date limiter was used in any search strategy

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Set	Key terms	Results
S1	MJEMB.EXACT.EXPLODE("health care utilization") OR (MJEMB.EXACT.EXPLODE("cost control") OR MJEMB.EXACT.EXPLODE("cost utility analysis") OR MJEMB.EXACT.EXPLODE("cost minimization analysis") OR MJEMB.EXACT.EXPLODE("cost benefit analysis") OR MJEMB.EXACT.EXPLODE("cost effectiveness analysis") OR MJEMB.EXACT.EXPLODE("cost of illness") OR MJEMB.EXACT.EXPLODE("economic evaluation")) OR (MJEMB.EXACT.EXPLODE("hospital purchasing") OR MJEMB.EXACT.EXPLODE("hospital finance") OR MJEMB.EXACT.EXPLODE("hospital cost") OR MJEMB.EXACT.EXPLODE("hospitalization cost") OR MJEMB.EXACT.EXPLODE("hospital running cost")) OR (MJEMB.EXACT.EXPLODE("drug utilization") OR MJEMB.EXACT.EXPLODE("drug cost"))	59412
S3	(resource NEAR/3 utili?ation) OR (nhs NEAR/3 cost*) OR (national near/5 health near/5 service near/5 cost) OR (cost near/3 benefit near/3 analysis) OR (cost near/3 effectiveness near/3 analysis) OR (cost near/3 illness) OR (cost near/3 control) OR (financial near/3 management) OR (health near/3 care near/3 cost) OR (health near/3 care near/3 finan*)	553790
S7	(hospital NEAR/3 cost*) OR (cost* NEAR/3 minimi?ation NEAR/3 analysis) OR (cost* NEAR/3 estimate*) OR (unit* NEAR/3 cost*) OR (resouce near/3 valuation) OR (resource near/3 use)	151101
S8	(MJMESH.EXACT.EXPLODE("Resource Allocation") OR MJMESH.EXACT.EXPLODE("Health Care Rationing:I.01.261.750.500") OR MJMESH.EXACT.EXPLODE("Relative Value Scales:N.04.452.313.500")) OR (MJMESH.EXACT.EXPLODE("Costs and Cost Analysis") OR MJMESH.EXACT.EXPLODE("Cost Control") OR MJMESH.EXACT.EXPLODE("Cost Allocation") OR MJMESH.EXACT.EXPLODE("Economics, Pharmaceutical") OR MJMESH.EXACT.EXPLODE("Cost Savings"))	50104
S9	s1 or s8	109516
S10	s3 or s7	630547
S11	s9 or s10	663990
S12	(wegener* NEAR/3 granulomatosis) OR (granulomatosis NEAR/3 polyangiitis) OR (wegener* NEAR/3 disease)	18023
S13	MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.14.907.940.897.249.750") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.20.111.193.875") OR MJMESH.EXACT.EXPLODE("Wegener Granulomatosis:C.08.381.483.950")	4267
S14	MJEMB.EXACT.EXPLODE("Wegener granulomatosis")	6063
S15	s1 or s2	18023
S16	s1 or s3	18023
S17	s4 or s5	18023
S18	(microscopic near/3 polyarteritis) OR (microsopic near/3 polyangiitis)	447
S19	MJEMB.EXACT.EXPLODE("microscopic polyangiitis")	382
S20	MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.20.111.193.750") OR MJMESH.EXACT.EXPLODE("Microscopic	124

	Polyangiitis:C.14.907.940.897.249.500") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.14.907.253.329.600") OR MJMESH.EXACT.EXPLODE("Microscopic Polyangiitis:C.10.228.140.300.275.600")	
S21	s7 or s8	804
S22	s7 or s9	570
S23	s10 or s11	841
S24	MJMESH.EXACT("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis")	286
S25	MJEMB.EXACT.EXPLODE("ANCA associated vasculitis")	837
S26	anca near/3 associated near/3 vascul*	2446
S27	s13 or s15	2476
S28	s14 or s15	2446
S29	s16 or s17	2476
S30	s18 or s12 or s6	20917
S31	s30 and s11	68
S32	s31	73
S33	s31 AND (human(yes) AND human(yes))	67
S34	s31 AND la.exact("English")	64
S35	s31 AND (human(yes) AND human(yes) AND la.exact("English"))	63

Table 83: Search strategy EED

Set	Key Terms	Results
S1	(granulomatosis polyangiitis) OR (microscopic polyangiitis) OR (Wegener) OR (anca associated vasculitis)	13

Three of the 13 records identified in NHS EED have also been identified in MEDLINE, MEDLINE In-Process, EMBASE and EMBASE-alerts.

Table 84: Search strategy EconLit

Set	Key Terms	Results
S1	microscopic polyangiitis	0
S2	wegener's disease	0
S3	granulomatosis polyangiitis	0

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

A search of Roche's internal literature database PubCenter on 05/02/2013 yielded no additional results. PubCenter contains publically available articles along with company presented posters and abstracts

10.10.6 The inclusion and exclusion criteria.

Inclusion Criteria

- Records not relating to humans
- Records not written in the English language
- Studies that look at resource utilization of treating patients with either MPA or GPA
- Any study in any geographical location

Exclusion Criteria

- Any geographical location
- Studies that do not look at resource utilization of treating patients with either MPA or GPA

10.10.7 The data abstraction strategy.

Data were exported from ProQuest into a PDF