NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

RITUXIMAB FOR THE TREATMENT OF RELAPSED FOLLICULAR LYMPHOMA

Roche Submission to the
National Institute for Health and Clinical Excellence
13th June 2007

Contents

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

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

Brand name: MabThera

Approved name: Rituximab

Therapeutic class: Antineoplastic chimeric monoclonal antibody

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

This submission, as per the Scoping Document issued by NICE, concerns the use of rituximab in relapsed follicular lymphoma. Within this broad indication rituximab has three approved indications:

Monotherapy

In June 1998 rituximab received a pan-European Marketing Authorisation for *"the treatment of patients with stage III/IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy"*

Re-induction Followed by Maintenance

In July 2006 a pan-European Marketing Authorisation was granted for *"the use of rituximab as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera".* This Marketing Authorisation was based primarily on a trial of patients in their first or second relapse with follicular lymphoma randomly allocated to rituximab maintenance or observation after achieving remission with induction treatment consisting of CHOP chemotherapy with or without rituximab. Data from this study are included in the current MabThera SmPC.

This addition to the SmPC thus covers two new ways of using rituximab:-

- As maintenance after successful induction of remission regardless of the chemotherapy regimen used to induce remission (any chemotherapy regimen, with or without rituximab)

- In conjunction with cytotoxic chemotherapy in order to induce remission in relapsed follicular lymphoma. (list first?)

The pivotal trial carried out for regulatory purposes demonstrated that rituximab improves the efficacy of CHOP chemotherapy as an induction regimen, and results from this study are included in the SmPC. However, the EMEA recognized that the benefits of adding rituximab to induction chemotherapy are not specific to CHOP and so the SmPC permits the use of rituximab with any cytotoxic regimen used for re-induction in relapsed follicular lymphoma.

It should be noted that this submission does *not* concern itself with the treatment of previously untreated follicular lymphoma or diffuse large B cell lymphoma which are also covered by the MabThera Marketing Authorisation (say why briefly or refer to section which explains why)

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

As outlined above, this submission concerns only those indications for the use of rituximab in relapsed follicular lymphoma with regulatory approval as of May 2007. These are detailed above.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Roche market research (Synovate for Roche UK, 2007) indicates that rituximab is widely used in the treatment of relapsed follicular lymphoma with around half of all patients receiving the drug as part of their second-, third- or fourth-line treatment, usually in conjunction with cytotoxic chemotherapy to induce remission.

Rituximab monotherapy has little usage, with around 2% of patients receiving it at their first relapse rising to around 10% at fourth line. Monotherapy use has declined significantly in recent years with increased use of the drug in combination with chemotherapy earlier in the course of patients' disease.

The same research indicates that rituximab maintenance following induction of remission in relapsed follicular lymphoma is not as yet? Commonly used in the UK outside of Scotland, where there has been significant uptake following the SMC endorsement of this treatment last year.

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

MabThera has widespread regulatory approval on a global basis. Within Europe all regulatory reviews have been conducted by the EMEA so that the Marketing Authorisations are the same throughout Europe. The indications under consideration

have also been approved in many non-European countries, a complete list of which can be provided on request.

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

In December 2006 the Scottish Medicines Consortium (SMC) completed its review and recommended that rituximab be made available within NHS Scotland *"as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab".*

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Vials containing 100 mg and 500 mg rituximab solution for dilution to form an IV infusion are available.

The 100 mg vials come in packs of two while the 500 mg vials come individually packed.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

A single dose of rituximab is 375 mg/m^2 body surface area.

Monotherapy

For patients receiving rituximab monotherapy for stage III-IV follicular lymphoma that are chemoresistant or in second or subsequent relapse this dose is given weekly for 4 weeks.

Rituximab plus chemotherapy for induction of remission in relapsed follicular lymphoma

For patients requiring remission induction with chemotherapy this dose is given with each cycle of chemotherapy

Maintenance

For patients requiring maintenance of remission after remission induction with chemotherapy with or without rituximab this dose is given every 3 months until relapse or for a maximum of 2 years (total of 8 doses).

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

Assuming an average patient body surface area of between 1.6 -1.87 m^2 a patient will require 1 x 500 mg and 2 x 100 mg vials to provide the 375 mg/m^2 dose described above.

The cost per 100 mg vial is £174.63 and £873.15 per 500 mg vial. This results in a basic NHS cost of £1222.41 per cycle of rituximab.

Thus for a patient receiving 4 weekly cycles of monotherapy the total acquisition cost is £4889.64, for a patient receiving an 8 dose maintenance course the cost is £9779.28 spread over 2 years. For a patient receiving a course of 6 doses with chemotherapy for remission induction the rituximab cost is £7334.46 (excluding chemotherapy costs).

1.10 What is the setting for the use of the technology?

Rituximab is administered by intravenous infusion typically in a hospital chemotherapy day-case unit or outpatient clinic.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No additional tests or investigations are required to select relapsed follicular lymphoma patients for maintenance treatment with rituximab. IV administration of rituximab does utilise healthcare resources, these vary with the schedule used:-

Monotherapy

When rituximab is administered as monotherapy for the induction of remission in patients with relapsed/refractory follicular lymphoma four additional day-case visits are needed for drug administration.

Rituximab plus cytotoxic chemotherapy for remission induction

When rituximab is added to chemotherapy as part of treatment to induce remission the antibody can be administered during hospital day-case visits for chemotherapy and no additional hospital visits should be required, though visits when rituximab is administered with chemotherapy will take longer.

Maintenance

In order to receive maintenance rituximab, which is given as an intravenous (IV) infusion, an additional 8 outpatient treatments will be required. It is likely that these will, generally, be incorporated into routine follow-up appointments, which are generally scheduled in 2-3 monthly intervals, so that they will not require patients to make extra hospital visits.

Whenever rituximab is administered, patients require routine nursing observation for the duration of rituximab infusion, in case of toxicity that may require intervention (usually in the form of interruption or slowing of the rituximab infusion). It has been reported that a patient's first rituximab infusion takes a mean of 5.2 hours, with subsequent infusions typically taking about 3.5 hours (McLaughlin et al. 1998) when the licensed infusion schedule is followed.

However, it should be noted that significant infusion reactions appear to be less frequent when rituximab is used in the maintenance setting. This should permit more rapid dose escalation of the drug infusion rate, reducing total administration times compared with those previously reported for patients receiving rituximab for remission induction.

Roche is also aware that an accelerated infusion schedule is increasingly being adopted by UK treatment centres. This unlicensed schedule allows most patients to receive second and subsequent infusions of rituximab over 90 minutes (Sehn et al. 2004, 2007).

Since rituximab is already widely used for the treatment of non-Hodgkin's lymphoma (NHL) within the NHS, staff treating follicular lymphoma patients will be familiar with the monitoring required during drug infusion and it is not anticipated that any additional training will be required.

2 Statement of the decision problem

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

A review of existing NICE guidance is triggered by "any new evidence on the technology".

Roche will demonstrate, on the basis of a systematic review of literature, that no new evidence has accrued on the use of rituximab monotherapy for the treatment of *"patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy"* since this indication was reviewed in NICE Technology Appraisal 37 (TA37). As such no new evidence is presented and we would therefore propose that the original guidance on the use of rituximab in this setting should stand.

This leaves two remaining licensed indications that fall within the scope of this appraisal:

- The use of rituximab in combination with cytotoxic chemotherapy in order to induce remission in patients with relapsed follicular lymphoma
- The use of rituximab as maintenance therapy in patients with relapsed follicular lymphoma in whom remission has been achieved by the use of cytotoxic chemotherapy with or without concurrent rituximab.

As shown in Table 1 below, for each of these indications there are differences between the final scope and the decision problem being addressed in this appraisal. At a meeting between Roche and the NICE technical team on 9th May 2007 Roche were able to provide clarification (subsequently verified by Roche Regulatory Affairs and reiterated in a letter sent to NICE on 25th May 2007) on the Marketing Authorisation for MabThera that underlies these differences.

Table 1: Differences between scoping document for this appraisal and the decision problems addressed in this submission

	Final scope issued by NICE	Decision problem addressed in the submission
Population	For induction of remission Adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. For maintenance therapy Adults with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab.	For induction of remission using rituximab monotherapy* Adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. For induction of remission using chemotherapy plus rituximab Adult patients with stage III-IV follicular lymphoma who are in relapse after previous chemotherapy, who are still suitable for chemotherapy For maintenance therapy As scope. Responding meaning having achieved at least a partial response.
Intervention	Rituximab as induction and as maintenance therapy.	For induction of remission in patients who are chemoresistant or in 2nd or subsequent relapse* Four, weekly doses of rituximab alone For induction of remission in relapsed follicular lymphoma patients in conjunction with chemotherapy One dose of rituximab with each chemotherapy cycle For maintenance therapy. One dose of rituximab alone every 3 months for two years

Comparator(s)	• Cyclophosphamide, hydroxydaunomycin (doxorubicin), Oncovin (vincristine), and prednisone (CHOP) • Fludarabine, as a single agent, or in combination with mitoxantrone and dexamethasone (FMD). • Cyclophosphamide, vincristine, and prednisone (CVP) • Chlorambucil • Best supportive care (BSC)	<u>For induction of remission using rituximab monotherapy*</u> Best supportive care, other active treatment options having been exhausted. Chemotherapy would be an option according to Manufacturing Authorisation but not within existing NICE guidance. With no new data this guidance should stand <u>Rituximab plus chemotherapy for induction of remission in relapsed follicular lymphoma</u> Chemotherapy alone. As will be explained in Section 4.1, CHOP and, fludarabine-containing chemotherapy are the dominant cytototoxic regimens used in relapsed follicular lymphoma and are the most appropriate comparators. These will be considered. Chlorambucil, BSC alone and CVP are little used in this setting and therefore will not be considered as comparators. <u>Rituximab maintenance</u> The only comparator considered by Roche will be “no treatment” since patients in remission currently get no treatment until relapse.
Outcomes	The outcome measures to be considered include: • Partial/complete response rates • Duration of response/remission • Health related quality of life • Event free survival • Time to new anti-	The end-points appropriate to rituximab use vary according to the way in which rituximab is employed: <u>All situations</u> • Health related quality of life (seldom collected in lymphoma interventional studies and dealt

	lymphoma treatment/ time to progression • Overall survival • Adverse effects of treatment, including serious infection/ immunologic competence	with by reference to general evidence of the quality of life benefit to patients of being in remission and off chemotherapy) • Adverse events of treatment <u>Rituximab maintenance after induction</u> • Event-free survival/Progression -free survival/disease-free survival • Time to new antilymphoma treatment/progression • Overall survival <u>R-CHOP as part of induction therapy prior to maintenance</u> • Response rate • Event-free survival/Progression -free survival/disease-free survival • Overall survival
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 time horizon for the economic evaluation should be based on life expectancy. Costs should be considered from a NHS and Personal Social Services perspective.	The submission will generate 2 separate cost effectiveness results the first will be the cost effectiveness of rituximab as a maintenance therapy only (following response to an induction therapy) compared to observation only (no treatment until relapse). This will be referred to as the 2-arm model. The second will have an earlier starting time-point for the analysis and will evaluate whether the use of rituximab as an induction therapy in addition to maintenance therapy is cost effective. This will be referred to as the 4-arm model. This will compare 4

		options; R-CHOP induction followed by maintenance therapy, R-CHOP induction followed by observation, CHOP induction followed by rituximab maintenance and CHOP induction followed by maintenance alone. The economic evaluation will estimate costs and consequences over the remaining life-time of each patient from the NHS perspective.
Special considerations and other issues		

** As explained above Roche will demonstrate that there is no new information in this area since its original review by NICE in TA37. As such no new case will be presented and the existing guidance should stand*

Section B

3 Executive summary

Scope of Appraisal

This submission concerns the use of rituximab (MabThera) in relapsed follicular lymphoma. Within this remit, rituximab currently has the following indications:

- ***Monotherapy (current NICE Guidance TA37)***
  In June 1998, rituximab received a pan-European marketing authorisation for *"the treatment of patients with stage III/IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy".* This indication for rituximab was appraised by NICE in Technology Appraisal 37 which concluded that the use of rituximab monotherapy for the induction of remission should be restricted to patients considered chemotherapy intolerant or chemotherapy refractory, i.e. for those patients in whom conventional cytotoxic chemotherapy was not an option.

- ***Reinduction followed by maintenance (new indication)***
  In July 2006, a pan-European marketing authorisation was granted for *"the use of rituximab as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera".*

This addition to the marketing authorisation was based primarily on the results of a trial of patients in their first or second relapse with follicular lymphoma (EORTC20981) randomly allocated to rituximab maintenance or observation after achieving remission with induction treatment consisting of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy with or without rituximab. Data from this study are included in the current MabThera SmPC. The marketing authorisation covers two new ways of using rituximab:

1) In conjunction with cytotoxic chemotherapy in order to induce remission in relapsed follicular lymphoma.

2) As maintenance therapy after successful induction of remission, regardless of the chemotherapy regimen used to induce remission (any chemotherapy regimen, with or without rituximab)

This submission will therefore present the clinical and economic evidence supporting the use of rituximab in these two situations.

However, the scope for this appraisal also requires a review of the evidence base for the current guidance on remission induction with rituximab monotherapy that was given in TA37. We present evidence from a comprehensive literature review that confirms that there is no new relevant evidence on rituximab used in this specific manner. We show from market research that rituximab is still used in this way in a small and diminishing group of patients. We would therefore propose that the original TA37 guidance on the use of rituximab monotherapy for remission induction should stand and be included within the guidance from this appraisal.

Rituximab Dosing and Frequency

Vials containing 100mg and 500mg rituximab solution for dilution to form an IV infusion are available. The 100mg vials come in packs of two while the 500mg vials come individually packed. A single dose of rituximab is 375mg/m^2 body surface area. For patients receiving rituximab monotherapy for stage III-IV follicular lymphoma that are chemoresistant or in second or subsequent relapse this dose is given weekly for 4 weeks. For patients requiring remission induction with chemotherapy this dose is given with each cycle of chemotherapy. For patients requiring maintenance of remission after remission induction with chemotherapy with or without rituximab this dose is given every 3 months until relapse or for a maximum of 2 years (a total of 8 doses).

Comparators

For the induction element of the new indication, CHOP chemotherapy is considered the most relevant comparator. It is widely used in the UK and is the comparator in the main licensing study. However, as rituximab is licensed for use in combination with “chemotherapy” and not only CHOP, evidence evaluating the efficacy of rituximab in combination with FCM (fludarabine, cyclophosphamide, mitoxantrone) chemotherapy compared to FCM alone will also be presented. CHOP and fludarabine-based combination chemotherapy are the predominant chemotherapy regimens given to patients with follicular lymphoma in first and second relapse in the UK. The potential impact on the ICER of assuming alternative comparator costs and effects is evaluated within the economic section of our submission.

Decision Problem Overview

The licensed indications for rituximab in follicular lymphoma, how these relate to current standard practice in the UK and the corresponding questions answered in this submission are summarised in the flow diagram below.

Disease setting	Current standard of care in England	Relevant rituximab license indication	Questions for this appraisal
1st-line untreated follicular lymphoma	Chemotherapy (predominantly alkylator-based e.g. CVP, single agent chlorambucil)	*"treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy"(*1 dose per cycle of CVP)	None. Only relapsed follicular lymphoma is under review. TA110 relates.
Patients with relapsed follicular lymphoma considered sensitive to and tolerant of further cytotoxic therapy on basis of previous response	Cytotoxic chemotherapy +/- rituximab. Alkylator based chemotherapy may be used if patients had a long remission after first-line therapy. If not, an anthracycline (doxorubicin as part of CHOP) or fludarabine are added – neither is clearly superior and both are used. At next relapse the remaining unused agent (doxorubicin/fludarabine) will typically be used. Currently there is minimal use of maintenance therapy to keep patients in remission once this has been achieved, where this is used, it will be with rituximab alone (as it is in Scotland).	*"**maintenance** therapy* (1 dose every 3 months for 2 years) *is indicated for patients with relapsed/refractory follicular lymphoma responding to **induction therapy** with chemotherapy* **with or without Mabthera***"*(1 dose per cycle of chemotherapy)	1. Is rituximab when given as a maintenance therapy to patients in remission clinically and cost effective? 2. Is rituximab when given with cytotoxic chemotherapy for remission induction followed by rituximab maintenance therapy, clinically and cost effective?

Patients with relapsed follicular lymphoma considered refractory to or intolerant of further chemotherapy	Rituximab monotherapy weekly for 4 weeks to induce remission	*"patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy* (one dose weekly x 4 weeks)	Is there any new evidence that requires revision of NICE guidance (TA 37) in this area?

Clinical Effectiveness Evidence

Follicular lymphoma is characterised by periods of active disease, during which patients are symptomatic, separated by remissions induced by effective, systemic antitumour chemotherapy (cytotoxic chemotherapy and/or rituximab). The main goal of therapy is to induce durable remissions during which patients are free of disease symptoms, the psychological burden of active life-threatening illness and the toxicity of antilymphoma chemotherapy. Until the introduction of rituximab into clinical practice, improvement in life expectancy was not viewed as a realistic therapeutic goal.

Evidence to support the use of rituximab in conjunction with chemotherapy to induce remissions in relapsed follicular lymphoma and its use, alone, to maintain remissions following successful induction therapy comes from two large randomised controlled trials – the EORTC20981 study (the Roche pivotal regulatory study) and the GLSG-FCM study (an investigator led study which has been the subject of peer reviewed publications).

In EORTC 20981 patients with relapsed follicular lymphoma were randomised to induction therapy with CHOP chemotherapy with or without rituximab (R-CHOP). Those in remission after completion of 6 cycles of CHOP+/-R were subject to a second randomisation to observation only or 8 x infusions of maintenance rituximab given every 3 months for 2 years with the aim of prolonging remissions.

In GLSG-FCM, similar hypotheses were tested to those examined in EORTC20981, though in this case induction treatment was with 4 cycles of FCM (+/-rituximab) and the maintenance therapy was delivered as 2 x 4 weekly treatment blocks 3 months and 6 months from randomisation (although note that this maintenance schedule is different to the marketing authorisation for rituximab).

The most complete data set available is from the EORTC 20981 study and shows (see table below) that adding rituximab to chemotherapy in relapsed follicular lymphoma improves

response rate and long-term disease outcomes. One of the most important effects of the addition of rituximab added to induction chemotherapy is to increase the percentage of patients who achieve remission and thus become eligible for rituximab maintenance.

Impact of the addition of rituximab to standard cytotoxic induction therapy with CHOP for relapsed follicular lymphoma in study EORTC 20981 (regulatory analysis December 2004)

Parameter	CHOP N=231	R-CHOP N=234	Magnitude of benefit	p-value	Risk reduction (95% CI)[1]
Primary ORR	74%	87%	13%	<0.001	
CR	16%	29%	13%	0.0005	
PR	58%	58%		0.9449	
Secondary Median OS (months)	nr	nr		0.0508	32% (0-54%)
Median PFS (months)	19.4	33.2	13.8 months	0.0001	38% (21-52%)

Abbreviations: *CI, confidence interval; CR, complete response rate; nr, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response*

As shown in the table below, the addition of rituximab maintenance after successful induction therapy substantially improves progression-free survival regardless of whether or not patients had already received rituximab as part of their induction treatment.

Impact of rituximab maintenance therapy on progression-free survival in sub-groups of patients recruited in study EORTC 20981 (regulatory analysis December 2004)

Patient group	Median progression-free survival (months)			Risk reduction (95% CI)
	Observation	Rituximab	p-value (Log-Rank)	
All patients	14.3	42.2	<0.0001	61% (45-72%)
CHOP induction	11.6	37.5	<0.0001	71% (54-82%)
R-CHOP induction	22.1	51.9	0.0071	46 % (15-65%)

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response

Extending progression-free survival almost three-fold is clearly very valuable to patients – keeping them free of disease symptoms, treatment toxicity and the psychological burden of disease progression for, on average, 42 months longer than would otherwise be the case. In addition, rituximab maintenance extends overall survival, reducing the risk of death by by 56% (p=0.0039) demonstrating, once again, that the inclusion of rituximab in drug regimens

for the treatment of follicular lymphoma can achieve this crucial but, until recently, elusive, outcome.
Using a different induction chemotherapy regimen, the GLSG-FCM study confirmed that the benefits of adding rituximab to induction treatment for relapsed follicular lymphoma are not regimen specific, as reflected in the licensed indication. The addition of rituximab to FCM chemotherapy increased the overall response rate from 70% to 94% (p=0.011), and significantly improved in median progression-free survival (not yet reached *versus* 21 months; p=0.0139) and produced a clear trend towards improved 2 year overall survival (90% *versus* 70%; p=0.0943) despite limited follow-up.

The GLSG-FCM study also confirmed that 8 doses of maintenance rituximab administered to patients in remission extends their duration of response (median not reached *versus* 26 months; p=0.0035) and produces a clear trend towards improved overall survival, though survival data from this study are, as yet limited (3-year overall survival 77% *versus* 57%; p=0.1).

Thus, two large well-designed RCTs demonstrates that for patients with relapsed follicular lymphoma, the optimum treatment strategy consists of the clinician and patient's chemotherapy of choice administered with rituximab, followed (for patients where this achieves remission) by 8 doses of maintenance rituximab. This dramatically improves the treatment outcome traditionally targeted (time in remission) as well as achieving something previously thought unrealistic – improvement in overall survival. These important benefits are achieved with minimal extra burden of treatment being put upon patients such as very modest additional toxicity, generally limited to the days when rituximab is administered. This is in total a maximum of 8 additional days when IV drug treatment is administered, typically performed during hospital visits that would have been required for routine patient follow-up.

Cost Effectiveness Evidence

A cost utility economic model was developed in two parts based upon the results of the EORTC20981 study to evaluate two decision problems. Firstly, is rituximab cost effective when used as a maintenance therapy (the 2-arm part) and secondly, is rituximab cost effective when used as an induction therapy followed by maintenance therapy? (the 4-arm part).

The model design reflects both the design of the EORTC20981 study, with its two separate randomisation time-points and also the variety of treatment strategies presented by the new rituximab license.

Is rituximab cost effective when used as a maintenance therapy? - 2 Arm Model

Methods

A health state transition model with 3 health states (progression-free, progressive disease and death) was created utilising the Kaplan Meier progression-free and overall survival data from the EORTC20981 for the first 24 months of the model. A Weibull parametric function was then utilised for the remaining lifetime time-horizon of the model, selected on goodness of fit, relative to alternative functions. The assumed treatment effect of rituximab was limited to 5 years in the model, thereafter rituximab patients subsequently had a monthly risk of death and disease progression equivalent to the observation group. QALYs were derived using utility scores from a UK survey of over 200 follicular lymphoma patients using the EQ-5D instrument, valued from the societal perspective. Post protocol treatments were included, estimated from the EORTC20981 study, routine patient monitoring, drug administration and adverse event costs were also included.

Results

Maintenance therapy with rituximab when compared to observation was cost-effective against commonly applied UK thresholds. The incremental cost per QALY gained was £7,721. The table below presents a detailed breakdown of the results.

Incremental cost-effectiveness of rituximab maintenance compared to observation

Treatment group	Total cost	QALYs gained	Incremental cost per QALY gained	Life years gained	Incremental cost per life-year gained
Rituximab	£21,608	4.2250		5.8694	
'Observation'	£14,722	3.3331		4.8693	
Incremental	£6,886	0.8919	**£7,721**	1.0001	**£6,885**

These results were very robust when subject to extensive uni-variate and probabilistic sensitivity analysis. The incremental cost of rituximab is largely accounted for by the drug acquisition costs of rituximab. Even when the duration of the treatment benefit of rituximab is restricted to only that observed in the EORTC 20981 clinical trial, rituximab remains a cost effective treatment option within this setting. Probabilistic sensitivity analyses indicate that the likelihood of the ICER being below £10,000 is 90%.

Is rituximab cost effective when used as an induction therapy followed by maintenance therapy? - 4 Arm Model

Methods

Four separate treatment strategies, observed within the EORTC20981 study were evaluated within this part of the model:

- R-CHOP induction followed by rituximab maintenance
- R-CHOP induction followed by observation
- CHOP induction followed by rituximab maintenance
- CHOP induction followed by observation.

A health state transition model with 5 health states (progression-free in the induction setting, progression free in the maintenance setting, progression free but not in the induction or maintenance setting, progressive disease and death) was created utilising the Kaplan Meier progression-free and overall survival data from the EORTC20981 for the first 24 months of the model. A Weibull parametric function was then utilised for the remaining lifetime time-horizon of the model, selected on goodness of fit, relative to alternative functions. Individual survival curves were estimated for each sub-group within the analysis. The assumed treatment effect of rituximab maintenance was limited to 5 years only in the model (which approximates to the longest follow-up time point in the pivotal study). Thereafter, maintenance rituximab patients subsequently had a monthly risk of death and disease progression equivalent to CHOP followed by observation alone intervention in the 4 arm model. The QALYs and costs applied in the 4-arm model are the same as those described above and applied in the 2-arm model.

Results

The four-arm economic evaluation illustrated that the greatest clinical effectiveness (i.e. the highest QALYs) is achieved by R-CHOP followed by rituximab maintenance treatment strategy. The four-arm model illustrates that this intervention was also cost effective with an incremental cost effectiveness ratio of £16,749 per QALY when compared to the 2nd most clinically effective intervention of CHOP induction followed by rituximab maintenance therapy.

Incremental cost-effectiveness of R-CHOP-R versus CHOP-R in patients presenting for induction therapy

Treatment and comparator groups	Costs	QALYs	Incremental cost per QALY gained
R-CHOP-R	£28,585	4.0906	
CHOP-R	£22,389	3.7207	
Incremental	£6,196	0.3699	£16,749

Again these results have been demonstrated to be very robust when subject to both uni-variate and probabilistic sensitivity analysis and are not dependent upon the assumption of a long-term treatment effect associated with rituximab. The ICER was not sensitive to alternative costs and efficacy assumptions associated with potential alternative chemotherapy treatment comparators. Probabilistic sensitivity analyses indicate that the likelihood of the ICER being below £30,000 is 82%.

NHS Budget Impact

The introduction of maintenance rituximab at 2nd line will result in patients staying in remission for longer and therefore deferring the cost of later line treatments to the NHS in England and Wales to some time in the future. It is estimated that 20% of all 2nd line patients receiving treatment, 268, will be treated with R-CHOP induction at 2nd line, with 183 responding patients going on to receive maintenance rituximab in the first year. The number of patients estimated to receive R-CHOP induction is assumed to grow at a rate of 20% per annum.

In the first year following an endorsement by NICE, the cost of R-CHOP induction at 2nd line, followed by maintenance rituximab is estimated to be approximately £2,7m, rising to approximately £6.5m in the 2nd year and £10.6m in the 3rd year.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

4.1.1 What is follicular lymphoma?

Follicular lymphoma represents 22% a group of diseases known collectively as non-Hodgkin's lymphomas (NHLs) - cancers arising from the lymphoid cells of the immune system. These cells normally have a key role in protecting the body from pathogenic microorganisms.

4.1.2 Presentation of follicular lymphoma

Malignant transformation of lymphocytes results in their uncontrolled replication. This usually starts within the lymph nodes, mainly those of the neck, armpits and groin. Swelling of these structures often provides the first clinical manifestation of illness, though other symptoms including fever, drenching night sweats, weight loss (so-called B-symptoms) and tiredness may also be present at diagnosis or develop later.

4.1.3 Prognosis in follicular lymphoma

Survival for patients with follicular lymphoma is prolonged. Different figures for median survival have been reported, but 8-10 years from diagnosis is typical (Horning and Rosenberg, 1984; Lister, 1991). However, these are likely to be underestimates since there is good evidence from recent large population-based (Swenson et al. 2005) and single institution studies (Liu et al. 2003; Dillman and Chico, 2005; Fisher et al. 2005) that survival is improving. This is probably as a consequence of improved treatment, especially the introduction of rituximab, which is the first drug treatment for this disease to demonstrate an

ability to improve overall survival in randomised clinical trials (reviewed by Marcus and Hagenbeek, 2007).

Despite recent improvements in treatment, most patients with follicular lymphoma ultimately die of their disease. For example, amongst a group of 147 patients followed for over 15 years from diagnosis by Lister (1991), 94 died during the observation period, with 76 deaths attributed to progressive lymphoma.

Prognosis is partly determined by the extent of disease at diagnosis, which is usually described using the Ann-Arbor staging system, as shown in Table 2.

Table 2: Ann-Arbor staging system of non-Hodgkin's lymphoma (Carbone et al. 1971)

Stage I	Involvement of a single lymph node region (I), or localised involvement of a single extralymphatic organ or site (IE).
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II), or localised involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm (IIE).
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), that may also be accompanied by localised involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Other factors besides disease stage have been identified as having prognostic significance. Five of these were incorporated into the International Prognostic Index (IPI) which allows a composite IPI score to be calculated (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). This has been shown to be highly predictive of long-term survival. Although the IPI was formulated for aggressive lymphomas it was also applied to more indolent forms of the disease, like follicular lymphoma. More recently, the Follicular Lymphoma Prognostic Index (FLIPI) has been devised specifically for this type of lymphoma (Solal-Céligny, 2004).

Although the FLIPI is well accepted as having prognostic significance, it is not routinely used to guide treatment, which is generally determined by disease stage plus clinician and patient preference for a particular chemotherapy regimen.

4.1.4 General principles in the treatment of follicular lymphoma

4.1.4.1 Stage I/II disease

Approximately 15% of patients present with early-stage disease (Shipp et al. 1997), defined as localised or Stage I or II disease, which is not the subject of this submission. Stage I/II disease can be managed by regional radiotherapy with excellent results. Around half of patients so treated are free of relapse after 5 years. Patients who reach this point have a very low risk of future relapse. In one large series (McManus and Hoppe, 1996), relapse-free survival rates were 55%, 44%, 40% and 37% at 5, 10, 15 and 20 years, respectively, suggesting that only a subpopulation of patients will have a prolonged disease-free interval after radiotherapy, but that for this group, relapse more than 10 years after treatment is rare.

4.1.4.2 Stage III/IV disease

Treatment of the 85% of follicular lymphoma patients who present with stage III/IV disease (Shipp *et al.* 1997) is shaped by several important considerations:-

- Stage III/IV disease has already disseminated and systemic therapy is required. Until recently cytotoxic chemotherapy represented the only systemic option. To this can now be added immunotherapy with rituximab.

- Early intervention in patients not experiencing troublesome symptoms has not been shown to alter the long-term outcome in this disease (Ardeshna et al. 2003). Therefore, a watch-and-wait policy is normally adopted, where systemic treatment, which inevitably has associated toxicity, is withheld until the patient is symptomatic.

- Stage III/IV follicular lymphoma is generally considered incurable. This means that the main aim of treatment is induction of remission. The ideal treatment will induce a prolonged remission, with acceptable acute toxicity and no significant chronic toxicity to impair quality of life during disease remission.

- Remission induction is of great value to patients. Rituximab-induced remissions are associated with resolution of disease symptoms (Davis et al. 1999). In addition, a recent study (Wild et al. 2006) conducted amongst 222 patients with follicular lymphoma demonstrated that they valued time free of disease progression substantially more than life with progressive disease. Furthermore, response, particularly complete response, to induction chemotherapy has repeatedly been reported to predict for better long-term outcomes including prolonged overall survival (Gallagher et al. 1986; Weisdorf et al. 1992; Montoto et al. 2002). Finally, prolonged remission defers the diagnosis of relapse, which in cancer management generally has been shown to be extremely traumatic – typically more so than the initial diagnosis of cancer (Cella *et al.* 1990)

- Typically, a patient will require several episodes of treatment during the decade or more that they live with their disease. As illustrated in Table 3, it is accepted that with each successive treatment the chances of remission are lower and the duration of the remissions achieved, shorter (Gallagher et al. 1986; Wahl et al. 2001). Therefore, it is important that early treatment remissions are maintained for as long as possible.

Table 3: Decreasing response to treatment in patients with relapsed follicular NHL (based on Gallagher *et al.* 1986)

Parameter	Course of treatment				
	Initial therapy	First relapse	Second relapse	Third relapse	Fourth relapse
Number of patients	110	68	44	27	18
Response rate	70%	59%	59%	44%	39%
Median response duration (months)	16	11.2	9.6	3.2	Not reported

4.1.5 The treatment pathway in Stage III/IV disease

4.1.5.1 First-line treatment

Once patients become symptomatic, treatment with systemic cytotoxic chemotherapy is commenced. However, the selection of a first-line and subsequent cytotoxic regimens for

use in follicular lymphoma treatment is not straightforward as there is no universally accepted gold-standard regimen or treatment sequence.

In a previous submission to NICE (TA110) Roche presented an analysis of the treatments received by 662 patients with follicular lymphoma receiving their first systemic chemotherapy treatment and entered into the Scottish and Newcastle Lymphoma Group's Vanguard database. This database revealed that no less than 37 different first-line regimens had been used in a four year period (Scottish and Newcastle Lymphoma Group, 2004).

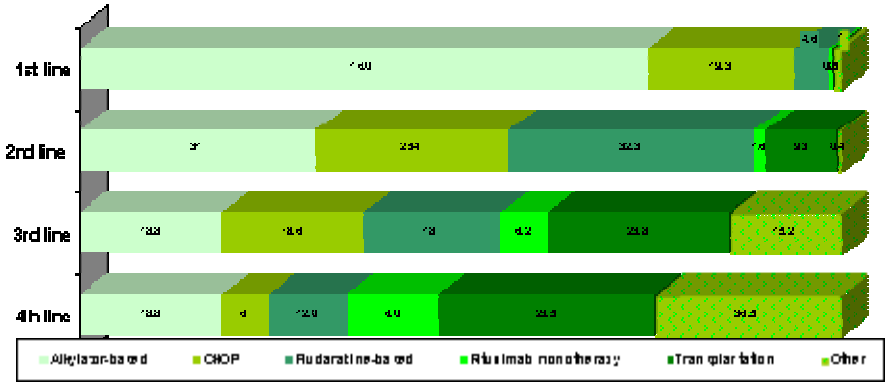
Virtually all of these regimens were based on alkylating agents (usually cyclophosphamide or chlorambucil) with or without a corticosteroid (usually prednisolone). Choice of alkylator is not critical and chlorambucil has been shown, in a comparative trial, to produce similar outcomes to the cyclophosphamide-based regimen CVP (Lister et al. 1978).

Although, entry of new patient data on the Vanguard database ceased some years ago Roche's recent market research (as shown in Figure 1) indicates that alkylator therapy +/- corticosteroids still dominates first line chemotherapy and that there is still diversity of choice in this area, with some clinicians opting to add in either fludarabine or doxorubicin – the two most active, non-alkylator cytotoxic drugs used in follicular lymphoma.

Doxorubicin and fludarabine appear to improve speed and extent of tumour shrinkage. However, the evidence from randomised trials indicates that the long-term outcomes of first-line chemotherapy based on alkylators alone, fludarabine and

Doxorubicin are similar (Zinzani et al 2004; Hagenbeek et al 2006). Therefore as fludarabine and doxorubicin undoubtedly add to treatment toxicity, many UK clinicians only use these agents first-line for individuals who they consider need more aggressive therapy or rapid cytoreduction. For example, those whose tumour histology shows characteristics of more aggressive lymphoma, those who have a high bulk of disease, and those whose tumour is compressing a vital structure.

Figure 1: Current treatment of follicular lymphoma in the UK (Market Research conducted by Synovate for Roche UK in January 2007)



Note: See appendix 12 for clearer version.

It should be noted that this variety of first-line chemotherapy regimens is not a UK phenomenon and that current European (Hagenbeek, 2005) and US guidelines (National Cancer Institute, 2005) on the first-line treatment of follicular lymphoma offer 10 possible chemotherapy options

It has recently been demonstrated in several large clinical trials (see Marcus and Hagenbeek, 2007) and a meta-analysis (Schulz et al 2007) that rituximab added to first-line chemotherapy for Stage III-IV follicular lymphoma improves all important clinical outcomes including overall survival – something never demonstrated with a cytotoxic drug regimen in this setting - and chemotherapy plus rituximab is now accepted as the standard of care in the first-line setting including the UK where both NICE and the SMC have endorsed the clinical and cost-effectiveness of rituximab plus CVP chemotherapy.

4.1.5.2 Treatment at relapse

For patients relapsing after first-line treatment, re-induction therapy is indicated. Again, there is no standard treatment at this point and treatment is largely guided by previous lines of therapy and patients' and doctors' preferences. For patients who experienced a prolonged remission (at least 6 months) after initial alkylator therapy an attempt may be made to reinduce using the same regimen.

However, it is well established that the chances of achieving remission fall with each subsequent relapse as drug resistance develops. For this reason it is common practice to add in either doxorubicin or fludarabine when the response to a prior alkylator-based regimen is deemed inadequate, with a switch to the other agent at next relapse. There are

very few data on the merits of any particular chemotherapy regimen over any other in relapsed disease and none on treatment sequences. Treatment is individualised based on the response of patients to their last treatment, what drugs they have yet to receive and other patient characteristics which might rule out individual drugs e.g. cardiac problems which make anthracyclines unsuitable.

Typically, by the time patients have relapsed twice they will have received three lines of treatment starting with an alkylator-based regimen without fludarabine or an anthracycline, then either CHOP (the predominant doxorubicin containing regimen) or a fludarabine-based regimen at second line then CHOP or a fludarabine-based regimen (whichever has not been used before) at third-line.

There is attrition at each relapse with only a minority of patients receiving fourth and subsequent-line treatment. Market research carried out on behalf of Roche in January 2007 (Synovate for Roche UK) indicates that of patients presenting with Stage III-IV follicular lymphoma 82%, 58%, 30% and 8% get 1, 2, 3 and 4 lines of treatment respectively. This rate of drop out from active treatment is remarkably similar to that reported by Gallagher et al. 20 years ago (see Table 3)

Again, because of extensive trial evidence that rituximab enhances the efficacy of chemotherapy there is significant use of rituximab in conjunction with chemotherapy used to induce second and subsequent remissions.

4.1.5.3 Treatment of relapse in patients unsuitable for chemotherapy

Many patients eventually reach a point where further cytotoxic chemotherapy is not an option because they have become chemotherapy refractory or intolerant. A patient who achieves no remission or a very short remission after their last chemotherapy and for whom no further obvious cytotoxic options remain can be described as chemotherapy refractory. A patient who can be expected to suffer unacceptable treatment toxicity from the cytotoxic options that remain because of, for example, a high cumulative dose of anthracyclines or poor bone marrow function can be considered as chemotherapy intolerant.

In response to evidence that chemotherapy refractory patients can achieve durable responses to rituximab monotherapy without the characteristic toxicities of cytototoxic treatment, NICE allowed the use of the 4 x weekly dose schedule of rituximab for chemotherapy refractory and resistant patients in TA37 in 2002. There continues to be low

level usage of rituximab monotherapy rising from 2% of first-line induction treatment to 10% of fourth-line induction (down from 1.3% and 52.6% at fourth-line in 2004). This pattern of usage strongly suggests that within the UK currently, remission induction with rituximab monotherapy is reserved for patients who are chemotherapy refractory or intolerant and who have no further treatment options i.e. that the guidance in TA37 is being followed and the group of patients identified therein as being appropriate for rituximab monotherapy though small and shrinking still exists.

4.1.5.4 Maintenance therapy in remission

Since one of the key problems in relapsed follicular lymphoma is the poor durability of remissions, the concept of ongoing maintenance therapy is an attractive one. There are limited data that maintenance with cytotoxic chemotherapy can extend remissions but not overall survival (Ezdinli et al. 1985; Steward et al. 1988; Peterson et al. 2003). However, the toxicity of maintenance chemotherapy is such that it is not used in clinical practice. Similarly, although there is evidence from a meta-analysis of randomised trials (Rohatiner et al. 2005) that use of interferon alfa may prolong remissions when used post-induction, this too suffers from poor tolerability (Solal-Celigny 1993; Solal-Celigny 1998; Fisher et al. 2000; Rohatiner et al. 2001) and it is not used for this purpose in the UK.

Market research evidence (Synovate for Roche UK, January 2007) suggests that at present the use of rituximab maintenance for patients in remission after induction treatment is minimal, though it is, significant in Scotland where the SMC has endorsed the use of rituximab in this way.

4.1.6 Consideration of comparators for current review

The intricate and highly individualised treatment pathways used in follicular lymphoma make the choice of comparators for this review complex, this section explains Roche's approach

The comparator for rituximab monotherapy for induction therapy in relapsed lymphoma is straightforward. NICE in TA37 identified that this treatment was a useful option for patients for whom cytotoxic chemotherapy was no longer an option by virtue of disease resistance or intolerance, but who still require treatment for the relief of their disease symptoms. For these patients no other systemic antitumour treatment has significant use in the UK. Under these

circumstances the appropriate comparator is BSC as it was at the time of preparation of TA37. In the light of the lack of new data in this area (which is demonstrated later in this document) Roche are submitting no further clinical or economic evidence and propose that the guidance in TA37 therefore remains unchanged.

The comparator for rituximab maintenance after induction of remission in relapsed follicular lymphoma is no further active treatment until relapse. Patients who have achieved remission (regardless of induction regimen) currently receive no further treatment until relapse. Consequently, the introduction of an active comparator in this setting would not be representative of current UK clinical practice.

The comparator for rituximab plus chemotherapy for remission induction in relapsed follicular lymphoma is chemotherapy alone. The key Roche regulatory study in this area used CHOP chemotherapy +/- rituximab. As CHOP is one of the most widely used chemotherapy regimens in UK practice it is a highly relevant comparator and the CHOP versus R-CHOP comparison will form the main evidence base for Roche's clinical and economic case in the induction setting.

Since Roche's Marketing Authorisation permits the use of rituximab in combination with other induction chemotherapy regimens used for relapsed follicular lymphoma, clinical data will also be presented from an independently conducted clinical trial examining the addition of rituximab to fludarabine-based induction chemotherapy, which demonstrates that the clinical benefits of adding rituximab to induction chemotherapy are not regimen specific.

It can also be argued that R-CHOP should also be compared with alternative cytotoxic induction regimens used alone. From a clinical perspective the available trial evidence suggests that induction chemotherapy regimens are similar in efficacy making a formal indirect comparison of this type unnecessary – if R-CHOP produces better long-term outcomes compared to CHOP it can reasonably be assumed that it will also be superior to other induction chemotherapies.

Sensitivity analysis will demonstrate the impact that alternative comparator costs and effects in the induction setting will have on the final ICER of rituximab.

4.2 What was the rationale for the development of the new technology?

Early clinical trials demonstrated the efficacy of rituximab used alone in relapsed follicular lymphoma, whilst subsequent studies demonstrated its efficacy when given in conjunction

with cytotoxic chemotherapy in a variety of newly diagnosed B-cell lymphomas. Against this background it was logical to explore its use in conjunction with cytotoxic chemotherapy to induce remissions in relapsed follicular lymphoma.

Additionally, the excellent safety and tolerability of rituximab coupled with its convenient administration schedule suggested rituximab as a good candidate for maintenance therapy in follicular lymphoma i.e. as a treatment administered after induction of remission to delay relapse and the return of symptomatic disease. Earlier studies with maintenance chemotherapy and interferon alfa had already established the principle that antilymphoma therapy administered after successful induction can prolong remission duration (see Section 4.1) but these older treatments proved too toxic for routine administration to patients in remission.

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

Rituximab is a humanized monoclonal antibody that binds selectively to the CD20 cell surface marker found on the surface of mature B lymphocytes and lymphoma cells. It causes depletion of normal and malignant B cells. Although its mechanism of action is not precisely defined, antibody-directed cytotoxicity, complement-dependent cytotoxicity, induction of apoptosis and sensitisation of cells to conventional cytotoxic drugs are all likely to be important (Reff et al. 1994; Demidem et al. 1997; Anderson et al. 1997).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/ condition?

Within the scope of this appraisal three uses of rituximab in the treatment of relapsed follicular lymphoma are under consideration:

- Administration in conjunction with standard induction chemotherapy to increase the frequency and durability of disease remissions. This usage is already a well established part of clinical practice within the UK. Based on Market Research (Synovate for Roche UK, 2007) Roche estimates that around half of patients in first or second relapse receive rituximab in conjunction with chemotherapy for remission induction.

- Administration as a maintenance therapy to patients whose disease is in remission after cytotoxic chemotherapy (+/- rituximab) with a view to extending the duration of

the remission, keeping patients free of disease symptoms and the need for toxic re-induction therapy for longer. Patients in remission currently receive no active antilymphoma therapy.

- Administration in order to induce disease remission in relapsed patients for whom further chemotherapy is not an option by reason of their disease being judged chemotherapy resistant or the patient being deemed unable to tolerate further cytotoxic treatment. This use of rituximab, as allowed by NICE in TA37 is already part of the standard treatment pathway in relapsed follicular lymphoma for this small group of patients.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Patients with relapsed follicular lymphoma generally receive several courses of induction chemotherapy during the course of their disease. There is a lack of certainty over which is the optimum treatment sequence and treatment pathways for individual patients are individualised according to a variety of factors, including:-

- Response to prior therapy- is it worth repeating the same or a similar regimen?
- Patient characteristics which may preclude certain drugs e.g. doxorubicin in patients with cardiac impairment.
- General patient fitness which determines their suitability for more aggressive combination chemotherapy regimens or transplantation.

4.6 Provide details of any relevant guidelines or protocols.

Within the UK there are no comprehensive management guidelines for follicular lymphoma and the British Society for Haematology's position paper on rituximab (Johnson, 2000) is now outdated. However, both NICE and the SMC have issued guidance on aspects of the use of rituximab in relapsed follicular lymphoma:-

- In Technology Appraisal 37 (2002), NICE endorsed the use of rituximab for the last-line treatment of patients who are chemo-resistant or chemo-intolerant

- In November 2006 the SMC accepted rituximab for use within NHS Scotland “as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab”.

Globally there are many guidelines offering advice or guidance on different aspects of the treatment of follicular lymphoma. In many cases, such as the European Society for Medical Oncology Minimum Standards (European Society for Medical Oncology, 2007), these cover only first line treatment. However the National Cancer Institute (NCI) in the USA does discuss the treatment of relapsed indolent lymphoma in its “PDQ” guidance, commenting on the value of rituximab used alone or in conjunction with chemotherapy as induction treatment and alone as maintenance therapy (National Cancer Institute, 2005).

5 Clinical evidence

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both 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. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY), Embase alerts (EMBA) and Biosys (BIYY).

Blood online was searched for abstracts relating to economic evaluations presented at the American Society of Hematology Annual Meetings

The Cochrane Library controlled trials database was searched for clinical trials of rituximab in relapsed or refractory follicular lymphoma.

Wherever possible databases were searched from 01/01/2000 to the present.

The results of these searches and, where possible, a copy of the search strategy are appended (see Appendix 2).

Additionally the Roche application for a Type II variation to the MabThera Marketing Authorisation (EU/1/98/067/001-002) was reviewed for the relevant study reports and any other information not obtained elsewhere.

5.2 *Study selection*

5.2.1 Complete list of RCTs

Provide a list 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 assessors.

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

Table 4 provides a list of all literature references found to RCTs fitting the description above. Where more than one report has been identified pertaining to the same study these have been included in the same row of the table.

Table 4: RCTs comparing rituximab containing regimens with other interventions in relapsed follicular/indolent lymphoma

Study identifier	Literature Refererences	Included in list of relevant studies? Reason if excluded
1	Gordon LI *et al*. Clin Lymphoma 2004; **5**: 98-101 Wiseman GA *et al*. *Blood* 2000; **96** (11 Part 1):734a Wiseman GA *et al*. *Blood* 2001, **98** (11 Part 2): 236b Wiseman G *et al. Crit Rev Oncol Hematol* 2001; **39**: 181-194 Wiseman GA *et al Cancer Biother Radiopharmaceut* 2003, **18**: 253-258 Witzig TE *et al Blood* 2000; **96** (11 Part 1): 831a Witzig *et al. J Clin Oncol*. 2002; **20**: 2453-2463	No Comparator is radioimmunotherapy product hardly used in the UK and agreed by NICE as being an inappropriate comparator during scoping

2 GLSG-FCM	Dreyling M *et al Blood* 2003; **102** (11): 103a Dreyling M *et al. Proc Am Soc Clin Oncol.* 2006a; **24**: 422s (abstr 7502)* Dreyling M *et al Blood* 2006b; **108** (11 Part 1): 784a Forstpointer R *et al Dtsch Med Wochenschr* 2002; **127**: 2253-2258 **Forstpointer *et al. Blood* 2004; 104: 3064-3071** **Forstpointer *et al. Blood* 2006; 108: 4003-4008** Hiddemann W *et al Blood* 2001; **98** (11 Part 1): 844a Hiddeman W *et al. Semin Oncol*. 2003; **30** (Suppl 2: 16-20) Hiddemann W *et al* **Blood** 2005; **106** (11 Part 1): 270a	Yes
3. SAKK 35/98	Ghielmini M *et al Blood* 2002; **100** (11): abstr 604 Ghielmini M *et al Blood* 2004; **103**:4416-4423	No Concerns rituximab maintenance after rituximab induction – non-licensed indication using non-licensed schedule
4	Eugen L *et al Blood* 2002; **100** (11): abstr 4745	No Small phase 2 study of non-licensed schedule.Only 7 patients randomized all had rituximab (in 2 different schedules)
5. EORTC	Van Oers MHJ *et al Ann Hematol* 2002; **81**: 553-557 Van Oers, MHJ *et al Blood* 2004; **104** (11	Yes

20981	Part 1): 169a Van Oers MHJ *et al Blood* 2005; **106** (11 Part 1), p107a **Van Oers MHJ *et al Blood* 2006; 108: 3295-3301** **Roche Study Report 1016350 December 2005**	

** Not identified during formal search strategy but known to author*

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Three RCTs comparing rituximab with another intervention in relapsed follicular/indolent lymphoma were excluded as not being relevant to this appraisal for the reasons given in Table 4.

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

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

Relevant RCTs are identified in Table 4 along with the publications arising from them.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

None considered relevant.

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

None known

Figure 2: CONSORT flow chart for study selection process for this review

Publications identified	
Medline, EmBase, EmBase Alerts	58
ASH Abstracts via Biosys	55
Medline in process	9
Cochrane	32
EMEA submission	1
Total	155

Publications excluded on first screen (all RCTs versus rituximab in relapsed follicular/indolent lymphoma)	**No. excluded**
Based on title	41
Based on abstract	81
Based on publication	10
Publications excluded at second stage as "irrelevant" to decision problem	
Based on abstract	10
Total publications excluded	142

Reasons for exclusion	**No excluded (1st /2nd stage)**
Duplicates	15/0
No rituximab used	6/0
Not Follicular lymphoma	5/0
Not relapsed patients	6/0
No non-rituximab arm	12/1
Not RCT	82/0
No clinical data	6/0
Unlicensed indication	0/2
Irrelevant comparator	0/7

Total included:

13 publications from 2 studies (includes 1 not identified during formal search)

Note that two randomised studies excluded during the above process concerned the use of rituximab maintenance after induction of remission using rituximab monotherapy. The LYM-5 study (Hainsworth *et al.* 2005) study recruited only relapsed patients whilst the SAKK 35/98 study (Ghielmini *et al* 2004) recruited a mixture of newly diagnosed and relapsed patients. Although these studies were excluded because they use non-licensed rituximab maintenance schedules in a non-approved indication both were highly supportive of the efficacy of maintenance rituximab in maintaining remissions regardless of how these are induced or the precise rituximab schedule. Similarly, another excluded RCT, the ECOG 1496 study (Hochster *et al* 2005) which concerned the use of rituximab maintenance after first-line chemotherapy also demonstrated the general utility of this approach.

5.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Trial design details for the two relevant studies are summarised in Table 5 and Figure 6.

Table 5: Trial design for studies EORTC 20981 and GLSG-FCM

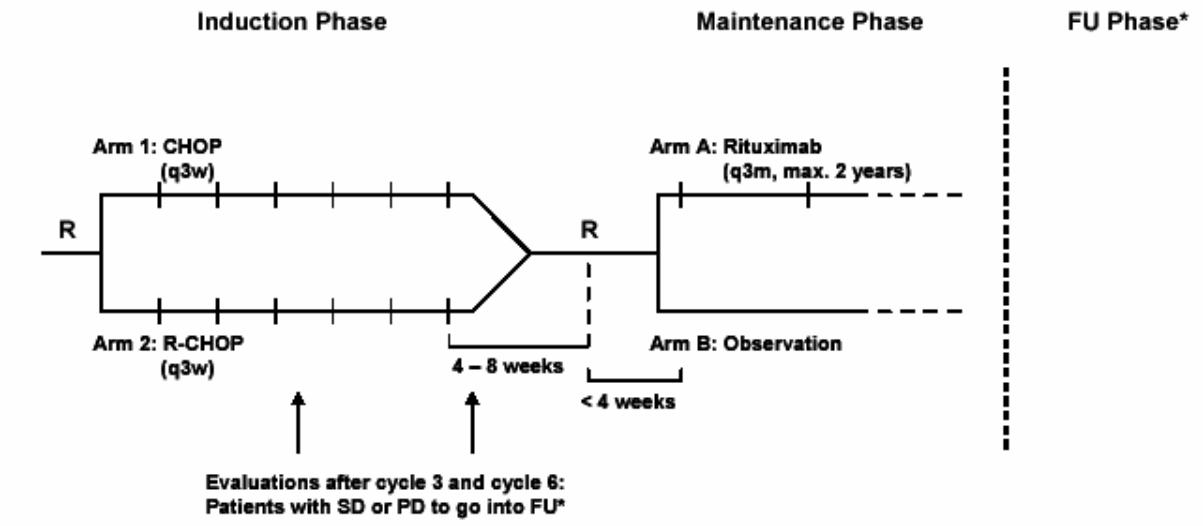
	Trial	
	EORTC 20981	**GLSG-FCM**
Objectives stated by investigators	To establish the effect of the addition of rituximab to CHOP induction chemotherapy on response rate and quality of response in patients with relapsed/refractory, low-grade non-Hodgkin's lymphoma) To establish the effect of maintenance treatment with rituximab on progression-free survival in patients with relapsed, low-grade non-Hodgkin's lymphoma after CHOP+/-rituximab treatment.	To determine whether the addition of rituximab to FCM induction chemotherapy for patients failing to respond to or relapsing after at least one prior chemotherapy regimen for indolent lymphoma could increase remission rate To determine whether 8 doses of rituximab maintenance therapy administered during remission could increase progression-free survival compared with observation alone.
Overall design	Patients randomised to induction with 6 cycles of CHOP+/-R. Patients achieving PR/CR after 6 cycles (3 if stopped early for CHOP toxicity) randomised to 2 years of maintenance with rituximab or observation.	Patients randomised to induction with 4 cycles of FCM chemotherapy+/-R Patients achieving PR/CR after induction randomised to 8 further doses of rituximab delivered as 4 week blocks 3 months and 6 months after completion of induction

Rationale	• *Induction*: Rituximab has single-agent activity in relapsed FL and is synergistic with cytotoxic chemotherapy with non-overlapping toxicity. CHOP acceptable to all participants • *Maintenance*: 3-monthly dosing maintains serum levels above those required for therapeutic effect (Berinstein *et al* 1998) and would be expected to be well tolerated	Broadly similar to EORTC 20981, with two major differences in design: • *Induction* Fludarabine-based induction chemotherapy used due to greater use of CHOP first-line in Germany • *Maintenance.* Doses split into blocks of 4 as this scheduling already established effective in remission induction
Participating research groups	Coordinated by the EORTC: • EORTC Lymphoma Group • Australia and New Zealand Lymphoma Group • National Cancer Institute of Canada Clinical trials Group • British National Lymphoma Investigation • Swiss Group for Clinical Cancer research • Nordic Lymphoma Group • South African NHL Clinical Trials Group	German Low-grade Lymphoma Study Group (GLSG) with some centres in Austria and Australia
Overall patient population description	Follicular Lymphoma in relapse after 1 or 2 chemotherapy regimens	Indolent (follicular, mantle cell or lymphocytoid) lymphoma relapsing after, or failing to respond to, at least one prior chemotherapy regimen.
Number of patients randomised induction/maintenance	465/334	147/195 (randomisation induction closed after superiority of R-FCM over FCM demonstrated in first 147 patients)
Recruitment periods • induction • maintenance	 10/11/98-16/4/04 29/04/99-23/04/04	 • 11/98-6/01 • 11/98-04/05

Blinding	Open-label study	Open-label study
Randomisation technique	Centrally conducted,either directly via the EORTC data centre computer, 24 hours a day, seven days a week or by telephone during office hours. Randomisation to both phases done on a 1:1 basis using a minimisation procedure according to Pocock and Simon. *Induction randomisation* Stratified by institution, previous treatment with purine analogues (no *vs* yes), age (<65 *vs* >/=65 years), number of previous induction treatments (1 *vs* 2), best response previously obtained (CR *vs* PR *vs* no change [NC] *vs* stable disease *versus* progressive disease [PD]), time since diagnosis (</= 2 *vs* > 2 years) and bulky disease (size of largest tumour mass < 10 *vs* >/= 10 cm). *Maintenance randomisation* Stratified for institution, treatment allocation at the first randomisation (CHOP *vs* R-CHOP) and the quality of response (CR *vs* PR)	*Induction randomisation:* Centrally, conducted by telephone, using a computer programme, stratified for histology, response to preceding chemotherapy, and number of previous chemotherapies using random permutated blocks. *Maintenance randomisation:* Centrally, conducted by telephone, using a computer programme, stratified for histology, response to preceding chemotherapy or rituximab plus chemotherap, and number of previous chemotherapies using random permutated blocks.
Interventions	**Induction treatment** **R-CHOP**: Cyclophosphamide 750 mg/m^2 IV Day 1, doxorubicin 50 mg/m^2 IV Day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) IV Day 1; rituximab 375 mg/m^2 as a slow IV infusion Day 1, prednisolone 100 mg orally, Days 1 to 5 every 21 days. **CHOP**: As R-CHOP without rituximab **Maintenance rituximab**: Rituximab 375 mg/m^2 as a slow IV infusion once every 3 months for 8 doses (24 months) or until disease progression.	**Induction treatment** **R-FCM** Fludarabine 25 mg/m^2 IV Days 1-3, cyclophosphamide 200 mg/m^2 IV Days 1-3, mitoxantrone 8 mg/m^2 IV Day 1, rituximab 375 mg/m^2 as a short IV infusion Day -1 every 28 days. **FCM** As R-FCM but without rituximab **Maintenance rituximab** Rituximab 375 mg/m^2 as a short IV infusion weekly x 4 at 3 months and 6 months after completion of induction therapy (total 8 doses).

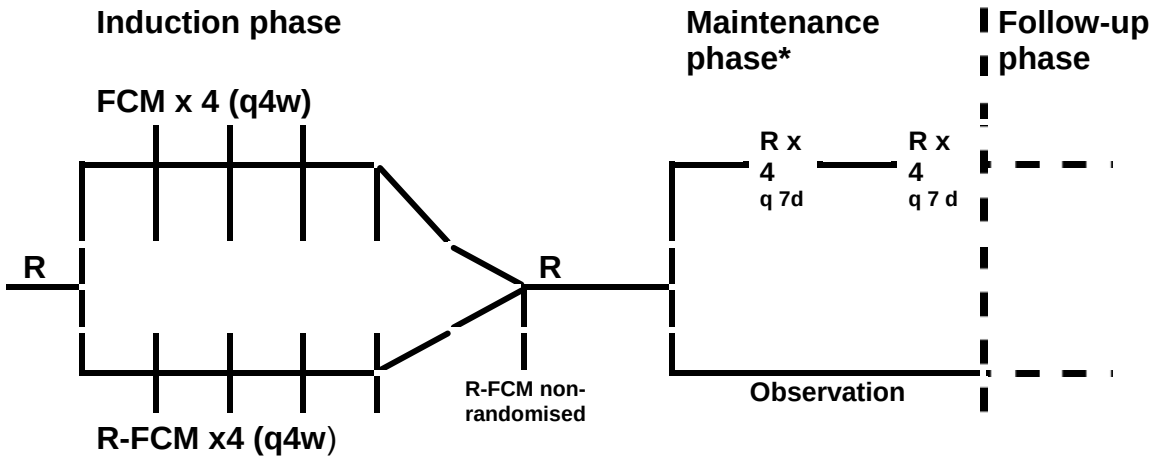
Figure 3: Schematic diagram of trial protocol for studies EORTC 20981 and GLSG-FCM

A. EORTC 20981



* After either completion of planned therapy or early termination, patients went into the follow-up phase (one visit every 4 months)
R = randomization; q3w = once every three weeks; q3m = once every three months

B. GLSG-FCM



5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Table 6 details the inclusion and exclusion criteria for entry into studies EORTC 20981 and GLSG-FCM

Table 6: Inclusion and exclusion criteria for studies EORTC 20981 and GLSG-FCM

	Trial	
	EORTC 20981	**GLSG-FCM**
Induction Phase	**Inclusion:** • Ann Arbor Stage III or IV follicular lymphoma • Relapsed disease after a maximum of one or two (but not more) adequate non-anthracycline containing chemotherapy regimens (4 consecutive months or more of single agent therapy or 4 or more consecutive cycles of polychemotherapy – modified in June 2000 [Protocol Ammendment 4] to 2 consecutive months or 2 consecutive cycles) • No prior treatment with anthracyclines, mitoxantrone or rituximab • Circulating tumour cells < 10 x 10^9/L • Remission to at least one of the prior chemotherapy regimens (modified in June 2000 to include patients with stable disease as their best prior response) • Response duration of 3 months or more to one prior chemotherapy (modified in June	**Inclusion:** • Relapsed or refractory follicular, mantle cell or lymphocytoid lymphoma, with histology centrally confirmed • Not responding to or relapsing after at least 1 preceding chemotherapy regimen **Exclusion:** • Pregnancy • Breast-feeding • Patients of child-bearing potential not using reliable contraception

	2000 to at least 4 weeks) • CD20 positive follicular lymphoma according to the REAL classification • At least one bidimensionally measurable lesion • Age 18 years of age or older • WHO Performance status 0, 1, or 2 • Patient had given written informed consent (which covered both phases of the study) and was capable of and willing to meet the schedule of hospital appointments required by the study. • ***Patients were excluded if any of the following applied:*** • Severe cardiac disease • Serum creatinine, BUN, alkaline phosphates or bilirubin =/> 2.5 times the upper limit of normal, unless clearly related to lymphoma • Pregnancy • Prior malignancy, except non-melanomatous skin cancers, cervical carcinoma *in situ* and cancers cured by surgical resection > 5 years ago. • HIV positivity • Uncontrolled asthma • IgG levels <6g/L (reduced to 3g/L in June 2000) • Prior stem cell transplantation • Planned peripheral blood stem cell collection using *chemotherapy* for mobilisation.	

Maintenance phase	**Inclusion** • Complete or partial remission (CR or PR) of at least 4 weeks duration after the last cycle of CHOP+/- rituximab • For patients receiving rituximab during remission induction: no rituximab-related toxicity necessitating stopping rituximab. • Time interval since last cycle of CHOP+/- rituximab 4-8 weeks. • IgG levels <6g/L (reduced to 3g/L in June 2000) • No active infection.	**Inclusion** • CR or PR after FCM+/R during induction phase

The baseline demographic, disease and treatment characteristics of patients recruited into the two phases of study EORTC 20981 are presented in Table 7. This demonstrates not only that the randomisation process resulted in well balanced induction treatment groups, but also that the broad similarity of patients between treatment groups was maintained after second randomisation and that the study population as a whole were a group that would be deemed as being in need of active treatment (more than one-quarter had B symptoms, most had bone marrow involvement, 69% had Follicular Lymphoma Prognostic Index (FLIPI) scores of 2 or more) by UK clinicians.

Table 7: Characteristics of patients randomised between CHOP and R-CHOP induction and between rituximab maintenance and observation in study EORTC 20981

Characteristic	Induction Phase			Maintenance Phase*		
	CHOP N=231	R-CHOP N=234	All N=465	Observation N= 167	Maintenance N=167	All
Gender						
Male	118 (51%)	107 (46%)	225 (48%)	83 (50%)	78 (47%)	161 (48%)
Female	113 (49%)	127 (54%)	240 (52%)	84 (50%)	89 (53%)	173 (52%)
Age						
Median	54.0	54.0	54.0	55.0	53.0	54.0
Range	27-78	26-80	26-80	27-80	29-76	27-80
Ann Arbor stage						
I	1 (<1%)	4 (2%)	5 (1%)	3 (2%)	2 (1%)	5 (1%)
II	1 (<1%)	2 (<1%)	3 (<1%)	2 (1%)	-	2 (<1%)
III	74 (32%)	73 (31%)	147 (32%)	56 (34%)	57 (34%)	113 (34%)
IV	155 (67%)	155 (66%)	310 (67%)	106 (63%)	108 (65%)	214 (64%)
Bulky disease						
No	200 (90%)	194 (85%)	394 (87%)	146 (88%)	143 (89%)	289 (89%)
Yes	22 (10%)	35 (15%)	57 (13%)	19 (12%)	18 (11%)	37 (11%)
WHO Performance status						
0	135 (58%)	134 (57%)	269 (58%)	99 (59%)	100 (60%)	199 (60%)
1	79 (34%)	84 (36%)	163 (35%)	61 (37%)	58 (35%)	119 (36%)
2	17 (7%)	15 (6%)	32 (7%)	7 (4%)	9 (5%)	16 (5%)
3	-	1 (<1%)	1 (<1%)	-	-	-
B-symptoms present						
No	168 (73%)	174 (74%)	342 (74%)	128 (77%)	125 (75%)	253 (76%)
Yes	62 (27%)	60 (26%)	122 (26%)	39 (23%)	41 (25%)	80 (24%)
Bone marrow involvement						
No	85 (39%)	96 (42%)	342 (74%)	74 (45%)	58 (36%)	132 (41%)
Yes	131 (61%)	132 (58%)	122 (26%)	89 (55%)	102 (64%)	191 (59%)
FLIPI prognostic score (derived)						
0	1 (<1%)	3 (1%)	4 (<1%)	3 (2%)	1 (<1%)	4 (1%)
1	67 (30%)	63 (28%)	130 (29%)	45 (28%)	56 (35%)	101 (31%)
2	73 (33%)	74 (33%)	147 (33%)	51 (32%)	56 (35%)	107 (33%)
3	52 (23%)	60 (27%)	112 (25%)	45 (28%)	40 (25%)	85 (26%)
4	28 (13%)	23 (10%)	51 (11%)	14 (9%)	9 (6%)	23 (7%)
5	3 (1%)	1 (<1%)	4 (<1%)	2 (1%)	-	2 (<1%)
Extra nodal disease sites						
0-1	219 (95%)	220 (94%)	439 (94%)	155 (93%)	161 (96%)	316 (95%)
>1	12 (5%)	14 (6%)	26 (6%)	12 (7%)	6 (4%)	18 (5%)
Number of prior chemotherapies						
1	189 (82%)	183 (78%)	372 (80%)	137 (82%)	138 (83%)	275 (82%)
2	41 (18%)	50 (21%)	91 (20%)	30 (18%)	29 (17%)	59 (18%)
3	1 (<1%)	1 (<1%)	2 (<1%)	-	-	-
Best response to prior therapy						
CR	72 (31%)	76 (32%)	148 (32%)	52 (31%)	62 (37%)	114 (34%)
PR	120 (52%)	120 (51%)	240 (52%)	86 (51%)	86 (51%)	172 (51%)
NC	26 (11%)	23 (10%)	49 (11%)	22 (13%)	11 (7%)	33 (10%)
PD	13 (6%)	15 (6%)	28 (6%)	7 (4%)	8 (5%)	15 (4%)

***Abbreviations**: CR, complete response; FLIPI, Follicular Lymphoma International Prognostic Index; NC, no change; PD, progressive disease; PR, partial response*

** Characteristics recorded at time of study entry not at time of randomisation to maintenance/observation.*

For study GLSG-FCM the situation is more complex due to the way in which data has been presented so far. The first full publication (Forstepointer et al 2004) from this study reported on the first 147 patients entered into the study and the impact of their randomisation to FCM induction chemotherapy+/-R. It gives details of the characteristics of evaluable patients only (n=128) for the population as a whole and for the two major histological sub-groups (follicular and mantle cell lymphomas). For each of these groups patient demographics, disease details and treatment history were well balanced. In the second publication (Forstepointer et al 2006) patient characteristics are given only for the follicular lymphoma (n=125, 64%) and mantle cell (56, 29%) subgroups of the total 195 patients randomised to maintenance or

observation, this time on an intent-to-treat (ITT) basis. Again patient characteristics were broadly balanced between the control and experimental arms. The characteristics of the (majority) follicular lymphoma sub-groups from the induction and maintenance phases of the study that are of relevance to this appraisal are shown in Table 8.

Table 8: Characteristics of patients with relapsed follicular lymphoma entered into the induction and maintenance phases of study GLSG-FCM

Characteristic	Induction n=65*		Maintenance/ Observation n= 105**	
	FCM n=30	R-FCM n=35	Obs n=53	Maint n=52
Age				
Median	59.5	60	61	52
Range	35-77	42-80	35-80	41-78
Gender, no. (%)				
Male	13 (43)	16 (46)	27 (51)	22 (42)
Female	17 (57)	19 (54)	26 (49)	30 (58)
No. of prior therapies, %				
1	53	66	73	67
2	30	23	17	27
More than 2	17	11	9	6
Previous PBCT, %	13	9	4	8
Remission to prior therapy %	90	86	89	94
Extranodal involvement, %				
Bone marrow	55	49	52	43
Liver	4	9	6	0
GI tract	0	9	4	2
Spleen	23	20	27	20
B-symptoms, %	30	29	28	21
LDH elevated, %	17	23	20	20
Initial therapy, no. (%)				
FCM	NA	NA	13 (25)	11 (21)
R-FCM	NA	NA	40 (75)	41 (79)

**Assessable patients **Intent-to-treat population*
Abbreviations: NA, not applicable; Obs, Observation; Maint, maintenance.

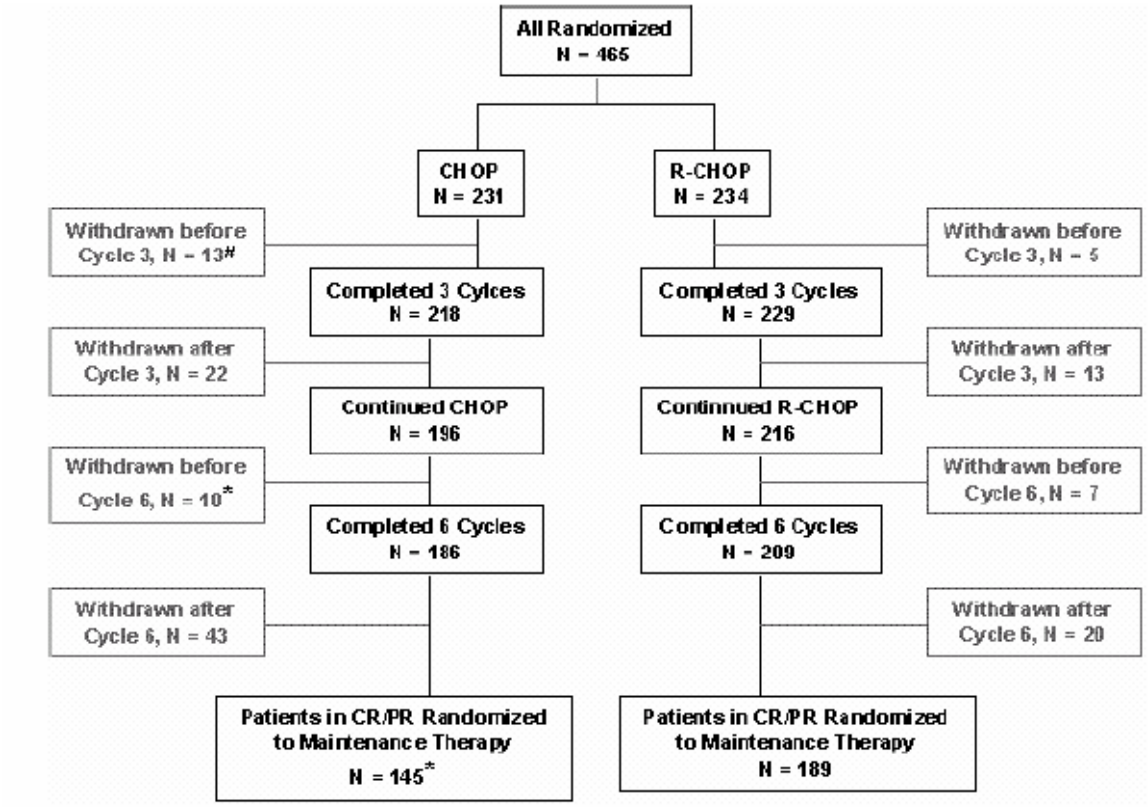
5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, 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/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

The disposition of patients entered into study EORTC 20981 is shown in Figure 4.

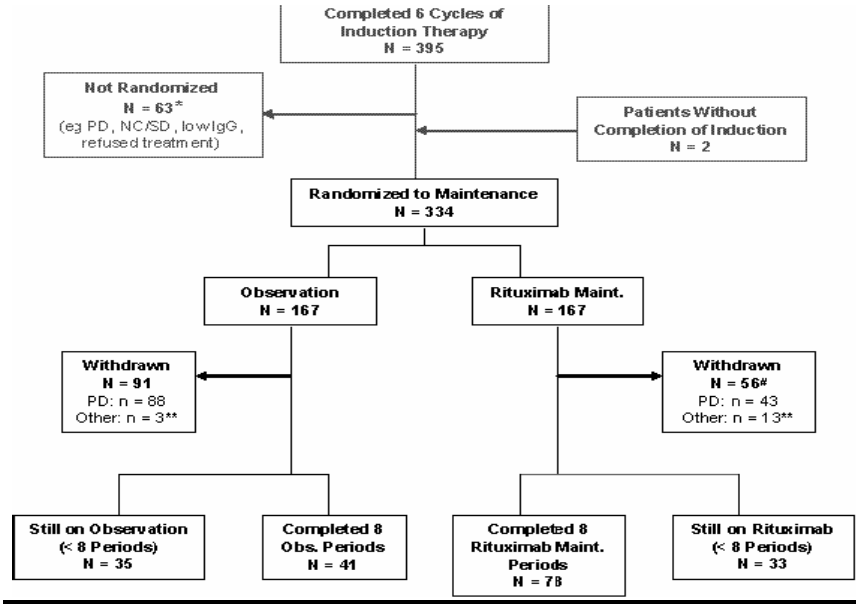
Figure 4: Disposition of patients entered into study EORTC 20981

A Induction phase



Includes 3 patients who did not receive any treatment at all.
* Includes 2 patients who discontinued induction treatment due to toxicity, but who had responded and were randomised in the maintenance phase.

B Maintenance Phase



**Includes 9 compassionate cases offered maintenance without randomisation when study closure was recommended.*

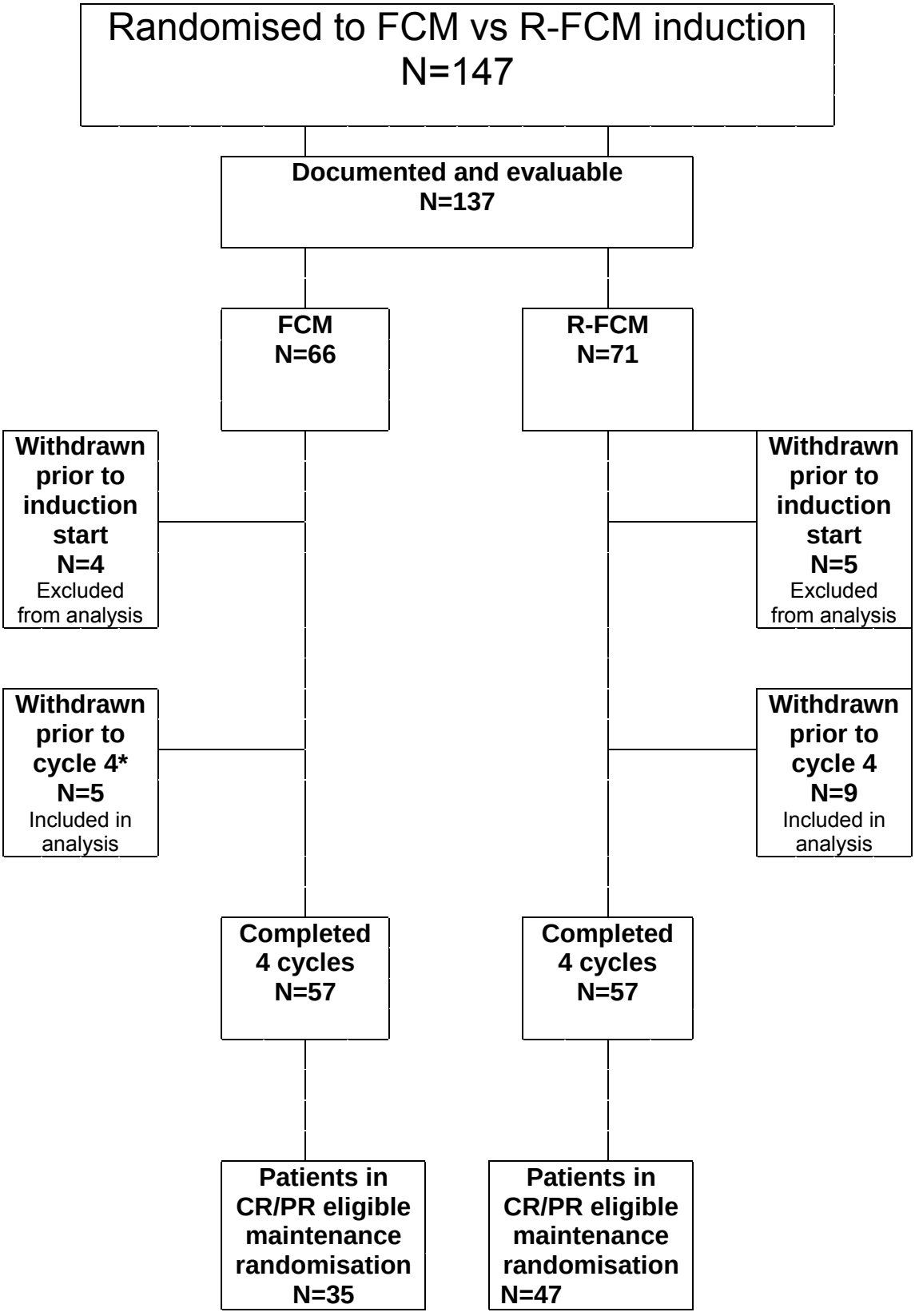
***6 treatment toxicity, 3 treatments refused for reasons other than toxicity, 2 deaths for reasons unrelated to lymphoma or treatment; 2 other.*

 # One patient only received 7 doses of rituximab during the maintenance phase and was included as withdrawn in the rituximab maintenance arm. However, the investigator considered this patient to have completed the maintenance phase.

Constructing a flow diagram for the disposition of patients in the GLSG-FCM trial is complicated by the fact that the impact of induction and maintenance have been the subject of two separate publications based on analyses at two different times. At the time of the first publication (impact of rituximab on induction) 128 patients were deemed evaluable, but by the time of the second-publication response rates were included on 133 randomised patients, presumably because of further patient data received by the trial centre. Thus, there is a discrepancy between the number of patients reaching the bottom of the induction phase flow diagram (Figure 5A) based on Forstpointer et al. (2004) and the number of patients from this phase of the study included at the start of the maintenance phase flow diagram (Figure 5B) where they are joined by patients treated with R-FCM without randomisation. For the maintenance phase, it is unclear from published information how many patients finished the maintenance treatment.

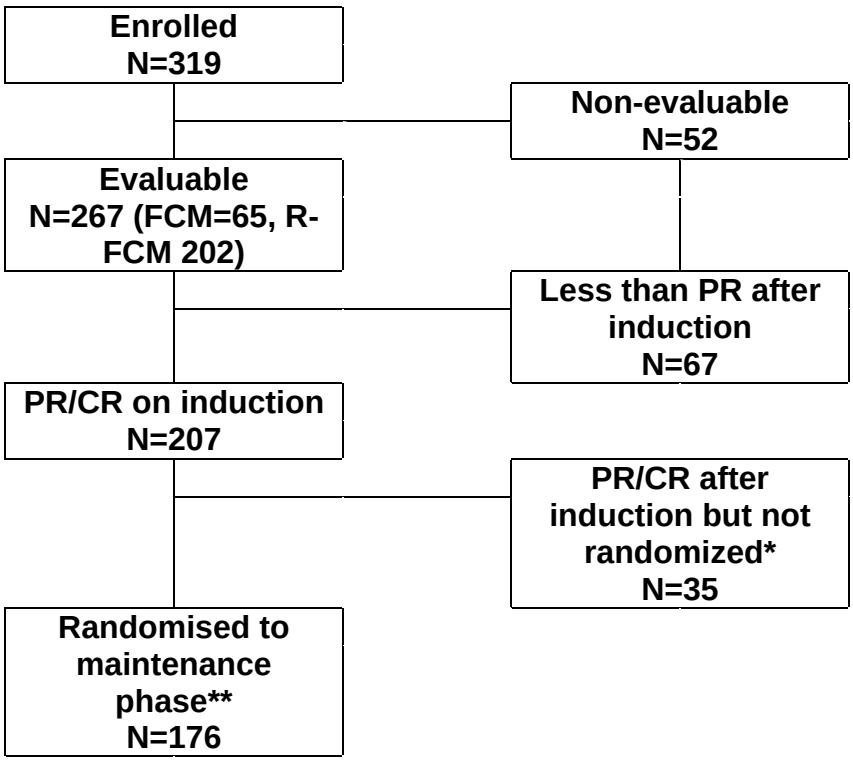
Figure 5: Patient disposition in study GLSG-FCM

A Induction phase



*4 patients withdrawn after 3 cycles (1 PR, 1 minor response, 2 SD); 1 withdrawn after 2 cycles with SD
**1 death during cycle 1 with no rituximab administered; 2 withdrawn after 2 cycles (1 CR, 1 SD); 5 withdrawn after 3 cycles (5 PR, 1 SD)*

B Maintenance phase



*14 patients terminated initial therapy early, 12 patients or clinicians declined further therapy, 5 had initial allergic reactions to rituximab, 4 developed new concomitant diseases

**Includes 4 patients not in remission after induction (protocol violation)

Abbreviations: CR, complete response, PR, partial response, SD, stable disease

5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

Study EORTC 20981

The study end-points in EORTC 20981were as follows:

- **Induction phase**
    - **Primary end-point**
      Last tumour response rate (RR)
    - **Secondary end-points**
      Overall survival (OS)
      Event-free survival (EFS)
- **Maintenance phase**
    - **Primary endpoint**
      PFS
    - **Secondary end-points**
      OS
    - **Exploratory endpoints**
      Time to new antilymphoma treatment or death (TNLT)
      Disease-free survival (DFS)
- **Safety in both phases**
    - All adverse events regardless of causality occurring during or up to 30 days after the last treatment cycle/observation period.

The end-points listed above were defined as follows:

Last RR: Response rate according to the LEXCOR criteria (Grillo-Lopez et al. 1997) using the last assessment made (RR was assessed after 3 cycles and 6 cycles of induction chemotherapy – specifying last RR avoided inflation of the response rate by inclusion of patients with a transient response after cycle 3 as responders).

OS (induction phase): Time from first randomisation to death from any cause. Patients still alive or lost to follow-up were censored at the last date they were known to be alive (last contact date).

OS (maintenance phase): Time from second randomisation to death from any cause. Patients still alive or lost to follow-up were censored at the last date they were known to be alive (last contact date)

EFS: The interval from the date of first randomisation to the date of documented progression, relapse or death, whichever occurred first. Patients who did not achieve at least a PR after at least 3 cycles of CHOP+/-R were considered treatment failures with EFS set to zero. Patients without an event were censored at the last date seen or at the end of the treatment period, whichever occurred first.

PFS (induction phase): The interval between the date of the first randomisation to the date of disease progression/relapse or death, whichever occurred first. Otherwise patients were censored at the last date the patient was assessed for tumour response.

PFS (maintenance phase): The interval between the date of the second randomisation and the date of relapse, progression, or death, whichever occurred first. Otherwise patients were censored at the date they were assessed for response.

TNLT: The interval between the date of the second randomisation and the start of the first new antilymphoma treatment or the date of death, whichever occurred first. Patients who reported neither a new lymphoma treatment nor death were censored at the last visit at which it was confirmed that the patients had not received NLT.

DFS: Disease-free survival only applied to patients randomised in the maintenance phase who had achieved a CR with induction therapy. It was was defined as the interval between the date of first documented CR and the date of relapse or death, whichever occurred first. Patients alive and without relapse were censored at the last assessment.

Follow-up

At the time of the analysis carried out for regulatory purposes in December 2004 median follow-up of patients was 31 months from the first (induction) randomisation and 28.3 months from the second (maintenance randomisation). At the time of the EORTC analysis used in the peer-reviewed publication arising from this study in September 2005 median follow-up had been extended to 39.4 months from study entry (33.3 months from maintenance randomisation).

Study GLSG-FCM

Very limited data are available on study GLSG-FCM. Publications and presentations to date state only that the end-points of the induction and maintenance phases of this study were RR assessed according to International Working Group criteria (Cheson et al. 1999) and risk of relapse, respectively. Response to induction therapy was assessed after the first 2 cycles of therapy and 4 weeks after completion of the fourth course. Response duration was assessed every 3 months. The frequency and severity of adverse events was also recorded using National Cancer Information Center (NCIC) Common Toxicity Criteria (CTC).

At the time of the second peer-reviewed publication of data from this study (Forstpointer et al. 2006) median follow-up was stated to be 39.4 months from study entry.

5.3.5 Statistical analysis and definition of study groups

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

Study EORTC 20981

Hypotheses under test and statistical tests used.

Induction phase

The primary hypothesis under test was that the addition of rituximab improves the overall response rate to induction chemotherapy by 10% in absolute terms. Response rates (CR, PR and no response) were analysed using a chi-square test for trend. The threshold for defining results as significant was P<0.001. The threshold for statistical significance was set at p<0.001, based on the Haybittle-Peto rule, with early stopping allowed if this threshold was crossed.

The primary analysis for the secondary end-points EFS, OS and the exploratory endpoint PFS was based on the log-rank test using a two-sided alpha level of 5%. Kaplan-Meier curves were constructed to graphically show the unadjusted difference between the treatment arms for all endpoints. Secondary analysis and the results were presented as risk ratios including 95% confidence intervals.

Maintenance phase

The primary analysis for PFS was based on a log-rank test stratified by induction treatment (CHOP versus R-CHOP) and quality of response after induction treatment (CR versus other) at second randomisation. The threshold for statistical significance was set at p<0.001, based on the Haybittle-Peto rule, with early stopping allowed if this threshold was crossed. The primary analysis for the secondary endpoint OS was based on an unstratified log-rank test using a two-sided alpha level of 5%. Secondary analyses were done by the Cox-regression analysis and the results presented as risk ratios including 95% confidence intervals.

The additional/exploratory endpoints, TNLT and DFS were analysed based on the non-stratified log-rank test.

Safety

Safety evaluation included all randomised patients who received study drug and had safety follow-up.

Sample size

The initial protocol planned to recruit 600 patients. However, the sample size was increased to 752 on June 28th 2000 when a protocol amendment opened recruitment to patients refractory to their last treatment. Such patients generally have a worse response to chemotherapy and it was assumed that their response rate to CHOP would be 55% rather than 75% (as assumed in the original protocol which included only chemotherapy sensitive

patients), and an increase in sample size was needed to detect the 10% increase in response rate being targeted.

Analysis plan

The statistical analysis plan for the study allowed for interim analyses after 50 evaluable patients (i.e. at least the result of 3 x CHOP must be known) and after 200, 400 and 600 evaluable patients, with results only disclosed to investigators if they resulted in the Independent Data Monitoring Committee (IDMC) recommending anything other than continued recruitment as per protocol.

Three interim analyses were performed. The first, with a cut off date of March 6th 2002 was carried out after 275 patients had been included in the induction phase and 148 randomised to maintenance or no maintenance. This revealed no reason for not continuing to recruit to the study as originally planned.

The second interim analysis (cut off date February 27th, 2004; 461 patients included in induction analysis; 319 patients included in the maintenance analysis) demonstrated a significant difference in overall and complete response rates for induction therapy with R-CHOP (as well as a significant increase in PFS). In both cases, the statistical significance crossed the formal threshold for early stopping and the IDMC recommended that the first randomisation be stopped. This was done on April 23rd 2004 and a major protocol amendment was prepared changing the study objective to assessment of the efficacy of rituximab maintenance treatment following R-CHOP induction therapy.

Before the study was re-opened with the amended protocol a third interim analysis was conducted, with a data cut-off of September 27th 2004. At this analysis the benefit of rituximab maintenance on PFS met the protocol determined level of significance for early stopping of the study. Consequently, no patient was recruited to the revised protocol and the study was closed to recruitment and fully analysed. The EORTC defined this as the final study analysis. Investigators were informed that the trial would not be re-opened on October 17th 2004. This announcement did not result in any early study withdrawals or cross-over of randomised patients from observation to maintenance and will not have materially altered study outcomes.

In addition to the above analyses conducted by the EORTC, a further analysis was carried out for regulatory purposes with a data cut-off of December 2004. This analysis is the most extensive to which Roche has access and forms the basis of the clinical and pharmacoeconomic case presented here. However, key efficacy data from the recent peer-

reviewed publication of the final analysis of the study (van Oers et al. 2006) are also included in the clinical section. These demonstrate that the benefits of rituximab are robust after further follow-up and are, in fact, increasing with time. As such, the economic case - where modelling was completed before the publication of the September 2005 analysis – based on the earlier analysis - represents a conservative estimate of the cost-effectiveness of the interventions under consideration.

Patient populations as defined for analytical purposes

The protocol specified that all efficacy analyses would be conducted on an “Intent-to-Treat” (ITT) basis and defined the ITT population as all randomised patients less those who were objectively demonstrated post-hoc to be ineligible for entry. During the course of the study EORTC Standard Operating Procedures were modified to define ITT populations as all randomised patients without exclusion. Efficacy analyses were carried out on this basis with two populations defined:

Induction ITT population (I-ITT). All patients randomised to induction analysed according to treatment allocated at randomisation

Maintenance ITT population (M-ITT). All patients randomised to maintenance analysed according to treatment allocated at randomisation

Similarly, two safety populations were defined:

Induction safety population (I-SAP). All patients who received at least one dose of induction therapy analysed according to treatment received (in all cases the treatment they were randomised to)

Maintenance safety population (M-SAP). All patients who received at least one dose of maintenance therapy analysed according to treatment received during first maintenance period (in 2 cases this was not the randomised therapy).

Study GLSG-FCM

Hypotheses under test and statistical tests used.

Induction phase

The comparison between FCM and R-FCM was designed to detect a 20% increase in response rate, assuming a response rate to FCM alone of 57%. The study utilised a 1-sided triangular sequential test with a working significance level of 0.05, which allowed detection of

the assumed superiority of R-FCM over FCM with a probability of 95% with recruitment to be stopped as soon as the level of significance was reached. This approach was designed to be equivalent in power and working significance to a fixed sample test with 228 observations. Exploratory analyses were done for histological subgroups, the progression-free survival from the start of therapy and overall survival using the Fisher test for binary responses and the log-rank test and univariate Cox regression for time-censored observations.

Induction phase

The comparison of rituximab maintenance with no further treatment was designed to test whether maintenance could reduce the risk of relapse by 50%. A 1-sided triangular sequential test with a working significance level of 0.05 was applied, allowing detection of the assumed superiority of maintenance over observation with a probability of 95% and halting of the trial as soon as significance was reached. This approach was designed to be equivalent in power and working significance to a fixed sample test with 91 events. Exploratory analyses were done for histological subgroups and overall survival. The Fisher test was used for comparison of binary responses and the log-rank test and univariate Cox regression for the analysis of time-censored events.

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

Table 9: Critical appraisal of RCTs included in this review

Criterion	ECOG 1496	GLSG-FCM
Concealment of allocation	Open-label study. Placebo control for a study involving IV rituximab administration and oral and IV pre-medication would been very difficult and probably considered unethical during maintenance/observation End-points are fairly objective and placebo effect not likely to	Open-label study As ECOG 1496

	be a major problem	
Randomisation technique	An appropriate technique was used: centralised using minimisation approach of Pocock and Simon	An appropriate technique was used: centralised using permutated block approach
Sample size justified adequately?	Yes. Though given there was no data on which to base any assumption on the efficacy of rituximab maintenance at the time of protocol development	Yes Comment as for EORTC 20981
Adequate follow-up	Yes Closure of first- and second-randomisations was mandated by independent monitoring given highly statistically significant differences in outcomes, making further follow-up very unlikely to change outcomes materially. Follow up appropriate to trajectory of disease with follow-up being longer than the median PFS after induction therapy	Yes Statistical design mandated that study end was determined by adequate events for statistical certainty so follow-up was self correcting. Again, follow-up appropriate to trajectory of disease with follow-up being longer than the median PFS after induction therapy
Assessors aware of treatment allocation?	Unclear Although no reference made to blinding of assessors it is likely that scan results which would determine response/progression would, in most cases, be reported by radiologists with no interest in the study	As EORTC 20981
Parallel group/cross-over	Parallel-group Primary end-points in both parts of study not influenced by post-study treatment	Parallel-group Primary end-points in both parts of study not influenced by post-study treatment
Carried out in UK?	International study including UK There were 37 UK study centres who recruited 102 of the 465 patients randomised. Indicating that UK clinicians found this study pertinent to	No However there are no obvious differences between the study population and non-trial patients requiring treatment for relapsed follicular lymphoma in the UK, except,

	their practice and had plenty of patients fitting the study entry criteria within their clinical population. As explained in Section 4.1 the control treatment in this study (induction with CHOP followed by no further treatment until relapse) is used in routine clinical practice in the UK	perhaps that the study patients are slightly younger . However, disproportionate recruitment of younger patients is a general problem in oncology clinical trials – the study had no upper age limit for participation. As explained in Section 4.1 the control treatment in this study (induction with fludarabine-based chemotherapy followed by no further treatment until relapse) is used in routine clinical practice in the UK
Dosage regimen	For both induction and maintenance portions of the trial dosage regimens accord with SmPC recommendations	The SmPC does not make specific recommendations on the combination of FMD and rituximab, but the use of 1 dose per cycle is consistent with all other recommendations for the use of rituximab given concomitantly with cytotoxic chemotherapy The maintenance schedule (8 doses of rituximab delivered in 2 block of 4 weekly doses 3 and 6 months after completion of induction therapy) is not consistent with the SmPC, which recommends 8 x 3-monthly doses, but does deliver the same total dose of rituximab as maintenance
Study groups comparable?	Yes See Section 5.3.2	Yes See Section 5.3.2
Appropriate statistical tests?	Yes. See Section 5.3.5. Note that statistical analysis in this study has been subjected to both peer-review for publication and EMEA scrutiny	Yes. See Section 5.3.5. Note that statistical analysis in this study has been subjected to peer-review for publication
ITT analysis?	Yes for both induction and maintenance portions of study	No for induction phase. Although investigators report that analysis was done on an ITT basis, they excluded 10 patients from the original published analysis on the basis of inadequate documentation and 9 who were withdrawn between randomisation and receiving any study treatment Yes for maintenance portion, though in 19 patients documentation was not available at the time of analysis

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

5.4.1 Use of rituximab with chemotherapy to achieve remission in relapsed follicular lymphoma

As shown in Table 10, EORTC 20981 achieved the primary endpoint specified for the induction part of the study. The addition of rituximab to CHOP chemotherapy administered for remission induction significantly increased the quantity (ORR) and quality (percentage CR) of objective responses obtained. PFS was also significantly improved by this intervention and the risk of death was improved by a substantial amount that approached statistical significance (P=0.0508). Again, these changes are of a magnitude that makes them highly relevant to patients.

Table 10: Impact of the addition of rituximab to standard cytotoxic induction therapy with CHOP for relapsed follicular lymphoma in study EORTC 20981

Parameter	CHOP N=231	R-CHOP N=234	Magnitude of benefit	p-value	Risk reduction (95% CI)[1]
Primary					
ORR					
Dec 2004 analysis	74%	87%	13%	<0.001	-
Sept 2005 analysis	72.3%	85.1%	12.8%	<0.0001	-
CR[2]					-
Dec 2004 analysis	16%	29%	13%	0.0005	
Sept 2005 analysis	15.6%	29.5%	13.9%	0.0001	
PR[2]					-
Dec 2004 analysis	58%	58%		0.9449	-
Sept 2005 analysis	56.7%	55.6%		Not significant	
Secondary					
Median OS (months)	nr	nr		0.0508	32% (0-54%)
Median PFS (months)					
Dec 2004 analysis	19.4	33.2	13.8 months	0.0001	38% (21-52%)
Sept 2005 analysis	20.2	33.1	12.9 months	0.0003	35% (not reported)

Abbreviations: *CI, confidence interval; CR, complete response rate; nr, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TNLT, time to next antilymphoma treatment.*
[1] Estimates were calculated by hazard ratios
[2] Last tumour response as assessed by the investigator

As shown in Table 11 a very similar outcome from the use of rituximab alongside induction therapy was reported in study GSG-FCM, where addition of rituximab to fludarabine-based combination chemotherapy increased response rate by 44%, meeting the primary end-point of the study, as well as significantly extending PFS producing a clear trend towards improved overall survival.

Table 11: Impact of the addition of rituximab to FCM chemotherapy as induction treatment for relapsed indolent lymphomas in study GSG-FCM (based on Forstpointer et al. 2004).

Parameter	FCM	R-FCM	p-value
Primary (response rates)			
All patients			
No. evaluable*	62	66	
CR, no. (%)	8 (13)	22 (33)	0.005
PR, no. (%)	28 (45)	30 (45)	NS
MR, no. (%)	4 (6)	1 (2)	NS
SD, no. (%)	3 (5)	3 (5)	NS
PD, no. (%)	16 (26)	8 (12)	NS
Death, no. (%)	3 (5)	2 (3)	NS
CR+PR, no. (%)	36 (58)	52 (79)	0.01
Follicular lymphoma			
No. evaluable*	30	35	NS
CR, no. (%)	NS (23)	NS (40)	NS
PR, no. (%)	NS (47)	NS (54)	NS
PD, no. (%)	NS (17)	NS (3)	NS
CR+PR, no. (%)	NS (70)	NS (94)	0.011
Secondary			
All patients			
Median PFS (months)	10	16	0.0381
Median OS (months)	24	NR	0.003
2 year survival	53%	73%	NS
Follicular lymphoma			
Median PFS (months)	21	NR	0.0139
Median OS (months)	NR	NR	
2 year survival	70%	90%	0.0943

Abbreviations: *CR, complete response; MR, minor response; PD, progressive disease; SD, stable disease; NR, not reportedNS, not stated; OS, overall survival; PFS, progression-free survival.*
** Evaluable patient pool of 128 excludes 10 patients with incomplete documentation and 9 withdrawn between randomisation and therapy*

The response data from the induction portion of GLSG-FCM was updated by Forstpointer et al. (2006) in their publication dealing with the maintenance phase of the study. With data now available on 133 patients (65; FCM, 68, R-FCM), the ORR was 58% versus 79% for all patients treated with FCM and R-FCM, respectively, and 71% versus 94% in the sub-group of 68 patients with follicular lymphoma (P=0.01).

Although the inferences that can or should be drawn from cross-trial comparisons are limited, it is interesting to note that although CHOP (in EORTC 20981) and FCM (in GLSG-FCM) induction therapies are both improved by the addition of rituximab the outcome of both

R-CHOP (85.1% ORR; median PFS 20.2 months from second randomisation i.e 24-26 months response duration) and R-FCM (94% ORR; median duration of response 26 months) followed by observation are broadly similar. Thus, it would appear that in the same way that fludarabine-based chemotherapy and CHOP are considered to be of similar efficacy as induction regimens in patients who are naïve to both, so R-CHOP and R-FCM seem to be similarly efficacious as induction regimens

5.4.2 Use of rituximab maintenance therapy to extend remissions in relapsed follicular lymphoma induced by administration of cytototoxic chemotherapy given alone or in conjunction with rituximab.

5.4.2.1 Impact of rituximab maintenance on progression-free survival

The ability of rituximab to keep patients in remission was the primary end-point in the maintenance portion of both the EORTC 20981 and GLSG-FCM studies. This accords with the primary aim of current treatments in follicular lymphoma – to keep patients in remission (and, therefore, symptom- and treatment-free) for as long as possible.

EORTC 20981

At the time of the data cut-off for the regulatory analysis of the study, 103 patients (62%) on observation and 61 patients (37%) in the rituximab maintenance arm had progressed/relapsed or had died. The majority of patients had progression as their first event (100 observations, 61 rituximab) and only 8 patients (3 observations, 5 rituximab) had died without progression. As shown in Table 12 rituximab maintenance had almost tripled PFS from 14.3 months to 42.2 months ($P<0.001$) corresponding to a reduction in risk of disease progression of 61% with the lower boundary of the 95% confidence interval at 45%.

The robustness of this result is underscored by the final EORTC analysis of the study carried out 9 months later in September 2005. This showed that the improvement in median PFS associated with rituximab maintenance therapy had increased by 8.7 months from 27.9 months to 36.6 months

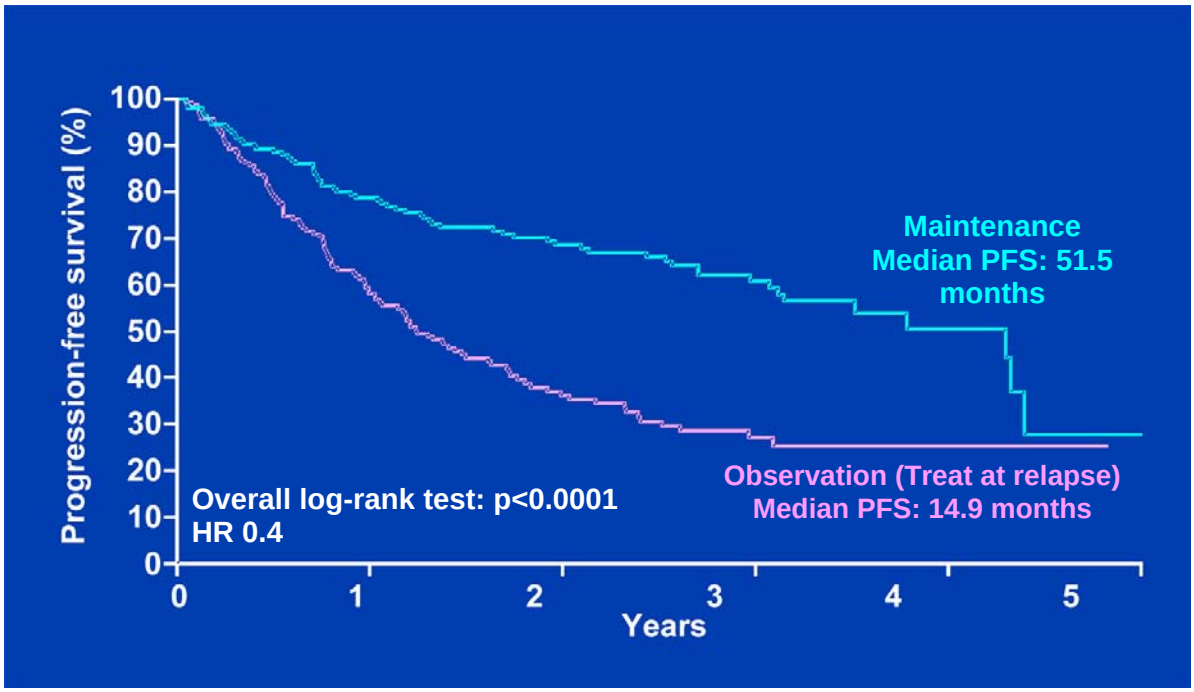
Table 12: Impact of rituximab maintenance therapy on progression-free survival in sub-groups of patients recruited in study EORTC 20981

Subgroup	Median progression-free survival (months)			Risk reduction (95% CI)
	Observation	Rituximab	p-value (Log-Rank)	
Overall				
Dec 2004 analysis	14.3	42.2	<0.0001	61% (45-72%)
Sept 2005 analysis	14.9	51.5	<0.0001	60% (not available)
CHOP induction				
Dec 2004 analysis	11.6	37.5	<0.0001	71% (54-82%)
Sept 2005 analysis	11.6	42.2	<0.0001	70% (not available)
R-CHOP induction				
Dec 2004 analysis	22.1	51.9	0.0071	46 % (15-65%)
Sept 2005 analysis	23.0	51.8	0.0043	46% (not available)
CR after induction	14.3	52.8	0.0008	64% (33-81%)
PR after induction	14.3	37.8	<0.0001	54% (33-69%)

Abbreviations: *CI, confidence interval; CR, complete response; PR, partial response*

The extent of the reduction in the risk of disease progression is illustrated graphically below in Figure 6.

Figure 6: Kaplan-Meier graph of progression-free survival in EORTC 20981 in patients receiving and not receiving maintenance rituximab in the M-ITT population (see Section 5.3.5)



Given the design of the study it is possible to suggest that all of the advantage of receiving maintenance rituximab accrued to patients who had not received the drug during remission induction i.e. that EORTC 20981 was, in effect a study of early (induction) versus late (maintenance) rituximab. To examine this, a sub-group analysis was conducted examining the impact of maintenance therapy according to induction treatment. The results of this are

shown in Table 12. From this, it is clear that maintenance with rituximab, after successful induction, is valuable in extending PFS regardless of exposure to rituximab during induction. Indeed, in patients who had received rituximab as a component of R-CHOP induction therapy, rituximab maintenance more than doubled PFS from less than 2 years to more than 4 years (p=0.0071), corresponding to a 46% reduction in the risk of disease progression.

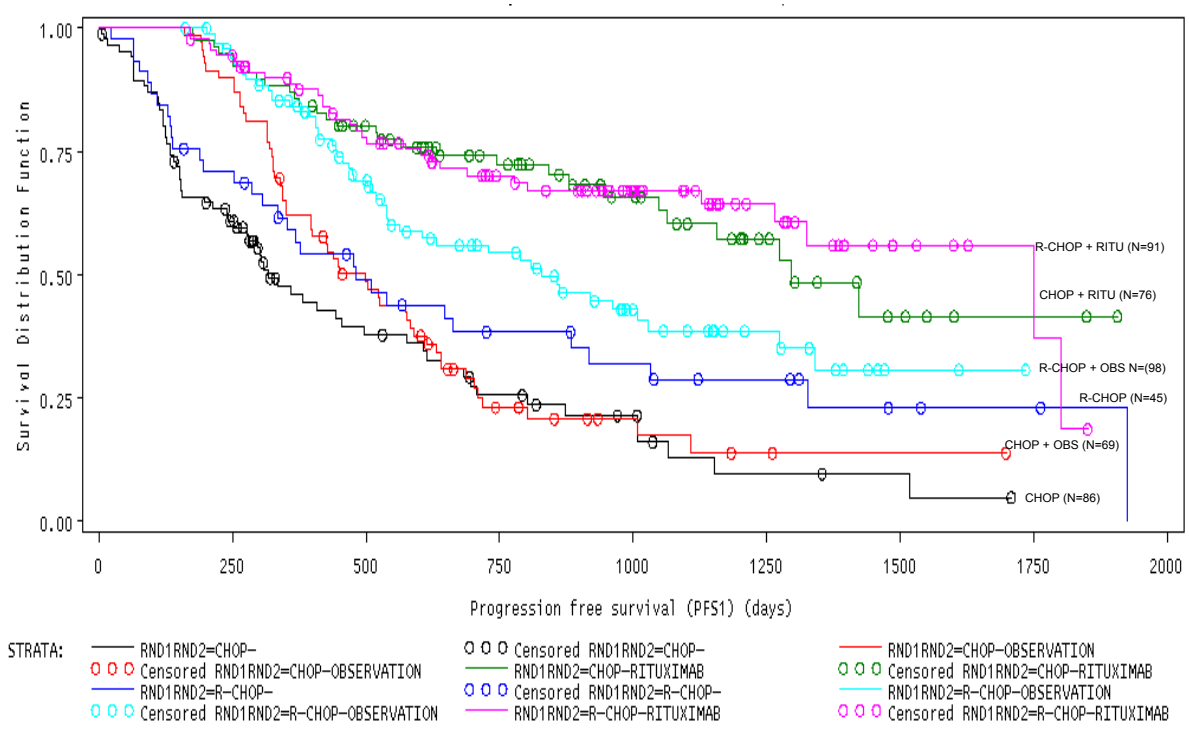
Regardless of whether patients received CHOP or R-CHOP induction, the benefit of receiving rituximab maintenance was stable over time with similar PFS gains reported in the analyses of December 2004 and September 2005 (see Table 12).

It should be noted that these subgroup analyses do not capture the full extent of benefit to patients of receiving rituximab as part of induction and maintenance since they do not reflect the greater chance of patients being eligible for maintenance when they first receive rituximab together with their CHOP induction (R-CHOP having a higher response rate than CHOP alone). Sub-group analysis also revealed that rituximab maintenance was of value to patients in both PR and CR after initial induction therapy. Indeed, the magnitude of the benefit is, if anything, slightly greater in patients receiving rituximab maintenance after achieving CR. This strongly suggests that the impact of maintenance goes beyond improving the quality of response in patients who failed to achieve CR in initial induction.

Overall, sub-group analysis supports the concept that rituximab maintenance therapy is of value regardless of the induction regimen used and the quality of response achieved with it.

The value of receiving rituximab maintenance in extending PFS regardless of initial induction treatment is well illustrated in Figure 7 which shows PFS for all possible combinations of induction treatment and maintenance.

Figure 7: Impact of rituximab maintenance on progression-free survival for all possible treatment combinations in study EORTC 20981



NB Blue and black curves represent patients failing to achieve remission after induction and, therefore, not subjected to second randomisation.

The most favourable outcome in terms of PFS was seen in patients receiving R-CHOP followed by rituximab maintenance, followed by those receiving rituximab as maintenance only and then those receiving rituximab as part of induction only. The trend towards increased benefit from receiving rituximab as induction and maintenance over those receiving rituximab as induction or maintenance only is clear. The cost effectiveness of using rituximab in these various schedules will be evaluated in section 6 below.

GLSG- FCM study

As in EORTC 2098, the maintenance phase of this study also prolonged response duration compared with observation after induction of remission with FCM+/-R (see Table 13).

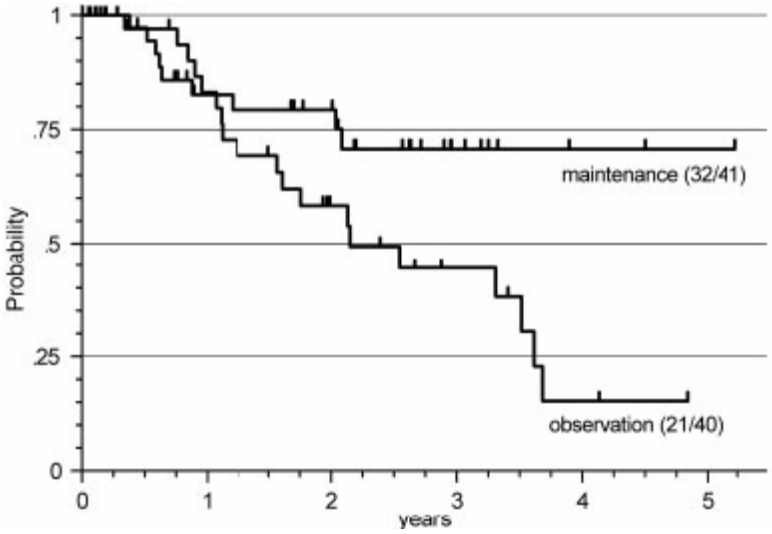
Table 13: Impact of the addition of rituximab maintenance after successful induction of remission by FCM+/-rituximab in study GLSG-FCM

Subgroup	Median duration of response (months)		
	Observation	Rituximab	p-value (Log-Rank)
Overall (N=176)	17	NR	*P*<0.001
Follicular lymphoma after R-FCM induction (n=81)	26	NR	*P*=.035
Mantle cell lymphoma after R-FCM induction (n=47)	12	14	NS

176 of 195 randomised patients were evaluable and 19 inevaluable (19 incomplete documentation, 1 patient moved to another institution, 1 patient record inaccessible, 3 inadequate staging documentation at the end of induction)

Again, the impact of 8 maintenance doses of rituximab in delaying relapse can clearly seen by reference to the Kaplan Meier curves for response duration presented in Figure 8

Figure 8: Kaplan Meier curves for response duration for patients with follicular lymphoma receiving rituximab maintenance or no further therapy prior to relapse after induction with R-FCM in trial GLSG-FCM



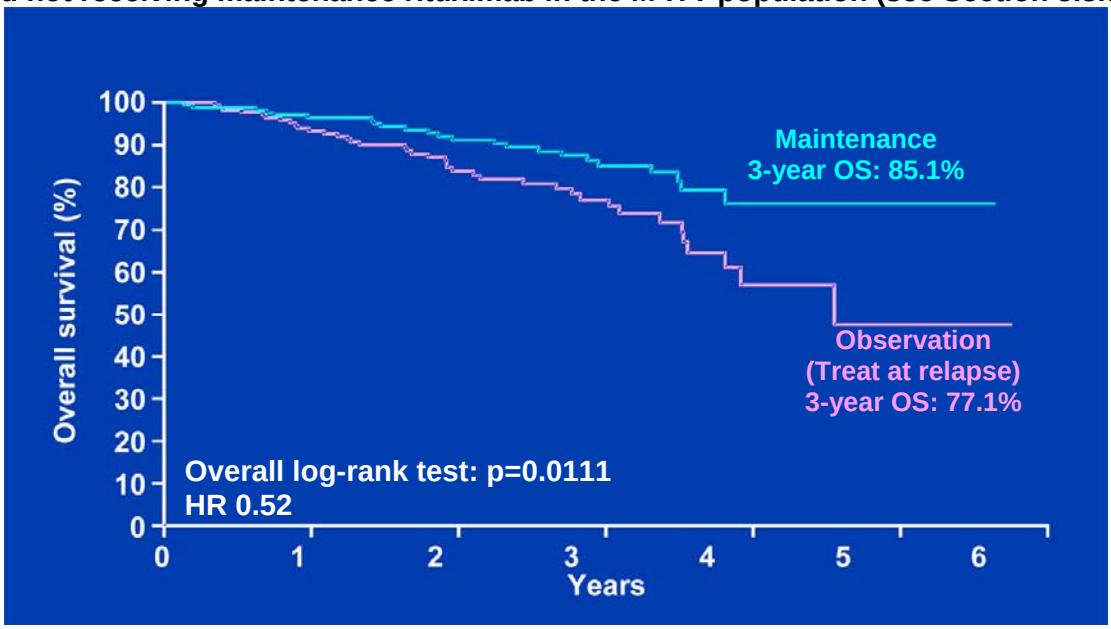
5.4.2.2 Impact of rituximab maintenance on overall survival

EORTC 20981

After a median of 28 months follow-up, there had been relatively few deaths (36 [21.6%] in the observation arm and 18 [10.8%] in the rituximab arm) amongst study patients and the median OS could not be calculated. However, the risk of death had been significantly reduced by 56% (p=0.0039) by the use of rituximab maintenance therapy. The impact of rituximab maintenance on overall survival can be seen clearly in Figure 9.

A similar reduction in the risk of death (48%) was reported in the final analysis of the study by the EORTC in September 2005. In this publication, van Oers et al. (2006) also note than the use of rituximab maintenance improves 3 year overall survival from 77.1% to 85.1% (p=0.011 log-rank test).

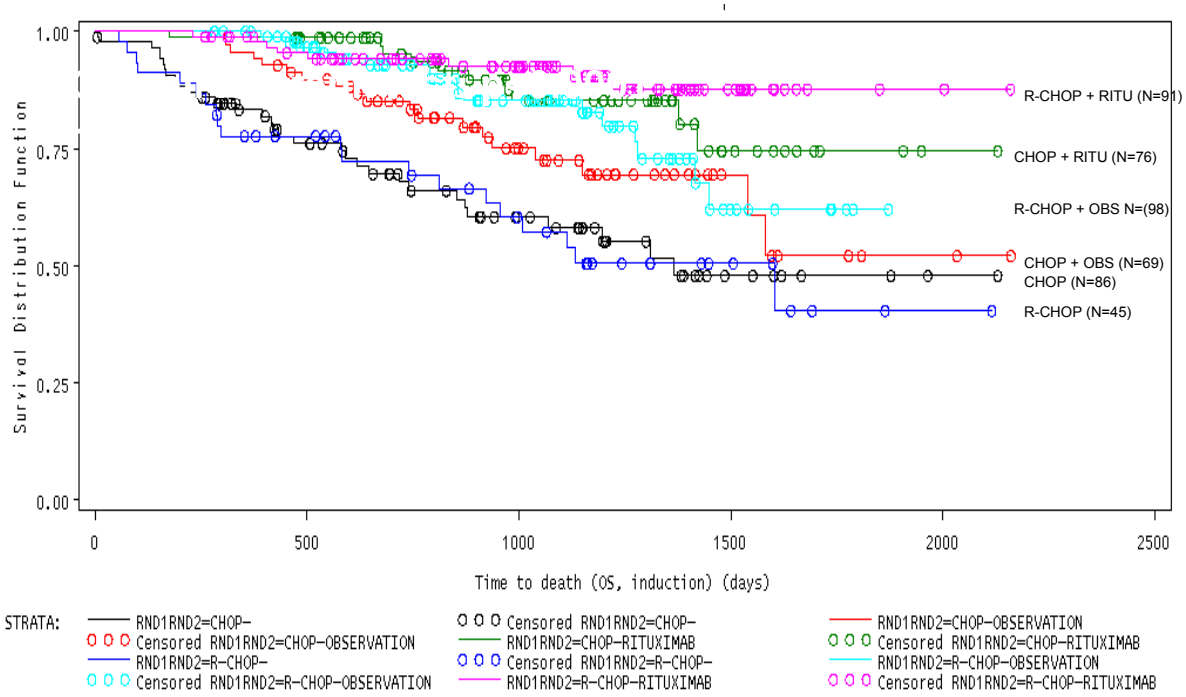
Figure 9: Kaplan-Meier graph of overall survival in EORTC 20981 in patients receiving and not receiving maintenance rituximab in the M-ITT population (see Section 5.3.5)



As with PFS, it is worthwhile to investigate whether the beneficial impact of rituximab on OS is restricted to patients receiving chemotherapy alone as induction treatment. As shown in Figure 10, when OS is used as the end-point, the optimum treatment approach is still rituximab at both induction and maintenance. Indeed the reduction in the risk of death associated with rituximab maintenance compared with observation is very similar for patients receiving CHOP (HR 0.498; 95% CI, 0.228-1.088; log-rank p value 0.0743) and R-CHOP (HR 0.438; 95% CI, 0.188-1.101; log-rank p value 0.0483) induction.

Again, it must be remembered that this presentation of the data underestimates the benefit to patients of receiving rituximab with induction and as maintenance by failing to reflect the increased percentage of patients achieving a response to induction with R-CHOP and hence eligible to receive and benefit from maintenance therapy.

Figure 10: Impact of rituximab maintenance on overall survival for all possible treatment combinations in study EORTC 20981



GLSG-FCM

Very limited data are available concerning the impact of rituximab maintenance as used in this study on overall survival. In the peer reviewed publication by Forstpointer *et al* (2006) it is reported that the estimated proportion of patients alive at 3 years increases from 57% after observation only to 77% after rituximab maintenance (P=0.1). Although this difference is not statistically significant it demonstrates a clear trend towards improved overall survival with the use of rituximab maintenance, even after a limited number of deaths.

5.5 Meta-analysis

The two relevant studies (EORTC 20981 and GLSG-FCM) reached similar conclusions:

- that addition of rituximab to induction chemotherapy in relapsed follicular lymphoma improves response rate (the primary end-point in both studies), PFS and OS. Both R-FCM and R-CHOP produce broadly similar outcomes (see Section 5.4.1 above)

- that the use of maintenance rituximab improves PFS/duration of response with a clear trend towards improved OS that reaches statistical significant in the EORTC 20981 study

However, there are significant differences between the treatments used in the two studies (induction chemotherapy regimen, number of cycles of induction therapy used and rituximab maintenance schedule used) and the presentation of data from them (duration of response versus PFS; reduction in risk of death versus percentage of patients alive at 3 years).

To meta-analyse these studies would not be practical on the basis of published information and even if it were there would be little value in it. The qualitative results of both studies are already known to be the same, and any pooling of data would produce a quantitative measures of treatment effect that would be an average of the treatment effects of two different treatment approaches (one using an unapproved maintenance schedule) – it would not produce a more precise estimate of either of the individual treatment schedules.

5.6 Indirect/mixed treatment comparisons

No information on mixed or indirect comparisons will be presented due to the availability of phase III randomised control trial evidence that included the relevant comparator.

5.7 Safety

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

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

5.7.1 Safety of rituximab in combination with cytotoxic chemotherapy for remission induction.

EORTC 20981

The excellent safety and tolerability of rituximab added to conventional cytotoxic chemotherapy is well established and has been extensively reviewed in previous NICE submissions.

As shown in Table 14 the addition of rituximab to conventional induction therapy with CHOP induction chemotherapy in study EORTC 20981 added little to the overall toxicity of treatment. There was a small increase in Grade 3 and 4 adverse events but no increase in the rates of toxicity-related study withdrawal or death during induction, both of which are low in both treatment arms.

Table 14: Overview of safety of rituximab added to induction chemotherapy with CHOP in study EORTC 20981

	CHOP N=222	**R-CHOP N=234**
All adverse events	223 (98%)	233 (100%)
Grade 3 and 4 adverse events	152 (67%)	185 (79%)
Toxicity-related study withdrawals	6 (3%)	8 (3%)
Deaths during induction therapy	2 (<1%)*	1 (<1%)**

**1 sepsis, 1 respiratory distress syndrome*
***pneumonia*

Few adverse events were reported amongst R-CHOP patients with a frequency 5% or more in excess of that reported amongst CHOP recipients, the exceptions being those affecting the skin (alopecia, rash/itch, others), infections, allergies and neutropenia.

A similar pattern was seen for Grade 3-4 events with relevant differences (>/=4%) seen only for blood and marrow toxicity (55% of R-CHOP patients versus 47%), skin reactions (14% versus 7%, no grade 4) and allergies (4% versus 0%). It should be noted that despite the higher incidence of neutropenia and infections amongst R-CHOP patients, there was no increase in the incidence of Grade 3 or 4 infections in the R-CHOP group (20% versus 18%)

Allergic and skin reactions are, almost certainly manifestations of rituximab infusion reactions whilst at least some of the modest increases in neutropenia, infection and alopecia

are probably related to more patients in the R-CHOP arm completing the planned 6 cycles of induction therapy and so receiving more chemotherapy.

Infusion reactions are the hallmark toxicity associated with rituximab and are discussed in Section 5.7.2.1.

For Grade 3 and 4 adverse events relevant differences (>/=4%) were seen only for blood and marrow toxicity (55% of R-CHOP patients versus 47%), skin reactions (14% versus 7%, no grade 4) and allergies (4% versus 0%). It should be noted that despite the higher incidence of neutropenia and infections amongst R-CHOP patients, there was no increase in the incidence of Grade 3 or 4 infections in the R-CHOP group (20% versus 18%)

The addition of rituximab to FCM induction chemotherapy in the GLSG-FCM study was similarly well tolerated with few differences noted in the tolerability of FCM with or without rituximab – asymptomatic lymphopenia was significantly more common during R-FCM (51% of treatment courses) than FCM (39%) treatment.

Additionally, and as expected, some acute reactions to rituximab infusion were seen, predominantly during the first infusion. These required the early termination of rituximab in 4 patients.

5.7.2 Safety of rituximab administered as maintenance after induction of remission with chemotherapy with or without rituximab

EORTC 20981

The most complete data on the safety of rituximab maintenance comes from study EORTC 20981. As shown in Table 15, rituximab maintenance therapy was generally well tolerated in this study. Importantly, no death was attributed to the treatment and just 4% of patients discontinued treatment prematurely for safety reasons. Rituximab maintenance was equally well tolerated in study GLSG-FCM, with just a single patient stopping treatment early because of a severe allergic reaction to rituximab.

In comparing the rates of adverse events in patients assigned to maintenance rituximab or observation two factors should be considered which bias such the comparison against the rituximab group:-

Patients on observation arm tended to progress earlier. At progression adverse event data collection ceased, resulting in a shorter period during which adverse events could be reported for observed patients compared with those receiving rituximab.

The studies were open-labelled. This may have resulted in under-reporting of non-serious adverse events in the observation groups.

In addition, the maintenance/observation period starts immediately after patients have completed induction chemotherapy. This has significant short- and long-term toxicities which spill over into the early weeks of maintenance therapy. This is illustrated by the decline in adverse event frequencies between the first and final 3-month maintenance/observation periods in study EORTC 20981 and the high proportion of adverse events in the control arm considered to be treatment related, as shown in Table 15.

Table15: Overview of safety of rituximab maintenance/observation after induction with CHOP+/-rituximab in study EORTC 20981

	Observation N=166	**Rituximab N=166**
All adverse events Whole observation period First 3 month observation period Eighth 3 month observation period	 130 (78%) 102 (62%) 61 (37%)	 149 (90%) 119 (72%) 83 (50%)
Grade 3/4 adverse events	38 (23%)	61 (37%)
Treatment-related adverse events	91 (55%)	128 (77%)
Toxicity related withdrawals	NA	6 (4%)
Deaths (not related to treatment)	3 (2%)	4 (2%)
Deaths (related to treatment)	NA	0 (0%)

Abbreviation: *NA, not applicable.*

Adverse event categories that were reported at a higher incidence (>/= 5% difference) with rituximab compared to observation in study EORTC 20981 were: flu-like symptoms (mainly lethargy, myalgia and arthralgia), neurologic (mainly sensory and pain), infections, blood/bone marrow (mainly leucopenia and neutropenia) pulmonary (mainly cough and shortness of breath), “other” and allergy. As with rituximab used for induction most of these rituximab-associated adverse events are symptomatic of acute reactions occurring during rituximab infusion.

As shown in Table 16, when Grade 3 or 4 toxicities reported during the maintenance phase of EORTC 20981 are considered alone, those affecting blood/bone marrow and infections are still more common amongst rituximab recipients and account for most of the excess events in the rituximab arm. However, neurological problems and ‘flu-like symptoms are

actually more common amongst observation patients, with other events infrequent and similar in the two study arms.

Table 16: Grade 3-4 adverse events by NCIC class for patients in the maintenance phase of study EORTC 20981

NCIC-CTC class	Observation N=166 No. (%)	Rituximab N=166 No. (%)
Patients not assessed	4 (2)	1 (<1)
Total patients with at least one adverse event	38 (23)	61 (37)
Total number of adverse events	54	85
Blood/bone marrow	12 (7)	22 (13)
Cardiovascular	9 (5)	11 (7)
Infection	3 (2)	17 (10)
Neurologic	9 (5)	7 (4)
Gastrointestinal	5 (3)	10 (6)
'Flu-like symptoms	8 (5)	2 (1)
Skin	2 (1)	3 (2)
Bone	1 (<1)	3 (2)
Pulmonary	-	1 (<1)
Cancer related	1 (<1)	1 (<1)
symptoms	1 (<1)	1 (<1)
Genito-urinary	-	2 (1)
Other	-	1 (<1)
Allergy	1 (<1)	-
Coagulation	1 (<1)	-
Endocrine	-	1 (<1)
Hepatic	1 (<1)	-
Metabolic	-	1 (<1)
Weight		

GLSG-FCM

In study GLSG-FCM the pattern of adverse events during rituximab maintenance was similar to that seen in the EORTC 20981 study with events in the following categories reported at a higher incidence (>/= 5% difference) in maintenance recipients than controls: blood/bone marrow (mainly leucopenia and granulocytopenia), infection, fever, diarrhoea, pulmonary toxicity and liver enzyme elevation, but none of these differences were statistically significant

When Grade 3 and 4 adverse events are considered, only blood and bone marrow events (mainly leucopenia) and fever were reported at a higher frequency (>/=4%) for the maintenance group compared to controls.

5.7.2 Comments on specific adverse events

Specific comment is appropriate on adverse events affecting the blood/bone marrow and infections which constitute the majority of the excess Grade 3 or 4 events amongst rituximab patients and infusion reactions which are the characteristic toxicity associated with rituximab elsewhere.

5.7.2.1 Infusion reactions

These are known to be a frequent complication of rituximab treatment for lymphoma. When the drug is used as monotherapy for relapsed indolent lymphoma more than 50% of patients experience infusion reactions and, in about 10% of cases, these are complicated by bronchospasm or hypotension (see SmPC). Symptoms attributable to infusion reactions were reported amongst rituximab recipients in both the induction and maintenance phases of the two studies reviewed here. However, the severity appeared to be lower than that described in the original monotherapy studies.

For example, in EORTC 20981 the absolute difference in the percentage of patients experiencing 'flu-like symptoms in rituximab maintenance and observation groups was only 10% (48% versus 38%) with "allergy" reported in another 7% of rituximab recipients.

Similarly in GLSG-FCM the percentage of patients reporting those symptoms most likely to describe rituximab infusion reactions was only slightly greater in the rituximab maintenance group than amongst controls: allergy (4% versus 2%), exanthema (6% versus 5%), fever (11% versus 3%) or pulmonary toxicity (7% versus 2%).

Furthermore, severe or life-threatening 'flu-like symptoms, pulmonary problems or allergy were reported in 1%, 2% and <1% of rituximab recipients respectively. The corresponding frequencies for observed patients being 5%, <1% and 0%, respectively. n GLSG-FCM Grade 3 or 4 fever and pulmonary toxicity were reported in 4% and 1% of rituximab maintenance patients, respectively but none in the observation group.

There are three plausible reasons for apparently low frequency and modest severity of infusion reactions in these studies:

- Patients on CHOP induction receive high dose steroids as part of their chemotherapy regimen, these blunt any immune-mediated part of rituximab infusion reactions
- Severe infusion reactions are known to be more common in patients with a high tumour burden. Patients in these studies received effective cytotoxic chemotherapy from the

start of their rituximab treatment. This would have led to a rapid reduction in tumour bulk reducing the likelihood of severe rituximab infusion reactions during induction

- 55% and 79% of patients receiving rituximab maintenance in studies EORTC 20981 and GLSG-FCM, respectively, had already received the antibody as part of their induction. The frequency and severity of infusion reactions is known to decrease with successive infusions.

Although clinicians are well used to administering rituximab to lymphoma patients and to dealing with any resultant infusion reactions, the reduced severity of such reactions in the maintenance setting will be welcomed by both patients and those treating them. In other settings, infusion reactions have been the most prominent subjective toxicity of rituximab and reduction in their severity makes an already well tolerated treatment even easier for patients to cope with. It also makes treatment quicker and easier to administer – the recommended way of dealing with such reactions is to slow down or temporarily suspend drug infusion. This requires nursing intervention and extends treatment times, reducing the capacity of busy treatment clinics, but is less likely to be required in the maintenance setting.

5.7.2.2 Infections

In both the EORTC 20981 and GLSG-FCM studies, infections were more common in patients receiving rituximab maintenance than amongst those in the observation group. In EORTC 20981 43% and 22% experienced at least one infection, respectively, and in GLSG-FCM infection was reported in 28% of patients receiving rituximab maintenance and 19% of observed controls.

In EORTC 20981, the difference remained after adjustment for time under observation, with the estimated frequency of infective episodes being 0.264 per patient year in the observation arm and 0.620 per patient year in the rituximab maintenance arm. The most common sites of infection were ear, nose and throat, lung and skin/subcutaneous. Despite the higher incidence of infection in this study, only 8 patients (5%) receiving rituximab maintenance – compared with none on observation - had infections that were classified as Serious Adverse Events and they only contributed to the premature cessation of treatment in 4 patients.

Likewise, in GLSG-FCM the incidence of Grade 3 or 4 infections in the maintenance arm was low (4%) with no serious or life-threatening infections reported amongst controls.

5.7.4 Blood and bone marrow

The higher incidence of adverse events in this category amongst rituximab recipients compared to observation patients in study EORTC 20981 (shown in Table 16) is accounted for by more rituximab patients experiencing leucopenia (29% versus 21%) and neutropenia (23% versus 12%). The incidence of Grade 3 and 4 haematological events was also higher (13% versus 7%) amongst patients in the rituximab maintenance group.

However, for both observation and rituximab groups the incidence of blood/bone disorders was highest in the first 3 month maintenance period (21% and 25%, respectively) declining to 5% and 6%, respectively in the 8th 3 month period. This suggests that many of the abnormalities in white blood counts detected during the maintenance phase represent residual toxicity from the induction schedule, which gradually resolves regardless of ongoing rituximab treatment. Of 49 patients with documented neutropenia at the end of induction therapy, and randomised to rituximab maintenance, 33 recovered during the first 3 months of maintenance treatment and 12 during months 3-6.

A similar picture of increased lymphopenia and granulocytopenia was seen in patients receiving rituximab maintenance in GLSG-FCM.

It is important to understand that abnormalities in white blood cell numbers are laboratory measures that do not, in themselves, cause problems to patients, though they may predispose to infection. However, as discussed above, the use of rituximab maintenance seems to increase only very modestly the risk of significant infection.

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

5.8.1 Summary of methodology of relevant non-RCTs

No non RCT evidence will be presented

5.8.2 Critical appraisal of relevant non-RCTs

Not relevant

5.8.3 Results of the relevant non- RCTs

Not relevant

5.9 Interpretation of clinical evidence

5.9.1 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 relevance of the evidence base must be judged with reference to the therapeutic goals in stage III-IV follicular lymphoma and the principles of treatment outlined in Section 4.1.

Relevance of end-points in clinical studies to patients with relapsed Stage III-IV follicular lymphoma

As explained, stage III-IV follicular lymphoma is generally considered incurable and patients are treated when they become symptomatic with a view to inducing remission, thereby alleviating symptoms. Patients in remission are not only free of the symptoms caused by overt disease, but also from the inconvenience and toxicity of the chemotherapy that will be required when they relapse, not to mention the psychological trauma that attends relapse with a disease that is, in most cases, ultimately fatal. There is a clear understanding amongst clinicians that remissions are of immense value to patients. Therefore, treatments which can induce more frequent or longer lasting remissions represent developments which are extremely relevant to patients and their carers.

Relevance of the impact of adding rituximab to induction chemotherapy in relapsed follicular lymphoma.

In this submission evidence has been presented from two well-conducted RCTs that rituximab, when added to induction chemotherapy in relapsed follicular lymphoma, increases the proportion of patients entering remission and the durability of those remissions. As explained in Section 4.1.4 achievement and maintenance of remission is invaluable to patients associated as it is with relief of symptoms, freedom from the requirement for chemotherapy and psychological burden of progressing or relapsing disease. The impact of adding rituximab to induction chemotherapy was similar for both anthracycline-based (CHOP) and fludarabine containing (FCM) chemotherapy with the already high response rates increased by 17-34% and progression-free survival extended by around 50% (the absolute duration of PFS in the R-FCM study is shorter because of the inclusion of mantle cell lymphomas which have a poorer prognosis). These differences are not only highly statistically significant, but also of a magnitude that would be expected to make a real difference to patients, especially as the “cost” to patients in terms of additional treatment burden is minimal – rituximab infusions are administered at the same time as IV chemotherapy and add little to treatment toxicity .

Relevance of the impact of administering rituximab maintenance after successful remission induction in relapsed follicular lymphoma.

Additionally, evidence is provided that when rituximab maintenance is administered to patients in remission, responses can be extended by an extent that is statistically and clinically of great significance – using the licensed 8 x 3-monthly maintenance schedule of rituximab after CHOP+/-R induction PFS was almost tripled from 14.3 to 42.2 months. A similar benefit was reported after the use of a different 8 dose maintenance schedule administered after R-FCM (median response duration not reached after 26 months observation in the maintenance group versus 26 months in the observation group). Clinically important prolongation of remission were seen regardless of whether patients had received rituximab as part of their induction chemotherapy, and clear evidence is presented that the optimum treatment strategy in relapsed follicular lymphoma consists of rituximab plus chemotherapy for induction followed by rituximab maintenance for those patients who achieve remission.

Additionally, sub-group analysis of EORTC 20981 shows that that the benefit of maintenance rituximab is not restricted to patients achieving a PR during induction – maintenance therapy is not just compensating for an inadequate response to induction therapy and is relevant to patients in PR and CR after completion of induction.

Until recently there was no evidence that any treatment could improve survival in stage III-IV follicular lymphoma and improved survival was not considered a realistic treatment goal, though it is of obvious relevance to patients suffering from a condition that is likely to kill them. Presented in this submission is clear evidence that the addition of rituximab to induction chemotherapy based on an anthracycline (Risk reduction 32%, P=0.0508) or fludarabine (3 year overall survival including poor-prognosis mantle cell lymphomas 82% versus 55%, P=0.056) produces a strong trend towards improved overall survival and that the use of maintenance rituximab improves overall survival after induction with CHOP+/-R (reduction in risk of death 56%, P=0.0039) and FCM+/-R ((3 year overall survival including poor-prognosis mantle cell lymphomas 77% versus 57%, P=0.056). Again, a sub-group analysis of patients entered in study EORTC 20981 demonstrated that the overall survival benefit resulting from maintenance rituximab was similar whether or not patients received rituximab as part of their induction chemotherapy.

Burden of rituximab treatment on patients

In a disease where cure is impossible and treatment is intended to enhance the amount of time spent in remission and symptom-free, the tolerability of maintenance therapy is also very relevant. The toxicity data from EORTC 20981 and GLSG-FCM are highly reassuring in this regard. Apart from some largely asymptomatic changes in laboratory parameters, treatment toxicity is mostly restricted to acute reactions during drug infusion. These reactions are short-lived and have only a minor impact on patients. Additionally, delivery of maintenance requires just 8 additional outpatient treatment appointments (each typically lasting half a day), which can usually be combined with the routine follow-up visits, which patients are normally required to attend regardless of maintenance therapy. Overall, the burden of maintenance therapy on patients is trivial relative to the benefits.

In summary, rituximab administered concomitantly with remission induction therapy for relapsed follicular lymphoma, and as maintenance therapy for responders, not only results in very substantial improvements in the conventional measures of treatment effectiveness in this disease – frequency and duration of disease remissions, it also improves overall survival which is clearly of importance to patients. These advances are offset by only modest increases in treatment toxicity and burden of drug administration.

5.9.2 Identify any factors that may influence the applicability 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 suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

5.9.2.1 Patient groups in trials versus clinical practice

Trial patients would have been actively treated by UK clinicians

In routine clinical practice patients with Stage 3-4 follicular lymphoma will undergo several courses of treatment interspersed with treatment-induced remissions. Treatment is triggered by symptoms experienced by the patient or clinical evidence that disease is compromising the function of other organs. As such patients with relapsed follicular lymphoma requiring treatment are a group that would be well recognised by UK clinicians treating follicular lymphoma in clinical practice. All patients in the EORTC 20981 study and the majority of those in the GLSG-FCM study had follicular lymphoma, with data presented separately on this group.

Additionally, a retrospective analysis was conducted on patients entering the EORTC study to ensure that they fitted generally accepted criteria for “requiring treatment”. This found that 73% of patients had characteristics that would be generally accepted as indications for active intervention Given the number of treatment triggers not included in the baseline data collected on study entrants(e.g. serous effusion, compression syndrome, symptomatic splenomegaly, leukemic phase with abnormal, lymphocyte count > 5,000 x 10^9/L, pruritus, and localized bone lesions as seen on x-ray or isotope scan) it seems highly likely that most or all of the patients in this study would have been viewed as needing active treatment by UK clinicians in routine clinical practice. Less information is available on study GLSG-FCM but, here too, 24-30% of patients had B-symptoms and 25-30% of patients had elevated lactate dehydrogenase levels, suggesting that recruits to this study also correspond to a group who would be treated with chemotherapy upon presentation to a UK clinician.

Prior chemotherapy treatments received by trial patients relevant to UK practice

There are no data from EORTC 20981 or GLSG-FCM on exactly what prior treatment had been received. In EORTC 20981 we know that patients had received adequate courses of 1 or 2 prior non-anthracycline chemotherapy regimens. Patients in first or second relapse who

are anthracycline naïve would be a familiar group to UK clinicians. In GLSG-FCM there appear to have been no limitations on prior chemotherapy with patients simply required to have had at least one prior chemotherapy regimen. Given that the principles of treatment in follicular lymphoma are universally accepted and that the drugs available in Germany much the same as in the UK, it seems unlikely that the prior chemotherapy received by patients entering the GLSG-FCM study would be much different to those received by UK patients at this point in their disease, though the introduction to Forstpointer et al. 2004, indicates that many study entrants had already received CHOP (in contrast to EORTC 20981 where none had received this regimen). As such GLSG-FCM complements EORTC 20981 very well, since it provides reassurance that rituximab during re-induction or remission works well whether or not patients have received the widely used CHOP regimen earlier in their disease.

Prior exposure to rituximab

One point of difference between the trial and clinical practice populations is that with the greater use of rituximab as part of first-line therapy a significant proportion of patients relapsing in clinical practice will be rituximab experienced, whereas patients entering EORTC 20981 were treatment naïve. Patients entering the GLSG-FCM could have received earlier rituximab, though only a minority did so.

However it is unlikely that the impact of prior rituximab exposure would have been large. Several lines of evidence support this-

- Some patients in the GLSG-FCM study were rituximab experienced and this study produced outcomes comparable to those achieved in the EORTC 20981 study where patients were all rituximab naïve. In a retrospective sub-group analysis of this study Dreyling et al. (2006a) concluded that pre-trial exposure to rituximab did not prejudice outcomes to treatment with R-FCM.

- The impact on rituximab maintenance in study EORTC 20981 was similar regardless of whether patients had received rituximab as part of their prior induction regimen. Similarly, the benefits of rituximab maintenance seen in the GLSG-FCM study were of a similar magnitude to those seen in the EORTC study, despite the majority of patients in the maintenance phase of the German study having received rituximab as part of their on-study induction therapy. Thus the use of rituximab in the first-line setting would be unlikely to reduce the impact of rituximab maintenance used in a subsequent remission

- There is evidence from other situations that retreatment with rituximab of patients who initially responded to the drug produces similar outcomes to those achieved with initial therapy. For example Weide et al. (2006) reported that when administered in a 62 patient phase II study the efficacy of an induction chemotherapy regimen of bendamustine, mitoxantrone and rituximab was similar in patients who had previously received rituximab (RR 75%, CR 38%) and those who were rituximab-naïve (RR 88%; CR 36%)

- Similarly Hainsworth et al. (2005, 2006) showed that the majority of patients in a study of rituximab maintenance or retreatment at relapse, following remission induction with rituximab monotherapy, retain sensitivity to rituximab even when relapsing after receiving 2 years of rituximab. A variety of other smaller studies support the concept that patients with follicular lymphoma still respond well to rituximab when rechallenged with it (Igarashi et al. 1999; Lopez et al. 2001; Reiser et al. 2003)

5.9.2.2 Control treatments

The two studies described above used CHOP and fludarabine-based combination chemotherapy as the standard induction treatments to which concomitant and maintenance rituximab was added. These are highly relevant to UK clinical practice – they are the predominant chemotherapy approaches used once regimens based on alkylating agents are deemed no longer appropriate. It can be seen that rituximab added to and given after either CHOP or fludarabine-based chemotherapy is similarly effective but raises the question of whether rituximab would add to efficacy of reinduction regimens based on alkylators alone? The landmark phase III study conducted by Marcus et al. (2005), comparing CVP chemotherapy with and without rituximab, in chemotherapy naïve patients provides compelling evidence that rituximab also dramatically increases the power of alkylator-based induction chemotherapy. Similarly, maintenance rituximab has been shown to prolong remissions induced not only by CHOP+/-R and FCM+/-R used in relapse but also after alkylator-based CVP chemotherapy used first-line (Hochster et al. 2005)and rituximab monotherapy (Ghielmini et al. 2004; Hainsworth et al. 2005)

In short, there is strong evidence that rituximab enhances the efficacy of induction chemotherapy with which it is combined and, when used as maintenance, prolongs remissions, however these are induced.

5.9.2.3 Relevance of dosing schedules used in clinical trials

The main study used in support of this submission - EORTC 20981- used the induction and maintenance schedules referred to in the MabThera SmPC for all patients

In the supportive study GLSG-FCM a different scheduling was used for the 8 rituximab maintenance doses, though the total rituximab maintenance dose delivered was the same. For induction, one dose of rituximab was used with each cycle of cytotoxic treatment. Although the MabThera SmPC makes no specific reference to the use of rituximab with fludarabine containing chemotherapy (it refers to induction chemotherapy with rituximab and cites the clinical data from the EORTC 20981 study by way of illustration) in all other indications where rituximab is combined with chemotherapy, one dose is administered per 3 week chemotherapy cycle. As such the induction schedule used by the GLSG is compatible with the SmPC.

Overall, despite the inevitable minor differences between clinical trials and routine practice it is possible to be confident that rituximab, used according to its SmPC, will improve outcomes in relapsed follicular lymphoma when used alongside induction chemotherapy and as a maintenance therapy for patients in remission. Furthermore, we can be confident that the benefits of rituximab used in this way are of a magnitude sufficient to be highly significant to patients.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

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 in appendix 3, section 9.3.

The search strategy aimed to identify all publications relating to rituximab and follicular lymphoma. Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study design.

6.1.2 Description of identified studies

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. Where studies have been identified and not included, justification for this should be provided.

Please see Appendix 10 for a description of the studies identified and studies included and excluded. See Appendix 4 for the overview of papers included.

6.2 De novo economic evaluation(s)

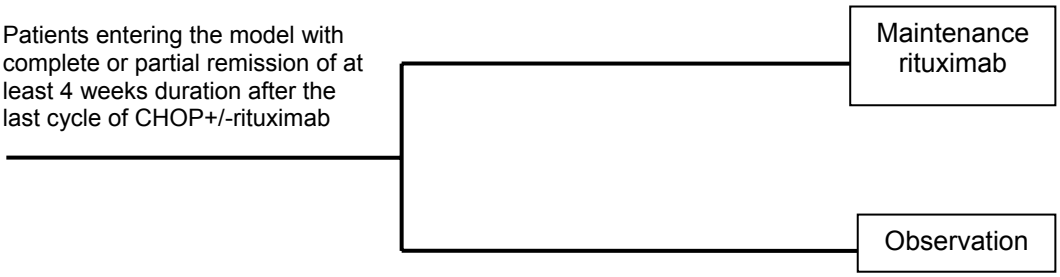
Introduction

Rituximab in combination with chemotherapy has previously been considered to be a cost effective treatment for the first line treatment of both follicular and diffuse large B-cell non-Hodgkin's lymphoma and as a monotherapy treatment for relapsed indolent NHL by NICE.

The recently updated licensed indication for rituximab now permits the use of rituximab as both an induction and maintenance treatment for relapsed follicular lymphoma patients.

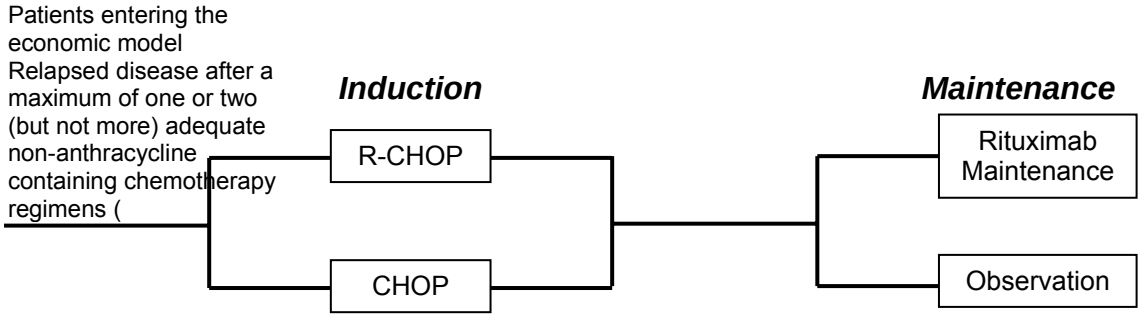
Consequently our pharmacoeconomic evaluation has been designed to firstly evaluate the cost effectiveness of rituximab as a maintenance therapy only (following response to an induction therapy) compared to observation only (no treatment until relapse). This will be referred to as the 2-arm model.

Figure 11: 2-arm model



Secondly a further version of the model has been developed to evaluate whether the use of rituximab as an induction therapy in addition to maintenance therapy is cost effective. This will be referred to as the 4-arm model. The choice of model designs reflects the nature of the EORTC20981 trial which has both a first and second randomisation.

Figure 12: 4-arm model



It is important to note that whilst the EORTC 20981 trial allows the comparison of the 4 alternative treatment strategies contained within the trial, the trial was not powered or designed for this specific purpose. However considering the available treatment strategies contained within the licence, Roche considered this an appropriate exercise to undertake given the decision problem that is being appraised.

Throughout the sections below, responses have been split for the 2-arm and 4-arm models, where the responses have not been split, our response is common to both models and any assumptions common to both models have been highlighted accordingly.

Data sources

Please note that the data set which Roche had access to from the EORTC in order to construct the economic model was the same dataset used in the regulatory submission. The van Oers publication was based on a slightly longer follow-up data set which Roche does not have access to. Consequently the data set used is from the regulatory submission with a median follow-up of 31 months for the economic evaluation, this explains why some figures within the economic section do not align with the van Oers publication or elements of the clinical section above that refer to this publication.

For example, the overall response rates listed in the clinical and economic section differ slightly, as the ORR in the economic section represents only those patients who were eligible for and received maintenance therapy. The overall response rate in the clinical section of 87% for R-CHOP and 74% for CHOP refers to all patients who respond to treatment, including those who do not then go on to receive maintenance treatment. However, response rates in the economic section of 80.8% for R-CHOP and 62.8% for CHOP refers only to those patients who respond to induction and were then randomized a 2nd time to receive maintenance treatment within the EORTC20981 registration trial.

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

Maintenance rituximab (2-arm model)

In the economic model it is assumed that maintenance rituximab is administered as a single agent therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without rituximab. It is assumed in the model that patients receive maintenance therapy with rituximab given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years.

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

In the economic model it is assumed that patients with relapsed/refractory follicular lymphoma receive 6 cycles of induction CHOP chemotherapy (cyclophosphamide 750mg/m2intravenously, day 1; doxorubicin 50mg/m2 intravenously, day 1; vincristine 1.4mg/m2 intravenously, day 1; and prednisone 100mg/d orally, days one to five; once every 3 weeks) with or without rituximab. Patients responding to induction therapy will go on to receive maintenance rituximab, as a single agent, once every 3 months until disease progression or for a maximum period of two years as described above. The licensed dose of rituximab in both the induction and maintenance indications is 375 mg/m^2 body surface area. It is modelled that patients will receive maintenance treatment until they relapse or for a maximum period of two years.

In both models the actual trial dose received by patients is used, this is explained in more detail in section 6.2.9.6.

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? 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?

Maintenance rituximab (2-arm model) & Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

The economic evaluation is based on the EORTC20981 trial. Therefore the population in the economic evaluation is reflected by the population enrolled and randomised in the maintenance phase of EORTC20981. This population is relevant for the economic evaluation because it accurately reflects the patient population likely to present for induction and subsequently maintenance therapy in the clinical setting for the treatment of relapsed follicular lymphoma. The table below outlines the patient characteristics for this patient pool.

Table 17: Baseline characteristics according to treatment group within the 2-arm and 4-arm economic models

Characteristic	Induction Phase			Maintenance Phase		
	CHOP N=231	R-CHOP N=234	All N=465	Observation N= 167	Maintenance N=167	All
Gender						
Male	118 (51%)	107 (46%)	225 (48%)	83 (50%)	78 (47%)	161 (48%)
Female	113 (49%)	127 (54%)	240 (52%)	84 (50%)	89 (53%)	173 (52%)
Age						
Median	54.0	54.0	54.0	55.0	53.0	54.0
Range	27-78	26-80	26-80	27-80	29-76	27-80
Ann Arbor stage						
I	1 (<1%)	4 (2%)	5 (1%)	3 (2%)	2 (1%)	5 (1%)
II	1 (<1%)	2 (<1%)	3 (<1%)	2 (1%)	-	2 (<1%)
III	74 (32%)	73 (31%)	147 (32%)	56 (34%)	57 (34%)	113 (34%)
IV	155 (67%)	155 (66%)	310 (67%)	106 (63%)	108 (65%)	214 (64%)
Bulky disease						
No	200 (90%)	194 (85%)	394 (87%)	146 (88%)	143 (89%)	289 (89%)
Yes	22 (10%)	35 (15%)	57 (13%)	19 (12%)	18 (11%)	37 (11%)
WHO Performance status						
0	135 (58%)	134 (57%)	269 (58%)	99 (59%)	100 (60%)	199 (60%)
1	79 (34%)	84 (36%)	163 (35%)	61 (37%)	58 (35%)	119 (36%)
2	17 (7%)	15 (6%)	32 (7%)	7 (4%)	9 (5%)	16 (5%)
3	-	1 (<1%)	1 (<1%)	-	-	-
B-symptoms present						
No	168 (73%)	174 (74%)	342 (74%)	128 (77%)	125 (75%)	253 (76%)
Yes	62 (27%)	60 (26%)	122 (26%)	39 (23%)	41 (25%)	80 (24%)
Bone marrow involvement						
No	85 (39%)	96 (42%)	342 (74%)	74 (45%)	58 (36%)	132 (41%)
Yes	131 (61%)	132 (58%)	122 (26%)	89 (55%)	102 (64%)	191 (59%)
FLIPI prognostic score (derived)						
0	1 (<1%)	3 (1%)	4 (<1%)	3 (2%)	1 (<1%)	4 (1%)
1	67 (30%)	63 (28%)	130 (29%)	45 (28%)	56 (35%)	101 (31%)
2	73 (33%)	74 (33%)	147 (33%)	51 (32%)	56 (35%)	107 (33%)
3	52 (23%)	60 (27%)	112 (25%)	45 (28%)	40 (25%)	85 (26%)
4	28 (13%)	23 (10%)	51 (11%)	14 (9%)	9 (6%)	23 (7%)
5	3 (1%)	1 (<1%)	4 (<1%)	2 (1%)	-	2 (<1%)
Extra nodal disease sites						
0-1	219 (95%)	220 (94%)	439 (94%)	155 (93%)	161 (96%)	316 (95%)
>1	12 (5%)	14 (6%)	26 (6%)	12 (7%)	6 (4%)	18 (5%)

Number of prior chemotherapies 1 2 3	189 (82%) 41 (18%) 1 (<1%)	183 (78%) 50 (21%) 1 (<1%)	372 (80%) 91 (20%) 2 (<1%)	137 (82%) 30 (18%) -	138 (83%) 29 (17%) -	275 (82%) 59 (18%) -
Best response to prior therapy CR PR NC PD	72 (31%) 120 (52%) 26 (11%) 13 (6%)	76 (32%) 120 (51%) 23 (10%) 15 (6%)	148 (32%) 240 (52%) 49 (11%) 28 (6%)	52 (31%) 86 (51%) 22 (13%) 7 (4%)	62 (37%) 86 (51%) 11 (7%) 8 (5%)	114 (34%) 172 (51%) 33 (10%) 15 (4%)

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

Maintenance rituximab (2-arm model) & Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

The economic evaluation was not carried out for any patient subgroups. The effect of rituximab maintenance therapy over observation was consistent across all subgroups evaluated for efficacy parameters PFS and OS, regardless of disease risk at study entry, the type of induction regimen and the quality of response to induction treatment as discussed in clinical section, question 5.4.2.1. Also, there is no published evidence to suggest that the clinical effectiveness of rituximab varies across patient types.

Therefore, the economic evaluation was performed based on the ITT population from the clinical trial. It was considered that this population is relevant for the economic evaluation because it accurately reflects the patient population likely to present for induction in the clinical setting in the UK.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

No economic evaluation according to sub-groups was performed for either of the analyses, for the reasons outlined in question 6.2.2.2 above.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Maintenance (2-arm model)

Patients enter the economic model following a response to 2nd line CHOP induction therapy with or without rituximab. Once entering the model patients will either receive treatment with maintenance rituximab until disease progression or for a maximum of 2 years or will be observed until disease progression. Patients will only exit the model due to death.

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

Patients enter the economic model upon commencement of 2nd line treatment with CHOP with or without rituximab. Responders to 2nd line treatment will then go on to receive maintenance treatment with rituximab until relapse or for a maximum of 2 years or will be observed until disease progression. Patients will exit the model only due to death.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A)

Maintenance (2-arm model)

Currently within UK clinical practice no other maintenance treatment is provided for relapsed/refractory follicular lymphoma following a successful response to induction therapy, therefore the comparator assumed in the 2-arm economic model, as the EORTC trial reflects, is observation alone until relapse.

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

CHOP is considered the relevant comparator to R-CHOP as an induction regimen prior to maintenance therapy. CHOP was the comparator in the EORTC20981 phase III trial and a recent survey of 50 UK haematologists revealed that CHOP is a predominant second-line treatment, given to 25.4% of patients in the UK (Synovate Market Research, January 2007). As described in the clinical section, no notable variations in clinical outcomes have been observed across the current alternative 2nd line induction therapies; therefore CHOP can be viewed as a reliable clinical proxy for other potential alternative comparators in the induction setting.

Also by using CHOP as the comparator in the economic model the trial with the lowest relative benefit is being used, as the table below outlines. Therefore, the cost effectiveness ratios generated by the models are conservative and biased against rituximab.

Table 18: Response with induction therapies with and without rituximab

Study	Patient Population	Induction treatment / No of Patients Enrolled	Overall response rates	Absolute risk difference
Forstpointer (GLSG)	Relapsed/refractory FL* and MCL	R-FCM n=66 FCM n=62	79% (*94%) 58% (*70%)	21% (*24%)
EORTC	Relapsed/refractory FL	R-CHOP n= 234 CHOP n= 231	87% 74%	13%

Constructing alternative economic models to evaluate alternative comparators was not considered appropriate due to the lack of evidence to suggest CHOP is significantly different to the cost and outcomes of other current 2nd line induction therapies. Furthermore no direct clinical evidence comparing R-CHOP to alternative comparators is yet available.

However to help manage any uncertainty this may generate, a series of threshold analyses were instead performed to evaluate the impact on the ICER if alternative costs and effectiveness assumptions are made for the comparator arm within the model. This is presented in section 6.3.1.1 below.

Baseline clinical evidence

It was not considered necessary to build an entirely separate model based upon the R-FCM/FCM data. Firstly, the incremental cost is assumed to be similar or less and secondly when comparing the relative treatment effects, the EORTC20981 study is the more conservative choice. Therefore, if rituximab can be considered cost effective based on the EORTC20981 it would be fair to assume that rituximab would be cost effective in the context of the R-FCM/FCM study.

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen

The perspective taken when estimating costs within the economic evaluations is that of the NHS in England and Wales. All relevant direct healthcare costs are evaluated. The health outcomes measured in the economic model (quality adjusted life-years) are calculated from the perspective of the patient with values from the general public applied. Any indirect costs and benefits are excluded from the analysis.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

A lifetime time horizon of 30 years has been used in both analyses, thereby capturing the lifetime costs and health outcomes of patients in each of the treatment groups. A time horizon of less than the life-time of the patient population would not be sufficient to capture the total costs and total benefit consequences of the treatments under evaluation. The duration impact of the assumed time horizon is evaluated in the sensitivity analysis.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

6.2.6.1 *Maintenance (2-arm)*

– **A description of the model type.**

A health state transition model with three health states was used to model costs and effects of rituximab compared to observation alone. The three health states of the model were progression free survival (PFS), progressive disease (PD) and death, as defined in the EORTC20981 trial. Patients in the economic evaluation were followed through the three

health states in monthly cycles over a period of 30 years in order to capture the entire lifetime costs and effects of the population.

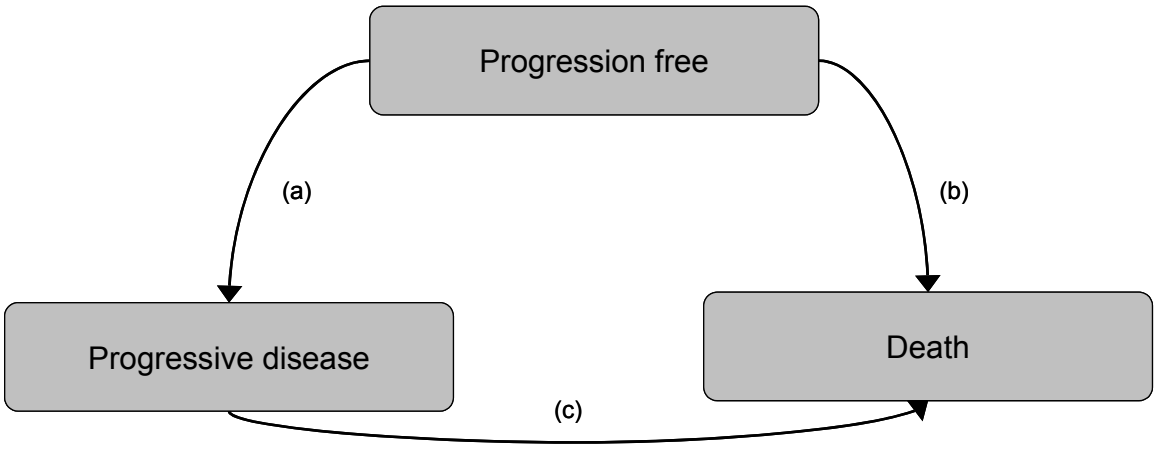
The same model structure was used for both interventions; however, the hazard rates of disease progression and death were different between the two interventions. These hazard rates were taken directly from the EORTC20981 trial data up to month 24 for both progression-free and overall survival respectively in the model. For years 2 to 30, the hazard of disease progression and death were derived from a parametric extrapolation of the EORTC 20981 survival curves over the remaining time horizon in the model.

To avoid the potentially over-optimistic assumption that rituximab produces a treatment effect and a reduced hazard of disease progression and death over the entire time horizon of the model; the hazard of progression and death for rituximab was assumed equivalent to the baseline risk after year 5 of the model. Variations in the assumed duration of treatment effect were explored in the sensitivity analysis.

– **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

The structure of the model and possible transitions between the health states can be seen in the figure below. A description of each of the health states follows.

Figure 13: Structure of the Health state transition model



Key:

a) The transition from progression free to progressive disease is derived from the PFS observed in EORTC20981 and the corresponding Weibull parametric extrapolation

b) The transition from progression free to death is based on the overall survival observed in EORTC20981 and the corresponding Weibull parametric extrapolation

c) The transition from progressive disease to death is based on the overall survival observed in EORTC20981 and the corresponding Weibull parametric extrapolation

Progression free survival (PFS health state)

All patients in the model began in the PFS health state and remained in that health state until disease progression or death (whichever occurred first). The PFS and PD health state was modelled to account for the higher quality of life and lower treatment costs for patients free of progression relative to those with progressive disease. Time to progression for each of the treatment groups was derived from the EORTC20981 trial for each of the treatment groups.

Progressive Disease (PD health state)

Patients could enter the PD health state from the PFS health state. The definition of a progressed disease was one in which there was a >50% increase from nadir in the sum of the products of the two largest perpendicular diameters of one or more measurable and evaluable lesions, or new lesions (EORTC20981). Once in the PD health state a patient could either remain in the PD health state or die. Patients in the PD health state accrued higher management/surveillance costs than those free of progression. These patients also accrued treatment costs upon relapse. A monthly cost was calculated based on the post-protocol treatment recorded in the EORTC20981 and was estimated separately for observation and maintenance to account for any downstream treatment differences between the two groups.

Death

The model utilised overall survival data from EORTC20981 and therefore does not distinguish between different causes of death. No costs of death were included in the economic evaluation.

- **A list of all variables that includes their value, range (distribution) and source**

The parameters included in the probabilistic sensitivity analysis are discussed in section 6.2.11.2 and presented in more detail in Appendix 9.

Table 19: 2-arm Model: Model Parameters and Values

Model Variable	Value	Source
Transition Probabilities		
PFS to Progression	• 0-24 months values taken from the EORTC20981 trial data	Health state transition model
Progression to Death		
PFS to Death		

	• Values from 24 months extrapolated out for 30 years time dependent based upon Weibull extrapolations of the PFS and OS trial curves	
Utilities		
Progression Free Survival	0.805	Oxford Outcomes Utility Study, 2005
Progression	0.618	Oxford Outcomes Utility Study, 2005
Costs		
Drug costs		
Rituximab drug costs per dose	£1,325	See 2-arm economic model
Mean cost per administration	£86	NHS Reference costs 2004, TOPS FU 303
Mean number of rituximab doses per patient	5.93	EORTC20981
Total rituximab drug costs per patient	£7,739	See 2-arm economic model Variable list sheet
Total rituximab administration costs per patient	£502	See 2-arm economic model Variable list sheet
Adverse Event (AE) Costs		
Serious adverse events		
Patients experiencing serious adverse events - Rituximab	0.180	EORTC20981 database
Patients experiencing serious adverse events – Observation	0.006	EORTC20981 database
Unit cost per serious adverse event - Rituximab	£1,051	See 2-arm economic model, Variable list sheet
Unit cost per serious adverse event - Observation	£1,177	See 2-arm economic model Variable list sheet
Expected cost of serious AEs - Rituximab	£188.90	See 2-arm economic model Variable list sheet
Expected cost of serious AEs - Observation	£7.05	See 2-arm economic model Variable list sheet
Non-serious adverse events		
Number of non-serious adverse events per patient - Rituximab	1.605	EORTC20981 database
Number of non-serious adverse events per patient - Observation	1.443	EORTC20981 database
Unit cost per non-serious adverse event – Both Tx groups	£86	NHS Reference costs 2004, TOPS FU 303
Expected cost of non-serious AEs - Rituximab	£138.01	See 2-arm economic model Variable list sheet
Expected cost of non-serious AEs - Observation	£124.11	See 2-arm economic model Variable list sheet
Treatment costs upon relapse		
Expected cost per treatment received	£6,870.57	See 2-arm economic

upon relapse – Rituximab		model Variable list sheet
Expected cost per treatment received upon relapse - Observation	£6,858.44	See 2-arm economic model Variable list sheet
Frequency of treatment received upon relapse		
Number of years between each line of therapy whilst in the PD health state – Rituximab & Observation	2 (years)	Assumption
Average post protocol treatment costs upon relapse per cycle of the health state transition model in the PD health state		
Rituximab	£286.27	See 2-arm economic model Variable list sheet
Observation	£285.77	See 2-arm economic model Variable list sheet
Cost of non-drug resources (routine management / surveillance) by health state		
Cost per month Rituximab - Progression free	£28.67	See 2-arm economic model Variable list sheet
Cost per month Observation - Progression free	£28.67	See 2-arm economic model Variable list sheet
Cost per month in PD health state	£86	See 2-arm economic model Variable list sheet
Cost per month whilst Dead	£0	Assumption
Discount rate		
Costs	3.5%	Guide to Methods, NICE
QALYs	3.5%	Guide to Methods, NICE

Note: For a thorough breakdown of all variables included in the model please see Sheet entitled "Variable List" in the 2-arm model.

- **A separate list of all assumptions and a justification for each assumption**

Survival assumptions

- For the first 24 months of the model, Kaplan Meier (KM) data from EORTC20981 was used. After the 24 month period, the disease progression and mortality hazards from parametric curve fitting was used. The Weibull model provided the best goodness of fit of the trial data (see section 6.2.6.8 and Appendix 5).

- The hazards for disease progression and death for the rituximab maintenance group are assumed to be equivalent to those in the observation group after 5 years. The duration of this assumed treatment benefit and its impact on the cost effectiveness ratio is tested in the sensitivity analysis.

Quality of life assumptions

- The utility score reported for PFS and PD were directly applied to the PFS and PD health states in the health state transition model. It is assumed that these utilities do not change over time as the values represent an average or midpoint estimate of this disease state.

- It is appreciated that this approach to utility valuation does not explicitly capture the variable quality of life for patients within the progressive disease health state. That is, patients will continue to receive treatment after progression and may well return to the progression free health state. However, the reason for not attempting to further model the changes in quality of life over time in the PD state is that the sample used in the progressive disease state was mixed, with patients in the group receiving between 0 to 5 previous treatments (Oxford Outcomes 2005). This meant that the utility value applied in the economic evaluation is assumed to be representative of the variable nature of NHL within the PD health state. It is argued that any attempts to model the longer term effects of the natural history of NHL on quality of life would introduce levels of complexity and uncertainty into the economic evaluation which outweigh the benefits of such an approach. Uncertainty around the value of the utility score in the progressive health state is explored in the sensitivity analysis.

Drug utilisation

- Rituximab patients received 5.93 cycles as observed in the EORTC20981 study. This calculation excluded “censored” patients still taking maintenance rituximab, but included the 134 patients who either completed all 8 cycles, stopped maintenance medication for other reasons.

Costs

- Each non-serious AE was assumed to accrue a cost of £86 per event and was based on the haematology outpatient visit (NHS reference costs 2004; TOPS FU 303).

- An average monthly cost of post-protocol treatment was assumed based on the average cost of those treatments observed in the EORTC20981 study post-protocol and the assumed frequency of further lines of treatment.

- It is assumed that patients in each group will receive a further anti-NHL treatment following relapse every two years. This assumption was based on the approximate

time to first progression observed in EORTC2091. The frequency and associated unit costs of this assumption are tested in sensitivity analysis.

- Patients in the progressive disease health state were assigned a cost of an outpatient visit every month (£86; NHS reference costs 2004; TOPS FU 303).

- Patients who were progression free were attributed the cost of an outpatient visit every 3 months (£28.67) per cycle of the health state transition model; £86/6). These values were tested in sensitivity analysis, including the extreme case where there is no difference in the cost of routine management/surveillance resources between patients with progressive disease and those who are progression free.

- The cost of rituximab administration was assumed to be equivalent to an outpatient visit of £86.

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

- ***A description of the model type***

A health state transition model with five health states was used to model costs and effects of the four treatment strategies. The same structure was used for all groups in the model, however, the hazards between the health states were different between the four groups, as according to the EORTC20981 trial data.

The economic evaluation included four treatment groups representing the two induction combinations and the two maintenance options (R-CHOP-O, R-CHOP-R, CHOP-O, CHOP-R). To model the impact of the induction treatment it was necessary to account for patients who were not eligible for the maintenance phase of the EORTC20981 trial. The results of EORTC20981 and how these are then applied to the economic evaluation are presented in the table below. The difference in the proportion of patients eligible for maintenance therapy between the R-CHOP and CHOP induction treatment groups was statistically significant (chi-squared $p < 0.0001$).

Table 20: Outcome of induction therapy from EORTC20981 and applied to the modelled economic evaluation

Parameter	R-CHOP	CHOP	Reference
Patients starting induction therapy	234	231	EORTC20981
Patients eligible for maintenance therapy (%)	189 (80.8%)	145 (62.8%)	EORTC20981
Patients not eligible for maintenance therapy (%)	45 (19.2%)	86 (37.2%)	EORTC20981

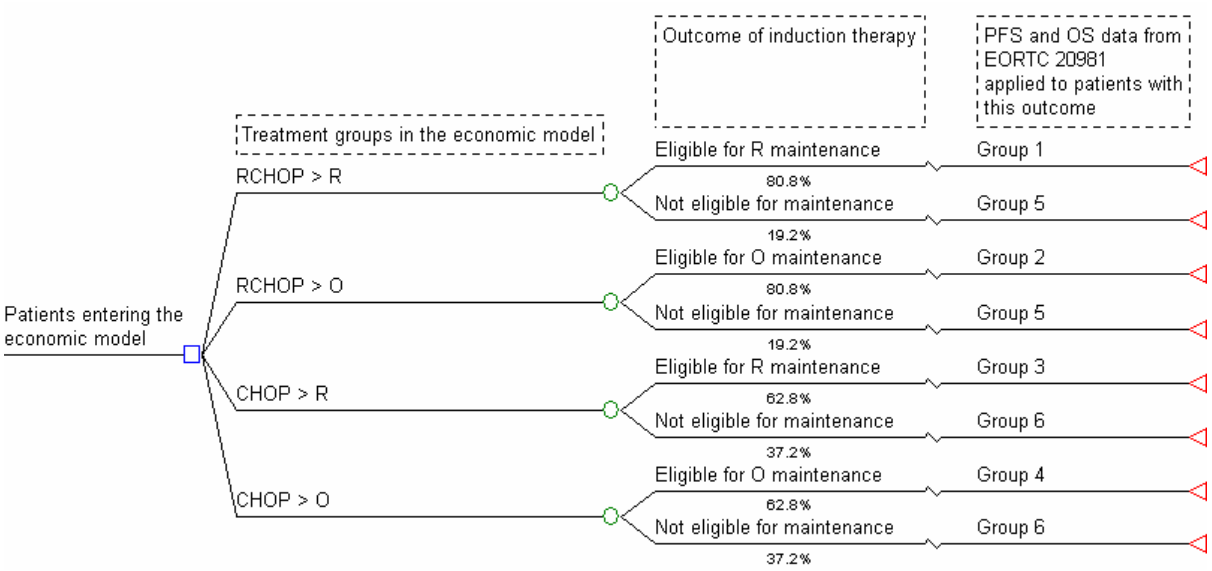
As presented in the introduction to the economic section there is a slight difference between the response rates quoted here and those quoted in the clinical section. This is because the response rates quoted here refer only to those patients who responded to induction treatment and were then randomized again to receive maintenance treatment.

Progression free and overall survival used in the model were contingent on both the outcome of induction therapy and the maintenance therapy received in each of the treatment groups. This meant that there were six possible outcomes across the four treatment groups that could be identified from the EORTC20981 study. These were:

1. patients who had received R-CHOP, were eligible for maintenance and were receiving rituximab
2. patients who had received R-CHOP, were eligible for maintenance and were in the observation group
3. patients who had received CHOP, were eligible for maintenance and were receiving rituximab
4. patients who had received CHOP, were eligible for maintenance and were in the observation group
5. patients who had received R-CHOP, but were not eligible for maintenance
6. patients who had received CHOP, but were not eligible for maintenance

The six groups for which clinical data (in terms of PFS and OS) are applied in the economic model are presented in the figure below.

Figure 14: Identifying the appropriate clinical trial data for each of the health states in the Health state transition model



The above table and figure show how the patients are allocated to one of the six potential survival curves from the EORTC20981 study within the 4-arm model. Clinical trial data was used to estimate the time to progression and death of each of the health states. The time spent in each health state of the health state transition model reflect the differences in terms of progression-free and overall survival observed in EORTC20981. For the first 24 months of the model the actual EORTC20981 trial data was used, in the form a Kaplan Meier curve presented below in the 2 sets of figures. This 24 month period was applied in the economic model because it included the majority of the ITT population. After this point, it was decided that the Weibull model, was a better estimator of survival than the Kaplan-Meier model. This is tested in sensitivity analysis.

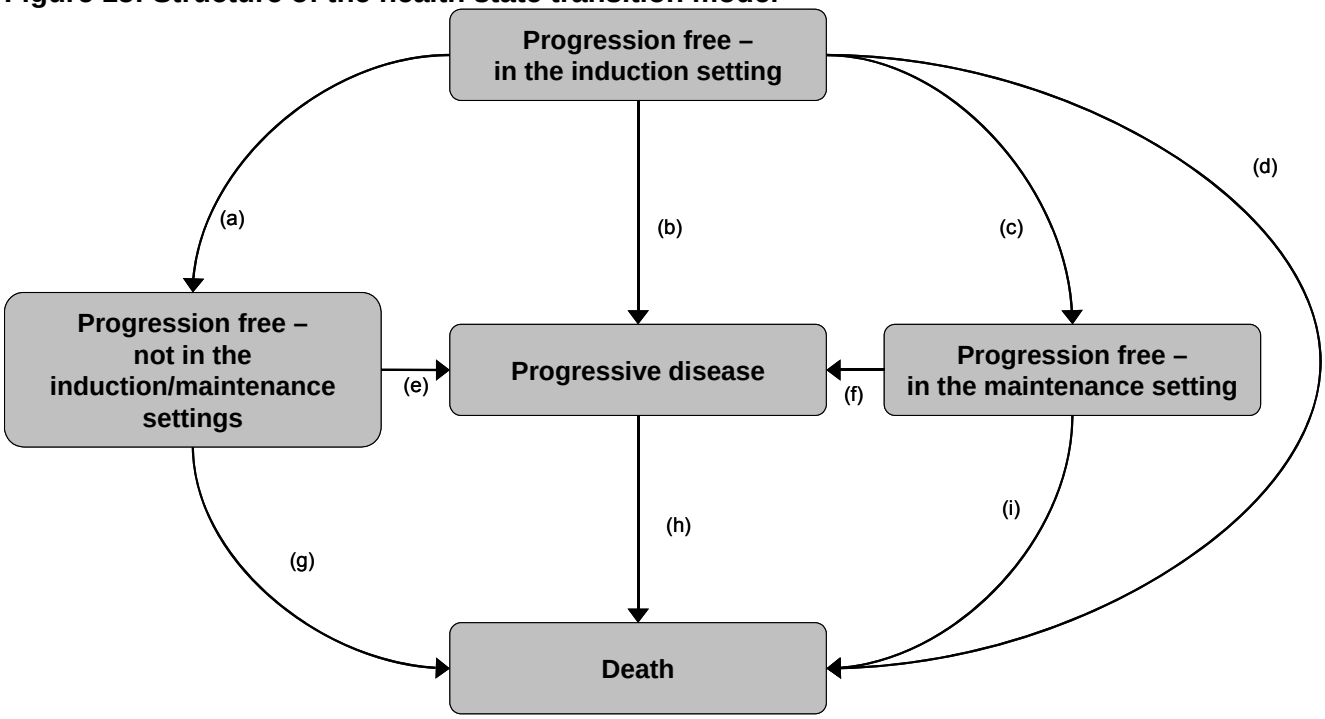
Patients in the economic evaluation were followed through the five health states of the Health state transition model in monthly cycles over a period of 30 years. This time horizon was used in order to capture the full life time of the patients in the model and therefore accurately measure the life expectancy in each of the treatment groups (the duration of the model is tested in sensitivity analysis). The five health states of the model were:

i) progression free – in the induction setting
ii) progression free – in a maintenance setting
iii) progression free – but not in the induction or maintenance settings
iv) progressive disease
v) death

The structure of the model and possible transitions between the health states is presented in the figure below (in addition to the transitions presented in the figure, it is possible for

patients in the Health state transition model to remain in the same health state from one cycle to the next). A description of each of the health states follows.

Figure 15: Structure of the health state transition model



***Key**:*

- *(a) The transition from the induction setting to "Progression free – not in the induction/maintenance settings" is based on results of EORTC20981. Those patients who complete induction therapy without progressive disease but who did not qualify for maintenance therapy according to the EORTC20981 protocol will enter this health state*
- *(b) The transition to progressive disease is based on the PFS and OS observed in EORTC20981*
- *(c) The transition from the induction setting to "Progression free –in the maintenance setting" is based on results of EORTC20981. Those patients who qualified for maintenance therapy according to the EORTC20981 protocol will enter this health state*
- *(d) The transition to death is based on the overall survival observed in EORTC20981*
- *(e) The transition to progressive disease is based on the PFS and OS observed in EORTC20981*
- *(f) The transition to progressive disease is based on the PFS and OS observed in EORTC20981*
- *(g) The transition to death is based on the overall survival observed in EORTC20981*
- *(h) The transition to death is based on the overall survival observed in EORTC20981*
- *(i) The transition to death is based on the overall survival observed in EORTC20981*

Model overview / Progression free – in the induction setting

All patients enter the model in the induction setting. Whilst receiving induction patients will remain in the progression free (in the induction setting) health state. Following induction, patients will transit to maintenance therapy (if they are eligible according to EORTC20981); progressive disease (according to PFS in EORTC) or will not be eligible for maintenance due to lack of response and/or toxicity (again, this is according to EORTC). The probability of disease progression, eligibility for, and withdrawal from, maintenance therapy are based on

EORTC and are contingent on the induction therapy being received in the respective treatment groups. Treatment costs accrued for patients entering this health state reflects the cost of the induction therapy received (R-CHOP or CHOP). The utility value for patients in this health state reflects that of a progression-free population.

Progression free – in the maintenance setting (PFS maintenance health state)

Patients completing the induction phase of EORTC20981 will enter this health state if they have qualified for the maintenance phase of EORTC20981. Patients will remain in this health state until disease progression and/or death. The probability of disease progression and/or death are contingent on the maintenance being received (rituximab or observation) as well as the induction therapy received during the induction phase (R-CHOP or CHOP). Treatment costs accrued for patients entering this health state reflects the cost of the maintenance treatment received. The utility value for patients in this health state reflects that of a progression-free population.

Progression free – not in the induction/maintenance settings (PFS withdrawn health state)

Patients completing the induction phase of EORTC20981 will enter this health state if they have not qualified for the maintenance phase of EORTC20981. Patients may not qualify for maintenance therapy due to adverse events and/or lack of response to the induction therapy. The probability of entering this health state after the induction is contingent on the induction therapy received (R-CHOP or CHOP). Patients will remain in this health state until disease progression and/or death. The probability of disease progression and/or death is based on the time to progression and overall survival for this sub-group of patients observed in EORTC20981. The utility value for patients in this health state reflects that of a progression-free population.

Progressive Disease (PD health state)

Patients could enter the progressed health state from PFS. The definition of a progressed disease was one in which there was a >50% increase from nadir in the sum of the products of the two largest perpendicular diameters of one or more measurable and evaluable lesions, or new lesions (Research Report 1016350). Once in the progressed health state a patient could either remain in the progressed health state or die. Patients in the progressed health state accrued higher management/surveillance treatment costs than those free of progression. These patients also accrued treatment costs upon relapse to reflect ‘treat on relapse’ practices. The cost of treatments upon relapse was entered into the model as a

monthly cost in the health state transition model. The monthly cost was calculated for each of the four arms of the model, based on the treatment upon relapse recorded in the trial and assuming a line of treatment upon relapse once every two years. The utility value for patients in this health state reflects that of a population with progressive disease.

Death

The model utilised overall survival data from EORTC20981 and therefore does not distinguish between different causes of death. No costs of death were included in the economic evaluation.

– **A list of all variables that includes their value, range (distribution) and source**

The parameters included in the probabilistic sensitivity analysis are discussed in section 6.2.11.2 and presented in more detail in Appendix 9.

Table 21: 4-arm Model: Model Parameters and Values

Model Variable	Value	Source
Transition Probabilities		
PFS in induction setting to PFS not in the induction/maintenance setting	• 0-24 months values taken from the EORTC20981 trial data • Values from 24 months extrapolated out for 30 years time dependent based upon Weibull extrapolations of the PFS and OS trial curves	Health state transition model
PFS in induction setting to PFS in the maintenance setting		
PFS in induction setting to Progressive disease		
PFS in induction setting to Death		
PFS not in induction/maintenance setting to Progressive disease		
PFS not in induction/maintenance setting to death		
PFS maintenance setting to Progressive disease		
PFS maintenance setting to Death		
Progressive disease to Death		
Response rates		
Patients becoming eligible for maintenance therapy - R-CHOP	80.8%	EORTC20981
Patients becoming eligible for maintenance therapy - CHOP	62.8%	EORTC20981

Utilities		
Progression Free Survival	0.805	Oxford Outcomes Utility Study, 2005
Progression	0.618	Oxford Outcomes Utility Study, 2005
Costs		
Drug costs		
Cost per administration visit	£86	NHS Reference costs 2004, TOPS FU 303
Induction drug costs per dose		
Rituximab	£1,325	See 4-arm economic model Variable list sheet
Cyclophosphamide	£9.47	See 4-arm economic model Variable list sheet
Doxorubicin	£186	See 4-arm economic model Variable list sheet
Prednisone	£3.45	See 4-arm economic model Variable list sheet
Regimen drug costs per dose R-CHOP	£1,545	See 4-arm economic model Variable list sheet
Regimen drug costs per dose R-CHOP	£220	See 4-arm economic model Variable list sheet
Number of induction doses per patient		
R-CHOP	5.6838	EORTC20981 trial database
CHOP	5.4474	EORTC20981 trial database
Total drug and administration costs per patient		
R-CHOP	£9,272	See 4-arm economic model Variable list sheet
CHOP	£1,699	See 4-arm economic model Variable list sheet
Rituximab maintenance drug costs		
Rituximab drug costs per dose	£1,325	See 4-arm economic model Variable list sheet
Mean number of rituximab doses per patient	5.9254	EORTC20981 trial database
Total rituximab drug and administration costs per patient	£8,241	See 4-arm economic model Variable list sheet
R-CHOP (Induction), R (Maintenance) Expected cost of maintenance	£6,656.28	See 4-arm economic model Variable list sheet
CHOP (Induction), R (Maintenance) Expected cost of maintenance	£5,172.99	See 4-arm economic model Variable list sheet
Cost of serious Adverse Events (AEs)		
R-CHOP (I), R (M) Expected cost of serious adverse events - induction	£528	See 4-arm economic model Variable list sheet

R-CHOP (I), R (M) Expected cost of serious adverse events - maintenance	£191	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M) Expected cost of serious adverse events - induction	£427	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M) Expected cost of serious adverse events - maintenance	£0	See 4-arm economic model Variable list sheet
CHOP (I), R (M) Expected cost of serious adverse events - induction	£376	See 4-arm economic model Variable list sheet
CHOP (I), R (M) Expected cost of serious adverse events - maintenance	£186	See 4-arm economic model Variable list sheet
CHOP (I), O (M) Expected cost of serious adverse events - induction	£301	See 4-arm economic model Variable list sheet
CHOP (I), O (M) Expected cost of serious adverse events - maintenance	£17	See 4-arm economic model Variable list sheet
R-CHOP (I), Not eligible (M) Expected cost of serious adverse events - induction	£744.25	See 4-arm economic model Variable list sheet
CHOP (I), Not eligible (M) Expected cost of serious adverse events - induction	£604.96	See 4-arm economic model Variable list sheet
Cost of non-serious adverse events by outcome of induction		
Cost per non-serious AE	£86	See 4-arm economic model Variable list sheet
R-CHOP (I), R (M) Expected cost of non-serious adverse events - induction	£188	See 4-arm economic model Variable list sheet
R-CHOP (I), R (M) Expected cost of serious adverse events - maintenance	£133	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M) Expected cost of serious adverse events - induction	£176	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M) Expected cost of serious adverse events - maintenance	£106	See 4-arm economic model Variable list sheet
CHOP (I), R (M) Expected cost of serious adverse events - induction	£173	See 4-arm economic model Variable list sheet
CHOP (I), R (M) Expected cost of serious adverse events - maintenance	£144	See 4-arm economic model Variable list sheet
CHOP (I), O (M) Expected cost of serious adverse events – induction	£172	See 4-arm economic model Variable list sheet

CHOP (I), O (M) Expected cost of serious adverse events - maintenance	£150	See 4-arm economic model Variable list sheet
R-CHOP (I), Not eligible (M) Expected cost of serious adverse events - induction	£290	See 4-arm economic model Variable list sheet
CHOP (I), Not eligible (M) Expected cost of serious adverse events - induction	£189	See 4-arm economic model Variable list sheet
Treatment costs upon relapse		
Expected cost of treatments received upon relapse R-CHOP (I), R (M)	£5,837	See 4-arm economic model Variable list sheet
Expected cost of treatments received upon relapse R-CHOP (I), O (M)	£6770	See 4-arm economic model Variable list sheet
Expected cost of treatments received upon relapse CHOP (I), R (M)	£8,195	See 4-arm economic model Variable list sheet
Expected cost of treatments received upon relapse CHOP (I), O (M)	£6,943	See 4-arm economic model Variable list sheet
Frequency of treatments received upon relapse: R-CHOP (I), R (M) R-CHOP (I), O (M) CHOP (I), R (M) CHOP (I), O (M)	2 (years)	Assumption
Treatment costs upon relapse per cycle of the health state transition model in the PD health state		
R-CHOP (I), R (M)	£243	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M)	£282	See 4-arm economic model Variable list sheet
CHOP (I), R (M)	£341	See 4-arm economic model Variable list sheet
CHOP (I), O (M)	£289	See 4-arm economic model Variable list sheet
Cost of non-drug resources (routine management/surveillance) by health state		
R-CHOP (I), R (M) Cost per month in PF	£28.67	See 4-arm economic model Variable list sheet
R-CHOP (I), O (M) Cost per month in PF	£28.67	See 4-arm economic model Variable list sheet
CHOP (I), R (M) Cost per month in PF	£28.67	See 4-arm economic model Variable list sheet
CHOP (I), O (M) Cost per month in PF	£28.67	See 4-arm economic model Variable list sheet

Cost per month in PD health state	£86	See 4-arm economic model Variable list sheet
Cost per month whilst dead	£0	Assumption
Discount rate		
Costs	3.5%	Guide to Methods, NICE
QALYs	3.5%	Guide to Methods, NICE

– **A separate list of all assumptions and a justification for each assumption.**

Survival assumptions

For the first 24 months of the model the actual EORTC20981 trial survival data was used, in the form of a Kaplan Meier curve. This 24 month period was applied in the economic model because it included the majority of the ITT population.

After this time-point a Weibull parametric survival curve was utilised to estimate the hazard of disease progression and death for both interventions, as it was assumed this would represent a better estimator of survival.

The hazards for the rituximab maintenance group are assumed to be equivalent to those in the CHOP-O group after 5 years.

Quality of life assumptions

The utility score reported for PFS and PD were directly applied to the PFS and PD health states in the health state transition model. It is assumed that these utilities do not change over time. It is appreciated that this approach to utility valuation does not explicitly capture the variable quality of life for patients with NHL following progression. That is, patients will continue to receive treatment after progression and may well return to the progression free health state.

However, the reason for not attempting to further model the changes in quality of life over time in the PD state is that the sample used in the progressive disease state was mixed, with patients in the group receiving between 0 to 5 previous treatments (Oxford Outcomes 2005). This meant that the utility value applied in the economic evaluation is representative of the variable nature of NHL within the PD health state. It is argued that any attempts to model the longer term effects of the natural history of NHL on quality of life would introduce levels of complexity and uncertainty into the economic evaluation which outweigh the benefits of such an approach. This assumption is explored in the sensitivity analysis.

Cost assumptions

- Each non-serious AE was assumed to accrue a cost of £86 per event and was based on the haematology outpatient visit (NHS reference costs 2004; TOPS FU 303).

- It is assumed that patients in each group will receive treatment costs upon relapse every two years. This assumption was based on the approximate time to first progression observed in EORTC2091. The frequency and associated unit costs of this assumption are tested in sensitivity analysis.

- Patients in the progressive disease health state were assigned a cost of an outpatient visit every month (£86; NHS reference costs 2004; TOPS FU 303). Patients who were progression free were attributed the cost of an outpatient visit every 3 months (£28.67) per cycle of the health state transition model; £86/6). These values were tested in sensitivity analysis, including the extreme case where there is no difference in the cost of routine management/surveillance resources between patients with progressive disease and those who are progression free.

6.2.6.2 Why was this particular type of model used?

NHL is a long term disease with several lines of treatment and relapse. To adequately capture the natural history of the disease would require a very complex model with many health states representing different lines of treatment and time spent in relapse and remission. The problem with creating this type of model, which would be a Markov model, is that there is an insufficient amount of data to adequately populate such a model. Several assumptions would have to be made about many of the transition probabilities. In order to develop a model that would adequately cover the history of the illness, as well as be parsimonious and use fewer assumptions, the clinical trial data was used to predict time in PFS as well as time in OS as these two end-points are ultimately what matters to the patient and are the main goal of treatment. By doing this, fewer assumptions were made, transition probabilities were not calculated and instead the observed clinical trial data was extrapolated in order to obtain unbiased mean estimates of survival.

This health state transition model was used for both models to capture the costs and benefits of relapsed/refractory follicular lymphoma patients as they transition between health states over the lifetime of the model. Non-Hodgkin's lymphoma is a long term disease, with survival rates long exceeding the time frame of the clinical trial. Therefore, in order to

estimate clinical outcomes and the subsequent costs beyond the trial follow-up some form of modelling was required. The health state transition model was considered the most appropriate as the disease can be classified into a number of broad health states.

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of the 2-arm and 4-arm models, where patients are broadly stratified into progression free, progression and death, is commonly used in the economic evaluation of oncology interventions. These health states were chosen to reflect the objective of treatment within this disease area, to place a patient into a progression-free health state for as long as possible. Also, the chosen health states within these models reflect the main outcomes of the EORTC20981 clinical trial.

A markov model that takes into account subsequent lines of treatment and potentially how patients transition between lines of treatment, response to treatment, time in relapse and remission would be a relevant alternative to the structure chosen here. However, the lack of data and the number of assumptions that would be required for this type of model made this approach an unfeasible development option, although it would have offered more flexibility in exploring certain assumptions. It was decided to sacrifice flexibility in order to remove the uncertainty that such an approach would introduce.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The main source of information that informed the model structure was the EORTC20981 clinical trial. This trial provided the probability of a patient remaining within the PFS health state for each cycle of the model and the response rates to induction therapy for the 4-arm model.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

It is believed that the model structure is robust in order to investigate the main treatment goals. The three broad health states of progression free, progression and death capture all the conditions relevant to the decision problem.

6.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length employed in the health state transition models is monthly. Rarely is clinical assessment and diagnosed clinical status performed on a more regular basis than every month. Consequently, it is unreasonable to assume that costs or clinical outcomes could change on a more frequent basis than every month.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction is applied in both models.

6.2.6.8 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 technology and its comparator?

The median length of follow-up of the EORTC20981 trial dataset utilised for the economic evaluation is 31 months, therefore to estimate the lifetime health benefits and associated costs of receiving induction chemotherapy with or without rituximab followed by maintenance rituximab, assumptions of the future disease progression and survival of these patients have to be made.

To develop a life time model it was necessary to extrapolate the KM data for both progression-free and overall survival from the trial period using parametric extrapolation.

This was performed for the survival curves following second randomisation in the EORTC 20981 study (2-arm model) and also for all six groups of patients / survival curves identified from the point of first randomisation included in the 4-arm model.

The major distributions that have been proposed for modelling survival (or failure) times are the log-logistic, the log-normal, the exponential, the Weibull and the Gompertz. (Chapman and Hall, 1984). OS and PFS in the health state transition model was derived from the observed PFS and OS data from EORTC20981 by fitting a Weibull distribution. The Weibull curve was selected on the basis of a series of goodness of fit evaluations; this analysis is presented in more detail in Appendix 5.

Sensitivity analysis includes results of the economic evaluation using different distributions to parameterise the EORTC20981 PFS and OS data and can be changed within the economic model.

Maintenance (2-arm model)

The OS and PFS data used in the economic evaluation for each of the treatment groups, based on the fitted Weibull distributions, are presented in the two figures below.

Figure 16: Overall survival by treatment group in EORTC20981 and applied in the economic evaluation

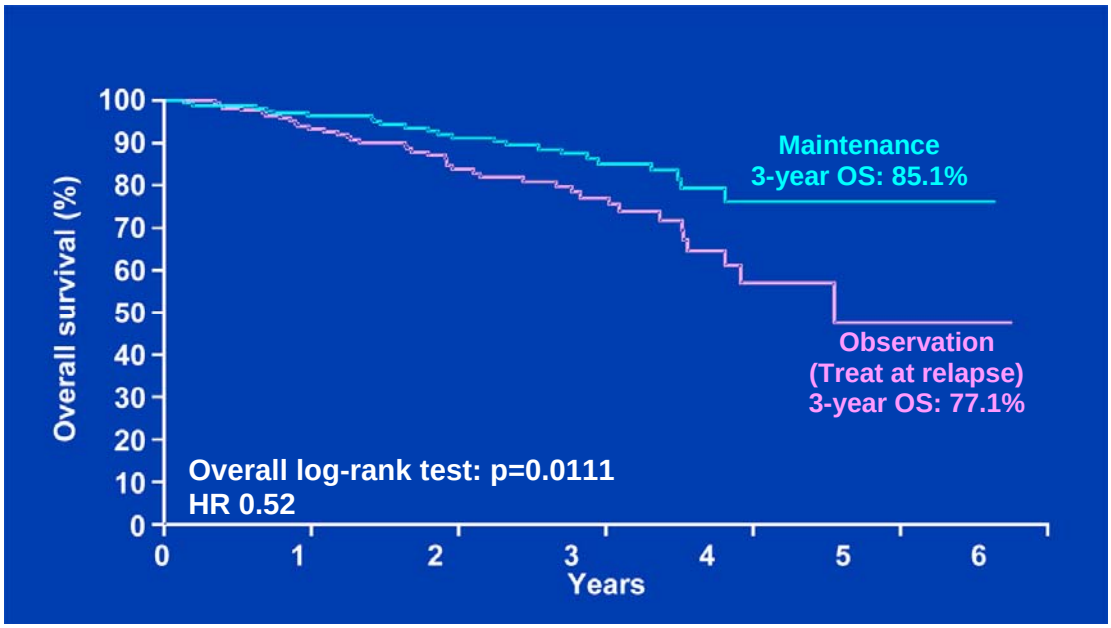
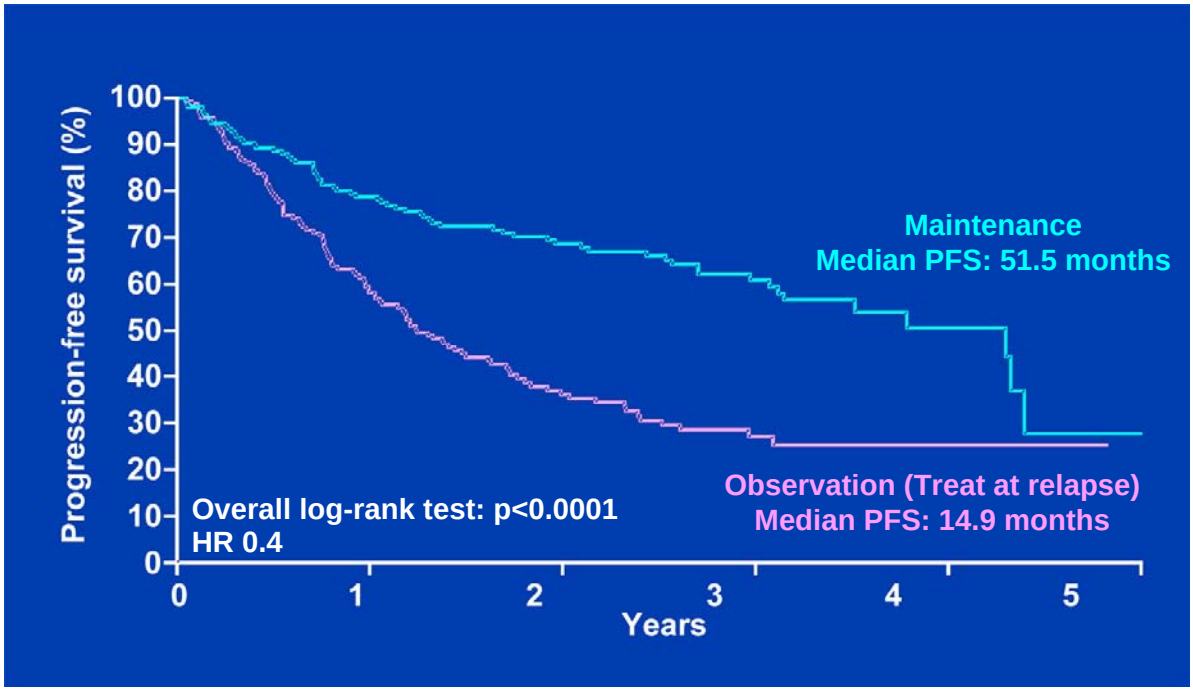


Figure 17: Progression free survival by treatment group in EORTC20981 and applied in the economic evaluation



Prior to fitting the parametric curves, the KM data was firstly truncated at 1500 days for both arms in order to reduce the uncertainty evident in the tail of the KMs due to the small number of remaining patients. This contrasted to the longest potential follow-up point for the KM curves.

The major distributions that have been proposed for modelling survival (or failure) times are the log-logistic, the log-normal, the exponential, the Weibull and the Gompertz. The Weibull distribution is a suitable distribution if events occur early in the follow-up period whereas the log normal and log logistic distributions have heavy right tails and are therefore suitable for situations in which events occur later in the follow-up period (Regression models for survival data: Keith R. Adams. In statistical analysis of medical data; new developments. Arnold 1998).

The table below shows the AIC (Akaike Information Criterion) and BIC (Schwarz's Bayesian Criterion) statistics for the five major distributions, for overall survival (OS) and progression-free survival (PFS) of paired treatment arms, that is, the maintenance and observation paired arms after R-CHOP induction, the maintenance and observation paired arms after CHOP induction, and the R-CHOP and CHOP induction paired arms that included patients withdrawn from the study prior to the second randomisation.

Table 22: Summary of Goodness of Fit by Treatment Comparators and Distribution

		BIC		AIC	
Treatment	**Distribution**	**OS**	**PFS**	**OS**	**PFS**
R-CHOP + (MabThera or Observation)	Exponential	-84.198	-185.837	-83.577	-185.216
	Log Logistic	-80.533	-178.553	-79.291	-177.311
	Log Normal	-80.828	-175.544	-79.587	-174.302
	Weibull	-80.326	-182.102	-79.085	-180.860
	Gompertz	NC	NC	NC	NC
CHOP + (MabThera or Observation)	Exponential	-84.669	-155.935	-84.181	-155.446
	Log Logistic	-82.061	-143.607	-81.084	-142.631
	Log Normal	-81.279	-142.960	-80.302	-141.984
	Weibull	-82.641	-147.304	-81.664	-146.327
	Gompertz	NC	NC	NC	NC
CHOP_ vs. R-CHOP_ (Non Responders)	Exponential	-143.739	-191.087	-143.301	-190.650
	Log Logistic	-146.031	-190.965	-145.156	-190.090
	Log Normal	-147.376	-191.320	-146.501	-190.444
	Weibull	-146.144	-193.401	-145.269	-192.526
	Gompertz	NC	NC	NC	NC

Note: The Gompertz model failed to converge for R-CHOP + (MabThera vs. Observation) and CHOP + (MabThera vs. Observeration)

The table shows that there is little difference between the fit of the different distributions, and that any of the log-logistic, log-normal, or Weibull distributions suitably describe the distribution of the survival times.

Given the age and health status of the patients it was felt that the shape of the Weibull distribution was the most appropriate for this analysis. The distributions were fitted to the first 1500 days of the clinical trial period. The decision to go with the 1500 days truncation point was used because it is at this point where all curves were flattening out and thus might unduly influence the parameter estimates.

The parameter values of the Weibull distributions used in the model are provided below.

Weibull Survival Function: $S(t) = \exp(-\lambda * t^{**}\gamma)$, where $\lambda=\exp(-\mu/\sigma)$ and $\gamma = 1/\sigma$ and μ = intercept + treatment effect)

Table 23: parameters used for the 2-arm model

	OS			PFS		
	intercept	MAB dummy	scale	intercept	MAB dummy	scale
MabThera	7.7576	0.3979	0.5274	6.813	0.6506	0.6792
Observation	7.7576		0.5274	6.813		0.6792

The table above presents the parameters used for the 2-arm model. Please refer to the sheet entitled “Variable list” in the 4-arm model for details on the parameters utilised in the 4-arm model.

Figure 16: Modelled OS for observation and rituximab maintenance treatment groups

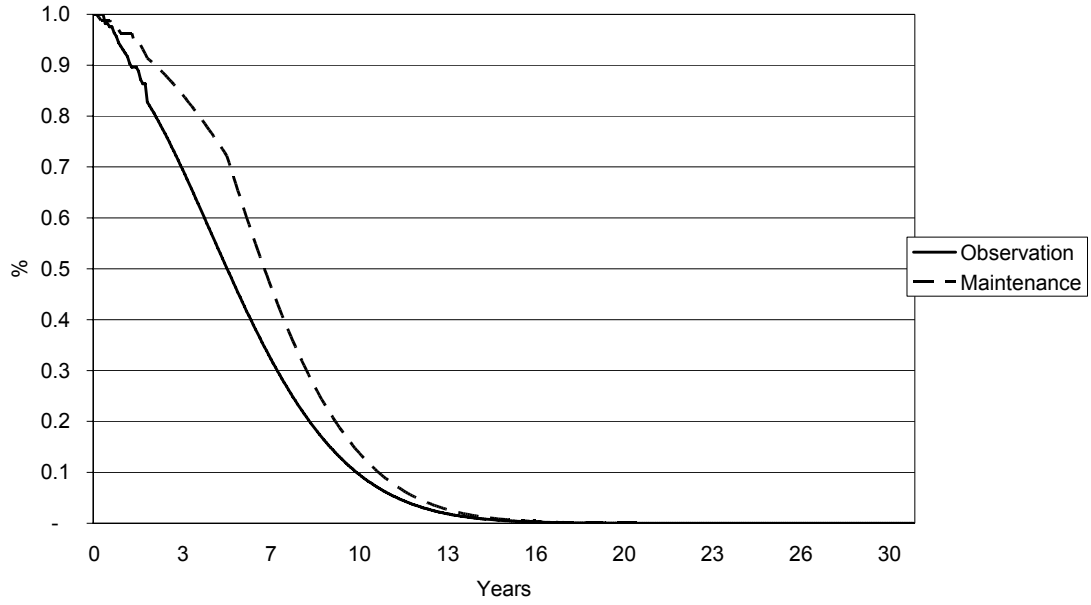
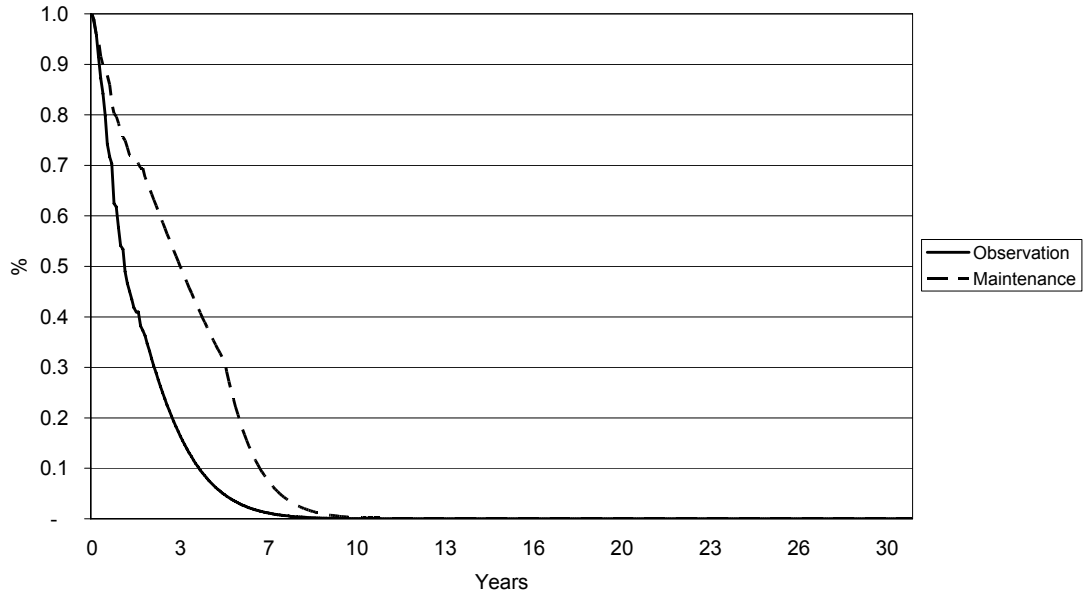


Figure 17: Modelled PFS for observation and rituximab maintenance treatment groups



The parametric curve fitting for each of the treatment groups implies different hazards across the treatment groups for the life time of the model. This is considered an unrealistic assumption and so the hazards for the rituximab maintenance group are assumed to be equivalent to those in the observation group after 5 years. This approximates the longest

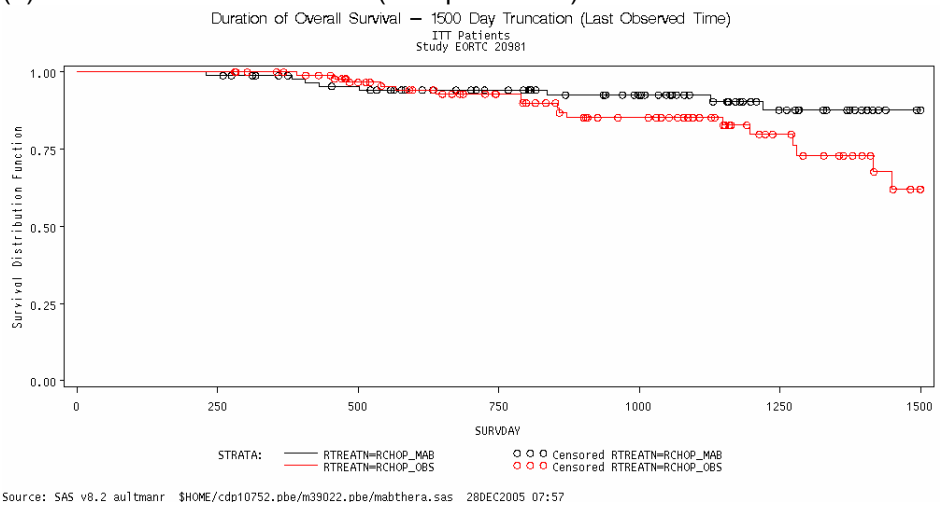
follow up from the EORTC trial, to assume any longer treatment benefit may appear optimistic in the absence of a clear evidence base to support this. This is reflected in the survival curves presented in above. The duration of this treatment benefit is tested in sensitivity analysis. The resulting curves were then used directly within the economic model to estimate the time spent in each health state and the corresponding life expectancy and total QALYs

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

To populate the 4-arm model six separate patient groups with corresponding PFS and OS survival curves were identified and consequently required extrapolating. The actual KM data for the six groups identified in section 6.2.6.1 above are illustrated below. These curves correspond with those illustrated in section 5.4.2.2 in the clinical section above.

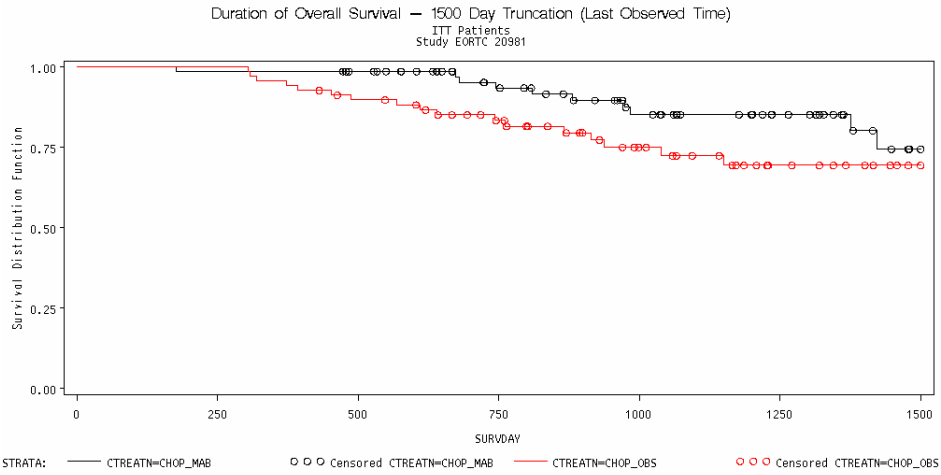
Figure 18: Overall survival by outcome of induction therapy and allocation of maintenance treatment – EORTC20981

(a) R-CHOP-R and R-CHOP-O (Groups 1 and 2)



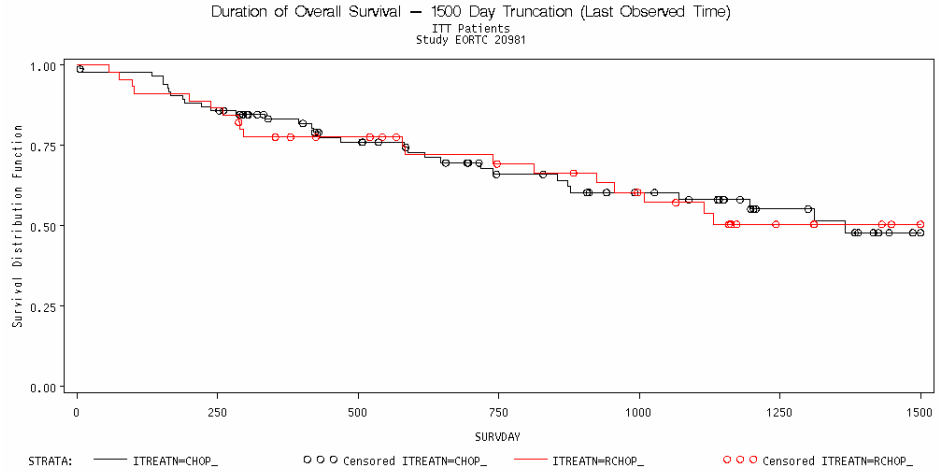
Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 07:57

(b) CHOP-R and CHOP-O (Groups 3 and 4)



Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 08:05

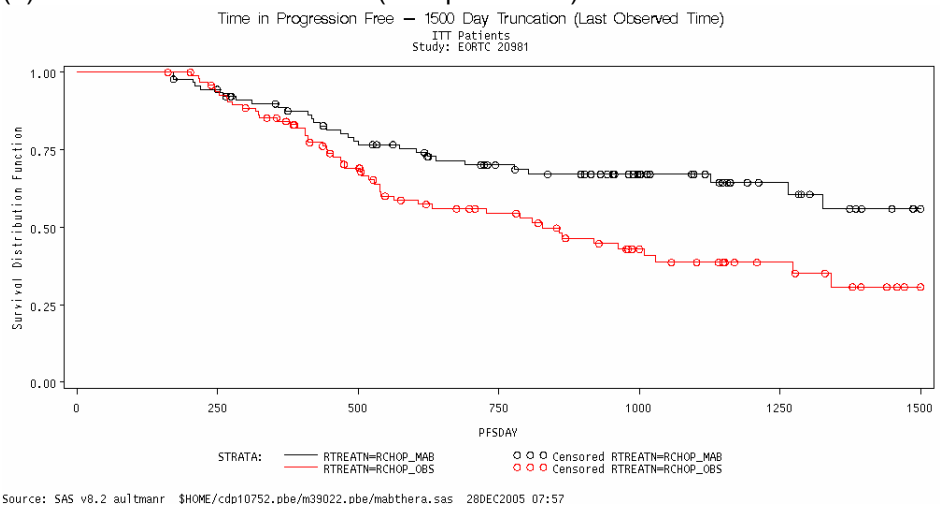
(c) R-CHOP>not eligible and CHOP> not eligible (Groups 5 and 6)



Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 08:05

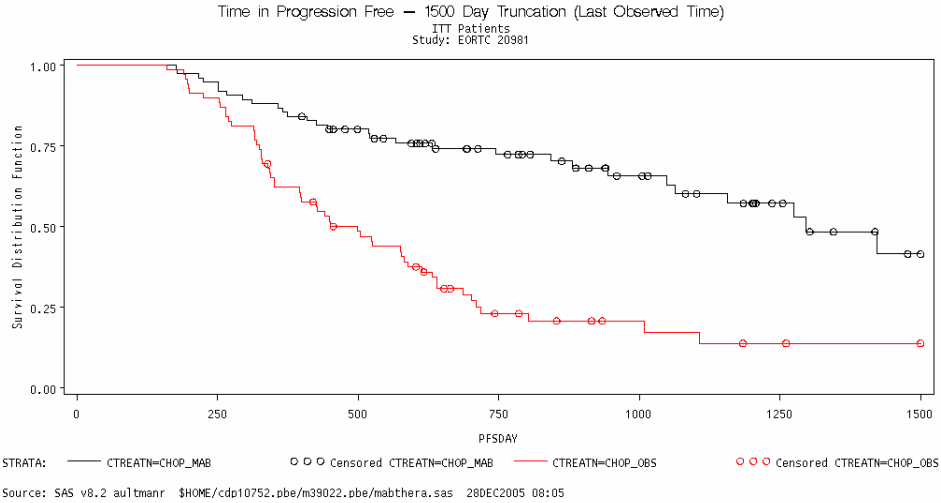
Figure 19: Progression free survival by outcome of induction therapy and allocation of maintenance treatment – EORTC20981

(a) R-CHOP-R and R-CHOP-O (Groups 1 and 2)



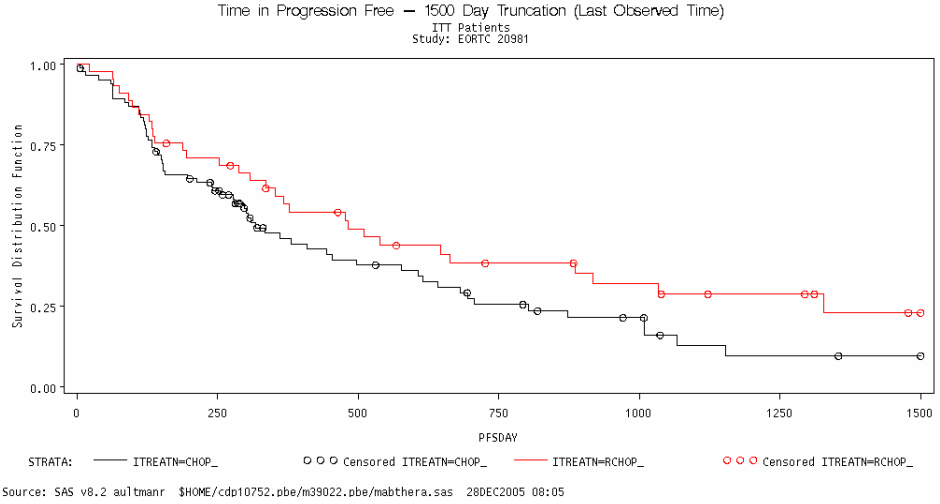
Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 07:57

(b) CHOP-R and CHOP-O (Groups 3 and 4)



Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 08:05

(c) R-CHOP>not eligible and CHOP> not eligible (Groups 5 and 6)

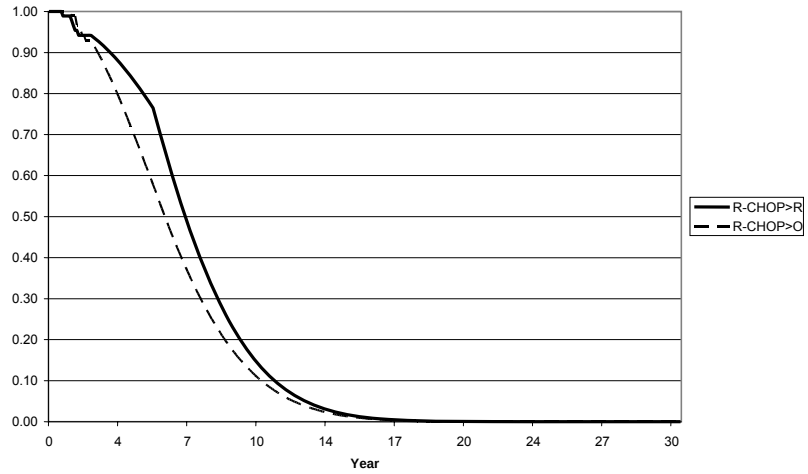


Source: SAS v8.2 aultmanr $HOME/cdp10752.pbe/m39022.pbe/mabthera.sas 28DEC2005 08:05

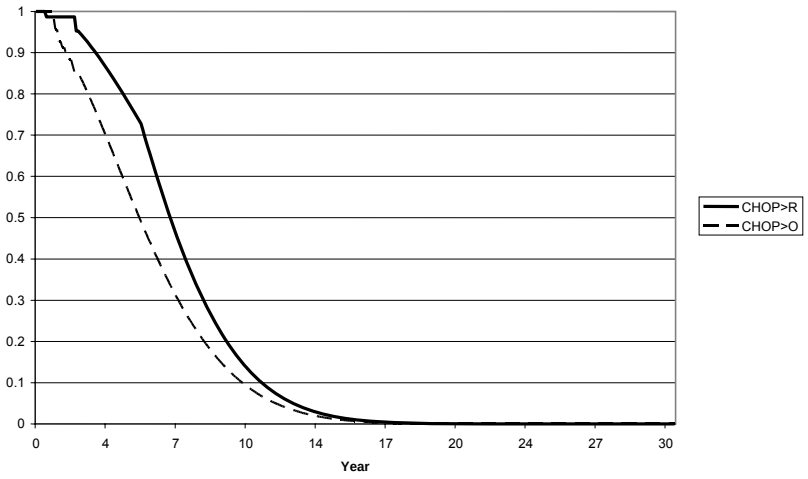
Similar to the 2-arm model the parametric curve fitting for each of the treatment groups implies different hazards across the treatment groups for the life time of the model. This is considered an unrealistic assumption and so the hazards for the rituximab maintenance group are assumed to be equivalent to those in the CHOP-O group after 5 years, as outlined in the 2-arm model. The OS and PFS curves are presented in the two sets of figures below.

Figure 20: Lifetime projection of overall survival by outcome of induction therapy and allocation of maintenance treatment – EORTC20981

(a) R-CHOP-R and R-CHOP-O (Groups 1 and 2)



(b) CHOP-R and CHOP-O (Groups 3 and 4)



(c) R-CHOP>not eligible and CHOP> not eligible (Groups 5 and 6)

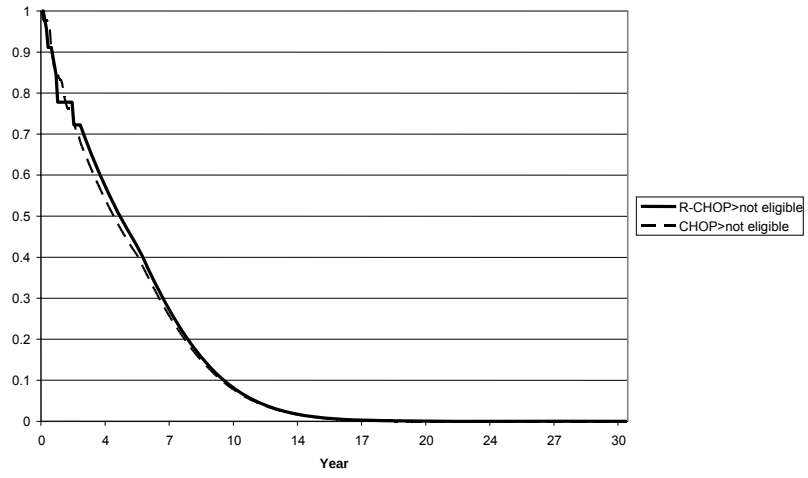
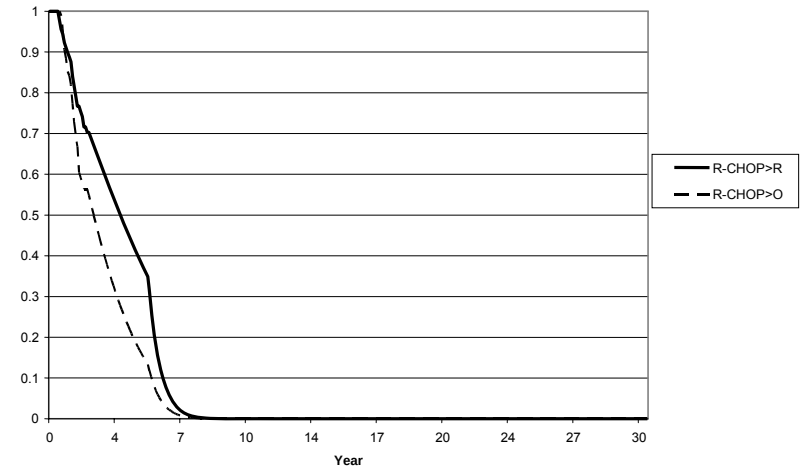
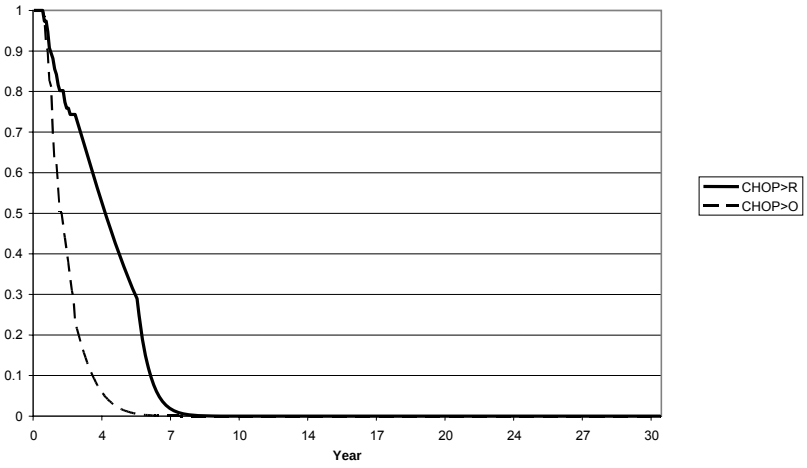


Figure 21: Lifetime projection of progression free survival by outcome of induction therapy and allocation of maintenance treatment – EORTC20981

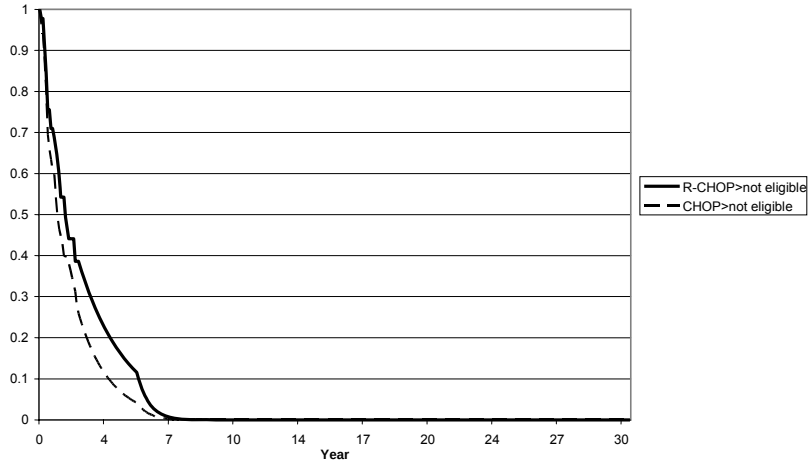
(a) R-CHOP-R and R-CHOP-O (Groups 1 and 2)



(b) CHOP-R and CHOP-O (Groups 3 and 4)



(c) R-CHOP>not eligible and CHOP> not eligible (Groups 5 and 6)



b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not applicable, economic models utilised.

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not applicable, economic models utilised.

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable, economic models utilised.

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable, economic models utilised.

6.2.6.13 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 any longer-term differences in effectiveness between the technology and its comparator?

Not applicable, economic models utilised.

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The “baseline risk” of disease progression relates to observation in the 2-arm model and CHOP arm followed by observation alone in the 4-arm model. The baseline risk was derived directly from the EORTC20981 trial as described in question 6.2.6.8.

6.2.7.2 How were the relative risks of disease progression estimated?

The transition probabilities of moving from PFS to the Progressed health state were estimated independently based on the Kaplan Meier data from the EORTC20981 study and parametric extrapolation for longer term outcomes as described above in question 6.2.6.8. Therefore the relative risks of disease progression and death were time dependent up to year 5 in the model, where upon due to the assumption of no treatment effect for rituximab, there was no relative risk reduction assumed.

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The progression free survival and progressed health states were linked to the final outcome of QALYs by multiplying the proportion of patients in each health state by the respective utility score for each cycle of the model. The sum of the quality adjusted PFS and progressed health states then generates the final mean QALY for each arm of the evaluation.

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The health effects of adverse events were not included in the economic evaluations as it was considered that there was no clinically significant difference between the rate or severity of adverse events observed in both arms of the clinical trial. Due to the long term nature of follicular non-Hodgkin's lymphoma it was considered that the impact of an adverse event, on a patient's quality of life, over the lifetime of the patient would be negligible. For this reason it was not considered necessary to incorporate the impact of adverse events.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Clinical expert opinion was not required to estimate any of the clinical parameters.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

The health effects of adverse events were not included in the economic models for the reasons outlined in section 6.2.7.4.

It was assumed that patients would relapse and receive treatment every two years, this assumption is based on the EORTC20981 trial which found that the approximate time for first progression was 2 years.

It is assumed that patients with progression free disease would attend hospital for routine management/surveillance every 3 months and patients with progressive disease attend hospital for routine management/surveillance every month.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Health benefits for patients have been measured using the QALY. Health effects associated with progression free survival and progressive disease have been measured. A study was commissioned by Roche (Oxford Outcomes, HRQoL in follicular lymphoma) in order to value progression and progression-free health states. In order to value the utility associated with each of these health states, accurate descriptions of the health states and adverse events that would be meaningful to members of the public were developed. These were then valued by 222 patients members of the general public using the EQ-5D instrument at eight centres throughout the UK. The health effects of adverse events have not been valued as outlined in question 6.2.7.4 above.

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

A quality of life study (Oxford outcomes quality of life study, 2005, data on file) was commissioned and subsequently presented at the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) conference (Wild D et al, 2006) to capture the health related quality of life from a cohort of follicular NHL patients in the UK. The study included the EQ-5D instrument to provide valuations from the societal perspective for the progression and progression-free survival health states constructed in the model.

In order to value the health effects of PD and PFS it is necessary to provide a valuation of HRQL that can be incorporated into cost-effectiveness calculations. Therefore the study valued the health status of patients in progression and progression-free survival which can then be applied to the differential durations of time spent in these health states. The health benefits valued were selected because they were relevant to the condition and the intervention being evaluated.

The table below summarises utility scores for the progression free and progression health states. For more details on the utility study please refer to the Appendix 11.

Table 24: Utility values

	Health State	
	Progression-Free	**Progression**
N	132	33
utility	0.805	0.618
SE	0.018	0.056

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

Health effects were measured and valued in a manner consistent with the NICE reference case. QALYs were measured incorporating valuations from the EQ-5D, meeting the NICE reference case requirement of a standardised and validated generic instrument that values changes in patients' HRQL (utilities) based on public preferences elicited using a choice-based method.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

The effect of adverse events upon health benefit and quality of life were excluded from the evaluation as it was considered that there was no clinically significant difference between the rate of adverse events observed in both arms of the clinical trial as outlined in question 6.2.7.4.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Not applicable, health effects were expressed in terms of QALYs.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

There were four major types of costs included in both the 2-arm and 4-arm economic models:

1. Study drug costs, including costs of administration (these costs were calculated separately from the health state transition model)
2. Adverse events (these costs were calculated separately from the health state transition model)
3. Treatment costs upon relapse (these costs were calculated in the health state transition model)
4. Cost of routine management / surveillance (these costs were calculated in the health state transition model)

The costs included in both models are presented below; cost variables which are common to both models will be highlighted.

Maintenance (2-arm model)

Study Drug Costs

Study drug doses were calculated based on rituximab usage during the EORTC20981 trial. The discounted total study drug cost (including administration) was £8,241 per patient in the rituximab maintenance arm and zero in the observation arm. The calculation of study drug costs is explained in more detail in section 6.2.9.6 below.

Cost of adverse events

There are differences in the number of adverse events and serious adverse advents in the clinical and economic sections. Included in the economic analysis are only those clinically significant AEs, which require some level of intervention. Also, to avoid double counting of hospital costs where serious AEs occurred simultaneously, only a single hospitalisation episode has been costed. The cost of adverse events in the economic evaluation was based on the incidence of serious and non-serious AEs reported in EORTC20981. Serious adverse events (SAE's) by definition are life threatening events, deaths, events related to persistent or significant disability, incapacity, congenital anomalies and events that led to hospitalisation or prolongation of hospitalisation. SAE's were categorised according to ICD-10 coding and the ICD-10 code was mapped to a UK NHS Healthcare Resource Group (HRG) to obtain a unit cost. Thus, each SAE received a unit cost specific to that condition to the extent that is possible with HRGs. The costs of SAE's in the economic evaluation are

presented in the table below. The single adverse event in the observation arm was heart failure/shock.

Table25: Total cost of serious adverse events by treatment group

Row	Parameter	rituximab	'observation'	Reference
A	Number of patients in EORTC	167	167	EORTC20981
B	Number of serious adverse events reported in EORTC	30	1	EORTC20981
C	Expected number of adverse events per patient	0.180	0.006	Row B / Row A
D	Unit cost per adverse event	Various	£1,177.38	Unit costs were specific to the type of adverse event experienced.
E	Expected cost of adverse events per patient	£188.90	£7.05	Row C * Row D

Non serious AEs are those that can be managed in the outpatient setting. The total number of non-serious adverse events was counted for each arm of the trial see table below. Each non-serious AE was assumed to accrue a cost of £86 per event and was based on the haematology outpatient visit (NHS reference costs 2004; TOPS FU 303).

Table 26: Total cost of non-serious adverse events by treatment group

Row	Parameter	rituximab	'observation'	Reference
A	Number of patients in EORTC	167	167	EORTC20981
B	Number of non serious adverse events reported in EORTC	268	241	EORTC20981
C	Expected number of adverse events per patient	1.605	1.443	Row B / Row A
D	Unit cost per adverse event	£86	£86	Assumption
E	Expected cost of adverse events per patient	£138.01	£124.11	Row C * Row D

The total cost of adverse events (serious and non-serious) applied in the evaluation for each of the treatment groups is presented in the table below.

Table 27: Total cost of all adverse events by treatment group

Row	Parameter	rituximab	'observation'	Reference
A	Cost of non-serious adverse events	£138.01	£124.11	See table above
B	Cost of serious adverse events	£188.90	£7.05	See table above
C	Total cost of adverse events	£326.91	£131.16	Row A + Row B

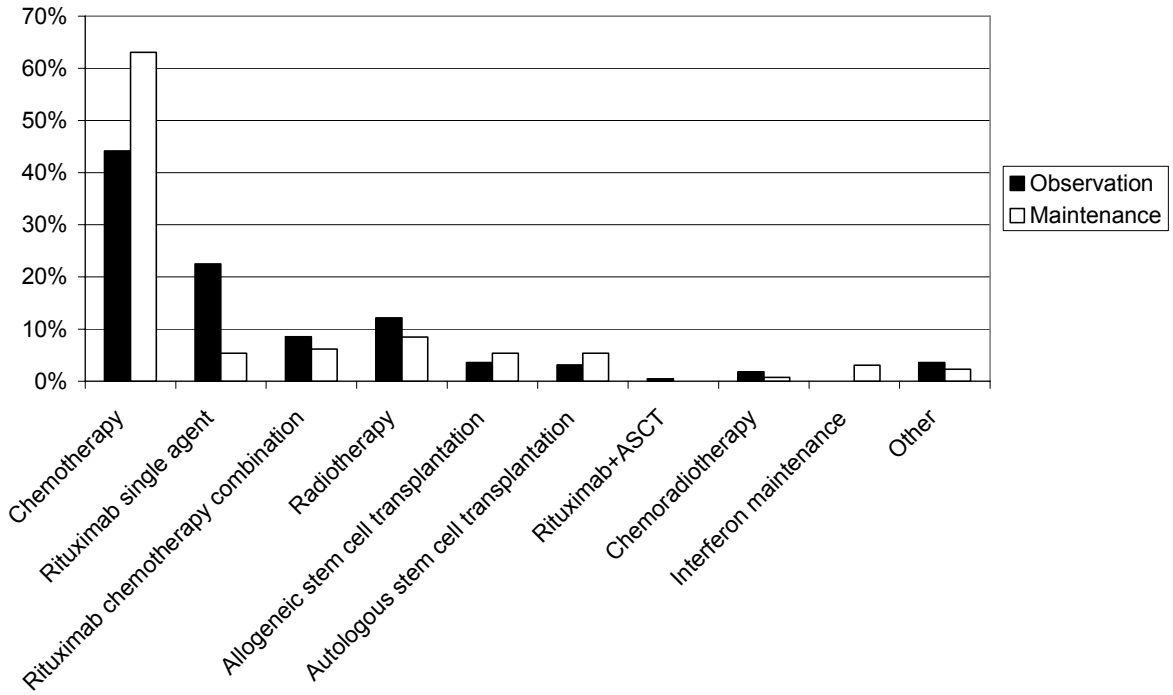
There were two possible forms of bias against rituximab in the collection and cost of AEs as described above in the 2-arm model. Firstly, because AE data was not collected after disease progression (at which point treatment upon relapse might commence), the shorter PFS in the observation arm effectively meant there was a shorter period of follow-up for AE's in the observation arm compared to the rituximab maintenance arm. Secondly, there could be a recording bias caused by the trial being open labelled. This is because physicians would be more likely to ignore medical conditions in the observation arm, on the grounds it is not significant and/or could not possibly be treatment-related, but would be more likely to record any event in the maintenance arm given the possibility it is a treatment-related AE. Given these biases, the economic evaluation is calculated without the cost of adverse events in sensitivity analysis. See Appendix 7 for a more detailed description of the AEs included in the analysis.

Treatment costs upon relapse

Treatment costs upon relapse were included in the economic evaluation to reflect the therapies this patient group receives upon disease progression and continue to receive through their remaining life expectancy. These costs are calculated based on data collected about the therapies received upon progression by patients in the EORTC20981 trial.

The figure below shows the distribution of the post-protocol therapy received by patients in maintenance and observation treatment groups. The data in the diagram incorporates post-protocol therapies received by all patients (observation and maintenance groups) in EORTC20981 and therefore is a reasonable representation of the expected utilisation and cost of the therapies this patient group receives upon relapse and continues to receive through their remaining life expectancy.

Figure 22: Post-protocol treatment distribution EORTC20981 (maintenance and observation) used to estimate treatment costs upon relapse



The table below uses the data in the above figure to calculate the expected cost of a single line of treatment costs upon relapse. The unit cost applied to each therapeutic option is derived from a variety of sources including the NHS Reference Cost Schedule 2004 and the BNF, see Appendix 8. It is estimated that the expected cost for each therapeutic option administered following progression is £6,858 per patient in the observation arm and £6,871 per patient in the maintenance arm.

Table 27: Expected cost of a single treatment costs upon relapse, by treatment group and across both treatment groups a

Treatment option (post progression)	Unit cost per treatment course	Number of treatment costs upon relapse administered		Proportion of all treatment costs upon relapse	
		OBS	RIT	OBS	RIT
Chemotherapy	£3,232	98	82	44%	63%
Rituximab single agent	£8,490	50	7	23%	5%
Rituximab chemotherapy combination	£11,206	19	8	9%	6%
Radiotherapy	£1,620	27	11	12%	8%
Allogeneic stem cell transplantation	£41,721	8	7	4%	5%
Autologous stem cell transplantation	£18,998	7	7	3%	5%
Rituximab+ASCT	£38,500	1	-	0%	0%
Chemoradiotherapy	£4,852	4	1	2%	1%
Interferon maintenance	£7,834	-	4	0%	3%
Other	£0	8	3	4%	2%
Average cost (per line of post progression treatment)		222	130	£6,858	£6,871

a. Source: Secondary displays of efficacy data. Protocol EORTC20981. Research Report 1016350

For the purpose of calculating the cost of all therapies after the maintenance setting, it is assumed that patients in each group will receive treatment costs upon relapse every two years. This assumption was based on the approximate time to first progression observed in EORTC2091. The cost per line of therapy was subsequently converted into a monthly cost and patients incurred this monthly cost while in the PD health state of the Health state transition model as presented in the table below. The frequency and unit costs are tested in sensitivity analysis. Therefore the longer predicted survival for rituximab patients within the model did incur an additional cost of post-protocol treatments for every additional month of survival.

Table 28: Treatment costs upon relapse, by treatment group

Row	Parameter	Observation	Maintenance	Reference
A	Cost per line of therapy	£6,858	£6,871	See table above
B	Average time between treatment	2 years	2 years	Assumption approximately based on the average time to first progression (EORTC20981 Research Report 1016350)
C	Expected annual cost for patients in the PD health state of the Health state transition model	£3,435	£3,429	A/B
D	Monthly cost for patients in the PD health state of the Health state transition model	£285.77	£286.27	C/12

Cost of routine management / surveillance

Patients incurred routine management / surveillance costs during each cycle of the health state transition model. These costs were included in order to capture those associated with the routine management of the underlying condition of patient's with NHL. It was assumed that both patients with progressive disease and those free of progression would require routine management. However, it was assumed that following a clinical consultation that patients with progressive disease would experience greater utilisation of health care resources. For simplicity and to avoid double counting of costs captured in other sections of the economic evaluation (adverse events, treatment costs upon relapse, drug administration), the routine management costs consisted of outpatient visits only. Patients in the PD health state were assigned a cost of an outpatient visit every month (£86; NHS reference costs 2004; TOPS FU 303). Patients who were progressive free were attributed the cost of an outpatient visit every 3 months (£28.67 per cycle; £86/3).

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

Study drug costs
Induction costs

The total induction study drug costs per patient treated with R-CHOP and CHOP were £9,272 and £1,669 respectively. This total cost included study drug costs and the costs of drug administration.

Maintenance costs

The maintenance drug costs are assumed to be the same as outlined above under the 2-arm, Study Drug Costs section 6.2.9.1.

The calculations for both induction and maintenance drug costs are outlined in more detail in section 6.2.9.6 below.

Cost of adverse events

The cost of adverse events in the economic evaluation were based on the incidence of serious and non-serious AEs reported in EORTC20981 in both the induction and maintenance phases of the trial. Serious adverse events (SAE's) were categorised according to ICD-10 coding and the ICD-10 code was mapped to a

UK NHS Healthcare Resource Group (HRG) to obtain a unit cost. Thus, each SAE received a unit cost specific to that condition to the extent that is possible with HRGs, as was done in the 2-arm model.

The costs of SAE in the economic evaluation estimated from EORTC20981 are presented in the table below. The costs in this table are calculated according to the induction and maintenance treatment groups (including those patients not eligible for maintenance therapy).

Table 29 Total cost of serious adverse events in the induction and maintenance phases of the economic evaluation, by treatment group and outcome of induction

Row	Parameter	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O	R-CHOP>not eligible	CHOP>not eligible	Reference
A	Number of patients in EORTC	91	98	76	69	45	86	EORTC20981
B	Number of serious adverse events reported in EORTC (induction and maintenance phases)	61 (45 and 16)	38 (38 and 0)	41 (27 and 14)	21 (20 and 1)	33 (33 and 0)	45 (45 and 0)	EORTC20981
C	Expected number of adverse events per patient	0.670	0.388	0.539	0.304	0.733	0.523	Row B / Row A
D	Unit cost per adverse event	Various	Various	Various	Various	Various	Various	Unit costs were specific to the type of adverse event experienced.
E	Expected cost of adverse events per patient	£719.83	£426.91	£561.96	£318.52	£744.25	£604.96	Row C * Row D

The total number of non-serious adverse events was also counted for each arm of the trial. Each non-serious AE was assumed to accrue a cost of £86 per event, as per the 2-arm model, and was based on the haematology outpatient visit (NHS reference costs 2004; TOPS FU 303).

Table 30: Total cost of non-serious adverse events in the induction and maintenance phases of the economic evaluation, by treatment group and outcome of induction

Row	Parameter	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O	R-CHOP>not eligible	CHOP>not eligible	Reference
A	Number of patients in EORTC	91	98	76	69	45	86	EORTC20981
B	Number of serious adverse events reported in EORTC (induction and maintenance phases)	340 (199 and 141)	322 (201 and 121)	280 (153+127)	258 (138 and 120)	152 (152 ad 0)	189 (189 and 0)	EORTC20981
C	Expected number of adverse events per patient	3.736	3.286	3.684	3.739	3.378	2.198	Row B / Row A
D	Unit cost per adverse event	£86	£86	£86	£86	£86	£86	Assumption
E	Expected cost of non-serious adverse events per patient	£321.32	£282.57	£316.84	£321.57	£290.49	£189.00	Row C * Row D

The total cost of adverse events (serious and non-serious) applied in the economic evaluation for each of the treatment groups is presented in the table below. The calculations in the table account for the difference in the proportion of patients eligible for maintenance therapy between the two induction treatment groups. Therefore the cost of adverse events represents an intention-to-treat analysis from the time of the first randomisation in EORTC20981.

Table 31: Total cost of all adverse events in the induction phase by treatment group

Row	Parameter	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O	Reference
A	Proportion of patients eligible for maintenance (n/N)	80.8%	80.8%	62.8%	62.8%	EORTC
B	Total cost of adverse events in patients eligible for maintenance (serious + non-serious)	£1,041.15 (719.83 +312.32)	£709.48 (426.91 +282.57)	£878.81 (561.96 +316.84)	£640.09 (318.52 +321.57)	See tables above
C	Total cost of adverse events in patients not eligible for maintenance (serious + non-serious)	£1,034.74 (744.25+290.49)	£1,034.74 (744.25+290.49)	£793.96 (604.96+189.00)	£793.96 (604.96+189.00)	See tables above
D	Total cost of adverse events	£1,039.92	£772.03	£847.22	£697.37	Row B * Row A+ Row C * (1-Row A)

There were two possible forms of bias against rituximab in the collection and cost of AEs as described in the 2-arm model above. See Appendix 7 for a more detailed description of the AEs included in the analysis.

Cost of treatments upon progression/relapse

The cost of treatment upon relapse by treatment group is as described above in the 2-arm model. Presented in the table below is the expected cost of a single line of treatment received upon relapse, by treatment group.

Table 32: Expected cost of a single line of treatment received upon relapse, by treatment group

Treatment option (post progression)	Unit cost per treatment course	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O
Chemotherapy	£3,232	68.5%	51.4%	56.1%	37.2%
Rituximab single agent	£8,490	4.1%	12.8%	7.0%	31.9%
Rituximab chemotherapy combination	£11,206	4.1%	4.6%	8.8%	12.4%
Radiotherapy	£1,620	8.2%	11.9%	8.8%	12.4%
Allogeneic stem cell transplantation	£41,721	2.7%	4.6%	8.8%	2.7%
Autologous stem cell transplantation	£18,998	5.5%	6.4%	5.3%	0.0%
Rituximab+ASCT	£38,500	0.0%	0.0%	0.0%	0.9%
Chemoradiotherapy	£4,852	1.4%	3.7%	0.0%	0.0%
Interferon maintenance	£7,834	5.5%	0.0%	0.0%	0.0%
Other	£0	0.0%	4.6%	5.3%	2.7%
Average cost (per line of post progression treatment)		£5,836	£6,770	£8,195	£6,943

a. Source: Secondary displays of efficacy data. Protocol EORTC20981. Research Report 1016350

For the purpose of calculating the cost of all therapies after the maintenance setting, it is assumed that patients in each group will receive a line of treatment upon relapse every two years. This assumption was based on the approximate time to first progression observed in EORTC2091. The cost per line of therapy was converted into a monthly cost and patients incurred this monthly cost while in the PD health state of the Health state transition model, see the table below. The frequency and cost of treatments upon relapse is tested in sensitivity analysis.

Table 33: Cost of treatment costs upon relapse applied in each cycle of the health state transition model, by treatment group

Row	Parameter	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O	Reference
A	Cost per line of therapy	£5,836	£6,770	£8,195	£6,943	See table above
B	Average time between treatments upon relapse	2 years	2 years	2 years	2 years	Assumption approximately based on the average time to first progression (EORTC20981 Research Report 1016350)
D	Monthly cost for patients in the PD health state of the Health state transition model	£243	£282	£341	£289	(C/2)/12

Cost of routine management / surveillance

The costs of routine management/surveillance are as outlined above in the 2-arm model description.

6.2.9.2 How were the resources measured?

Study drug & Administration

Drug utilisation was taken directly from the EORTC20981 trial as described above in section 6.2.9.1. Drug administration was assumed to be captured within the oncology outpatient unit cost.

Adverse events

The frequency and type of adverse events were taken directly from the EORTC20981 trial as described above in section 6.2.9.1.

Treatment upon relapse

The therapies used upon relapse were taken directly from the EORTC20981 trial as described above. The frequency of relapse, every 2 years, and therefore the rate at which this cost is incurred is an assumption based upon the approximate time to first progression observed in EORTC20981.

Routine management/surveillance

The assumed frequency of an outpatient visit for routine management for the progression free and progressive disease follicular NHL patients health states were based on expert clinical assumption.

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

The resource utilisation data for study drug utilisation, adverse events and treatment upon relapse were all taken from the EORTC20981 trial, as was the baseline and relative risks of disease progression. The resource use for routine management/surveillance was based on an assumption.

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Both economic models used a lifetime time horizon, therefore costs and benefits over the lifetime of the patient were captured in the models. Post-protocol treatments and routine monitoring beyond the initial treatment period are included in the model over the entire time horizon and outlined in greater detail above.

6.2.9.5 What source(s) of information were used to value the resources?

Study drug & Administration

Drug costs were sourced from the British National Formulary (BNF). The cost per administration of induction and maintenance treatment was based on the cost of a haematology outpatient visit of £86 sourced from the NHS reference costs 2004, TOPS FU 303. See Appendix 6 for more details.

Adverse event

Serious adverse events were assigned a code according to ICD-10 coding; this code was then mapped to a UK NHS Healthcare Resource Group (HRG) to obtain a unit cost.

Non serious adverse events were assumed to accrue a cost of £86 per event which was based on the cost of a haematology outpatient visit sourced from the NHS reference costs 2004, TOPS FU 303. See Appendix 7 for more details.

Treatment upon relapse

To calculate the cost of treatment upon relapse the unit cost applied to each therapeutic option is derived from the NHS Reference Cost Schedule 2004, BNF and other sources which are outlined in Appendix 7.

Routine management/surveillance

The costs associated with routine management/surveillance were sourced from the NHS reference costs 2004, TOPS FU 303.

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

There is a difference between the acquisition costs reported here and those reported in section 1. The costs reported here are based on drug usage during the EORTC20981 trial. The estimated drug costs in section 1 are based on assumed treatment duration of a maximum of 6 cycles in the induction setting and 8 cycles in the maintenance setting.

Maintenance (2-arm)

As outlined in section 6.2.9.1 above the discounted total study drug cost (including administration) was £8,241 per patient in the rituximab maintenance arm and zero in the observation arm. On average, patients received 5.93 cycles of rituximab during the maintenance phase of the EORTC20981 trial, with 8 being the maximum number of cycles, as shown in the table below. This calculation excluded ‘censored’ patients still taking maintenance medication, but included the 134 patients who completed all 8 cycles, progressed, or stopped maintenance medication for other reasons.

Table 34: Utilisation of rituximab maintenance in EORTC20981 and applied to the economic evaluation

Number of doses received by the patient	Number of patients[a]	Reference
0	1	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
1	14	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
2	10	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
3	12	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
4	5	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
5	7	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
6	4	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
7	3	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
8	78	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
Total doses	794	No. of patients * No. of doses (for each dose No.)
Number of patients	134	Sum the No. of patients
Mean number of doses per patient	5.9254	Total doses/No. patients
% doses during first year	58%	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)
% doses during second year	42%	EORTC20981 Research Report 1016350 (Table 54 and t_admbm_70000)

Drug costs of £7,739 were calculated based on a rituximab dosage of 375mg/m^2 and a mean dispensed dose of 759 mg per patient. Drug prices were sourced from the British National Formulary (BNF). The mean dispense dose accounted for wastage, which will occur when the vial size is not equal to the required dispense dose. The calculation of drug costs is summarised in the table below.

Table 35: Calculation of the cost of rituximab maintenance in the economic evaluation

Parameter	Value	Source/description
Cost of rituximab (per mg)	£1.75	BNF: Concentrate for intravenous infusion, rituximab 10 mg/mL, net price net price 10-mL vial = £174.63, 50-mL vial = £873.15. BNF prices represent the dispensed price (inclusive of pharmacy costs)
Rituximab dose (mg/m^2)	375	Regimen (maintenance): 375mg/m^2 iv infusion once every 3 months up to max. of 2 years (EORTC20981)
Estimated average dispensed dose accounting for wastage (mg)	759	Study mean and standard deviation dose applied to a normal distribution to calculate the proportion of all patients receiving each dispense dose.
Cost per rituximab maintenance dose	£1,325	= £1.75 * 759 [a]
Number of rituximab doses (per patient)	5.9254	See table above
Total cost undiscounted	£7,851	= 1,325*5.9254
Total discounted	£7,739	58% of doses in the first year, 42% in the second year. =£7,851*(58%*1+42%*1/(1.035))

The discounted administration cost per dose was calculated as £502 based on 100% outpatient treatment, as presented in the table below. The cost per administration of rituximab is based on the cost of a haematology outpatient visit (£86; NHS reference costs 2004; TOPS FU 303). Sweetenham et al. (1999) reported that of 327 visits for administration of rituximab, 71 (22%) were administered in the inpatient setting. However, the inpatient visits were required for the first rituximab dose in an induction setting (Sweetenham et al. 1999). Therefore, the administration cost applied in this economic evaluation was based on an outpatient visit.

Table 36: Cost of rituximab maintenance administration

Parameter	Value	Reference
Number of rituximab doses per patient	5.9254	See table above
Unit cost for the administration of a rituximab dose	£86	NHS reference costs 2004; TOPS FU 303
Total cost per patient of rituximab administration (undiscounted)	£510	=5.9254 *£86
Total cost per patient of rituximab administration (discounted at 3.5%)	£502	See table above; 58% of doses in the first year, 42% in the second year. =£510*(58%*1+42%*1/(1.035))

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

Induction costs

As presented in section 6.2.9.1 above the total induction study drug costs per patient treated with R-CHOP and CHOP were £9,272 and £1,669 respectively. This total cost included study drug costs and the costs of drug administration as presented in the two tables below.

The total cost per patient applied in the evaluation is based on the average number of induction cycles received in each of the EORTC20981 induction arms, presented in the table below. The mean dispense dose accounted for wastage, which can occur because the vial size is not normally exactly equal to the required dose (see Appendix 8 for a detailed description).

Table 37: Average number of induction cycles received

Number of induction cycles	CHOP Proportion of patients	R-CHOP Proportion of patients
1	2.6%	2.1%
2	1.8%	0.0%
3	9.6%	5.6%
4	2.6%	1.3%
5	1.8%	1.7%
6	81.1%	89.3%
8	0.4%	0.0%
Weighted average	5.447	5.6838

Source: EORTC20981 Research Report 1016350

Table 38: Cost of induction therapy, by treatment group

Parameter	Rituximab	Cyclophosphamide	Vincristine	Prednisone	Doxorubicin
Cost per unit mg [a]	£1.75	£0.01	£11	£0.01	£1.87
Daily dose	375 mg/m2	750 mg/m2	1.4 mg/m2	100 mg	50 mg/m^2
Mean dose [b]	758.75	1,643.40	2.00	500	99.50
Cost per cycle	£1,325	£9	£21	£3	£186
Total drug cost per cycle (R-CHOP)					£1,545
Total drug cost per cycle (CHOP)					£220

a. Unit prices sourced from BNF and represents the dispensed price (inclusive of pharmacy costs)
b. To account for wastage, the BSA of EORTC20981 patient population (mean BSA = 1.89, St dev m2 = 0.198) converted to a mean and standard deviation dosage for each drug and then applied to a normal distribution to determine the proportion of patients in each dosing quantity band. See appendices.
c. Note rounding differences might occur

Table 39: Total cost of induction therapy, including administration cost, by treatment group

Row	Parameter	R-CHOP	CHOP
A	Total drug costs per cycle	£1,545	£220
B	Unit cost per visit for drug administration	£86	£86
C	Total drug and administration costs per cycle	£1,631	£306
D	Number of cycles per patient	5.6838	5.4474
E	Total costs per patient	£9,272	£1,669

The assumption that administration costs are the same for both CHOP and R-CHOP is tested in the sensitivity analysis.

Maintenance costs

The rituximab maintenance drug costs were calculated in the same manner as outlined above in the Maintenance section of this question. Presented in the table below are the total study drug costs (induction and maintenance costs) for each of the four treatment groups in the economic model.

Table 40: Total study drug costs, induction and maintenance, across all four treatment groups

Row	Parameter	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O
A	Cost of induction therapy per patient	£9,272	£9,272	£1,669	£1,669
B	Cost of maintenance therapy per patient eligible for maintenance	£8,241	£0	£8,241	£0
C	Proportion of patients eligible for maintenance therapy	80.8%	80.8%	62.8%	62.8%
D	Expected cost of maintenance therapy across the entire treatment group	£6,656	£0	£5,173	£0
E	Total study drug costs (discounted)	£15,929	£9,272	£6,842	£1,669

6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

All resources, excluding routine surveillance, were measured from the EORTC20981 clinical trial, which can be used as a proxy for resources that the NHS would consume if rituximab was positively endorsed for this indication. Where possible resources were valued from the NHS perspective utilising NHS reference costs, BNF, HRG costs and other sources as outlined above in section 6.2.9.5.

6.2.9.8 Were resource values indexed to the current price year?

All costs employed in the model are from 2004-2006 sources. The major incremental cost of the model relates to the unit cost of rituximab which has not changed since 1998. Therefore an inflationary increase to all other costs was not considered necessary from the perspective of the anticipated incremental cost and also given the relatively contemporary nature of the unit costs utilised.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

- The administration costs applied in the economic models are based on the cost of a haematology outpatient visit. Sweetenham et al (1999) reported that of 327 visits for administration of rituximab, 71 (22%) were administered in the inpatient setting. Therefore, the administration cost applied is based on an outpatient visit.

- It is assumed that patients in each arm of the two models will receive a line of treatment upon relapse every two years. This assumption is based on the approximate time to first progression observed in EORTC20981.

- It was assumed that patients would receive routine check-ups regularly throughout the model. Patients who were progression free would be observed once ever three moths and patients with progressive disease would be observed once a month. These assumptions were tested further in the sensitivity analysis.

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Both costs and QALYs were discounted at the NICE reference case value of 3.5%.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

Variables that were included in the sensitivity analyses are highlighted below.

Maintenance 2-arm model

Table 41: Variables included in the sensitivity analysis (2arm model)

Variables tested	Description of sensitivity analysis	Value in sensitivity analysis
Distribution used for extrapolation of PFS and OS	Log-logistic	See appendix 5
Duration of treatment benefit	Applied observation arm hazards from PFS and OS in both arms from the end of the treatment benefit	2 years 30 years
Unit cost of non serious adverse event	Value halved	£43
	Value doubled	£172
Adverse events inclusion	Excluded from calculations	-
Unit cost per line of treatment upon relapse	Double costs in observation arm only	OBS: £13,741
	Double costs in both arms	OBS: £13,741 RIT: £13,717
Frequency of treatment upon relapse	Double frequency in observation arm only	OBS: Every year
	Double frequency in both arms	RIT and OBS: Every year

Cost of routine management / surveillance per cycle	Cost in PD health state equal to cost in PFS health state	£28.67
	Cost in PFS health state equal to cost in PD health state	£86
PFS utility values	Utility values equal to progressive disease	0.618
PD utility values	Utility values equal to PFS	0.805
Duration of follow up	4 years	
	50 years	
Discount rate	Costs and outcomes	undiscounted
	Costs	undiscounted
	Outcomes	undiscounted

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

Table 42: Variables included in the sensitivity analysis (2arm model)

Variables tested	**Description of sensitivity analysis**	**Value in sensitivity analysis**
R-CHOP and CHOP response rates	Lower 95% CI of difference between the groups (CHOP response rate kept constant)	0.727 and 0.628
	Upper 95% CI of difference between the groups (CHOP response rate kept constant)	0.888 and 0.628
Distribution used for extrapolation of PFS and OS	Log-logistic	See Appendix 5
Duration of treatment benefit	Applied CHOP-O arm hazards for PFS and OS in all arms from the end of the treatment benefit	2 years 30 years

Unit cost of non serious adverse event	Value halved	£43
	Value doubled	£172
Adverse events inclusion	Excluded from calculations	-
Administration costs	Value set to zero for CHOP arm	£0
Unit cost per line of treatment upon relapse	Double costs in R-CHOP-R arm only	OBS: £11,673
	Double costs in all arms	OBS: £11,673 RIT: £13,541 RIT: £16,390 RIT: £13,887
Frequency of treatment upon relapse	Double frequency in R-CHOP-R arm	R-CHOP-R arm only every year
	Double frequency in all arms	
PFS utility values	Utility values equal to progressive disease	0.618
PD utility values	Utility values equal to PFS	0.805
Duration of follow up	4 years	
	50 years	
Discount rate	Costs and outcomes	Undiscounted

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

PSA was carried out for both the 2-arm and 4-arm economic models. Please see Appendix 9 below for a through description of the PSA variables.

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

Structural uncertainties explored within the univariate sensitivity analysis of both the 2-arm and 4-arm models include the following:

- The model time horizon
- The parametric function used for extrapolation

- Time period over which the parametric curve is utilised
- Duration of treatment effect of rituximab

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Please see question 6.2.6.8 above.

6.2.12.2 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.

The transition probabilities for progression free survival to progression, progression to death and progression free survival to death are derived directly from the Kaplan Meier curves for the first 24 months and subsequently from the Weibull extrapolated curves and therefore capture the fact these probabilities may vary over time.

6.2.13 Validity

6.2.14 Describe the measures that have been undertaken in order to validate and check the model.

The model was validated by an external agency who checked for calculation errors, errors in structure as well as the plausibility of assumptions and data. The face validity of the model was checked by the agency's oncologists. The economic model assumptions were also validated by external UK clinicians at a UK Roche advisory board.

Life expectancy for relapsed/refractory follicular non-Hodgkin's lymphoma patients has been reported in the region of 8 to 10 years from the point of diagnosis (Sweetenham et al, 1999). The 2-arm model predicts that 2nd line maintenance

rituximab and observation patients have an average life expectancy of 6.6 and 5.4 years (undiscounted). The 4-arm model predicts that 2nd line R-CHOP induction followed by maintenance rituximab and CHOP induction followed by maintenance rituximab patients have an average life expectancy of 6.4 and 5.8 years. As the model excludes the duration of first line treatment and remission, these comparisons help illustrate that the model is making survival predictions within a plausible range.

6.3 Results

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

Maintenance (2-arm model)

Effectiveness Results

The average, discounted, life expectancy in the rituximab group was 1.00 year longer than in the observation group (5.87 vs. 4.87). Rituximab maintenance was associated with an additional 0.89 QALYs compared to the observation group (4.22 vs. 3.33). The rituximab maintenance group also spent 1.46 years longer in PFS. The table below presents the effectiveness of each of the treatment groups calculated in the modelled economic evaluation.

Table 43: Effectiveness of the treatment groups calculated in the modelled economic evaluation

Treatment group	QALYs (undisc.)	Life years (undisc.)	PFS years (undisc.)
Rituximab maintenance	4.2250 (4.7177)	5.8694 (6.5998)	3.1965 (3.4170)
'Observation'	3.3331 (3.6794)	4.8693(5.4092)	1.7322 (1.7993)
Incremental	0.8919 (1.0383)	1.0001 (1.1906)	1.4643 (1.6177)

The table below summarises the time spent in each health state. Patients in the rituximab maintenance group spent 1.62 years longer in the PFS health state than patients in the observation group (3.42 years v 1.80 years). The observation group accrued more time in the PD health state than the rituximab group (3.61 years v 3.18 years).

Table 44: Expected time in each health state (years undiscounted)

Treatment group	Time in PFS health state (years, undiscounted)	Time in PD health state (years, undiscounted)	Total time alive (years, undiscounted)
Rituximab maintenance	3.4170	3.1828	6.5998
'Observation'	1.7993	3.6099	5.4092
Incremental	1.6177	-0.4271	1.1906

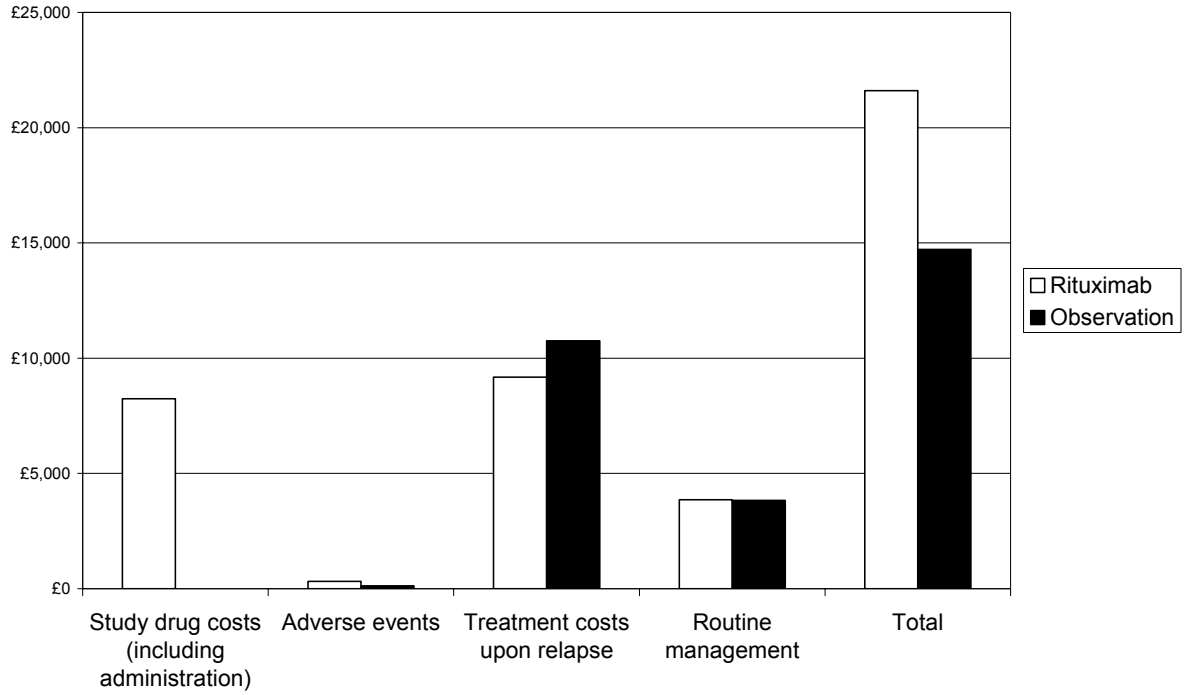
Costs

Total costs were £6,886 higher in the maintenance group than the observation group as outlined in the table below. The cost difference can be largely attributed to study drug costs in the rituximab group which was partly offset by the lower cost of treatment upon relapse in the maintenance arm due to a shorter time in the PD health state, as illustrated in the figure below. In the rituximab group, the slightly higher routine management costs were due to the greater life expectancy of this group. AE costs were higher in the rituximab group.

Table 45: Total costs by type of cost and treatment group estimated in the economic evaluation

Cost item	Rituximab (undisc.)	Observation (undisc.)	Incremental (undisc.)
Study drug costs	£8,241 (£8,361)	£0 (£0)	£8,241 (£8,361)
Adverse events	£327 (£327)	£131 (£131)	£196 (£196)
Treatment costs upon relapse	£9,182 (£10,934)	£10,758 (£12,379)	-£1,576 (-£1,445)
Routine management	£3,858 (£4,460)	£3,833 (£4,344)	£25 (£116)
Total costs	£21,608 (£24,082)	£14,722 £16,855)	£6,886 (£7,227)

Figure 23: Total discounted costs by type of cost and treatment group estimated in the economic evaluation



Incremental cost-effectiveness results

Maintenance therapy with rituximab when compared to observation was highly cost-effective. The incremental cost per QALY gained was £7,721. The table below presents a detailed breakdown of the results.

Table 46: Incremental cost-effectiveness of rituximab maintenance compared to observation

Treatment group	Total cost	QALYs gained	Incremental cost per QALY gained	Life years gained	Incremental cost per life-year gained
Rituximab	£21,608	4.2250		5.8694	
'Observation'	£14,722	3.3331		4.8693	
Incremental	£6,886	0.8919	**£7,721**	1.0001	**£6,885**

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

Effectiveness Results

Patients receiving R-CHOP induction followed by rituximab maintenance had the highest life expectancy (5.70 years; discounted) and quality adjusted life expectancy (4.09 years; discounted) (see table below). The next two most effective regimes were CHOP induction followed by rituximab maintenance and R-CHOP induction followed by observation. The least effective regime was when no rituximab doses were received, that is, CHOP induction followed by observation.

Table 47: Effectiveness of the treatment groups calculated in the modelled economic evaluation

Treatment group	QALYs (undisc.)	Life years (undisc.)	PFS years (undisc.)
R-CHOP-R	4.0906 (4.5619)	5.7035 (6.4110)	3.0262 (3.2081)
R-CHOP-O	3.6260 (4.0089)	5.1454 (5.7313)	2.3859 (2.4971)
CHOP-R	3.7207 (4.1324)	5.2479 (5.8723)	2.5534 (2.6916)
CHOP-O	3.0892 (3.4016)	4.5483 (5.0424)	1.4886 (1.5260)

The table below summarises the time spent in each health state. Patients in the CHOP-O group spent the most amount of time in the PD health state (3.52 years). This is an interesting result considering this group (CHOP-O) also had the lowest life expectancy of the four groups (5.04 years).

Table 48: Expected time in each health state (years undiscounted)

Treatment group	Time in any PFS health state – PFS induction, PFS maintenance or PFS withdrawn (years, undiscounted)	Time in PD health state (years, undiscounted)	Total time alive (years, undiscounted)
R-CHOP-R	3.2081	3.2029	6.4110
R-CHOP-O	2.4971	3.2342	5.7313
CHOP-R	2.6916	3.1806	5.8723
CHOP-O	1.5260	3.5164	5.0424

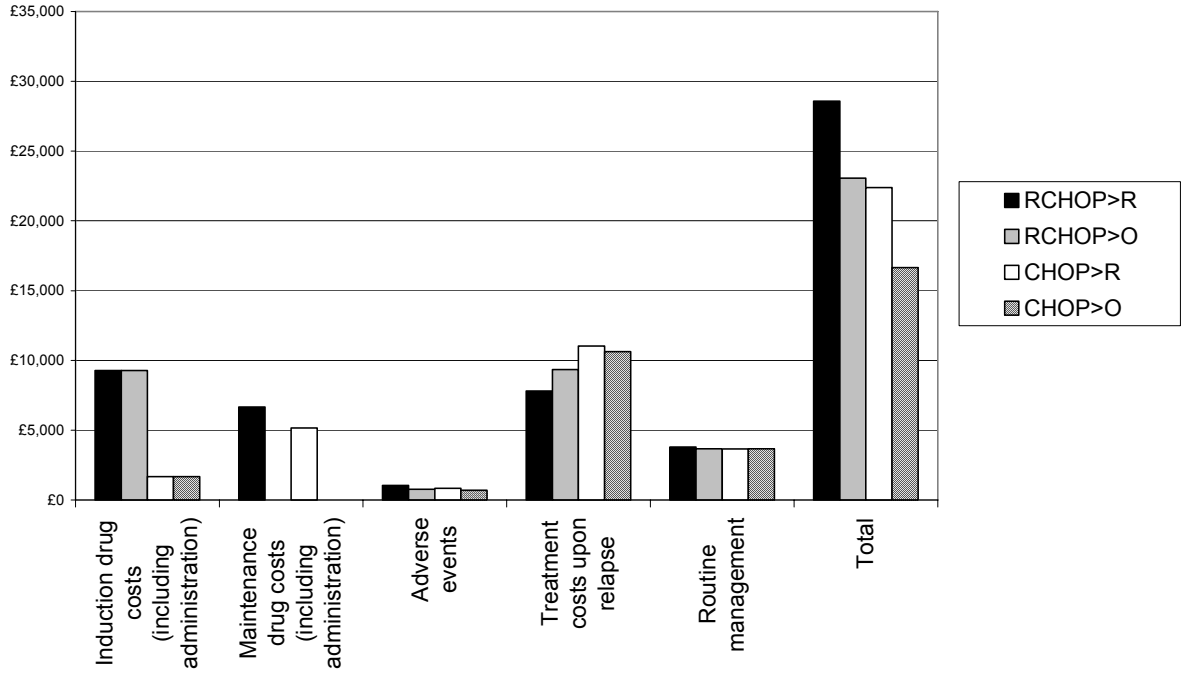
Cost Results

The total cost difference between the four groups was almost entirely attributable to the cost of rituximab. The total modelled cost of the R-CHOP-R group (£28,593 per patient) was greater than the three other groups (see table and figure below). The R-CHOP-O and CHOP-R groups had a similar total cost. The CHOP-O group had the lowest total cost (£16,652 per patient).

Table 49: Total costs by type of cost and treatment group estimated in the economic evaluation

Cost item	R-CHOP-R (undisc.)	R-CHOP-O (undisc.)	CHOP-R (undisc.)	CHOP-O (undisc.)
Total induction drug costs	£9,272 (£9,272)	£9,272 (£9,272)	£1,669 (£1,669)	£1,669 (£1,669)
Total maintenance drug costs	£6,656 (£6,753)	£0 (£0)	£5,173 (£5,248)	£0 (£0)
Adverse events	£1,040 (£1,040)	£772 (£772)	£847 (£847)	£697 (£697)
Treatments upon relapse	£7,813 (£9,347)	£9,341 (£10948)	£11,041 (£13,033)	£10,623 (£12,208)
Routine management / surveillance	£3,804 (£4,409)	£3,669 (£4,197)	£3,659 (£4,208)	£3,670 (£4,154)
Total costs	£28,585 (£30,821)	£23,054 (£25,189)	£22,389 (£25,005)	£16,658 (£18,728)

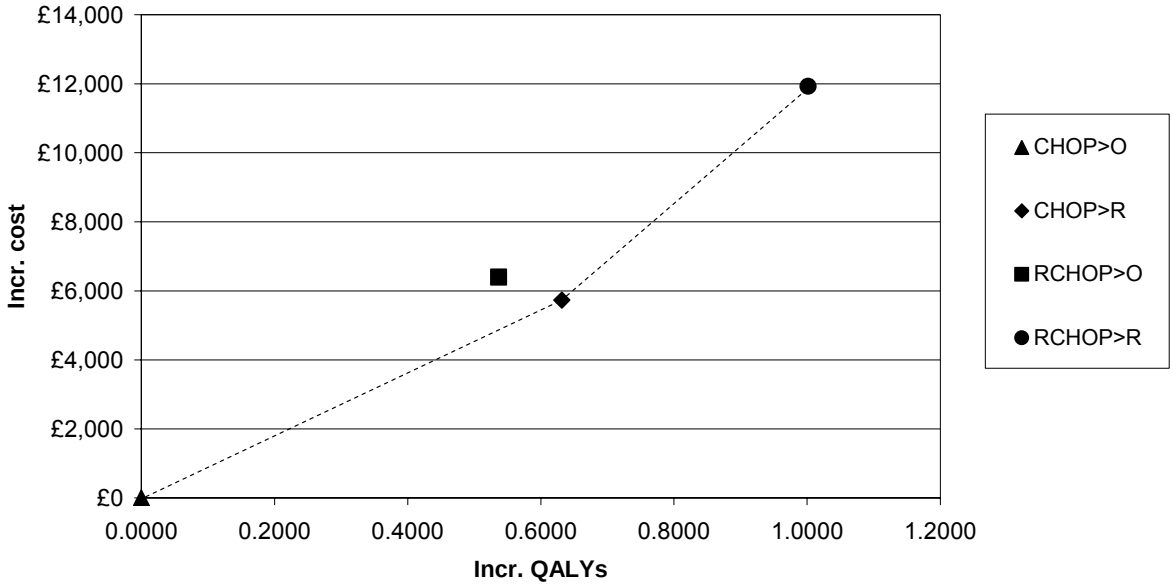
Figure 24: Total costs by type of cost and treatment group estimated in the economic evaluation (discounted)



Incremental cost effectiveness results

The figure below plots, on the cost-effectiveness plane, the incremental cost and QALYs of the three arms of the model relative to the CHOP-O group. The figure below can be used to determine which, if any, of the rituximab options represents the most cost-effective use of rituximab in patients presenting for induction therapy.

Figure 25: Results plotted on the cost-effectiveness plane



The figure above shows that R-CHOP followed by rituximab maintenance is the most effective intervention, gaining approximately 1 additional QALY compared to CHOP induction therapy alone (origin). Compared to the next most effective intervention (CHOP – R) R-CHOP followed by rituximab maintenance can be considered cost effective, with a cost per QALY of £16,749. R-CHOP-O is dominated by CHOP-R with a small advantage in QALYs and slightly reduced costs. Consequently the above evaluation illustrates that R-CHOP induction followed by rituximab maintenance appears to be the most cost-effective treatment strategy within the EORTC20981 study and consequently for relapsed follicular NHL patients.

Table 50: Incremental cost-effectiveness of a treatment strategy of CHOP-R versus a treatment strategy of CHOP-O in patients presenting for induction therapy

Treatment and comparator groups	Costs	QALYs	Incremental cost per QALY gained
CHOP-R	£22,389	3.7207	
CHOP-O	£16,658	3.0892	
Incremental	£5,731	0.6315	£9,076

However, this result does not necessarily imply that CHOP-R is the most efficient use of rituximab in this patient group. The gradient of the line joining the R-CHOP-R with the CHOP-R strategy reflects the incremental cost per QALY gained of R-CHOP-R compared to CHOP-R. This value is £16,749 and is also calculated, see the table below.

Table 51: Incremental cost-effectiveness of a treatment strategy of R-CHOP-R versus a treatment strategy of CHOP-R in patients presenting for induction therapy

Treatment and comparator groups	Costs	QALYs	Incremental cost per QALY gained
R-CHOP-R	£28,585	4.0906	
CHOP-R	£22,389	3.7207	
Incremental	£6,196	0.3699	£16,749

An incremental cost per QALY gained of £16,749 represents good value for money compared to other therapeutic interventions. Therefore, the most efficient use of rituximab in patients presenting for induction therapy is the R-CHOP-R strategy. This means a treatment strategy which includes induction with R-CHOP followed by maintenance therapy with rituximab will maximise the life expectancy of this patient group at a reasonable cost.

4-arm model Scenario Analysis

The current licence of rituximab permits its use as an induction agent for relapsed follicular lymphoma patients in combination with chemotherapy: “the use of rituximab as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MabThera”.

As presented throughout the economic section, this chemotherapy has been assumed to be CHOP for a number of reasons within the 4-arm model: (a) it is the chemotherapy used in the EORTC20981 registration trial, (b) it is a commonly used 2nd line chemotherapy treatment in the UK (c) also, because there is such a wide range of chemotherapies used to treat relapsed follicular NHL it is difficult to provide analysis for all available treatment options especially when there is a lack of comparative RCT data for these treatments.

However, to help illustrate that the choice of chemotherapy does not considerably impact the cost effectiveness of rituximab scenario analyses has been performed which will show (1) by how much the effectiveness/response rate to alternative chemotherapy will have to change for the cost effectiveness ratio to exceed the £30,000 threshold (2) the impact on the cost per QALY of utilising different chemotherapy costs in the comparator arm.

Table 52: 4-arm model scenario analysis

Scenario	Response rate	Cost per QALY
1	Response to chemotherapy – 70% (Rituximab incremental advantage – 10.8%)	R-CHOP-R V's CHOP-R £21,262
2	Response to chemotherapy – 75% (Rituximab incremental advantage – 5.8%)	R-CHOP-R V's CHOP-R £27,612
3	Response to chemotherapy – 77% (Rituximab incremental advantage – 3.8%)	R-CHOP-R V's CHOP-R £31,962
	Cost of alternative chemotherapy regimen	**Cost per QALY**
4	FCM	R-CHOP-R V's CHOP-R £9,414 R-CHOP-O V's CHOP-O £6,860
5	CVP	R-CHOP-R V's CHOP-R £15,052 R-CHOP-O V's CHOP-O £10,746
6	Chlorambucil	R-CHOP-R V's CHOP-R £17,342 R-CHOP-O V's CHOP-O £12,324

Scenarios 1 – 3 illustrate that as the absolute difference in response rates for R-chemotherapy and chemotherapy gets smaller the cost per QALY rises (base case difference 18%; R-CHOP 80.8% - CHOP 62.8%). Scenario 3 illustrates that for the ICER of R-chemotherapy to exceed £30,000 the absolute incremental advantage of adding rituximab to chemotherapy would have to be less than 4%.

Scenarios 4-6 examine the impact on the cost per QALY when the cost of the comparator induction chemotherapy used is varied. The analysis presented evaluates the cost of FCM, assuming patients receive four cycles of FCM, with or without rituximab, 6 cycles of CVP and Chlorambucil single agent therapy, with or without rituximab, are also examined. By assuming alternative costs for the induction chemotherapy used (£1.34 per day for chlorambucil, £600.47 per cycle for FCM and £41.37 per cycle for CVP), the ICER of rituximab within the 4-arm model does not exceed £20,000.

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No subgroup analysis was conducted for the reasons outlined in question 6.2.2.2.

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

The table below presents the results for the various sensitivity analyses explored in the model

Table 53: Sensitivity analysis results maintenance (2-arm model)

Variables	Assumptions (low and High)	Result (Cost per QALY)
Extrapolation	Weibull (Base case)	£7,721
	Log logistic	£6,040
Duration of treatment benefit	2 years	£18,124
	30 years	£6,270
Unit cost non-severe AEs	£43	£7,713
	£172	£7,736
Cost of AEs excluded	£0	£7,501
Unit cost per line of treatment upon relapse	Double costs in observation arm	Rituximab dominant
	Double costs in both arms	£18,016
Frequency of treatment upon relapse	Double frequency in observation arm	Rituximab dominant
	Double frequency in both arms	£18,016

Cost or routine management/surveillance per cycle	Cost in PD health state equal to cost in PFS health state	£8,079
	Cos in PFS health state equal to cost in PD health state	£8,850
Utility values for PFS	Utility value equal to PD	£11,141
	Utility value equal to PFS	£8,553
Duration of follow-up	4 years	£15,933
	50 years	£7,721
Discount rate for costs and outcomes	undiscounted	£6,960
Discount rate for costs	Costs undiscounted	£8,103
Discount rate for outcomes	Outcomes undiscounted	£6,632

Extrapolations

The table above presents the results of the sensitivity analysis for the extrapolation of overall survival and progression free survival. Using a Log-logistic, rather than a Weibull , distribution to extrapolate PFS and OS data improved the cost-effectiveness of maintenance therapy, with the ICER decreasing by approximately £1,700 (£7,721 to £6,040) for health effects measured in QALYs. This was because the OS and PFS curves based on a Log-logistic distribution did not slope as steeply as curves based on a Weibull distribution, resulting in patients living for longer in the Log-logistic model and the survival advantage of maintenance therapy being extended.

Treatment effect

To model the effect of the treatment benefit duration, the probability of moving between PFS, PD and death was set equal to the observation arm, for both arms of the model. The model's sensitivity to the duration of the treatment benefit decreased as the total number of patients alive decreased. Importantly, if the treatment effect associated with rituximab was limited to only the duration of the clinical evidence

base (3 years) then rituximab remained cost-effective (incremental cost per QALY ratio of £11,934).

Adverse events

The model was not sensitive to the cost of non-serious adverse events and there was little impact on the model when all adverse events were completely removed. The model is potentially sensitive to the cost of treatment upon relapse, due to its large total cost. Rituximab maintenance dominated observation if the frequency of the treatment upon relapse doubles in the observation arm but remained at the baseline level in the maintenance arm. Doubling the cost or frequency of treatments upon relapse in both arms of the model had little effect. The model was not particularly sensitive to the cost of routine management.

Quality of life

The model was not particularly sensitive to the difference in quality of life between the PD and PF health states.

Model structure

The model was sensitive to the model duration, but this sensitivity decreased over time as the total number of patients alive in the model decreased. As the model duration increased the cost-effectiveness of rituximab maintenance therapy increased. This is because patients in the maintenance arm lived for longer, meaning there was a greater time period for which to capture this survival benefit. The cost-effectiveness of maintenance decreased as the discount rate decreased. This is due to higher ‘up-front’ study drug costs in the maintenance arm. Removing the discount rate for outcomes improved the cost effectiveness of maintenance therapy due to the longer life expectancy in the maintenance arm of the model. Removing both the discount rate for both costs and effects also improved the cost-effectiveness of rituximab maintenance.

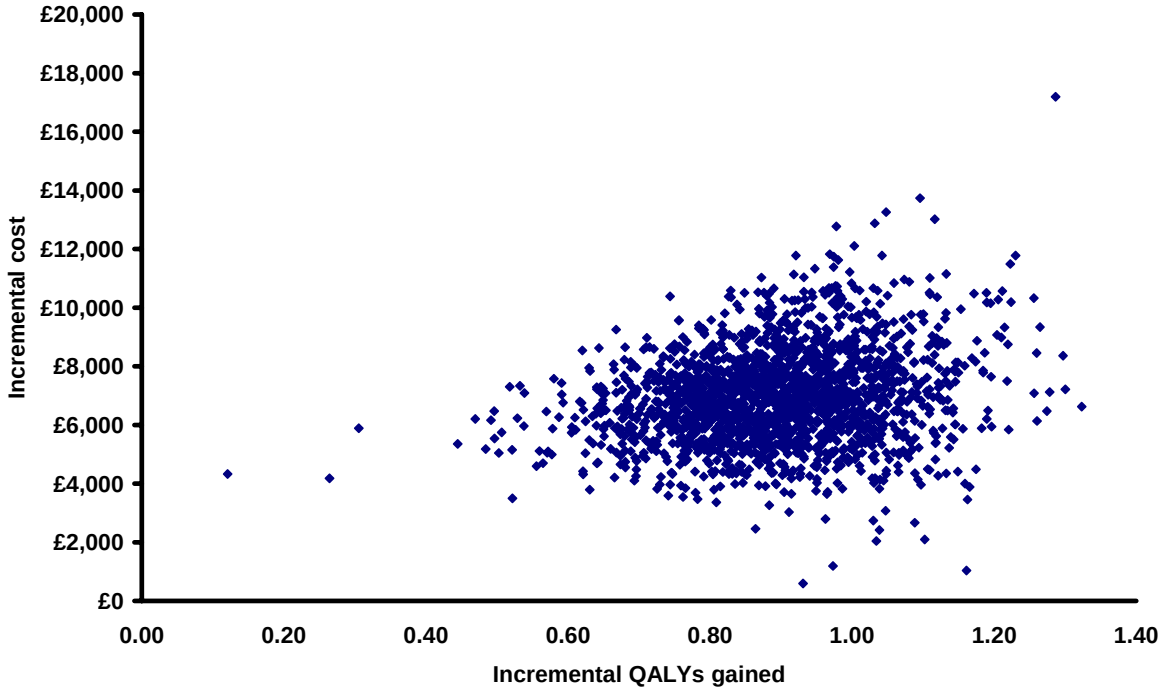
Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken by assigning an appropriate distribution to the clinical, resource utilisation, cost and other variables populating the model. See Appendix 9 for details of the distributions used. The model was calculated with 2000 simulations by sampling randomly from these distributions. The table below presents the mean costs and outcomes across the 2000 simulations.

Table 54: Summary statistics for 2000 simulations of the economic model

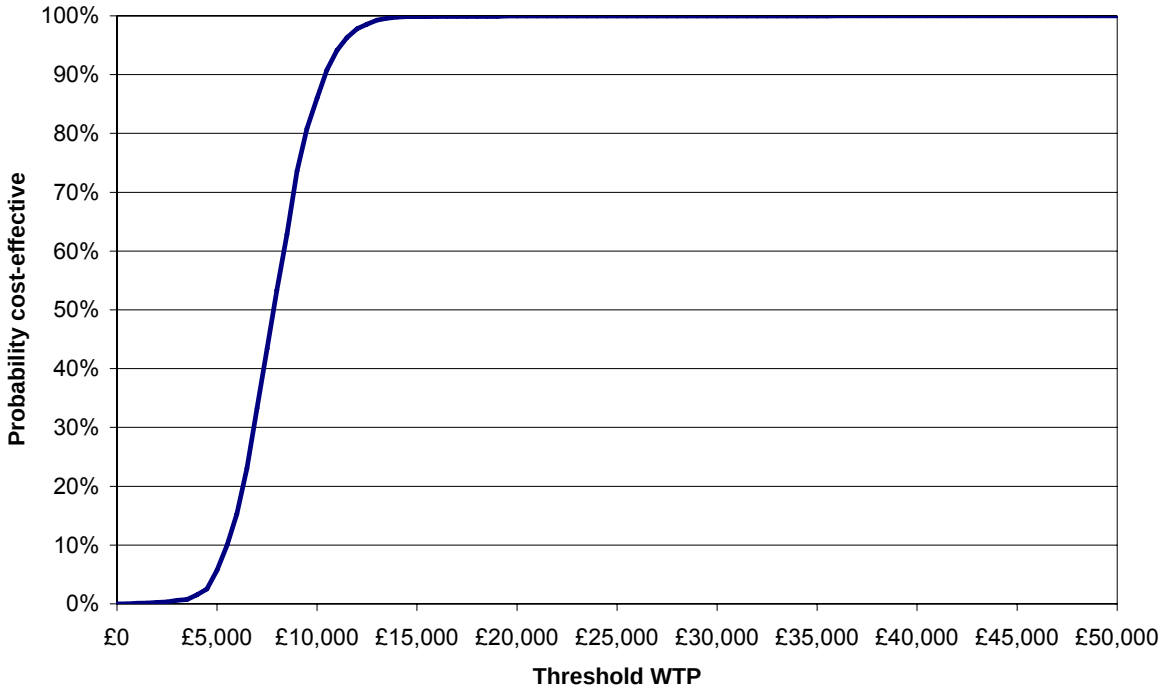
Statistic	Costs			QALYS		
	Rituximab	Observation	Incremental	Rituximab	Observation	Incremental
Number of simulations	2000	2000	2000	2000	2000	2000
Average	£21,872	£14,918	£6,955	4.2553	3.3608	0.8946
SE	£2,943	£2,470	£1,601	0.5345	0.4228	0.1325
Min	£12,487	£8,128	£595	2.3087	2.1878	0.1209
Max	£39,001	£26,214	£17,191	6.3827	5.0926	1.3232

Figure 26: Scatter plot showing incremental cost and effect of maintenance therapy over observation across 2000 simulations of the economic model



The scatter plots illustrate the all 2000 scenarios lie in the north-east quadrant of the cost effectiveness plane, with additional costs and additional QALYs from the introduction of rituximab.

Figure 27: Cost effectiveness acceptability curve –probability the incremental cost of rituximab maintenance over observation meets a WTP threshold



The cost-effectiveness acceptability curve above illustrate that rituximab is most likely to be cost-effective even at very low levels of the willingness to pay for an additional QALY. For example, at a willingness to pay of £10,000 per QALY gained, there is a greater than 90% chance that rituximab is cost-effective.

Induction therapy with R-CHOP followed by maintenance rituximab (4-arm model)

The table below presents the results for the various sensitivity analyses explored in the model.

Table 55: Sensitivity analysis results (4-arm model)

Variables	Assumptions (low and High)	Result (Cost per QALY)
R-CHOP and CHOP response rates	Lower 95% CI of difference between the groups (CHOP response rate kept constant)	R-CHOP-R V's CHOP-R £21,004 R-CHOP-R V's R-CHOP-O £11,654 R-CHOP-R V's CHOP-O £12,491
	Upper 95% CI of difference between the groups (CHOP response rate kept constant)	R-CHOP-R V's CHOP-R £14,541 R-CHOP-R V's R-CHOP-O £12,108 R-CHOP-R V's CHOP-O £11,452
Extrapolation	Log logistic	R-CHOP-R V's CHOP-R £9,835 R-CHOP-R V's R-CHOP-O £8,606 R-CHOP-R V's CHOP-O £8,528
Duration of treatment benefit	2 years	R-CHOP-R V's CHOP-R £36,497 R-CHOP-R V's R-CHOP-O £91,373 R-CHOP-R V's CHOP-O £28,400
	30 years	R-CHOP-R V's CHOP-R £8,907 R-CHOP-R V's R-CHOP-O £6,765 R-CHOP-R V's CHOP-O £8,052

Unit cost non-severe AEs	£43	R-CHOP-R V's CHOP-R £16,686 R-CHOP-R V's R-CHOP-O £11,870 R-CHOP-R V's CHOP-O £11,889
	£172	R-CHOP-R V's CHOP-R £16,874 R-CHOP-R V's R-CHOP-O £11,971 R-CHOP-R V's CHOP-O £11,953
Cost of AEs excluded	£0	R-CHOP-R V's CHOP-R £16,228 R-CHOP-R V's R-CHOP-O £11,328 R-CHOP-R V's CHOP-O £11,568
Unit cost of non-serious adverse events	£43	R-CHOP-R V's CHOP-R £16,686 R-CHOP-R V's R-CHOP-O £11,870 R-CHOP-R V's CHOP-O £11,889
	£172	R-CHOP-R V's CHOP-R £16,874 R-CHOP-R V's R-CHOP-O £11,971 R-CHOP-R V's CHOP-O £11,953
Unit cost per line of treatment upon relapse	Double costs in R-CHOP-R arm only	R-CHOP-R V's CHOP-R £37,868 R-CHOP-R V's R-CHOP-O £28,719 R-CHOP-R V's CHOP-O £19,712

	Double costs in all arms	R-CHOP-R V's CHOP-R £8,022 R-CHOP-R V's R-CHOP-O £8,614 R-CHOP-R V's CHOP-O £9,105
Frequency of treatment upon relapse	Double frequency in R-CHOP-R arm	R-CHOP-R V's CHOP-R £37,868 R-CHOP-R V's R-CHOP-O £28,719 R-CHOP-R V's CHOP-O £19,712
	Double frequency in all arms	R-CHOP-R V's CHOP-R £8,022 R-CHOP-R V's R-CHOP-O £8,614 R-CHOP-R V's CHOP-O £9,105
Administration costs	£0 (CHOP only arm)	R-CHOP-R V's CHOP-R £18,015 R-CHOP-R V's R-CHOP-O £11,904 R-CHOP-R V's CHOP-O £12,378
Utility values for PFS	Utility value equal to PD	R-CHOP-R V's CHOP-R £22,009 R-CHOP-R V's R-CHOP-O £16,037 R-CHOP-R V's CHOP-O £16,707
	Utility value equal to PFS	R-CHOP-R V's CHOP-R £16,896 R-CHOP-R V's R-CHOP-O £12,312 R-CHOP-R V's CHOP-O £12,826

Duration of follow-up	4 years	R-CHOP-R V's CHOP-R £48,116 R-CHOP-R V's R-CHOP-O £41,171 R-CHOP-R V's CHOP-O £25,278
	50 years	R-CHOP-R V's CHOP-R £16,749 R-CHOP-R V's R-CHOP-O £11,904 R-CHOP-R V's CHOP-O £11,910
Discount rate for costs and outcomes	undiscounted	R-CHOP-R V's CHOP-R £14,425 R-CHOP-R V's R-CHOP-O £10,001 R-CHOP-R V's CHOP-O £10,279

Response to induction

In the analysis the effect of the difference in the proportion of patients responding to induction therapy on the results of the economic model was tested. This variable had little impact on the outcome of the R-CHOP-R versus R-CHOP-O comparison since each of these strategies utilised the same induction regimen. The greatest impact of induction therapy was in the R-CHOP-R versus CHOP-R comparison where a better outcome in induction therapy has greatest value since rituximab maintenance has greater effectiveness than observation.

Extrapolation

Using a Log-logistic, rather than a Weibull, distribution to extrapolate PFS and OS data improved the cost-effectiveness of R-CHOP-R therapy. This was because the OS and PFS curves based on a Log-logistic distribution did not slope as steeply as curves based on a Weibull distribution, resulting in patients living for longer in the Log-logistic model and the survival advantage of R>CHOP being extended. To model the effect of the treatment benefit duration, the probability of moving between PFS, PD and death was set equal to the CHOP-O arm, for all four arms of the model, to

mark the end of the treatment benefit. The model's sensitivity to the duration of the treatment benefit decreased as the total number of patients alive decreased. Importantly, if the treatment effect associated with rituximab was limited to only the duration of the clinical evidence base (3 years) then R-CHOP-R remained under £30,000 per QALY gained.

Utilities

The sensitivity analysis looked at the impact of varying the utilities on the cost per QALY. Each of these analyses are biased against rituximab in that they assume an equal quality of life in the progressive disease and progression free health states. In each of these analyses, R-CHOP-R remains in the bounds of reasonable cost-effectiveness. R-CHOP-R was less cost-effective when the utility value of 0.618 was used for both health states.

Model structure

The model was sensitive to the model duration, but this sensitivity decreased over time as the total number of patients alive in the model decreased. As the model duration increased the cost-effectiveness of rituximab maintenance therapy improved. This is because patients in the maintenance arm lived for longer, meaning there was a greater time period for which to capture this survival benefit. The discount rate for costs had a minimal impact on cost-effectiveness with the impact varying depending on the comparator. The discount rate for outcomes had a bigger impact, and increased the cost effectiveness of maintenance therapy due to the longer life expectancy in the maintenance arm of the model. Removing both the discount rate for both costs and effects resulted in improving the cost-effectiveness of rituximab maintenance.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken by assigning an appropriate distribution to the clinical, resource utilisation, cost and other variables populating the model. See Appendix 9 for the details of the distributions used. The model was calculated with 2000 simulations by sampling randomly from these distributions. The table below presents the mean costs and outcomes across the 2000 simulations.

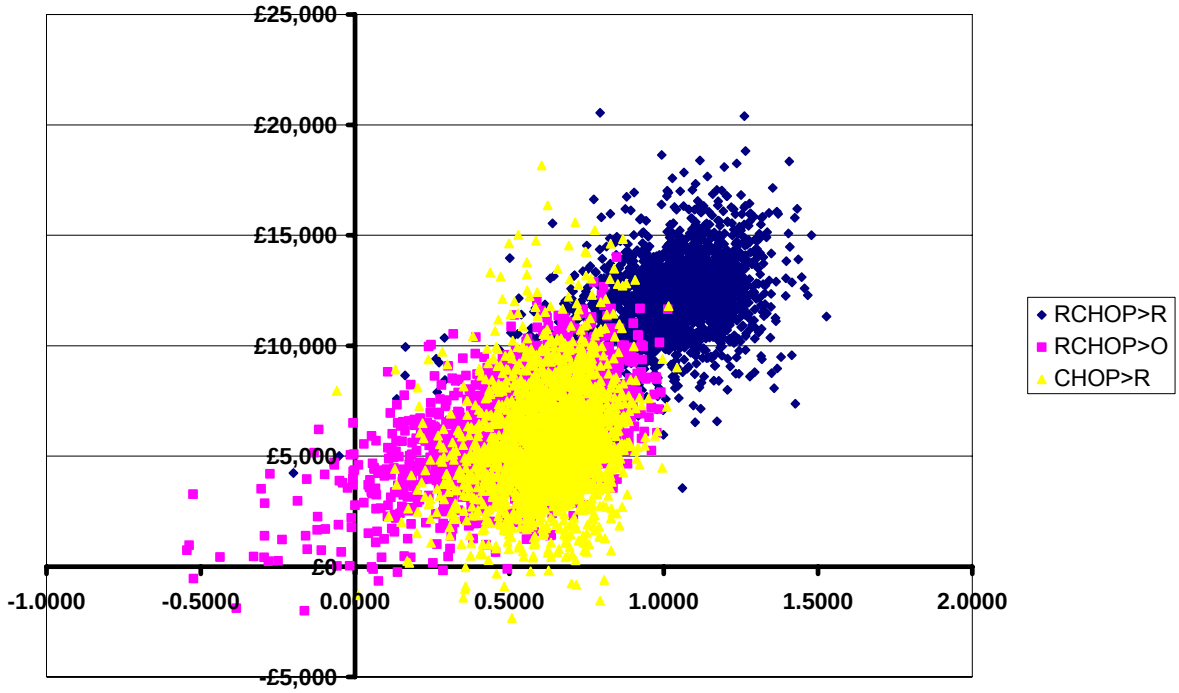
Table 56: Summary statistics for 2000 simulations of the economic model

Statistic	Costs				QALYs			
	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O	R-CHOP-R	R-CHOP-O	CHOP-R	CHOP-O
Number of simulations	2000	2000	2000	2000	2000	2000	2000	2000
Average	£28,554	£22,858	£22,122	£16,469	4.0442	3.5692	3.6435	3.0221
SE	£2,677	£2,569	£3,575	£2,720	0.4320	0.3848	0.4079	0.3915
Min	£21,632	£16,737	£13,239	£10,287	2.8874	2.5253	2.3320	1.9889
Max	£44,589	£34,859	£41,490	£28,771	5.8724	5.3745	5.6311	4.8787

The above table presents the results of the PSA in terms of the incremental costs and outcomes (QALYs gained) for rituximab maintenance compared to observation in each of the 2000 simulations.

The scatter plot below illustrates considerable overlap of costs and QALYs across the 4 treatment groups. This is consistent with the clinical evidence base (EORTC20981) which was not powered for the four-way comparison made in this economic evaluation.

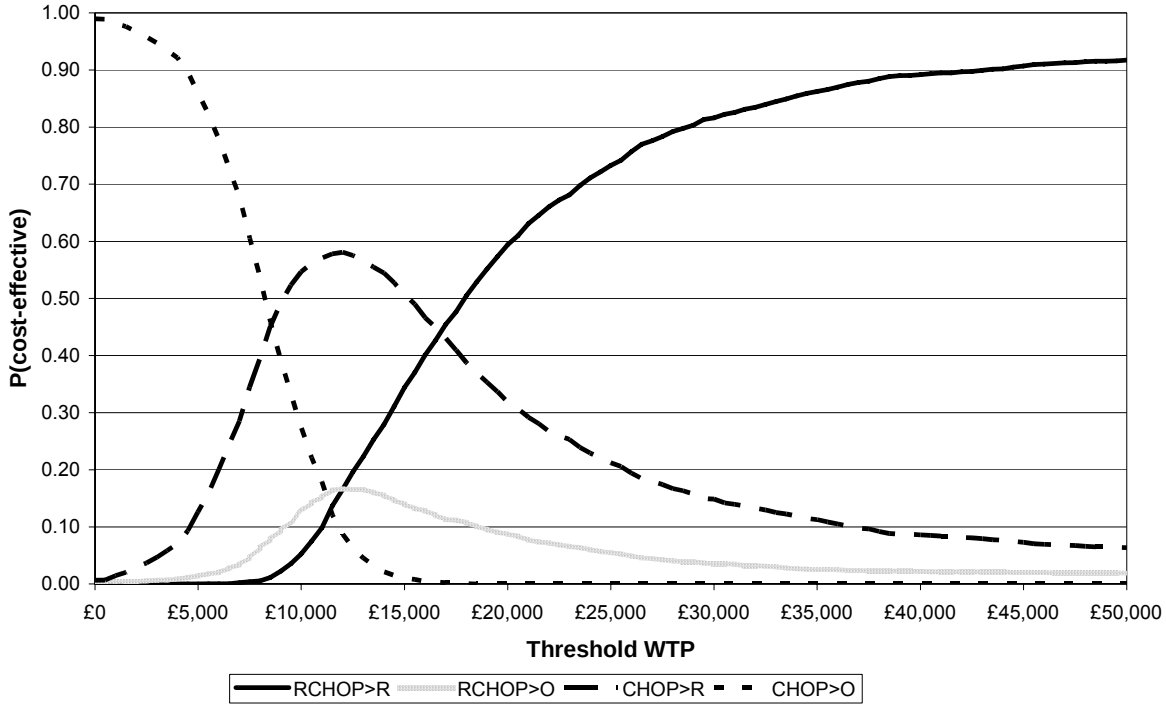
Figure 28: Scatter plot showing incremental cost and effect of maintenance therapy over CHOP-observation across 2000 simulations of the economic model



The cost-effectiveness acceptability curve in the figure below shows that at a WTP for a QALY of approximately £18,000 or greater, the R-CHOP-R treatment strategy

had the greatest probability of being cost-effective. Also, despite the clinical evidence base not having sufficient power for this comparison, the probability of the R-CHOP-R strategy being cost-effective is greater than 82% at a WTP threshold of £30,000 per QALY.

Figure 29: Cost effectiveness acceptability curve –probability that each treatment practice is cost-effective at a given WTP threshold



At very low willingness to pay thresholds CHOP followed by observation and CHOP followed by rituximab maintenance are the preferred treatment strategies.

6.3.4 Interpretation of economic evidence

6.3.4.1 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?

Rituximab is the first maintenance treatment available for relapsed refractory follicular non-Hodgkin's Lymphoma, therefore to date there has been no economic evaluation

of any NHL maintenance treatment to make a comment on consistency feasible. Nor has the cost effectiveness associated with R-CHOP compared to CHOP induction been previously investigated, as the literature review has highlighted, again making it difficult to comment on the consistency with the published economic literature.

As highlighted throughout Section 6 the 2-arm and 4-arm models are based on EORTC20981 clinical trial data which should lend credence to the model outcomes. Also, as highlighted in Section 6.2.13 the model outcomes in terms of clinical effectiveness are realistic, with life expectancy estimates aligning with published literature.

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation is based on the EORTC20981 trial. Therefore the population in the economic evaluation is reflected by the population enrolled and randomised in the maintenance phase of EORTC20981. It is believed this population accurately reflects the patient population likely to present for induction and therefore eligible for maintenance in a clinical setting.

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

Strengths

a) The incremental clinical effects of R-CHOP compared to CHOP and rituximab maintenance compared to observation are based upon a large randomised head to head control trial and not an indirect comparison of efficacy. Consequently the certainty of the evidence base surrounding the strong incremental clinical advantages of RHOP compared to CHOP and maintenance rituximab compared to observation is very strong. As this is the key driver of the cost effectiveness of rituximab, it is important that the clinical predictions of the model are based on robust clinical evidence.

b) The extrapolation of PFS and OS from the EORTC20981 study is based on a relatively long follow-up period of 1,500 days.

c) All potential areas related to parameter uncertainty have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be very stable to wide variations in model parameters.

d) Most of the key parameters have been taken directly from the EORTC20981 study to avoid utilising other sources e.g. post protocol treatments and corresponding survival, actual drug dosage/wastage. Consequently the observed survival outcomes are representative of the assumed treatments and dosages.

e) The model structure attempts and enables the evaluation of all 4 treatment strategies presented by both the new licensed indication and the design of the EORTC20981 study

f) Flexibility in the assumed parametric function, duration of treatment effect and model time horizon has been accounted for in the design of the model.

Weaknesses

a) The precision of the resource utilisation data and corresponding costs associated with drug administration and patient monitoring could be improved for example use of prospective time and motion data. However, as demonstrated in the sensitivity analysis by setting the cost of administration in the CHOP arm to zero the impact on the cost per QALY was not substantial, demonstrating that the cost per QALY is not sensitive to this.

b) The aggregated nature of the progressive disease health state may compromise the accuracy of the corresponding costs and utilities. However as the sensitivity analysis illustrates, despite a wide variation in the assumed value of these particular parameters (cost and utility of Progression health state) the ICER remains relatively insensitive to this aspect of the model structure.

c) The clinical data used to inform the 4-arm model is relatively under-powered compared to the 2-arm model. This is explained by the EORTC20981 study not being designed to evaluate the four treatment strategies required to inform the health economic decision problem presented by the licensed indication. However, as the threshold analysis presented in section 6.3.1.1 for the 4-arm model demonstrated

that for R-CHOP not to be cost effective the absolute incremental advantage of adding rituximab to chemotherapy would have to be less than 4%.

d) The inability of the model to account for any quality of life decrements associated with serious adverse events may be viewed as an incomplete aspect of the model. However, given the likely duration of any serious adverse events the final cost effectiveness ratio would not be sensitive to this.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

a) Utilisation of survival data from a longer follow-up of the EORTC20981 study as it emerges, which should be available in the later part of Q3 2007.

b) A prospective time and motion study capturing the resource requirements and consequent health care costs of administering both R-CHOP, CHOP and maintenance rituximab. This would help understand any potential marginal costs involved in administering R in addition to CHOP alone in greater detail. However, as the sensitivity analysis demonstrated the cost per QALY is not sensitive to changes in this variable.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

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

Induction therapy with R-CHOP followed by maintenance rituximab

Assuming a staggered uptake of 20% per annum over the next five years the estimated budget impact of R-CHOP induction therapy followed by maintenance rituximab is £2,764,931 in the first year following its introduction, £6,453,512 in the 2nd year, and £10,626,912 in the 3rd year. The budget impact for using rituximab maintenance alone, with no rituximab and chemotherapy induction would cost £896,002 in the first year, £2,696,966 in the 2nd year and £3,601,928 in the 3rd year.

The budget impact estimates presented above represent the maximum possible cost to the NHS during the first three years following positive NICE guidance. The above estimates assume that 100% of patients who respond to 2nd line induction therapy will be treated with maintenance rituximab, with all patients receiving the treatment for the maximum 2 year period. In reality we know not all patients responding to 2nd line induction will receive maintenance rituximab and many patients who do receive maintenance rituximab will relapse prior to the completion of the 2 year treatment.

7.2 What number of patients were assumed to be eligible? How was this figure derived?

It is estimated that within the first three years following positive NICE endorsement 268, 539 and 812 patients will be treated with R-CHOP induction treatment at 2nd line. Of this patient pool it is estimated that 183 patients in year 1, 368 in year 2 and 555 in year 3 will go on to received maintenance rituximab.

Table 57: Epidemiological Assumption
Estimated number of patients eligible to receive treatment

Assumptions	Percentage	Value Year 1	Value Year 2	Value Year 3
Local population		53,390,300	53,657,252	53,925,538
Prevalence of NHL	0.104%	55,526	55,804	56,083
Proportion of follicular lymphoma within NHL	22%	12,216	12,277	12,338
Proportion of follicular lymphoma patients that are Stage III/IV	85%	10,383	10,435	10,487
Proportion of Stage III/IV follicular lymphoma patients receiving 2nd line therapy	12.91%	1,340	1,347	1,354
Staggered uptake	Yr 1 – 20% Yr 2 – 40% Yr 3 – 60%	268	539	812
2nd line Response Rate				
Average Overall Response Rates	68%	183	368	555
Proportion of patients assumed to receive maintenance treatment with rituximab	100%	183	368	555

The population of England and Wales is currently 53,390,300 (National Statistics Online). It is estimated that there are 55,526 non-Hodgkin's lymphoma patients in England and Wales; this is assuming a prevalence of 0.104% as estimated by Globocan 2002 data. Globocan prevalence figures were estimated by combining the annual number of new cases and the corresponding probability of survival by time.

It is estimated that 22% of this patient pool will have follicular lymphoma (The Non-Hodgkin's Lymphoma Classification Project, Blood, 1997), of which 85% will have stage III/IV disease (Shipp et al, 1997).

Market research estimates that 12.91% of all stage III/IV follicular lymphoma patients receive 2nd line therapy in a year (Globocan Market Research, 2002). A staggered uptake of 20% per annum is assumed for the use of R-CHOP induction over the first five years following positive NICE endorsement. Of this patient pool who receive 2nd line chemotherapy it is estimated that on average 68% of patients will respond to 2nd line treatment. This average overall response rate is generated from 2 clinical trial papers, Klasa et al (2002) and Van Oers et al (2004) on 4 commonly used 2nd line treatments fludarabine, CVP, CHOP and R-CHOP. Those patients who respond to 2nd line treatment are eligible to receive maintenance rituximab. It is assumed that all eligible patients will receive maintenance rituximab.

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

As outlined in section 6.2.3 CHOP is a commonly used 2nd line treatment for relapsed/refractory follicular lymphoma. This model estimates the cost of adding rituximab to CHOP chemotherapy for 2nd line induction treatment.

Currently, there is no other maintenance therapy available for relapsed follicular NHL; therefore the cost of maintenance rituximab is not offset against any treatment.

It is assumed that there is a staggered uptake of the induction license at 2nd line of 20% per annum. All patients who respond to induction are considered eligible for maintenance rituximab and are assumed to receive treatment in this budget impact model.

7.4 What assumption(s) were made about market share (where relevant)?

Market share data is not required for the calculations in the budget impact model. The costs of R-CHOP or maintenance rituximab are not offset against any treatment as they are both additive treatment regimens.

7.5 What unit costs were assumed? How were these calculated?

The tables below present the treatment costs of (i) R-CHOP induction at 2nd line (ii) followed by maintenance rituximab. All cost data was sourced from BNF March 2006.

R-CHOP induction is administered every 3 weeks for a total of 6 weeks.

Table 58: R-CHOP 2nd line induction drug costs

Assumption	Value
Rituximab 2nd line induction	
Cost per administration (as above)	£1,222.41
Number of cycles	6
Total cost of 6 cycles of rituximab	**£7,335**
Cyclophoshamide	
Dose	750mg/m^2
Average dose required per administration	1,275mg
Vials required	1, 500mg 1, 1g
Cost per 1g vial	£5.04
Cost per 500mg vial	£2.88
Cost per cycle	£7.92
Total cost of 6 cycles of cyclophoshamide	**£47.52**
Doxorubicin	
Dose	50mg/m^2
Average dose required per administration	85mg
Vials required	1, 25mL 4, 5mL
Cost per 25mL vial	£103
Cost per 5mL vial	£20.60
Cost per cycle	£185.40
Total cost of 6 cycles of doxorubicin	**£1,112.40**
Vincristine	
Dose (Max 2mg per day)	1.4mg/m^2
Average dose required per administration	2mg
Cost per 2mg vial	£21.17
Cost per cycle	£21.17
Total cost of 6 cycles of vincristine	**£127.02**
Prednisolone	
Dose	100mg per day for 1st 5 days of each cycle
Number of tablets required per dose	4
Cost per 25 mg tablet	0.17
Cost per dose	0.69
Cost per cycle	£3.45
Total cost of 6 cycles of prednisolone	**£17.25**
Total R-CHOP costs (6 cycles)	**£8,642**

Maintenance rituximab is administered every three months over a two year period, resulting in a total of 8 administrations, 4 administrations per annum. The table below presents the cost of rituximab over a 2 year period.

Table 59: Maintenance rituximab drug costs

Assumption	Value
Dose	375mg/m2
Average adult body mass	1.7m2
Average adult dose	637.5
Dosing schedule	1 cycle every 3 months until relapse or for a maximum of 2 years
Retreat every (mths)	3
Number of vials required	1, 50ml
	2, 10ml
Cost per 50ml vial	£873.15
Cost per 10ml vial	£174.63
Cost per administration	£1,222
Assumed length of treatment (mths)	24
Number of administrations over assumed time	8
Total cost of 24 months of maintenance therapy	£9,779
Year 1 cost of maintenance rituximab	**£4,890**
Year 2 cost of maintenance rituximab	**£4,890**

The cost of R-CHOP induction and maintenance rituximab is spread over a three year period. The first year includes the cost of induction therapy (approximately 4 months duration) and 2 cycles of maintenance rituximab, the 2nd year looks at the cost of 4 cycles of maintenance and the 3rd year includes the cost of 2 cycles of maintenance therapy. The costs of R-CHOP 2nd line induction therapy are presented in the table below.

Table 60: R-CHOP induction followed by maintenance drug costs

Year 1 cost of 2nd line induction therapy and maintenance rituximab	**£11,087**
Year 2 cost of maintenance rituximab	**£4,890**
Year 3 cost of maintenance rituximab	**£2,445**

The drug costs are spread over a three period with a cost of £11,087 in the first year, £4,890 in the second and £2,445 in the third year per patient.

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Induction therapy with R-CHOP followed by maintenance rituximab

When rituximab is added to CHOP chemotherapy as part of treatment to induce remission the antibody can be administered during hospital day-case visits for chemotherapy and no additional hospital visits should be required.

Rituximab solution should be administered as an IV infusion through a dedicated line, once every 3 months until disease progression or for a maximum period of two years. Patients typically will receive rituximab in a hospital chemotherapy day-case unit or outpatient clinic.

In order to receive maintenance rituximab an additional 8 outpatient treatments will be required. It is likely that these will, generally, be incorporated into routine follow-up appointments so that they will not require patients to make extra hospital visits.

No additional tests or investigations are required to select relapsed follicular lymphoma patients for maintenance treatment with rituximab.

Whenever rituximab is administered, patients will require routine nursing observation for the duration of rituximab infusion, in case of toxicity that may require intervention (usually in the form of interruption or slowing of the rituximab infusion). It has been reported that a patient's first rituximab infusion takes a mean of 5.2 hours, with subsequent infusions typically taking about 3.5 hours (McLaughlin et al. 1998) when the licensed infusion schedule is followed.

However, it should be noted that significant infusion reactions appear to be less frequent when rituximab is used in the maintenance setting. This should permit more rapid dose escalation of the drug infusion rate, reducing total administration times compared with those previously reported for patients receiving rituximab for remission induction.

Roche is also aware that an accelerated infusion schedule is increasingly being adopted by UK treatment centres. This unlicensed schedule, allows most patients to receive rituximab over 90 minutes.

Since rituximab is already widely used for the treatment of non-Hodgkin's lymphoma (NHL) within the NHS, staff treating follicular lymphoma patients will be familiar with the monitoring required during drug infusion and it is not anticipated that any additional training will be required.

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

There were no estimates of resource savings calculated.

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

By treating 2nd line patients with maintenance rituximab and therefore increasing a patients' time in remission, the costs to the NHS of retreating patients at third line are deferred to some time in the future. Therefore, the NHS in England and Wales will save costs in the short run.

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9 Appendices

9.1 Appendix 1

Summary of Product Characteristics

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9.2 Appendix 2: search strategy for section 5

Refer to section 5.1 for details of the search strategy.

9.3 Appendix 3: search strategy for section 6

The following information should be provided.

9.3.1 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**
- **Health Economic Evaluation Database**
- **NHS Economic Evaluation Database (NHS EED).**

Dialog Datastar was used to search Medline (MEYY), Medline in process(MEIP), Embase (EMYY), Embase alerts (EMBA) and Biosys (BIYY for the American Society of Haematology conference proceedings).

Blood online was searched for abstracts relating to economic evaluations presented at the American Society of Haematology annual meetings.

The Cochrane Library controlled trials database was searched for clinical trials of rituximab in relapsed or refractory follicular lymphoma.

NHS EED and HEED were also searched for any health economic manuscripts.

The results of these searches and, where possible, a copy of the search strategy are appended. The dates when the searches were performed (saved) are also provided.

9.3.2 The date on which the search was conducted.

The literature searches were conducted on the 4th of May 2007.

9.3.3 The date span of the search.

Wherever possible databases were searched from 01/01/2000 to the present.

9.3.4 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).

The table below presents the search strategies used in the literature searches.

No.	Search terms
1	Monoclonal antibodies
2	Rituxan
3	CHOP
4	Rituximab
5	Economics
6	Follicular
7	Indolent
8	Economic evaluation
9	Cost benefit analysis
10	Cost effectiveness analysis
11	Cost minimization analysis
12	Cost utility analysis
13	Cost comparison
14	Nonhodgkin-Lymphoma
15	Follicular lymphoma
16	Quality Adjusted Life Years/QALY

Boolean search terms used were “AND” and “OR”.

9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

All searches have been outlined above.

Appendix 4 – Economic literature review

Study	Aims	Methods	Results	Relevance to decision making in England and Wales
Van Agthoven et al (2005)	Cost analysis of common treatment options for indolent follicular non-Hodgkin's lymphoma. To evaluate the direct health care costs associated with the most commonly prescribed treatments for indolent follicular non-Hodgkin's. Treatments evaluated include: CVP, CHOP (like), radiotherapy, chlorambucil, fludarabine, rituximab, stem cell transplantation,	A retrospective study was performed in 15 of the main Dutch hospitals treating patients with hematological malignancies. Patients were followed for three years to capture all resource use related to treatment or watchful waiting. All hospital resource use relating to follicular lymphoma during the data collection period was recorded, as well as medication used at home. A hospital perspective was adopted. Average unit costs were calculated for the most important resource use items, on the basis of financial data from five of the participating hospitals. For each unit cost, personnel costs, material costs and	Mean cost of allogeneic SCT were €45,326. Mean duration of hospitalization was 6.2 weeks. Mean cost of autologous SCT was €18,866. The mean treatment duration was 5.4 weeks. Mean per patient cost for a treatment with chlorambucil was €2,476. The CVP regimen was associated with mean per patient costs of €5,268. The mean treatment duration was 22.4 weeks during which 6.2 chemotherapy cycles were administered on average. A treatment with CHOP	Although the study was from a non-UK perspective it provided a recent (2005) and detailed breakdown of the treatment costs incurred by follicular lymphoma patients, the treatment group of interest in this study. More specifically the study reported the 2005 treatment costs for both rituximab and CVP, the treatments being compared in this analysis.

	interferon-α maintenance	overhead costs were included.	cost €7,547 on average and the mean duration was 16.2 weeks, with an average of 5.2 cycles administered. The mean cost of treatment with intravenous fludarabine was £10,651 for an average of 4.8 cycles of therapy. Radiotherapy mean per-patient costs were €4,218. Radiotherapy was applied over 3.3 weeks on average, with the mean number of sessions being 15.8. The mean cost of rituximab was €10,648, with 4 doses being administered. Additional resource use was low accounting for 19% of the total cost. Interferon-α was applied as maintenance treatment. The mean	

			cost was €13,396 with a mean duration of treatment of 87.7 weeks. Mean monthly costs of watchful waiting was €279 which mainly constituted of hospital admissions.	
Malliti et al (2003)	To evaluate the economic impact of using rituximab for the treatment of follicular non-Hodgkin's lymphoma (NHL) in comparison with the conventional chemotherapy protocols of CHOP and CHVP.	A retrospective study conducted between 1998 and 2000, the direct costs of treating NHL inpatients with rituximab or CHOP/CHVP were compared.	Including costs of administering chemotherapy and adverse events, the study showed that the average cost per patient was comparable for the two strategies: €9,700 euro for rituximab and €8,487 euro for conventional chemotherapy. In the rituximab group the costs were mostly due to drug purchases. In the conventional chemotherapy group outlays were related to drug-induced toxicity and longer hospital	The study is from a non-UK perspective. It was carried out in 2000 and reports the cost of treating patients with CHVP, CHOP and rituximab. The study provides a detailed breakdown of all costs incurred by a follicular lymphoma patient.

			stays. For first-line treatment, the difference in the cost effectiveness ratio between rituximab and conventional drugs might be smaller, but sound data are not yet available.	
Herold et al (2002)	This international analysis (Canada, Germany, Italy) was established to estimate the overall direct cost of treating patients with relapses indolent NHL and determine the main cost components of treatment. Treatments analyzed are CHOP, CVP and fludarabine.	A retrospective analysis of 424 patient's records was undertaken. Data was collected on treatment received and on any adverse events incurred. Overall costs for each selected regimen were calculated from the perspective of a third-party payer. Nationally, the unit costs for each treatment, test or procedure were used to calculate the cost per patient of a single cycle of chemotherapy. Unit costs were obtained from different sources, including published price lists,	Overall treatment costs were broken down into three components: (1) cost of drug acquisition, (2) cost of drug administration and (3) cost of monitoring and treating adverse events. The costs were presented as in-patient and out-patient costs and divided up by country. Total costs CHOP – Canada €12,892, Germany €9,733, Italy €6,430. CVP – Canada €10,612, Germany €11,107 FLU – Canada €13,942,	This study is from a European and Canadian perspective. The study reports the cost of treating relapsed indolent lymphoma patients, in 2002 prices, with commonly used chemotherapy regimens, including CVP.

		national and regional sources and previously published economic studies. Each cycle was assumed to be representative of the cycles making up the whole course of treatment for each patient. Results were expressed as an average treatment cost per patient for a complete course of chemotherapy (6 cycles). The average costs per patient were presented for both in-patient and out-patient treatment. A breakdown of the total cost of regimens was also reported to determine the biggest cost driver.	Italy €17,940. Drug acquisition costs made up less than half of the overall cost of treatment for most regimens.	
Sweetenham et al (1999)	To carry out a comparative study of CHOP, FLU and rituximab to determine the relative efficacy, toxicity and cost	Although no prospective trials have been conducted, the available literature suggests there is not a significant difference between CHOP, FLU and rituximab in terms of response rates and	No significant differences were found between the number and type of adverse events in the cycles of both CHOP and FLU. The major difference seen in the adverse	The study is from a UK perspective and reports in 1999 pounds sterling the costs associated with the active treatment of patients with relapsed indolent B-cell NHL and the cost of treating adverse events from these treatments.

	of the treatments.	response duration. However, there are apparent differences in the incidence and severity of drug-related adverse-events, which may impact on the economic implications of each regimen. A cost minimization analysis was used to determine the economic impact from a hospital perspective of the direct treatment costs associated with drug-related adverse events for the three regimens and, secondly, comparing total direct treatment costs including acquisition and administration costs associated with the regimens. Treatments were evaluated up to 6 months (full course for each regimen) and therefore discounting of costs was not employed, since the time frame was too short for this to be appropriate.	event profile were the absence of neutropenia and anemia for patients receiving rituximab. These differences in type and frequency of adverse events had a considerable impact on the economic implications of treating drug related adverse events. Per patient of adverse events: Rituximab - £109 FLU - £2,953 CHOP - £5,049 The total cost of therapy by each category including drug-related adverse events: FLU - £10,022 CHOP - £7,210 Rituximab - £6,080 The main cost driver for both FLU and rituximab was the actual acquisition cost of the drug regimen, in comparison to CHOP	The treatments considered in the analysis include rituximab.

			where the main cost driver was adverse events. For rituximab the high acquisition cost was greatly offset by savings from lower adverse event costs, making it the more attractive cost option.	
Schmitz et al (2006)	Sensitivity Analysis of Cost Factors for Various Therapy Options in the Treatment of Follicular Lymphoma	In Germany, patients with relapsed follicular non-Hodgkin's lymphoma do not all receive the same treatment. In this study, 3 therapy regimens were analyzed which were considered to be similar: CHOP, fludarabine and rituximab. With the goal of determining the treatment option with the lowest direct costs whilst maintaining the same degree of effectiveness, a cost analysis model was established and applied by way of example to the existing illness constellation. **Methods:** The German doctors' fee scale served	Therapy costs for the complete rituximab therapy calculated for the standard patient as defined by the model developed in the analysis: £12,192. Therapy costs for the complete fludarabine therapy calculated for the standard patient as defined by the model developed in the analysis: £9,272. Therapy costs for the complete CHOP therapy calculated for the standard patient as defined by the model developed in the analysis: £6,364.	This study looks at the costs associated with treatment options in follicular lymphoma two of which are analysed in this submission, CHOP and rituximab. However, the rituximab indication that this paper looks at is the 4 cycle monotherapy licence which is not being examined in this submission. The study is from the German health system perspective.

		as the basis for the calculation of medical services within the scope of the present statutory health insurance guidelines. A virtual standard patient was constructed for the cost model and treated with the different therapy regimens. The incidences of individual adverse events described in literature served as the basis for the characterization of the average toxicity of the respective treatment methods.		
Hutchinson et al (2006)	Costs of Chemotherapy for Indolent Follicular Non-Hodgkin's Lymphoma in the UK: An Observational Study	This analysis assessed the health service costs of patients receiving chemotherapy for indolent follicular NHL based on a retrospective analysis of patient records in the UK. Each patient was followed up for a period of 3 years or until death. The analysis included 181 patients, who received a total of 187 treatment periods. Costs were estimated from the	A total of 181 patients were included in the analysis. These patients received 187 courses of chemotherapy within the observed period. In 4 cases, the treatment episode was continuing when data collection ceased. A large number of different chemotherapies were identified. For the purpose of the analysis, the 187 episodes were	This study looks at the costs associated with treatment options in follicular lymphoma, two of which are analysed in this submission, CHOP and rituximab. The study is from the UK health system perspective and so is relevant to this submission.

		perspective of the UK National Health Service. A retrospective analysis was conducted of patient records in the UK. Twelve centres delivered data that were incorporated into the study database. The participating centres reflect the diversity of clinical practice in the NHS, with data collected from specialist centres, research hospitals and district general hospitals.	grouped into 7 categories: chlorambucil (n = 61), CHOP-like therapies (n = 29), CVP (n = 11), fludarabine (n = 29), rituximab (n = 13), other combination (n = 29) and other monotherapy (n = 15). Fludarabine was subdivided in the costing analysis and sensitivity analyses into monotherapy (n = 15) and combination therapy (n = 14). Mean cost per treatment period: chlorambucil £968, CHOP-like therapies £3,038, CVP £1,859, fludarabine mono £4,778, fludarabine combo £7,581 rituximab £5,413, other combination £2,597 and other monotherapy £2,044	
Kocs et al (2003)	Effect of Off-label Use of Oncology Drugs	To provide comprehensive and current information concerning the off-label	One hundred one patients received a total of 428 rituximab	This paper looks at costs associated with on-licence and off-licence usage of rituximab

	on Pharmaceutical Costs: The Rituximab Experience	use of oncology drugs and its effects on pharmaceutical costs. Patient diagnoses were linked to pharmacy records, and each administration of rituximab was classified as either on-label or off-label as defined by FDA-approved indications. The resultant utilization patterns were the foundation for a conceptual model designed to identify factors that influence off-label use of oncology-related therapeutics and forecast the effect of off-label use on aggregate oncology drug expenditures.	administrations during the study period. Most (320, 75%) of the administrations were for off-label indications. Although the extent of off-label and on-label use grew at a similar rate initially, off-label utilization increased nearly exponentially over time as on-label uses lessened. A conceptual model that describes factors that promote, inhibit, or have a mixed influence on off-label use may help predict future patterns of off-label utilization and allow better forecasting of oncology drug expenditures. During the study period, more than $1.1 million was spent on rituximab for off-label use, as compared with $355 000 for FDA-approved indications. These numbers do not include	from the US health care perspective. Some of the issues dealt with in this manuscript are not applicable to the UK, for example direct to consumer advertising and restricted access to therapy. However the paper does look at the costs associated with rituximab and therefore meets the inclusion criteria.

			costs in addition to those of this medical center's drug acquisition, such as pharmacy preparation, administration, managing adverse events, and indirect costs such as those incurred by the patients and their families.	
Hieke et al (2004)	Cost Evaluation of Rituximab Plus MCP vs. MCP Alone in Advanced Stage Indolent Non-Hodgkin's-Lymphoma Based on a Randomized Controlled Multicenter Trial.	To evaluate the health economic consequences of R-MCP vs. MCP from the perspective of a German payer (statutory sickness fund). Resource utilization data on 329 patients were collected and analyzed for the treatment phase (8 month). In addition, an interim analysis of the first 3 years of the subsequent observation period (planned: 7 years) was conducted. Data on resource utilization for initial chemotherapy, chemotherapy	Mean cost of the treatment phase in the base case analysis was EUR 35,890 for R-MCP and EUR 21,508 MCP per patient. Mean cost per active treatment cycle was EUR 4,932 for R-MCP and EUR 3,270 for MCP. Mean (undiscounted) cost per patient in the observation period amounted to EUR 9,973 for R-MCP and EUR 15,896 for MCP. Mean observation time, after end of active treatment, was similar in both arms, 28.5 months for	This analysis looked at the cost effectiveness of rituximab in combination with MCP, a different chemotherapy than that used in this submission. The analysis is from the German health care perspective.

		administration, treatment of adverse events, treatment of complications /progressive disease, subsequent chemotherapies and treatment for other reasons were collected.	R-MCP, 27.5 months for MCP. Costs for treatment of adverse events, new chemotherapies and other reasons were reduced by 23%–39%, cost for treatment of progressive disease by 76% in the R-MCP arm compared to MCP alone. Extrapolating data to a full 3-year observation period results in savings of EUR 8,214 per patient with R-MCP compared to MCP alone. This compensates approx. 60% of the higher costs from the treatment phase. Clinically, R-MCP resulted in an objective response rate of 85.6% vs. 65.5% with MCP. After two years, based on Kaplan Maier estimate, event free survival for R-MCP was 69% vs. 44% for MCP alone ($p < 0.001$) (For more detailed clinical	

			results see abstract by Herold et al.) Combined with the clinical superiority of R-MCP, a favorable cost-effectiveness ratio may be expected when more mature data are available.	
Leppa et al (2006)	Cost-Effectiveness of Rituximab Maintenance Treatment Versus Autologous Stem Cell Transplantation (ASCT) in Patients with Relapsed Follicular Lymphoma (FL).	The objective of this analysis was to estimate the incremental cost-effectiveness of rituximab maintenance compared to ASCT in patients with FL in first relapse. Efficacy data for rituximab maintenance treatment was derived from the EORTC 20981 trial (van Oers et al, ASH 2005). FL patients (n=334) were randomized to observation or rituximab maintenance treatment in first relapse. Rituximab maintenance treatment consisted of eight infusions during two years. The reported PFS for R-CHOP induction followed by maintenance	The cost of rituximab maintenance treatment was estimated to be approximately EUR 19.700. The actual cost of ASCT was approximately EUR 38.600. In terms of health benefits, rituximab maintenance seems to provide longer PFS after first relapse, with incremental difference of 17.8 mo, based on these early results reported. In the base case, therapy associated costs were lower in the rituximab maintenance treatment group.	This analysis looked at the cost effectiveness of maintenance rituximab compared to stem cell transplantation, whereas in this submission it is compared to observation. The analysis is from the Finnish health care perspective and has used up to date costs.

		arm was 51.9 mo, in comparison to 23.1 mo for observation arm. Efficacy data on ASCT and immunochemotherapy were derived from local experience during 1994–2005. Twelve patients with relapsed FL received ASCT, and had median PFS of 34.1 mo. In comparison, fifty patients who received immunochemotherapy without neither ASCT nor rituximab maintenance had a PFS of 21.8 mo, which is comparable to the outcome of R-CHOP treated patients in the observation arm of the EORTC 20981 study. To estimate the incremental resources involved therapy associated costs, and visit costs during the first two years were included. Rituximab maintenance costs included eight infusion visits, in addition to drug costs. Costs for ASCT were based on real data of		

		individual patients, collected from hospital's accounting systems. These costs are also used as prices charged by Helsinki University Hospital (HUCH) in Finland. The costs included only direct medical costs for hospital services and were calculated in 2004 prices.		

Appendix 5: Fitting distributions to observed survival data from EORTC20981 both the 2 arm and 4 arm models

2 arm	4 arm
Appendix Parametric curve fitting	Appendix Parametric curve fitting

Appendix 6: Calculation of the dispensed dose of rituximab maintenance therapy the EORTC20981 trial both the 2 arm and 4 arm models

2 arm	4 arm
 Appendix Dispensed dose calculations	 Appendix Dispensed dose calculations 4arı

Appendix 7: Calculation of the cost of adverse events reported in EORTC20981 both the 2 arm and 4 arm models

2 arm	4 arm
Error! Not a valid link.	 Appendix Cost of adverse events.doc

Appendix 8: Calculation of the cost of treatments upon relapse

2 arm	4 arm
Appendix Treatment cost upon relapse	Appendix Treatment cost upon relapse

Appendix 9: Description of probabilistic sensitivity analysis both the 2 arm and 4 arm models

2 arm	4 arm
 Appendix PSA details 2ARM	 Appendix PSA details 4arm.xls

Appendix 10: Economic literature review

Included and Excluded Publications  U:\MabThera RCVP\ MabMaintenanceAnd	**Publications identified by EMYY and MEYY searches**  U:\MabThera RCVP\ MabMaintenanceAnd
Publications identified by NHS EED and HEED searches  U:\MabThera RCVP\ MabMaintenanceAnd	**Publications identified by ASH search**  U:\MabThera RCVP\ MabMaintenanceAnd

Appendix 11: Utility study

Appendix 12: Current treatment of follicular lymphoma in the UK (market research conducted by Synovate for Roche UK- January 20