Non-Hodgkin's lymphoma:

diagnosis and management

NICE Guideline

Appendices A-F

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Appendix A: A cost-utility analysis of autologous and allogeneic transplantation for people with follicular lymphoma

A.1 Background

To date, there is no consensus on the optimal treatment strategies for people with relapsed follicular lymphoma. While there is some prospectively collected (pre-rituximab) evidence to suggest that autologous stem cell transplantation (ASCT) might be superior compared to conventional chemotherapy (Schouten et al.2003), the only prospective trial comparing allogeneic transplantation (allo-HSCT) to ASCT had to close prematurely due to insufficient patient recruitment (Tomblyn et al. 2011). Furthermore, no full economic evaluations have been published that would address the question of the optimal treatment strategy for people with relapsed follicular lymphoma. While ASCT is associated with acceptable toxicity and relatively low treatment-related mortality (TRM), concerns about late relapses and secondary malignancies remain. Allo-HSCT, on the other hand, offers the possibility of lasting remissions and curative potential with low late relapse rates but its high toxicity and TRM rates are limiting its application to a selected patient population in which the disease risk has to be outweighed against the procedure-related morbidity and mortality. Similarly, in the post-rituximab era, R-chemotherapy may also provide an appropriate treatment option for patients, particularly when not suitable for transplantation options e.g. based on a patient's co-morbidities. Considering the long natural history of the disease and the generally slow progression, it is important to evaluate the effectiveness of the treatment options against both risk and costs. As summarised in the clinical evidence review, the evidence base is of generally low quality consisting of mostly observational studies which report contradictory results on the clinical effectiveness of the different strategies at different time points. As well as the uncertainty around clinical effectiveness, the cost-effectiveness of these strategies in the UK context is as yet unknown.

A.1.1 Health Economics Priority

As decisions about the use of different transplantation strategies will significantly impact on NHS resources and patient benefits, this topic was identified as a high economic priority by the guideline committee (GC).

A.1.2 Existing Economic Evidence

No existing economic evidence as defined under the PICO for this guideline topic was identified after a systematic search of the literature.

A.2 De novo economic model (overview)

A.2.1 Aim

The aim of the economic evaluation was to estimate the cost-effectiveness of autologous transplantation and allogeneic transplantation compared to no transplantation (R-chemotherapy) for people with relapsed follicular lymphoma.

A.2.2 Population

The population for the economic analysis comprised adults and young people aged 16 years or over with a confirmed diagnosis of follicular Non- Hodgkin Lymphoma after first relapse. People with Grade IIIB, transformed or composite/discordant FL were excluded from the analysis. The economic analysis was concerned with treatment strategies at first and second relapse after initial first-line chemotherapy treatment for FL. No sub-groups were considered in the economic analysis.

A.2.3 Interventions and comparator

Table 1 summarises the interventions and comparator at first and second relapse.

Table 1: Summary of comparators included in the economic analysis

	Intervention	Intervention	Comparator
Second-line treatment following first relapse and response to second-line induction chemotherapy	ASCT	Allo-HSCT	R-chemotherapy + Rituximab maintenance
Third-line treatment following second relapse and response to third-line induction chemotherapy	ASCT (if not performed in second line)	Allo-HSCT (if not performed in second line	R-chemotherapy + Rituximab maintenance

In the base case, R-chemotherapy in second and third line was assumed to be R-CHOP due to limited data availability for other regimens.

A.2.4 Model structure

Since no current economic literature could be found to address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. An individual patient simulation model was developed using Microsoft Excel with coding in Visual Basic for Applications (VBA). VBA was chosen due to the complexity of the disease progression that had to be modelled. The fact that transition probabilities change with increasing length of remission and that there are certain constraints on the treatment options pushes the boundaries of the capabilities of a conventional Markov model and VBA patient level simulation deals well with any level of complexity.

Figure 1 illustrates the modelled treatment pathway, while Figure 2 shows the possible health states and transitions (Markov states).

Figure 1: Modelled treatment pathway

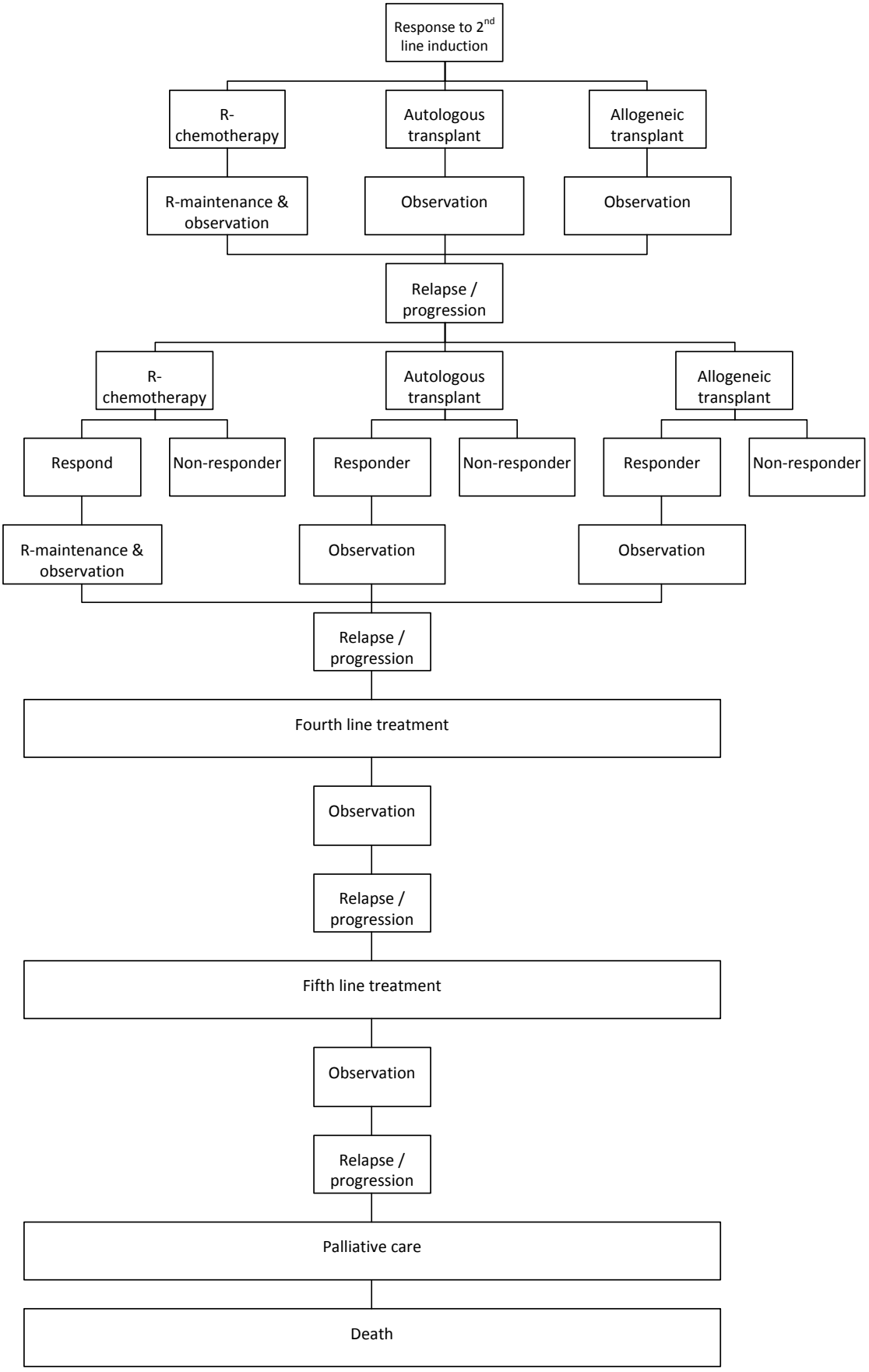
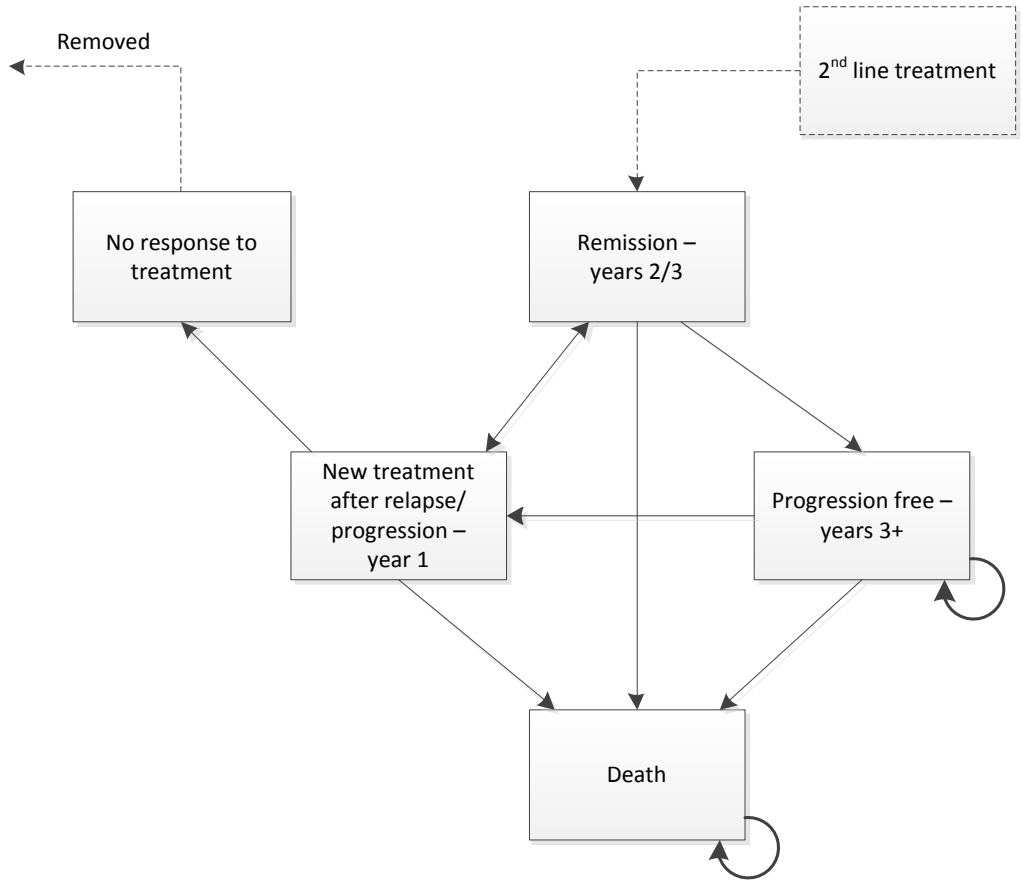


Figure 2: Possible health states and transitions (Markov states)



A decision tree model followed a cohort of 100,000 people with a starting age of 50 years suffering from follicular lymphoma who required second-line treatment after first relapse. They were assumed to have received R-chemotherapy in first line and responded to second-line induction chemotherapy.

The first decision in the model was the allocation of each person to their second-line treatment. They either received more R-chemotherapy, had an autologous transplantation or an allogeneic transplantation. Once allocated to their second-line treatment, they were assigned an initial health state for the next year (remission, death from treatment, death from cancer, all-cause death or relapse). This initial health state determined the clinical pathway that each patient would take. Transitions between health states were evaluated annually for a total modelling horizon of 35 years. Before moving onto the next time period, it was ascertained whether a patient experienced any adverse events linked with their treatment. These adverse events were counted and noted at each stage of treatment.

The model assumes that, if the patient was in remission after second-line treatment, they would remain on that same treatment pathway and receive either rituximab maintenance for two years after R-chemotherapy or if they were allocated to a transplantation arm they would be monitored over a period of two years. At any time during the two year maintenance/observation period, the patient could relapse or die of natural causes. If, after the two years, they still remained in remission they would receive no further treatment irrespective of treatment arm and would be monitored until they relapsed again or died.

People who experienced a relapse were once again assigned to one of the three treatment options(R-chemotherapy, autologous transplant or allogeneic transplant). The exact combinations which were allowed are outlined in Table 2.

Table 2: Possible treatment combinations

2nd Line treatment	3rd line treatment
R-Chemotherapy	R-Chemotherapy
	Autologous transplant
	Allogeneic transplant
Autologous	R-Chemotherapy
	Allogeneic transplant
Allogeneic transplant	R-Chemotherapy

Once the third line treatment was allocated, before determining the initial health state for the next time period, it had to be established whether the patients would respond to the third-line treatment or not (this was not required in second line as people only entered the model after initial response to induction). If they did not respond, they would drop out of the usual treatment pathway and be counted and noted. If they did respond they would then be allocated the initial health state for their treatment which was assumed to be the same as in second-line.

Upon relapse after third-line treatment at any stage (either during the treatment, maintenance or monitoring periods), they proceeded directly to fourth-line treatments. Data availability for fourth line treatments was limited and therefore the treatments were combined into one option (with one cost and utility attached to them). From here they could go into remission, relapse or die from any cause. No further rituximab maintenance was assumed at this stage and patients were monitored until relapse or death. Once they relapsed they would proceed directly to fifth-line treatments. Again, the simplified treatment option was utilised with the same health states as for fourth-line treatment.

Once a patient relapsed after fifth-line treatment, they progressed directly to palliative care, where they were assumed to remain for one year before death.

A UK NHS &PSS perspective has been adopted in the analysis, in line with NICE methodological recommendations. Health outcomes have been expressed in terms of quality-adjusted life years (QALYs) and costs and benefits were discounted at a rate of 3.5%. The analysis undertaken was a cost-utility analysis producing incremental cost-effectiveness ratios (ICERs) expressed as cost/QALY gained.

A.2.5 Key Model Assumptions

- The analysis follows current UK standard practice for treatment and surveillance post-treatment as advised by the GC.
- At model entry, all patients have a confirmed FL relapse, i.e. are in an existing cancer state based on their diagnosis after relapse from first-line treatment.
- All patients are assumed to have received and responded to induction therapy prior to the initial treatment strategy at model entry (ASCT, allo-HSCT or 3 cycles of R-chemotherapy).
- Total Body Irradiation (TBI) is not considered as a conditioning treatment pre-transplantation.
- All Allo-HSCT patients are assumed to be given a reduced-intensity conditioning regimen prior to transplant.
- Patients who complete R-chemotherapy are assumed to receive 8 cycles of rituximab maintenance therapy over a period of 2 years.

- After relapse from allo-HSCT, patients do not receive further transplantation and receive R-chemotherapy as the only treatment option (due to lack of outcome data).
- After first relapse from ASCT, patients can receive either allo-HSCT or R-chemotherapy but no second autologous transplantation (due to lack of outcome data).
- ASCT and allo-transplantations are only considered in second and third treatment line.
- After relapse following third-line treatment, all people are assumed to receive R-chemotherapy in fourth and fifth line.
- Secondary malignancies were not included in the model as an adverse event following GC advice.
- Serious adverse events included in the model are febrile neutropenia for all treatment strategies and graft versus host disease for patients who received allo-HSCT.
- After relapse following fifth-line treatment, all patients are assumed to be receiving palliative care until death.
- All patients remain in the model until death from any cause (disease-related, treatment-related or natural causes)

A.3 Cost-effectiveness analysis: inputs (base case)

The cost-effectiveness analysis required relevant clinical evidence, health utilities, health care resources associated with the treatment pathways and associated costs for the two transplant options and R-chemotherapy. Where possible, the clinical evidence review was used to provide data inputs with structured searches undertaken to identify other required parameters (e.g. utilities, risk increase and certain costs).

A.3.1 Clinical data

A considerable challenge during economic modelling was the paucity of high quality clinical evidence, as summarised in the evidence review. Of particular note is thereby the lack of randomised controlled trials providing direct comparisons of ASCT vs. allo-HSCT or allo-HSCT vs. R-chemotherapy. The strongest clinical evidence to inform the economic analysis was provided by Schouten et al. (2003), who compared ASCT to chemotherapy after first relapse in a randomised controlled trial. However, the study was conducted in the pre-rituximab era and therefore would not be fully reflective of current clinical practice and sample size was small (n=86). We used observational data reported by Robinson et al. (2013) for the direct comparative data of ASCT vs. allo-HSCT. This study was chosen due to its high quality methodology, large sample size (n=875) and completeness of reported outcome data. We utilised the 'best available' evidence from the clinical review and additional literature searches to populate parameters not covered by these studies to compare the three treatment options. All data inputs underwent full validation by the GC and uncertainty was considered within the sensitivity analysis.

A.3.1.1 Relapse rates

Robinson et al. (2013) report 1-year, 3-year and 5-year cumulative relapse incidence for people who underwent autologous and allogeneic transplantations. The number of prior treatment lines in this retrospective review was >3 for 45% of ASCT patients and 63% of allo-HSCT patients, respectively. Since transplantation was modelled only in second and third line, it was considered that the reported data was more representative of third-line treatment than second-line treatment. Data was adapted to second-line by applying a 20% risk increase per additional treatment line reported by Kothari et al. (2014) and also used in a recent comparable model by Prica et al. (2015). Relapse rates were converted into annual probability of relapse and, following GC advice, were staggered (see Table 3) to reflect the curative potential of ASCT and allo-HSCT apparent in the cumulative relapse incidence curves which show a decrease in relapse rate after year one and then again after year 3 for

ASCT and a marked decrease of relapse rate after year 1 for allo-HSCT3. Annual probability of relapse for allo-HSCT as a second transplant option could not be staggered as only 3-year CRI was reported. Annual probability of relapse for R-chemotherapy was calculated by applying the hazard ratio of 0.3 reported by Schouten et al. (2003) to the values for ASCT used in the model (see Table 3). While this RCT was conducted before the introduction of rituximab and the relapse rate for chemotherapy (CHOP) could be considered too high when applied for R-CHOP, the GC was of the opinion that it was appropriate for the higher risk population that would be considered for transplantation.

Table 3: Annual probability of relapse after third-line treatment

Comparator	P(relapse)	Source
R-chemotherapy	0.3975	Schouten et al. 2003 (based on hazard ratio)
Autologous transplantation (year 1)	0.2000	Robinson et al. 2013
Autologous transplantation (years 2/3)	0.0945	Robinson et al. 2013
Autologous transplantation (>3 years)	0.0461	Robinson et al. 2013
Allogeneic transplantation (year 1)	0.1700	Robinson et al. 2013
Allogeneic transplantation (>1 years)	0.0076	Robinson et al. 2013
Allogeneic transplantation as second transplant (<3 years)	0.1121	Robinson et al. 2013
Allogeneic transplantation as second transplant (>3 years)	0.0134	Assumption (based on 1.77 times higher relapse rate compared to allo-HSCT as first transplant in first 3 years)

The model was initially designed to calculate the cost-effectiveness of the treatment options in second and third line separately but due to lack of available data this could not be done. However, it was still considered more intuitive to use different relapse rate after different treatment strategies in subsequent treatment lines. This means that people who received an initial second-line R-chemotherapy course, relapsed and then underwent third-line transplantation were re-assigned a new relapse probability after their transplantation which reflected the efficacy of the last undergone treatment. This approach was chosen to reflect the very different effect on relapse rates observed for R-chemotherapy and transplantation options. However, since the relapse data available was based on cumulative relapse incidence, this approach might introduce bias as second and third relapses might be double-counted and relapse rates overestimated. The effect of this potential bias on the results has therefore been assessed in sensitivity analysis by applying the same relapse rate based on the first treatment throughout the model horizon.

A.3.1.2 Mortality

Disease-related mortality

Disease-related mortality was estimated using combined data from both treatment arms of Robinson et al. (2013). This equated to an annual estimate of disease-related mortality of 42.36%. The model links disease-related mortality to rate of relapse/progression and the annual probability of disease-related death applies only to people who have previously relapsed or progressed rather than the general cohort. Linking disease-related mortality to relapse rate resulted in staggered values for disease-related death which followed the relapse probabilities for each treatment arm and was again adapted to second-line treatment using a 20% risk increase per additional treatment line.

Non-cancer mortality

Death from other causes was captured using 2012-2014 life tables for England and Wales from the Office of National Statistics (ONS). These life tables give an estimate of the annual probability of death given a person's age and gender. A starting age of 50 years and a male proportion of 55% were applied in the model based on patient demographics from Robinson et al. (2013).

Treatment- related mortality

The high treatment-related mortality of allo-HSCT and to a lesser extent ASCT was considered a crucial parameter that could influence the potential cost-effectiveness of transplantation strategies compared to R-chemotherapy to a significant degree. Treatment-related mortality for ASCT and allo-HSCT was extrapolated from 1-year and 3-year non-relapse mortality (NRM) rates reported by Robinson et al. (2013), adjusted for the appropriate non-cancer mortality for the cohort (50 years, 55% male) and converted into annual probabilities. Following the NRM curves, probability of treatment-related death was staggered with a higher rate in year 1 and lower rates in years 2 and 3 (table 4). No treatment-related mortality was assumed beyond year 3 following transplantation.

Table 4: Annual probability of treatment-related death after third-line treatment

Comparator	P(TRD)	Source
R-chemotherapy	0.0040	vanOers et al. 2006
Rituximab maintenance	0.0000	vanOers et al. 2010
Autologous transplantation (year 1)	0.0274	Robinson et al. 2013
Autologous transplantation (years 2/3)	0.0074	Robinson et al. 2013
Allogeneic transplantation (year 1)	0.1674	Robinson et al. 2013
Allogeneic transplantation (years 2/3)	0.0227	Robinson et al. 2013
Allogeneic transplantation as second transplant†	0.1095	Robinson et al. 2013
†Allogeneic transplantation rates as a second transplant could not be staggered as only 3-year data was available.		

Due to lack of comparative data, treatment-related mortality for R-chemotherapy was taken from vanOers et al. (2006) where 1 of 234 participants died from treatment-related toxicity in the R-CHOP arm. Based on no treatment-related deaths in the rituximab maintenance arm of the same trial (vanOers et al. 2010), probability of treatment-related death was assumed to be 0.

A.3.1.3 Adverse events

Febrile neutropenia

Febrile neutropenia was identified by the GC as the adverse event that was most likely to result in significant costs of treatment. Probability of febrile neutropenia after transplantation was based on Leger et al. (2006) who reported that 98.3% of patients (n=60) undergoing ASCT were treated for febrile neutropenia post-transplant. This was assumed to be transferable to allo-HSCT. Reporting of febrile neutropenia rates for R-chemotherapy was found to be rare and thus was assumed to be 20% based on chemotherapy values reported in literature (Zinzani et al. 2006) and GC advice. Febrile neutropenia rate for rituximab maintenance was assumed to be 5%. Sensitivity analysis was performed to assess the effect of the uncertainty surrounding these values on the results.

Febrile neutropenia rates were only applied in the year of treatment.

Graft versus host disease

Graft versus host disease (GVHD) is a severe complication that is possible after an allogeneic transplantarion whereby T-cells in the donated bone marrow ('the graft') attack the patient's body ('the host'). In the allo-HSCT arm, we applied a probability of grade 3/4 acute GVHD of 12.08% based on 18 out of 149 people reported by Robinson et al. (2013) to have developed acute GVHD in the year of transplantation only. Additionally, an annual probability of chronic extensive GVHD of 13.69% was applied in years 2 and 3 only based on 38 of 149 affected people over 2 years reported by Robinson et al. (2013) and converted to annual probability.

A.3.104 Third-line treatment and probability of response

After having received R-chemotherapy, ASCT or allo-HSCT in second line, once people relapsed, they were eligible for third-line treatment according to predefined transition probabilities based on the previous treatment and values reported in literature (Table 5).

Table 5: Probability of third-line treatment options

Second-line treatment	Third-line treatment	P(combination)	Source
R-chemotherapy	R-chemotherapy	0.6952	1-(0.24+0.0648)
	Autologous transplant	0.2400	Le Gouill et al. 2011
	Allogeneic transplant	0.0648	Evens et al. 2013
Autologous transplant	R-chemotherapy	0.8100	1-0.19
	Autologous transplant	0.0000	Assumption
	Allogeneic transplant	0.1900	Robinson et al. 2013
Allogeneic transplant	R-chemotherapy	1.0000	Assumption
	Autologous transplant	0.0000	Assumption
	Allogeneic transplant	0.0000	Assumption

As now outcome data could be identified in the literature for second ASCT after previous ASCT or allo-HSCT after allo-HSCT, the model assumes that each transplantation option would only be performed once.

Due to the lack of relevant outcome data, length of previous remission and other clinical factors could not be taken into account when determining third-line treatment. However, it is assumed that the published mean data used would incorporate these parameters to a certain extent.

After third-line R-chemotherapy, 85.1% of people were assumed to achieve a response based on the overall response rate in relapsed patients after R-CHOP treatment reported by vanOers et al. (2010). Similarly, 98.5% of ASCT patients were considered to proceed with transplant after successful stem cell mobilisation as reported by Derenzini et al. (2013). No data could be identified for allo-HSCT and a base case value of 99% of people achieving transplant was assumed. Patients who did not respond to chemotherapy or proceed to transplantation were removed from the model and counted.

A.3.112 Costs

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. adverse events or death). Where possible, all costs were estimated in 2013-14 prices.

The majority of costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose information from the British National Formulary (BNF) and unit costs from the Electronic Market Information Tool (eMit). Other costs were estimated using the advice of the guideline committee.

A.3.2.1 Costs of treatment

R-chemotherapy and rituximab maintenance

Cost of second and third-line R-chemotherapy was assumed to be the cost of R-CHOP based on the outcome data being mainly reported for this regimen. The drug costs of R-CHOP and rituximab maintenance were estimated using dosages and unit costs from the British National Formulary (BNF) and the Electronic Market Information Tool (eMit). The cost associated with delivering rituximab and chemotherapy was estimated using cost codes for the delivery of chemotherapy (weighted for outpatient and daycase) from NHS reference costs 2013/14. The cost of R-CHOP and rituximab maintenance is shown in Table 6.

Table 6: Cost of second and third-line R-chemotherapy and rituximab maintenance

Chemotherapy cost element	Value	Source
Proportion delivered as outpatient	20%	NHS Reference costs 2013/14 – outpatient (SB14Z)
Proportion delivered as a day case	80%	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£265.85	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient deliver subsequent elements of a chemotherapy cycle	£313.80	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB15Z)
Rituximab		
375mg/m2 Rituximab given as an IV on day 1 of each cycle†	£1,222.41	Unit costs from BNF
R-CHOP		
Cyclophosphamide (750mg/m^2 IV day 1)†	£25.36	Unit costs from eMIT.
Doxorubicin (50mg/m^2 IV day 1)†	£8.82	Unit costs from eMIT.
Vincristine (1.4mg/m^2 IV day 1) †	£6.16	Unit costs from eMIT.
Prednisone or prednisolone (100mg/m^2 days 1-5) †	£83.15	Prednisolone unit cost from Emit. Prednisone unit cost from BNF.
CHOP cost per cycle	£823.30	
Cost per cycle of R-CHOP	**£2,045.71**	
Cost per cycle of rituximab maintenance	**£1,597.21**	
† Based on average body surface area for cancer patients from Sacco et al. 2010 (1.91m^2 for males and 1.71m^2 for females)		

Based on the advice of the guideline committee, it was assumed that granulocyte-colony stimulating factor (GCSF) would be used in 50% of patients receiving chemotherapy. The

unit costs associated with GCSF agents (lenograstim or filgrastim, including biosimilars) were sourced from the BNF as unit costs were not available from eMIT. It was assumed that GCSFs would be administered for seven days based on guidelines for the use of GCSF from St Luke's Cancer Alliance (Table 7).

Table 7: Cost of GCSF

GCSF cost element	Cost	Source
Lenograstim 263mcg	£62.54	Unit costs from BNF
Filgrastim† 300mcg	£55.78	Unit costs from BNF
Number of days that GCSF is administered	7.00	Guidelines for the Use of G-CSF Following Chemotherapy. St Luke's Cancer Alliance, Royal Surrey County Hospital
Average GCSF cost	**£414.10**	
†Average of Neupogen®, Nivestim®, Ratiograstim® and Zarzio®		

In second line, all patients entered the model after response to induction chemotherapy, so it was assumed that R-chemotherapy patients would receive a further 3 cycles of R-CHOP at a total cost of £6,758.29 (including GCSF). In third-line, people received 6 cycles of R-CHOP costing £13,516.58 (including GCSF) per patient.

The annual cost of rituximab maintenance was based on 6 cycles per year amounting to £9,583.28 and was applied for 2 years. No GCSF was assumed to be given to patients during rituximab maintenance treatments and delivery cost was applied for first attendance only.

Costs of transplantation

The cost of the autologous and allogeneic transplantation procedure was estimated to be £34,000 and £82,000, respectively based upon the tariff utilised by the transplanting haematologist on the guideline committee. It should be noted that alternative values of £16,359 and £36,288 were available from NHS Reference costs but they were thought to be considerable underestimates of the true cost and so were not used in the base case analysis. However, the impact of utilising the lower costs was explored in sensitivity analysis.

It was assumed that patients undergoing a transplant would first receive three cycles of salvage chemotherapy. Numerous chemotherapy regimens are used for this purpose in clinical practice but the guideline committee thought that the most commonly used regimens were R-ESHAP, R-DHAP, R-GDP or R-ICE. Therefore, the average cost of these chemotherapy regimens was applied in the economic analysis (assuming an equivalent weighting for each option i.e. a crude average).

The costs associated with delivering chemotherapy were sourced from NHS Reference costs. Based on the advice of the guideline committee, it was further assumed that R-ESHAP or R-DHAP would be delivered in an inpatient setting whereas R-GDP or R-ICE would be delivered in an outpatient setting. The costs associated with delivering outpatient chemotherapy were sourced from NHS Reference costs (using the same proportions as those used in the sections above). Following NHS Reference costs methodology the cost of inpatient chemotherapy was estimated using bed day costs (as there is no specific code for inpatient chemotherapy delivery). Therefore, inpatient chemotherapy costs were estimated using the average cost of an excess bed day in patients with malignant Lymphoma, including Hodgkin's and non-Hodgkin's (£348.88) multiplied by the number of days where chemotherapy is delivered.

1 The unit costs of drugs were sourced from Emit. Where eMIT costs were not available, BNF
2 costs were used (Table 8).

3 **Table 8: Cost of the chemotherapy regimens before transplant**

Chemotherapy cost element	Value	Source
Proportion delivered as outpatient	20%	NHS Reference costs 2013/14 – outpatient (SB14Z)
Proportion delivered as a day case	80%	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first Attendance	£265.85	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient delivery of subsequent elements of a chemotherapy cycle	£313.80	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB15Z)
Inpatient chemotherapy delivery cost (per day)	£384.88	NHS Reference costs 2013/14 - Weighted average cost of "Malignant Lymphoma, including Hodgkin's and non-Hodgkin's" (SA31) in elective Inpatients - Excess Bed Days
Rituximab		
375mg/m2 Rituximab given as an IV on day 1 of each cycle	£1,222.41	Unit costs from eMIT.
R-ESHAP (inpatient)		
4 doses of etoposide (40mg/m^2/day)†	£7.64	Unit costs from eMIT.
5 doses of methylprednisolone (500mg/day)	£23.30	Unit costs from eMIT.
1 dose cytarabine (2000mg/m^2)†	£40.25	Unit costs from eMIT.
3 doses of cisplatin (25mg/m^2/day)†	£35.25	Unit costs from eMIT.
6 doses of Corticosteroid eye drops e.g. Prednisolone 0.5%	£7.77	Unit costs from eMIT.
ESHAP cost per cycle	**£2,038.58**	
Total cost for 3 cycles of R-ESHAP	£11,380.19	
R-DHAP (inpatient)		
4 doses of dexamethasone (40mg)	£45.26	Unit costs from eMIT.
2 doses of cytarabine (2g/m^2)†	£60.26	Unit costs from eMIT.
1 dose of cisplatin (100 mg/m^2 on day 3)†	£31.15	Unit costs from eMIT.
6 doses of Corticosteroid eye drops e.g. Prednisolone 0.5%	£7.77	Unit costs from eMIT.
DHAP cost per cycle	£1,299.06	
Total cost for 3 cycles of R-DHAP	£9,161.62	
R-GDP (outpatient)		
2 doses of gemcitabine (1000mg/m^2)†	£62.72	Unit costs from eMIT.
4 doses of dexamethasone (40 mg)	£45.26	Unit costs from eMIT.
1 dose of cisplatin (75 mg/m^2)†	£25.34	Unit costs from eMIT.

Chemotherapy cost element	Value	Source
GDP cost per cycle	£833.13	
Total cost for 3 cycles of R-GDP	£7,763.82	
R-ICE (outpatient)		
1 dose of ifosfamide (5g/m^2)†	£624.98	Unit costs from BNF.
1 dose of Carboplatin AUC 5 (max 800mg)*	£21.74	Unit costs from eMIT.
3 doses of etoposide (100mg/m^2)†	£11.47	Unit costs from eMIT.
ICE cost per cycle	£1,357.99	
Total cost for 3 cycles of R-ICE	£9,338.43	
Average cost for chemotherapy regimens used before transplant	**£9,411.01**	
† Based on average body surface area for cancer patients from Sacco et al. 2010 (1.91m^2 for males and 1.71m^2 for females) * Carboplatin dose calculated using calvert formula: AUC 5 = 5*[GFR+25]. GFR calculated as: GFR = Gender (male = 1, females = 0.85) * [(140 - Age) / (SerumCreat)] * (Weight / 72). Average age and gender were that used in the model, while serum creatine and weight were based on a study by Craig et al. 2012‡		

As above, the cost of GCSF was added to the chemotherapy cost for 50% of the patients resulting in a cost per patient of £10,032.17 for chemotherapy prior to transplant.

Cost of subsequent lines of chemotherapy

As described in a previous section above, patients that experience a relapse after third-line treatment or beyond were assumed to receive further treatment with another immunochemotherapy regimen. The guideline committee provided a list of eleven immunochemotherapy regimens that might be used in this setting including R-CHOP, R-CVP, R-Bendamustine, R-ESHAP, R-DHAP, R-GDP, R-ICE, R-GEMP, R-FC, R-GCVP OR R-Mini-BEAM. The average cost associated with this basket of regimens was estimated (assuming an equivalent proportion of each regimen was used i.e. a crude average) and applied for each subsequent relapse.

As above, the costs associated with delivering chemotherapy were sourced from NHS Reference costs, with different costs used depending on whether the regimen is delivered on an outpatient, day case or inpatient basis (using the same methodology as above). The unit costs of drugs were sourced from Emit or the BNF (where eMIT costs were not available). However, in the case of carmustine, unit costs were not available from eMIT or the BNF. The guideline committee advised that this was due to a recent lack of availability of the drug, which is now only available through specialist importers. A pharmacy colleague of one of the guideline committee members provided the previous price paid for the drug (£358.80 for 100mg), which was utilised in the analysis. An alternative and much higher estimate was provided by the pharmacy colleague of another guideline committee member (£1,000 per 100mg), suggesting that there is considerable variability in the price of the drug. In order to address this uncertainty, a wide uniform distribution between the guideline committee's lower (£200) and upper estimates (£1,000) was utilised in the probabilistic sensitivity analysis.

The costs associated with each of the regimens as well as the overall average (£8,669) are shown in table 9 below. Note that full cost details are not shown for R-CHOP as it has already been presented in previous sections.

Table 9: Cost of subsequent lines of chemotherapy used in the model

Chemotherapy cost element	Value	Source
Proportion delivered as outpatient	20%	NHS Reference costs 2013/14 – outpatient (SB14Z)

Chemotherapy cost element	Value	Source
Proportion delivered as a day case	80%	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£265.85	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient delivery of subsequent elements of a chemotherapy cycle	£313.80	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB15Z)
Inpatient chemotherapy delivery cost (per day)	£384.88	NHS Reference costs 2013/14 - Weighted average cost of "Malignant Lymphoma, including Hodgkin's and non-Hodgkin's" (SA31) in elective Inpatients - Excess Bed Days
Rituximab		
375mg/m^2 Rituximab given as an IV on day 1 of each cycle	£1,222.41	Unit costs from BNF.
R-CHOP (outpatient)		
Total cost for 6 cycles of R-CHOP	£12,274.27	See sections above for full details and references
R-CVP (outpatient)		
Cyclophosphamide (750mg/m^2 IV day 1)†	£25.36	Unit costs from eMIT.
Vincristine (1.4mg/m^2 IV day 1)†	£6.16	Unit costs from eMIT.
Prednisone or prednisolone (40mg/m^2 days 1-5)†	£34.94	Prednisolone unit cost from Emit. Prednisone unit cost from BNF.
CVP cost per cycle	£766.26	
Total cost for 6 cycles of R-CVP	£11,932.05	
R-Bendamustine (outpatient)		
Bendamustine cost for 2 doses (90mg/m2 on days 1 and 2 of cycle)†	£446.51	Unit costs from BNF. Dosages from Rummel et al. 2013
Bendamustine cost per cycle	£1,146.32	
Total cost for 6 cycles of R-Bendamustine	£14,212.38	
R-ESHAP (inpatient)		
Total cost for 3 cycles of R-ESHAP	£11,380.19	See sections above for full details and references
R-DHAP (inpatient)		
Total cost for 3 cycles of R-DHAP	£9,161.62	See sections above for full details and references
R-GDP (outpatient)		
Total cost for 3 cycles of R-GDP	£7,763.82	See sections above for full details and references
R-ICE (outpatient)		
Total cost for 3 cycles of R-ICE	£9,338.43	See sections above for full details and references

Chemotherapy cost element	Value	Source
R-GEMP (outpatient)		
Gemcitabine (1000mg/m^2 IV Day 1, 8, 15)†	£94.08	Unit costs from eMIT.
Cisplatin (100mg/m^2 IV Day 15)†	£34.51	Unit costs from eMIT.
Methylprednisolone (1000mg IV Days 1 to 5)	£40.85	Unit costs from eMIT.
GEMP cost per cycle	£869.25	
Total cost for 4 cycles of R-GEMP	£8,366.64	
R-FC (outpatient)		
Fludarabine (30mg/m^2 per day for 3 days)†	£76.69	Unit costs from eMIT.
Cyclophosphamide (300mg/m^2 per day for 3 days)†	£26.61	Unit costs from eMIT.
FC cost per cycle	£803.11	
Total cost for 4 cycles of R-FC	£8,102.06	
R-GCVP (outpatient)		
Gemcitabine (1000mg/m^2 IV Days 1 and 8)†	£62.72	Unit costs from eMIT.
Cyclophosphamide (750mg/m^2 IV Day 1)†	£25.36	Unit costs from eMIT.
Vincristine (1.4mg/m^2 [max 2mg] IV Day 1)†	£6.16	Unit costs from eMIT.
Prednisolone or prednisone (100mg Days 1 to 5 oral)	£83.15	Unit costs from eMIT.
GCVP cost per cycle	£877.20	
Total cost for 3 cycles of R-GCVP	£7,896.05	
R-Mini-BEAM (inpatient)		
BCNU carmustine (60 mg/m^2 IV Day 1)†	£358.80	GC Correspondence
Cytarabine (100 mg/m^2 twice daily IV Days 2 to 5)†	£35.31	Unit costs from eMIT.
Etoposide (75 mg/m^2 IV Days 2 to 5)†	£39.69	Unit costs from eMIT.
Melphalan (30 mg/m2 IV Day 6)†	£129.81	Unit costs from BNF.
Total cost of R-Mini-BEAM inpatient	£2,872.87	
Total cost for 2 cycles of R-mini-BEAM inpatient	£11,384.98	
R-Mini-BEAM (outpatient)		
BCNU carmustine (60 mg/m^2 IV Day 1)†	£358.80	GC Correspondence
Cytarabine (150 mg/m^2 twice daily IV Days 2 to 4)†	£39.73	Unit costs from eMIT.
Etoposide (100 mg/m^2 IV Days 2 to 4)†	£21.39	Unit costs from eMIT.
Melphalan (30 mg/m^2 IV Day 5)†	£129.81	Unit costs from BNF.
Total cost of R-Mini-BEAM outpatient	£1,249.54	
Total cost for 2 cycles of R-mini-BEAM outpatient	£8,138.32	
Average cost for basket of immunochemotherapy regimens	**£9,995.90**	
† Based on average body surface area for cancer patients from Sacco et al. 2010 (1.91m^2 for males and 1.71m^2 for females)		

1 Cost of GCSF was added to the chemotherapy costs as described above resulting in a total
2 average cost of chemotherapy in fourth and fifth line of £10,772.34.

A.3.2.2 Costs of surveillance/follow-up

3 It was assumed that, at each follow-up visit, the patient would undergo a physical
4 examination and enquiry about symptoms as well as various tests including full blood count,
5 full profile (U&E, LFT, Ca), serum IgG, IgA, IgM and electropheresis. It was also assumed
6 that patients would receive a CT scan if relapse/progression was suspected or to evaluate

the response to treatment (e.g. to evaluate the response to rituximab at 12 months). The cost of follow-up investigations applied in the model are shown in Table 10.

Table 10: Cost of follow up

Follow-up item	Value	Source
Cost per consultation (physical examination and enquiry about symptoms)	£156.41	NHS reference costs 2013/14 - WF01A
Full blood count	£6.92	ScHARR report, which sourced costs from Sheffield Teaching Hospital Trusts (2005-6). Inflated to 2015 prices
Full profile (U&E, LFT, Ca) cost	£18.85	
Serum IgG, IgA, IgM and electropheresis cost	£27.67	
CT scan if relapse/progression is suspected or to evaluate treatment response		
Cost of computerised Tomography Scan, more than three areas	£147.17	NHS reference costs 2013/14 - RA14Z (Outpatient)

While there is likely to be some variation in clinical practice, the follow-up frequency reported in the BJH Guidance by McNamara et al. 201114 was thought to provide a good estimate of current UK practice and was therefore used as a basis in the economic model. People were assumed to receive a follow-up examination 3-monthly in year 1, 4 to 6-monthly in year 2 and 3 (equating to an average 2.47 follow-up visits per year) and annually thereafter.

A.3.2.3 Costs of adverse events

The cost of febrile neutropenia with malignancy was taken from NHS reference costs 2012/13 and inflated to 2015 prices and amounted to £6,226.29 per episode.

No reference costs could be found for graft versus host disease. All costs associated with transplantation up to 100 days post-transplant are included in the tariff. The cost of acute GVHD was therefore assumed to be £0 to avoid double counting.

Khera et al. (2014) analysed the medical costs of 311 patients who underwent allo-HSCT in the USA and found that extensive chronic GVHD increased the overall cost of allogeneic transplantation by 45%. Based on a transplant cost of £82,000, cost of extensive chronic GVHD was assumed to be £36,900 per patient in the economic evaluation.

A.3.2.4 Cost of death

Cost of disease-related death

The cost of disease-related death was based on the cost of palliative care using estimates from a costing report by the Nuffield Trust (Georghiou et al. (2014), 'Exploring the cost of care at the end of life'). A cost of £7,287 was applied based on the average resource use of patients with cancer in the last three months of life (Table 11).

Table 11: Palliative care costs

Type of care	Average cost per cancer patient	Source
Cost of all hospital contacts	£5,890	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	
District nursing care	£588	
GP contacts	£365	
Average palliative care cost per patient	**£7,287**	

It should be noted that this cost is generic to all cancers and is not specifically related to follicular lymphoma. However, in the absence of more robust data, it has been assumed that the costs in follicular lymphoma would not differ substantially.

It should also be noted that the costs of local authority-funded care may be an overestimate of the true cost because the data may include some patients that have made private contributions to partly cover the cost of care. However, since this aspect only makes up a small proportion of the overall average cost, the effect of this overestimate was thought to be negligible.

Cost of non-disease specific death

Cost of non-disease specific death was considered an unrelated cost and was omitted from the analysis.

Cost of treatment-related death

Cost of treatment-related death was assumed to be from septicaemia following infections due to treatment toxicity and costed using NHS reference costs at £4,211 (WA03A).

Cost of palliative care

After fifth-line treatment, the model assumes that people will receive palliative care or best supportive care for one year until death. The cost of £12,028.18 was taken from Prica et al. (2015) (converted to £ Sterling and inflated to 2015 prices).

A.3.3 Health-related quality of life

The model estimates effectiveness in terms of quality-adjusted life years (QALYs) so that both the quantity and quality of life are taken into account. QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. For the purposes of this economic evaluation, the QoL data shown in Table 12 below were utilised.

Table 12: Quality of life values applied in the model

Health state	Utility score	Source
Second and third line		
Treatment stage (year 1)	0.7363	Unpublished data from Wild et al. 2005 for "disease progression" from ScHARR
Maintenance stage (years 2/3 post - treatment)	0.8050	Unpublished data from Wild et al. 2005 for "progression free" patients from ScHARR
>3 years post-treatment	0.8800	Unpublished data from Wild et al. 2005 for "disease free" patients from ScHARR
Fourth and fifth line		
Treatment stage (year 1)	0.5300	Prica et al. 2015
>1 year post-treatment	0.6180	Unpublished data from Wild et al. 2005
Palliation	0.3800	Prica et al. 2015

The model assumes that quality of life is worst in the initial treatment stage and then increases the longer the patient remains progression free. This means that people who have been progression free for more than 3 years are assumed to have a higher QoL (0.88) compared to people whose remission length is still shorter than 3 years (0.8050). Furthermore, quality of life is assumed to be generally lower in fourth and fifth line compared to second and third line. Most QoL data were sourced from an unpublished Oxford Outcomes study (Wild et al. 2005) that was utilised in the NICE technology appraisal for Rituximab in

the first-line treatment of stage III-IV follicular lymphoma. Further details of the study were subsequently published in the accompanying technology assessment report by ScHARR. For QoL beyond fourth line, we followed the approach used by Prica et al. (2015) who assumed a deterioration of QoL in subsequent treatment lines and based utility values beyond second line on a cost-effectiveness analysis performed by Fagnoni et al. 200916 which was using data from the GOELAMS 072 study.

It should be noted that both, the Wild et al. (2005) and Fagnoni et al. (2009) studies have limitations. Wild et al. 2005 is unpublished and full details of the study are unavailable. Furthermore, the patient numbers are relatively small (particularly for the disease free health state) and in some cases it is not clear how values have been estimated. The GOELAMS 072 study was investigating ASCT as first-line treatment and did not produce QALYs as an outcome measure. For their economic evaluation, Fagnoni et al. 2009 weighted utility values from literature according to health state duration from the GOELAMS study which could introduce bias. However, as there is no better alternative data available, the use of this QoL data was thought to be appropriate. Both studies have also been used in previous economic evaluations making this analysis consistent with the existing economic literature. The effect of using alternative QoL values was explored in sensitivity analysis.

The model applies utility decrements for all three treatment options as well as for adverse events which were taken from literature (Table 13).

Table 13: Quality of life decrements

Event	Utility decrement	Source
R-chemotherapy	0.075	Hornberger et al. 2008†
Autologous transplantation	0.100	Hornberger et al. 2008†
Allogeneic transplantation	0.100	Hornberger et al. 2008†
Febrile neutropenia	0.018	ScHARR model (adverse event)
Acute GVHD	0.050	Assumption
Extensive chronic GVHD	0.100	Assumption

† Adapted to 1-year cycle length

Data availability for utility decrements was limited which led to some assumptions having to be made. Furthermore, the utility decrement values reported by Hornberger et al. (2008) were derived from utility registries and little is known about the methodology. While these limitations may introduce bias, it was considered important to account for the toxic effects of treatments and potentially severe adverse events in the model and uncertainty around the data was explored in sensitivity analysis.

A.4 Sensitivity analysis

Deterministic (one-way) and probabilistic sensitivity analyses were conducted to test the robustness of the results of the economic model.

A.4.1 One-way sensitivity analysis

Table 14 presents the range of parameter estimates applied to the comparison of autologous transplantation, allogeneic transplantation and R-chemotherapy during one-way sensitivity analysis.

Table 14: Parameter variation during one-way sensitivity analysis

Parameter varied	Low	High	Justification/source
Costs (£)			

Parameter varied	Low	High	Justification/source
R-chemotherapy	8,182.85	16,365.69	Varied number of R-CHOP cycles (4-8)
R-chemotherapy	11,932.05	14,212.38	Assumed R-CVP and R-bendamustine instead of R-CHOP
Autologous transplantation	16,359	34,000	NHS reference cost instead of tariff
Allogeneic transplantation	36,288	82,000	NHS reference cost instead of tariff
Utilities			
Utility of progression-free stage	0.8050	0.8800	No utility increase with increasing remission length assumed
Utility during subsequent treatment lines	0.5300	0.7363	Assumed no utility decrease with subsequent treatment lines
Utility after subsequent treatment lines	0.6180	0.8050	Assumed no utility decrease with subsequent treatment lines
Decrements associated treatment	0.00	0.20	No decrement and double decrements assumed for treatments
Decrements associated with adverse events	0.00	0.20	No decrement and double decrements assumed for adverse events
Rates			
HR to calculate R-Chemotherapy relapse rate	0.15	0.61	Upper and lower value of hazard ratio (Schouten et al., 2003)
Relapse rates	Uses values form Schouten et al. 2003 for chemotherapy and ASCT and HR from Robinson et al. 2013 for allo-HSCT (2.3) relapse rates		
Relapse rates transplantation	No staggering of transplantation relapse rate but use linear rate for ASCT (11.92% pa) and allo-HSCT (4.36% pa)		
R-Chemotherapy relapse rate	Staggering of R-chemotherapy relapse rate based on ASCT using HR=0.3 (Schouten et al. 2003) at each stage		
Relapse rates	Use relapse rate of first-line treatment throughout model horizon irrespective of subsequent treatments		
Risk increase in subsequent treatment lines	0%	20%	Assume no risk increase in subsequent treatment lines

A.4.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed to test the robustness of the modelling conclusions in the face of uncertainty surrounding the choice of modelling inputs. Parameter values were varied within a reasonable range in each of 10,000 runs and the results averaged across runs. Costs were sampled from gamma distributions, utilities from beta distributions and rates and probabilities from log normal or beta distributions. Due to the limitations of available data and the large number of parameters, the standard error of the mean was assumed to be 50% of the mean for all parameters where no uncertainty data (standard error, standard deviation, sample size, 95% confidence intervals) could be obtained.

A.5 Base case results

The model was run over a 35-year time horizon with total costs and QALYs estimated for each treatment strategy with future costs and benefits discounted at a rate of 3.5% per year as recommended by NICE.

The base case results of the analysis are presented in tables 15 and 16 below. It can be seen that, in comparison to R-chemotherapy, both autologous and allogeneic transplantation were found to be cost-effective with ICERs of £4,812 and £12,244 per QALY gained, respectively. Using dominance rank to ascertain the optimal strategy overall, it can be seen

that autologous transplantation is the most cost-effective strategy. Allogeneic transplantation was found to be slightly less effective with a substantially increased cost which means it is dominated by autologous transplantation as a first transplant option in second and third line.

Table 15: Base case cost-effectiveness results against common baseline (R-chemotherapy)

Treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
R-chemotherapy	£2,188,253,335	-	121,082.19	-	**-**
Autologous transplantation	£2,884,842,952	£696,589,617	265,849.28	144,767.09	**£4,812**
Allogeneic transplantation	£3,840,201,985	£1,651,948,650	256,004.00	134,921.81	**£12,244**

Table 16: Base case cost-effectiveness results using dominance rank

Treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
R-chemotherapy	£2,188,253,335	-	121,082.19	-	**-**
Autologous transplantation	£2,884,842,952	£696,589,617	265,849.28	144,767.09	**£4,812**
Allogeneic transplantation	£3,840,201,985	£955,359,033	256,004.00	-9,845.28	**Dominated**

A.6 Sensitivity analysis

A.6.1 Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in the Table 17 below.

Table 17: One-way sensitivity analysis results

Parameter change	Optimal strategy
Number of R-CHOP cycles = 4	ASCT
Number of R-CHOP cycles = 8	ASCT
R-chemotherapy is R-CVP	ASCT
R-chemotherapy is R-bendamustine	ASCT
Chemotherapy before transplant is R-CHOP	ASCT
NHS reference costs for transplantations	ASCT
No utility increase with increasing remission length	ASCT
No utility decrease with subsequent treatment lines	ASCT
No decrements assumed for treatments	ASCT
Double decrements assumed for treatments	ASCT
No decrements assumed for adverse events	ASCT
Double decrements assumed for adverse events	ASCT
Lower hazard ratio (0.15) for relapse rate of R-chemotherapy (79.5%)	ASCT
Upper hazard ratio (0.61) for relapse rate of R-chemotherapy (19.6%)	ASCT
Relapse rates form Schouten et al. 2003 used for chemotherapy (41.7%)	Allo-HSCT

Parameter change	Optimal strategy
and ASCT (21.26% - not staggered) and HR from Robinson et al. 2013 (2.3) for allo-HSCT (6.1% - not staggered) relapse rates	
No staggering of transplantation relapse rate but use linear rate for ASCT (11.92% pa) and allo-HSCT (4.36% pa)	Allo-HSCT
Staggering of R-chemotherapy relapse rate based on ASCT using HR=0.3 (Schouten et al. 2003) at each stage	ASCT
Use relapse rate of second-line treatment throughout model horizon irrespective of subsequent treatments	Allo-HSCT
Assume no risk increase in subsequent treatment lines	ASCT

It can be seen that the conclusion of the analysis is unchanged in most of the modelled scenarios i.e. autologous transplantation is the optimal strategy. In scenarios where relapse rates of ASCT are considerably higher compared to allo-HSCT the latter emerges as the optimal strategy being-cost-effective against both R-chemotherapy and ASCT.

Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values.

Tables 18 and 19 summarise the point estimate results of the probabilistic sensitivity analysis. The results of 10,000 runs of the probabilistic sensitivity analysis are shown using ICER scatterplot and a cost-effectiveness acceptability curve (CEAC) in Figures 3 and 4. The ICER scatter plot shows the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graph shows the probability of each diagnostic strategy being considered cost-effective at various cost-effectiveness thresholds.

Table 18: PSA cost-effectiveness results against common baseline (R-chemotherapy)

	Cost		QALYs		ICER (cost per QALY)
Treatment	Total	Incremental	Total	Incremental	
R-chemotherapy	£2,287,009,696	-	120,942.41	-	**-**
Autologous transplantation	£2,884,766,526	£597,756,830	267,995.87	147,053.46	**£4,067**
Allogeneic transplantation	£3,836,181,560	£1,549,171,864	259,692.45	138,750.03	**£11,169**

Table 19: PSA cost-effectiveness results using dominance rank

	Cost		QALYs		ICER (cost per QALY)
Treatment	Total	Incremental	Total	Incremental	
R-chemotherapy	£2,287,009,696	-	120,942.41	-	**-**
Autologous transplantation	£2,884,766,526	£597,756,830	267,995.87	147,053.46	**£4,067**
Allogeneic transplantation	£3,836,181,560	£951,415,034	259,692.45	-8,303.43	**Dominated**

Figure 3: ICER scatterplot of pairwise comparisons

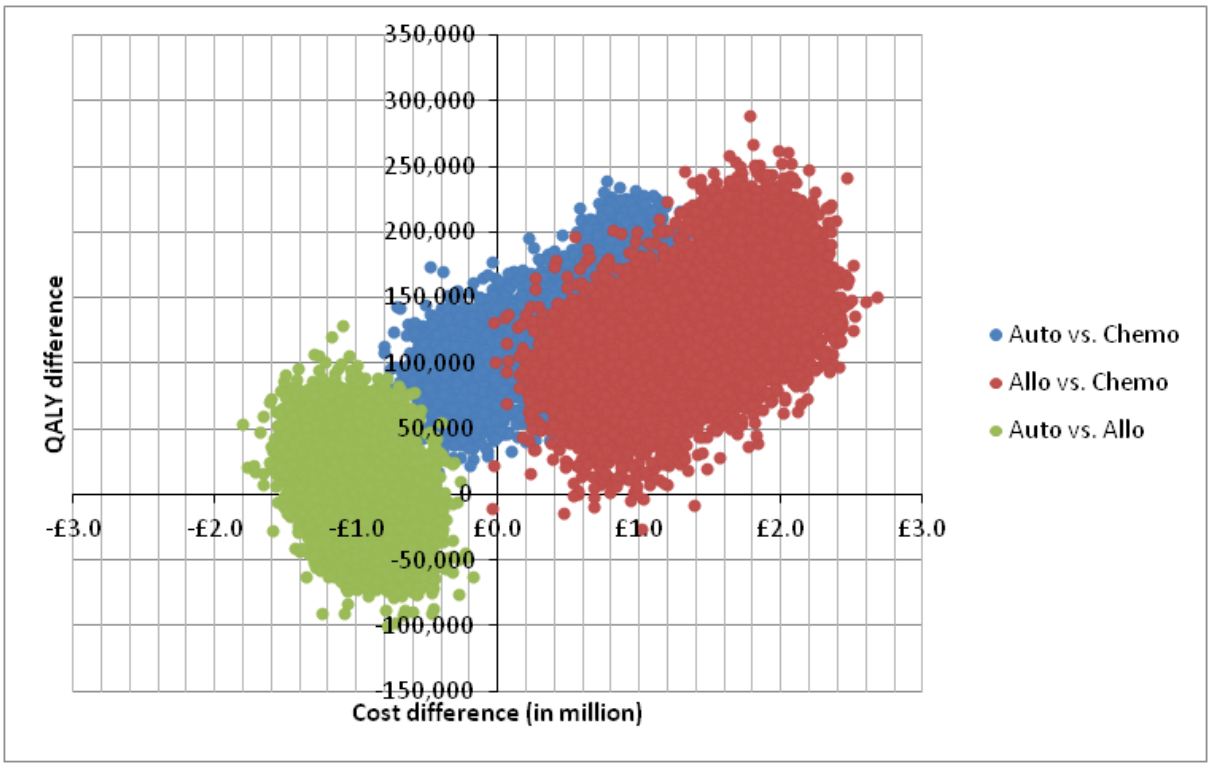


Figure 4: Cost-effectiveness acceptability curve (CEAC) of management strategies for relapsed follicular lymphoma

The ICER scatterplot depicted in Figure 3 shows the incremental cost-effectiveness of pairwise comparisons between the different treatment strategies. It can be seen that the

majority of the results for R-chemotherapy vs. allo-HSCT reside in the South West quadrant showing that R-chemotherapy was found to be less expensive but also less effective than allo-HSCT with most ICERs around £12,000 per QALY. For the comparison of allo-HSCT and ASCT, most results are located in the South East quadrant with allo-HSCT more expensive but less effective compared to ASCT (i.e. allo-HSCT is dominated). When comparing R-chemotherapy to ASCT, it can be seen that R-chemotherapy was found to be less expensive but less effective in some cases and more costly and less effective in other cases (i.e. R-chemotherapy is dominated).

In the CEAC presented in Figure 4 where all interventions are considered, it can be seen that, at a willingness to pay threshold of £20,000 per QALY, ASCT has a 94.8% probability of being cost-effective, while allo-HSCT has a 5.2% probability of being cost-effective and R-chemotherapy has 0% probability of being cost-effective.

A.7 Summary

The base case results suggest that both ASCT and allo-HSCT are cost-effective compared to R-chemotherapy with ICERs of £4,812 and £12,244, respectively. Allo-HSCT is more expensive and less effective compared to ASCT and is therefore dominated. Sensitivity analyses confirm these results. However, allo-HSCT does emerge as the optimal strategy in scenarios where ASCT relapse rates are increased compared to allo-HSCT. This result was also strengthened in the probabilistic sensitivity analysis where ASCT was found to be the optimal strategy in 94.8% of runs with allo-HSCT being the optimal strategy in the remaining 5.2% of runs. It can therefore be concluded that the economic evaluation provides robust evidence that ASCT is the most cost-effective treatment strategy for people with relapsed follicular lymphoma in second and third line. Furthermore, ASCT is the most cost-effective transplantation strategy at the point of first transplant. However, allo-HSCT can be cost-effective compared to ASCT in cases where ASCT is not expected to be successful.

A.8 Limitations of the analysis

While the model provides robust evidence for the cost-effectiveness of transplantation strategies for people with relapsed follicular lymphoma, the analysis is limited by the scarcity and quality of the available data used to populate the economic model.

Ideally, an indirect comparison would have been the method of choice to enable a comparison of allo-HSCT, ASCT and R-chemotherapy; however, due to the significant heterogeneity in the evidence, this was deemed unfeasible. Thus, the analysis focused on undertaking a pair-wise comparison (ASCT vs. R-Chemotherapy; ASCT vs. allo-HSCT; allo-HSCT vs. R-chemotherapy); with an additional analysis based on 3-way comparisons (ASCT vs. allo-HSCT vs. R Chemotherapy) based on the best available published pairwise comparisons and hazard and risk ratios.

Another challenge was the paucity of evidence regarding the length of remission time with no estimates available to provide robust and reliable estimates of the impact of length of remission on subsequent relapse and mortality rates. Thus, the analysis did not formally take into account the impact of previous length of remission on subsequent cancer outcomes. However, the impact of length of remission was indirectly taken into account by the staggering of relapse rates for ASCT and allo-HSCT (see above).

Due to the lack of available data, it was impossible to provide distinction between patients who achieved a CR or PR; thus, the model only distinguishes responders and non-responders in third line (all people are considered responders in second line at model entry) and relapse and mortality rates represent an average comprising both people achieving CR and PR.

Furthermore, lack of available data made it impossible to estimate the cost-effectiveness of ASCT and allo-HSCT in second and third line separately. The results therefore need to be interpreted with this in mind.

The model does not account for treatment discontinuation due to treatment toxicity. It is assumed that treatment discontinuation is incorporated in the non-responder rate which could underestimate this value.

The main data sources, Robinson et al. (2013) and Schouten et al. (2003), have limitations themselves. Especially, neither study reports UK specific data but is based on data from European centres. Robinson et al. (2013) is an observational study and gives little information about previous treatments and Schouten et al. (2003) reports data from the pre-rituximab era. Therefore, the data reported may not be entirely reflective of UK figures based on potential differences current clinical practice which could introduce bias. However, the GC was of the opinion that the data used in the model was reflecting UK practice to a satisfactory degree.

The model assumes that after relapse/progression and hence treatment failure, the benefits of the prior treatment are lost and patients continue through the model based on the benefits of the current treatment. This means that, for example, people who received ASCT in second line will transition through the model according to ASCT relapse rates until relapse but will change to allo-HSCT or R-chemotherapy relapse rate in third line depending on their third line treatment. This approach might introduce bias as the cumulative relapse incidence used to derive annual relapse probabilities would incorporate the possibility of several relapses and thus the relapse probability of subsequent treatments. However, it was considered by the GC that, based on the limitations of the data reported by Robinson et al. (2013) with a short median follow up of 60 months and a low number of events especially in the allo-HSCT arm (only 29 patients relapsed), this was the more intuitive and realistic approach. Sensitivity analysis was undertaken to estimate the effect of a constant relapse rate throughout the model horizon based on the rate of the initial treatment option on the results.

Febrile neutropenia was the only adverse event considered in the model (apart from graft versus host disease for allo-HSCT only). This approach was taken based on the GC's opinion that no other adverse event would cause significant costs to the NHS. Considering that treatment of adverse events up to 100 days following transplantation would be included in the tariff used in the base case, this omission will not affect the cost of transplantation but might slightly underestimate the cost of R-chemotherapy and at the same marginally overestimate the QALYs accumulated by all three treatments.

Due to the lack of comparative data (Schouten et al. 2003 does not report treatment-related mortality), TRM values for R-chemotherapy were taken from vanOers et al. (2006). While this has the potential to introduce bias, the GC considered the value to be a reasonable estimation.

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Appendix B: The role of immediate compared with deferred chemotherapy (watch and wait) in treating advanced asymptomatic follicular lymphoma

B.1 Background

Follicular lymphoma has a long natural history, the conventional view is that apart from very localised stage I disease, which may be ablated by local radiotherapy there is no advantage in terms of survival for immediate treatment compared to a watch and wait approach. This delays treatment until either the patient develops significant symptoms or there is risk of or actual dysfunction of a major organ system.

The evidence supporting this approach is based on data from the pre-rituximab era and there have been significant changes in the management of follicular lymphoma since then. In particular: immunochemotherapy achieves a higher number of responses and prolonged relapse free survival compared to chemotherapy alone; more intensive chemotherapy (CHOP) is more effective than previous approaches using oral chlorambucil or CVP; bendamustine is a new drug to the UK with high activity in follicular lymphoma which may now rival CHOP as the chemotherapy agent of choice; maintenance treatment continuing for two years beyond completion of immunochemotherapy further prolongs relapse free survival; a recent large trial of watch and wait compared to immediate immunotherapy with rituximab has found that twice as many patients in the watch and wait group required treatment after three years compared to those who received a short course of rituximab.

The availability of more effective treatment and the ability to identify those cases harbouring more aggressive lymphoma have led to uncertainty with regard to the role of a watch and wait approach. However it remains the case that 15-20% of patients may never need intervention over a period of 10-15 years for whom early chemotherapy would be unnecessary.

B.1.1 Aims

To estimate the cost-effectiveness of the following management strategies for people with advanced asymptomatic follicular lymphoma:

- Watchful waiting
- Rituximab induction
- Rituximab induction and maintenance

B.1.2 Existing Economic Evidence

A systematic literature review identified one paper that was deemed to be partially applicable to the current decision problem. Prica et al. (2015) was a Canadian study that assessed the cost-effectiveness of frontline rituximab monotherapy induction (with or without maintenance) versus a watch and wait approach for asymptomatic advanced stage follicular lymphoma.

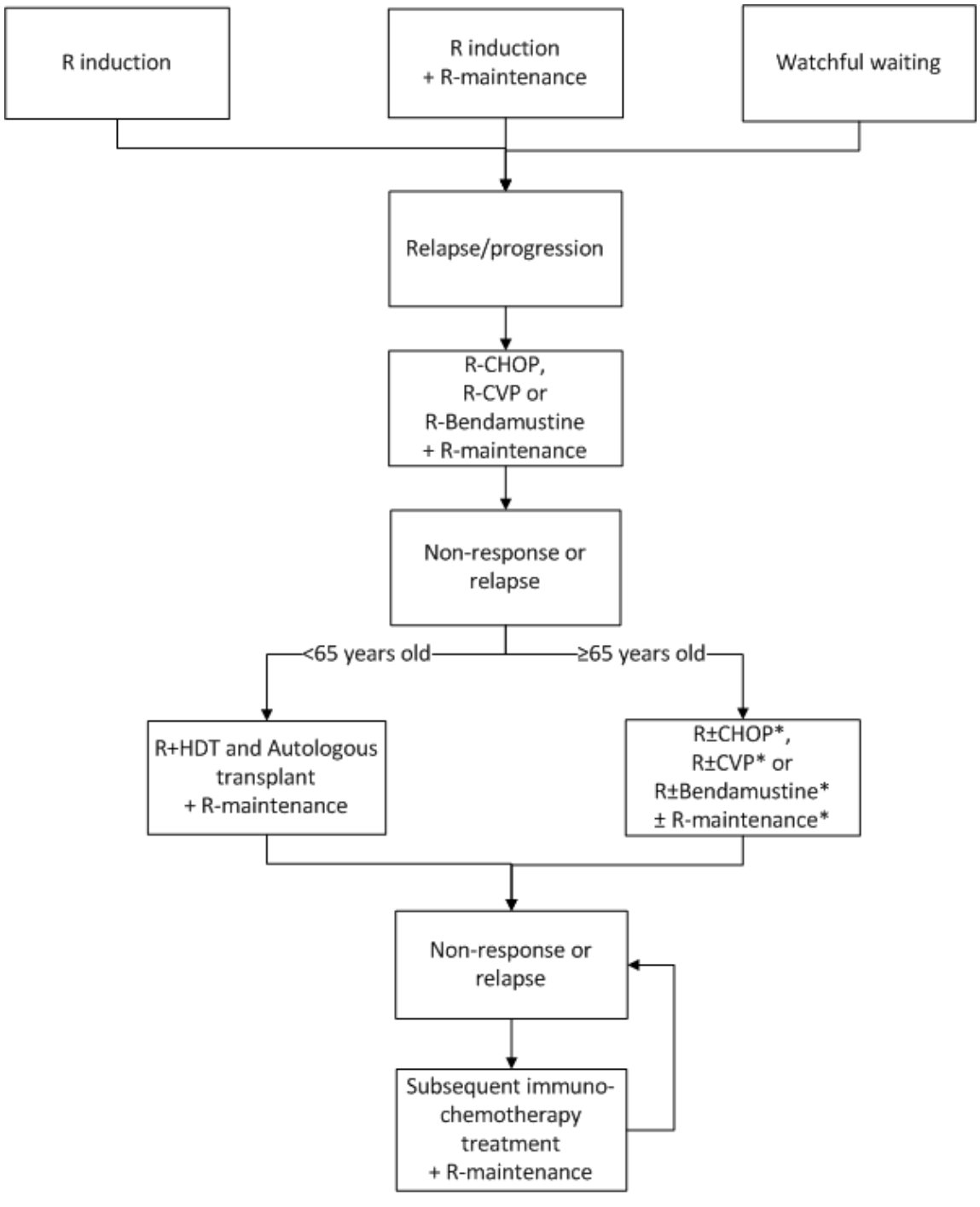
The results of the analysis showed that rituximab induction without maintenance was the preferred strategy. It was found to be both cheaper and more effective than watchful waiting (which was therefore dominated). Rituximab induction with maintenance was found to be marginally more effective than rituximab induction alone but also more costly and not cost-effective with an ICER of $62,350 per QALY.

While the analysis was thought to be of generally high quality, it was not deemed sufficient to address the decision problem in the UK context. .

B.2 De novo economic model

Since the current economic literature didn't adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. A Markov decision model was developed using Microsoft Excel. Figure 5 illustrates the modelled treatment pathway.

Figure 5: Modelled treatment pathway



Patients with asymptomatic follicular lymphoma enter the model at the point where a decision is being made between an active treatment (induction rituximab alone or rituximab induction and maintenance) and watchful waiting approach. Patients managed with the watchful waiting approach may eventually require treatment as a result of disease progression or patient preference. Likewise, patients initially treated with one of the rituximab treatment approaches may experience a relapse or disease progression at which point further treatment would be required.

For the purposes of the economic analysis, the further treatment received by patients at this point was termed “second line treatment” as either active treatment or watchful waiting were deemed to encompass “first line treatment”. Based on the advice of the guideline committee, patients were assumed to receive one of three immunochemotherapy regimens as second line treatment; R-CHOP, R-CVP or R-Bendamustine (in assumed equivalent proportions of 33% each). If induction immunochemotherapy was found to be successful then patients would receive rituximab maintenance.

If patients experience another relapse after second-line treatment, then they will receive a third treatment line which could be another chemotherapy regimen (an alternate regimen to that received as second line treatment) with or without rituximab (depending upon previous response) or an autologous transplantation. In the model, it was assumed that the latter option would only be given to patients <65 years old to reflect clinical practice whereby the procedure is only given to patients deemed fit enough to tolerate it. If the patient responded to treatment then patients would receive rituximab maintenance.

If patients experience a further relapse after third-line treatment or beyond, then it was assumed that they would receive another immunochemotherapy regimen. This reflects the guideline committee’s view that the vast majority of patients would be likely to receive an immunochemotherapy regimen at this point. It was assumed that patients may receive one of multiple immunochemotherapy regimens. This was inputted in the model as a ‘basket’ of eleven immunochemotherapy regimens (see cost section for more details) with rituximab maintenance.

Patients could also die from follicular lymphoma or other cause mortality at any point in the process.

B.2.1 Clinical data

B.2.1.1 Need for new treatment

The key clinical data utilised in the economic model was the number of patients receiving new treatment from Ardeshna et al. (2014). This outcome captures the number of patients in the watchful waiting arm that eventually require treatment or the number of patients initially treated with rituximab that require further treatment. The most likely reason for requiring treatment was disease relapse/progression but other reasons would also be captured in this measure including patient preference.

Ardeshna et al. (2014) reported that 54% of patients in the watchful waiting arm required new treatment after 3 years. The use of rituximab induction was shown to reduce the number of patients requiring new treatment with a HR of 0.35 [0.22-0.56] in comparison to watchful waiting (equating to 11% needing new treatment after 3 years). The use of rituxmab induction with maintenance was shown to further reduce the numbers of patients requiring new treatment with a HR of 0.21 [0.14-0.31] in comparison to watchful waiting (equating to 19% needing new treatment after 3 years).

For the purposes of the model, these values were converted to annual recurrence rates of 22.8%, 6.7% and 3.9% for the watchful waiting, rituximab induction and rituximab maintenance arms (assuming a constant rate of recurrence over the study period). In the

base case, these values were maintained over the time horizon of the model but variations in recurrences after 3 years were extensively explored in sensitivity analysis.

B.2.1.2 Subsequent relapse/progression rates

Patients may also experience a relapse/progression following subsequent lines of treatment. Subsequent progression rates were estimated from Salles et al. (2013), in which six-year progression free survival (59.2%) and overall survival data were presented for 505 follicular lymphoma patients treated with rituximab maintenance in the PRIMA trial. Based on the figures reported in Salles et al. (2013), it was estimated that there were 135 non-mortality related events over the six year period. This was converted to an annual recurrence estimate of 5.1%, which was applied for subsequent recurrences in the model.

Note that, for simplicity, a constant rate of relapse after subsequent treatments has been assumed in the model. While this approach is simplistic, it is also conservative, as progressively higher rates in subsequent treatment lines (which would effectively be the alternative approach) would favour initial treatment.

Another potential issue here is that the upfront use of rituximab may have consequences for the effectiveness of rituximab in subsequent lines (i.e. rituximab resistance). However, there is no evidence demonstrating such an effect (although longer-term follow-up from Ardeshna et al. (2014) may report data on this aspect). Due to the lack of evidence, in the base case, it has been assumed that there is no treatment resistance in subsequent lines.

Extensive sensitivity analysis has been performed on this subsequent relapse/progression rates utilised in the model (including the modelling of rituxmab resistance) to determine the overall influence of this aspect on the overall model result.

B.2.1.3 Disease related and other cause mortality

Ardeshna et al. (2014) reported no statistically significant difference in survival between the watchful waiting and rituximab arms. Therefore it has been assumed in the model that there is no difference in survival between the strategies.

Disease related mortality was captured in the model using combined data from the watchful waiting and rituximab arms from Ardeshna et al. (2014) (using data on cause of death reported in the supplementary appendix). The combined NHL related mortality rate over three years was 3.7%, this was converted to an annual estimate of 1.2% in the model (assuming a constant rate of mortality over the study period).

Note that, in order to maintain the survival equivalence reported in Ardeshna et al. (2014), disease-related mortality has been estimated independently of progression in the model (i.e. Linking progression and survival or assuming higher mortality in subsequent treatment lines would lead to a survival advantage to patients that are immediately treated).

Maintaining the conservative approach, treatment-related mortality was not considered in the base case analysis (the inclusion of such rates would favour active treatment upfront as these patients would be less likely to receive subsequent treatment). However, it was considered in sensitivity analysis.

Death from other causes was captured using 2011-2013 life tables for England and Wales from the office of national statistics (ONS). These life tables give an estimate of the annual probability of death given a person’s age and gender. A starting age of 60 and a male proportion of 46% were applied in the model based on averages from Ardeshna et al. (2014).

B.2.2 Costs

Modelled patients accrue costs associated with any treatment, monitoring or management strategy that they are undergoing. The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. These costs include drug costs, treatment costs and any other resource use that may be required (e.g. GP visit). Where possible, all costs were estimated in 2013-14 prices.

The majority of costs were sourced from NHS reference costs 2013/14 by applying tariffs associated with the appropriate HRG code. Drug costs were calculated using dose information from the British National Formulary (BNF) and unit costs from the Electronic Market Information Tool (eMit). Other costs were estimated using resource use and cost information from the Personal Social Services Research Unit (PSSRU) and the advice of the guideline committee.

B.2.2.1 Rituximab induction with and without maintenance

The drug costs of rituximab induction and maintenance were estimated using dosages and unit costs from the British National Formulary (BNF). The cost associated with delivering rituximab was estimated using cost codes associated with the delivery of chemotherapy at first attendance on an outpatient or day case basis (a weighted average of outpatient and day case costs was estimated using the number of procedures in NHS reference costs). The costs of rituximab induction and maintenance are shown in Table 20.

Table 20: Rituximab induction and maintenance costs

Treatment	Value	PSA distribution‡	Source
Proportion delivered as outpatient	20%	Beta (α = 20, β = 80)	NHS Reference costs 2013/14 – outpatient (SB14Z)*
Proportion delivered as a day case	80%	1-Beta (α = 20, β = 80). Remaining proportion estimated using PSA value above	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)*
Outpatient delivery cost	£265.85	Gamma (SE= 88.17, α =9, β = 29)	NHS Reference costs 2013/14 – outpatient (SB14Z)*
Day case delivery cost	£401.48	Gamma (SE= 161.26, α =6, β = 65)	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)*
Cost per dose (375 mg/m^2)†	£1,222.41	Gamma (SE= 906.16, α =2, β = 672)	British National Formulary (BNF)
Rituximab induction cost	**£6,388.85**		
Annual rituximab maintenance cost	**£9,583.28**		
*Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance			
† Based on average body surface area for cancer patients from Sacco et al. 2010 (1.91m^2 for males and 1.71m^2 for females)			
‡ PSA values for delivery costs were estimated using upper and lower estimates from NHS reference costs 2013/14. PSA values for proportions delivered as outpatient and day case were estimated by multiplying base case values by 100. In the absence of uncertainty data from the BNF, PSA values for Rituximab were based on upper and lower estimates of ± 50.			

B.2.2.2 Watchful waiting and follow-up costs

The only costs associated with watchful waiting are the costs of monitoring patients. Such costs would also be incurred in the active treatment arms as patients require regular follow-up after treatment in order to detect recurrences. Based on the advice of the guideline committee, it was assumed that the frequency and duration of monitoring as well as the investigations used would be the same in the watchful waiting and rituximab arms.

While there is likely to be some variation in clinical practice, the follow-up frequency reported in the BJH Guidance by McNamara et al. (2011) was thought to provide a good estimate of current UK practice and was therefore used in the economic model. The follow-up frequencies used in the economic model are shown in Table 21, note that they are inputted in the model as annual sessions (where a range of follow-up frequencies were reported, an average has been taken).

Table 21: Follow-up frequency and estimated annual number of sessions

Time	Follow-up frequency	Annual number of sessions	PSA distribution‡	Source
Year 1	3-monthly	4.00	Gamma (SE= 2.97, α =2, β = 2)	Frequency estimates based on BJH Guidance by McNamara et al. 2011
Years 2-5	4-6 monthly	2.47*	Gamma (SE= 1.83, α =2, β = 1)	
Year 6 and thereafter	Annual	1.00	Gamma (SE= 0.74, α =2, β = 1)	
‡PSA values estimated using upper and lower estimates of ± 50%				

It was assumed that, at each follow-up visit, the patient would undergo a physical examination and enquiry about symptoms as well as various tests; full blood count, full profile (U&E, LFT, Ca), serum IgG, IgA, IgM, electropheresis and lactate dehydrogenate. It was also assumed that patients would receive a CT scan if relapse/progression was suspected or to evaluate the response to treatment (e.g. to evaluate the response to rituximab at 12 months). The cost of follow-up investigations applied in the model are shown in Table 22.

Table 22: Follow-up costs

Follow-up item	Value	PSA distribution‡	Source
Cost per consultation (physical examination and enquiry about symptoms)	£156.41	Gamma (SE= 65.05, α =6, β = 27)	NHS reference costs 2013/14 - WF01A
Full blood count	£6.92	Gamma (SE= 5.13, α =2, β = 4)	ScHARR report, which sourced costs from Sheffield Teaching Hospital Trusts (2005-6). Inflated to 2015 prices
Full profile (U&E, LFT, Ca) cost	£18.85	Gamma (SE= 13.97, α =2, β = 10)	
Serum IgG, IgA, IgM and electropheresis cost	£27.67	Gamma (SE= 20.51, α =2, β = 15)	
Lactate dehydrogenate test cost	£13.99	Gamma (SE= 10.37, α =2, β = 8)	
CT scan if relapse/progression is suspected or to evaluate treatment response			
Cost of computerised Tomography Scan, more than three areas	£147.17	Gamma (SE= 51.35, α =8, β = 18)	NHS reference costs 2013/14 - RA14Z (Outpatient)
‡ PSA values for consultation and CT costs were estimated using upper and lower estimates from NHS reference costs 2013/14. PSA values for drug cost were estimated assuming upper and lower estimates of ± 50%.			

B.2.2.3 Second and third line treatment

As described in an earlier section above, patients will receive immunochemotherapy as second-line treatment and may receive autologous transplant (if they are less than 65 years old) or an alternative immunochemotherapy regimen as third line treatment.

B.2.2.4 Chemotherapy ± rituximab

Most patients experiencing a recurrence are likely to be treated with chemotherapy in combination with rituximab. Based on the advice of the guideline committee, it was assumed that patients would receive R-CHOP, R-Bendamustine or R-CVP. The costs associated with delivering chemotherapy were sourced from NHS Reference costs, with chemotherapy assumed to be delivered on an outpatient or day cases basis (a weighted average of outpatient and day case costs was estimated using the number of procedures in NHS reference costs). The unit costs of drugs were sourced from eMIT. Where eMIT costs were not available, BNF costs were used (Table 23).

Table 23: Chemotherapy ± rituximab costs (second and third line)

Chemotherapy cost element	Cost	PSA distribution‡	Source
Proportion delivered as outpatient	20%	Beta (α = 20, β = 80)	NHS Reference costs 2013/14 – outpatient (SB14Z)
Proportion delivered as a day case	80%	1-Beta (α = 20, β = 80). Remaining proportion estimated using PSA value above	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£265.85	Gamma (SE= 88.17, α =9, β = 29)	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient delivery of subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE= 265.61, α =1, β = 225)	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	Gamma (SE= 161.26, α =6, β = 65)	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	Gamma (SE= 137.17, α =6, β = 57)	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB15Z)
Rituximab			
375mg/m^2 Rituximab given as an IV on day 1 of each cycle†	£1,222.41	Gamma (SE= 906.16, α =2, β = 672)	British National Formulary (BNF)
R-CHOP			
Cyclophosphamide (750mg/m^2 IV day 1)†	£25.36	Gamma (SE=1.92, α =174, β =0)	Unit costs from eMIT.
Doxorubicin (50mg/m^2 IV day 1)†	£8.82	Gamma (SE=7.36, α =1, β =6)	Unit costs from eMIT.
Vincristine (1.4mg/m^2 IV day 1) †	£6.16	Gamma (SE=1.78, α =12, β =1)	Unit costs from eMIT.
Prednisone or prednisolone (100mg/m^2 days 1-5) †	£83.15	Gamma (SE=61.37, α =2, β 45=)	Prednisolone unit cost from Emit. Prednisone unit cost

Chemotherapy cost element	Cost	PSA distribution‡	Source
			from BNF.
CHOP cost per cycle	£823.30		
Total cost for 6 cycles of R-CHOP	£12,274.27		
R-CVP			
Cyclophosphamide (750mg/m^2 IV day 1)†	£25.36	Gamma (SE=1.92, α =174, β =0)	Unit costs from eMIT.
Vincristine (1.4mg/m^2 IV day 1)†	£6.16	Gamma (SE=1.78, α =12, β =1)	Unit costs from eMIT.
Prednisone or prednisolone (40mg/m^2 days 1-5)†	£34.94	Gamma (SE=25.76, α =2, β =19)	Prednisolone unit cost from eMIT. Prednisone unit cost from BNF.
CVP cost per cycle	£766.26		
Total cost for 6 cycles of R-CVP	£11,932.05		
R-Bendamustine			
Bendamustine cost for 2 doses (90mg/m^2 on days 1 and 2 of cycle)†	£446.51	Gamma (SE=330.99, α =2, β =245)	Unit costs from BNF. Dosages from Rummel et al. 2013
Bendamustine cost per cycle	£1,146.32		
Total cost for 6 cycles of R-Bendamustine	£14,212.38		
† Based on average body surface area for cancer patients from Sacco et al. 2010 (1.91m^2 for males and 1.71m^2 for females)			
‡ PSA values for delivery costs were estimated using upper and lower estimates from NHS reference costs 2013/14. PSA values for proportions delivered as outpatient and day case were estimated by multiplying base case values by 100. PSA values for drug costs sourced from eMIT were based on reported SDs. In the absence of uncertainty data from the BNF, PSA values for Rituximab and bendamustine were based on upper and lower estimates of ± 50.			

B.2.2.5 Autologous transplant

It was assumed that patients undergoing an autologous transplant would first receive three cycles of salvage chemotherapy. Numerous chemotherapy regimens are used for this purpose in clinical practice but the guideline committee thought that the most commonly used regimens were R-ESHAP, R-DHAP, R-GDP or R-ICE. Therefore, the average cost of these chemotherapy regimens was applied in the economic analysis (assuming an equivalent weighting for each option i.e. a crude average).

The costs associated with delivering chemotherapy were sourced from NHS Reference costs. Based on the advice of the guideline committee, it was assumed that R-ESHAP or R-DHAP would be delivered in an inpatient setting whereas R-GDP or R-ICE would be delivered in an outpatient or day case setting (using the same proportions as those used in the sections above). Following NHS Reference costs methodology the cost of inpatient chemotherapy was estimated using bed day costs (as there is no specific code for inpatient chemotherapy delivery). Therefore, inpatient chemotherapy costs were estimated using the average cost of an excess bed day in patients with malignant Lymphoma, including Hodgkin's and non-Hodgkin's (£348.88) multiplied by the number of days where chemotherapy is delivered.

The unit costs of drugs were sourced from Emit. Where eMIT costs were not available, BNF costs were used.

Table 24 shows the costs of the chemotherapy regimens used in the economic model.

Table 24: Autologous transplant costs

Chemotherapy cost element	Cost	PSA distribution‡	Source
Proportion delivered as outpatient	20%	Beta (α = 20, β = 80)	NHS Reference costs 2013/14 – outpatient (SB14Z)
Proportion delivered as a day case	80%	1-Beta (α = 20, β = 80). Remaining proportion estimated using PSA value above	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£265.85	Gamma (SE= 88.17, α =9, β = 29)	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient delivery of subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE= 265.61, α =1, β = 225)	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	Gamma (SE= 161.26, α =6, β = 65)	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	Gamma (SE= 137.17, α =6, β = 57)	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB15Z)
Inpatient chemotherapy delivery cost (per day)	£384.88	Gamma (SE= 148.49, α =7, β = 57)	NHS Reference costs 2013/14 - Weighted average cost of "Malignant Lymphoma, including Hodgkin's and non-Hodgkin's" (SA31) in elective Inpatients - Excess Bed Days
Rituximab			
375mg/m^2 Rituximab given as an IV on day 1 of each cycle, plus an additional dose (4 doses in total)	£1,222.41	Gamma (SE= 906.16, α =2, β = 672)	British National Formulary (BNF)
R-ESHAP (inpatient)			
4 doses of etoposide (40mg/m^2/day)†	£7.64	Gamma (SE= 2.99, α =7, β =1)	Unit costs from eMIT.
5 doses of methylprednisolone (500mg/day)	£23.30	Gamma (SE= 5.90, α =16, β =1)	Unit costs from eMIT.
1 dose cytarabine (2000mg/m^2)†	£40.25	Gamma (SE= 22.55, α =3, β =13)	Unit costs from eMIT.
3 doses of cisplatin (25mg/m^2/day)†	£35.25	Gamma (SE= 11.72, α =9, β =4)	Unit costs from eMIT.
6 doses of Corticosteroid eye drops e.g. Prednisolone 0.5%	£7.77	Gamma (SE= 5.76, α =2, β =4)	Unit costs from eMIT.
ESHAP cost per cycle	£2,038.58		
Total cost for 3 cycles of R-ESHAP	£11,380.19		
R-DHAP (inpatient)			
4 doses of dexamethasone (40mg)	£45.26	Gamma (SE=10.41, α =19, β =2)	Unit costs from eMIT.
2 doses of cytarabine (2g/m^2)†	£60.26	Gamma (SE= 46.96,	Unit costs from eMIT.

Chemotherapy cost element	Cost	PSA distribution‡	Source
		α =2, β =37)	
1 dose of cisplatin (100 mg/m^2 on day 3)†	£31.15	Gamma (SE= 14.53, α =5, β =7)	Unit costs from eMIT.
6 doses of Corticosteroid eye drops e.g. Prednisolone 0.5%	£7.77	Gamma (SE= 5.76, α =2, β =4)	Unit costs from eMIT.
DHAP cost per cycle	£1,299.06		
Total cost for 3 cycles of R-DHAP	£9,161.62		
R-GDP (outpatient)			
2 doses of gemcitabine (1000mg/m^2)†	£62.72	Gamma (SE= 47.69, α =2, β =36)	Unit costs from eMIT.
4 doses of dexamethasone (40 mg)	£45.26	Gamma (SE= 10.41, α = 19, β =2)	Unit costs from eMIT.
1 dose of cisplatin (75 mg/m^2)†	£25.34	Gamma (SE= 11.20, α = 5, β =5)	Unit costs from eMIT.
GDP cost per cycle	£833.13		
Total cost for 3 cycles of R-GDP	£7,763.82		
R-ICE (outpatient)			
1 dose of ifosfamide (5g/m^2)†	£624.98	Gamma (SE= 463.29, α =2, β =343)	Unit costs from BNF.
1 dose of Carboplatin AUC 5 (max 800mg)*	£21.74	Gamma (SE= 6.77, α =10, β =2)	Unit costs from eMIT.
3 doses of etoposide (100mg/m^2)†	£11.47	Gamma (SE= 4.49, α =7, β =2)	Unit costs from eMIT.
ICE cost per cycle	£1,357.99		
Total cost for 3 cycles of R-ICE	£9,338.43		
Average cost for chemotherapy regimens used before transplant	**£9,411.01**		
† Based on average body surface area for cancer patients from Sacco et al. (2010) (1.91m^2 for males and 1.71m^2 for females)			
* Carboplatin dose calculated using calvert formula: AUC 5 = 5*[GFR+25]. GFR calculated as: GFR = Gender (male = 1, females = 0.85) * [(140 - Age) / (SerumCreat)] * (Weight / 72). Average age and gender were that used in the model, while serum creatine and weight were based on a study by Craig et al. 2012			
‡ PSA values for delivery costs were estimated using upper and lower estimates from NHS reference costs 2013/14. PSA values for proportions delivered as outpatient and day case were estimated by multiplying base case values by 100. PSA values for drug costs sourced from eMIT were based on reported SDs. In the absence of uncertainty data from the BNF, PSA values for Rituximab, bendamustine and ifosfamide were based on upper and lower estimates of ± 50			

The cost of the autologous transplantation procedure was estimated to be £34,000 based upon the current tariff from NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplantation (tariff identified by transplanting haematologist on the guideline committee). It should be noted that an alternative value of £16,359 was available from NHS Reference costs but it was thought to be a considerable underestimate of the true cost and so was not used in the base case analysis. However, the impact of utilising the lower cost was explored in sensitivity analysis.

B.2.2.6 Subsequent immunochemotherapy treatment

As described in a previous section above, patients that experience a relapse after third-line treatment or beyond were assumed to receive further treatment with another immunochemotherapy regimen. The guideline committee provided a list of eleven

immunochemotherapy regimens that might be used in this setting; R-CHOP, R-CVP, R-Bendamustine, R-ESHAP, R-DHAP, R-GDP, R-ICE, R-GEMP, R-FC, R-GCVP OR R-Mini-BEAM. The average cost associated with this basket of regimens was estimated (assuming an equivalent proportion of each regimen was used i.e. a crude average) and applied for each subsequent relapse.

As above, the costs associated with delivering chemotherapy were sourced from NHS Reference costs, with different costs used depending on whether the regimen is delivered on an outpatient, day case or inpatient basis (using the same methodology as above). The unit costs of drugs were sourced from eMIT or the BNF (where eMIT costs were not available). However, in the case of carmustine, unit costs were not available from eMIT or the BNF. The guideline committee advised that this was due to a recent lack of availability of the drug, which is now only available through specialist importers. A pharmacy colleague of one of the guideline committee members provided the previous price paid for the drug (£358.80 for 100mg), which was utilised in the analysis. An alternative and much higher estimate was provided by the pharmacy colleague of another guideline committee member (£1,000 per 100mg), suggesting that there is considerable variability in the price of the drug. The alternative (higher) estimate was used in deterministic sensitivity analysis and in probabilistic sensitivity analysis, a wide uniform distribution between the guideline committee's lower (£200) and upper estimates (£1,000) was utilised.

The costs associated with each of the regimens as well as the overall average (£9,996) are shown in Table 25. Note that full cost details are not shown for chemotherapy regimens that have already been presented in previous sections (i.e. R-CHOP, R-CVP, R-Bendamustine, R-ESHAP, R-DHAP, R-GDP and R-ICE).

Table 25: Subsequent immunochemotherapy costs

Chemotherapy cost element	Cost	PSA distribution‡	Source
Proportion delivered as outpatient	20%	Beta (α = 20, β = 80)	NHS Reference costs 2013/14 – outpatient (SB14Z)
Proportion delivered as a day case	80%	1-Beta (α = 20, β = 80). Remaining proportion estimated using PSA value above	NHS Reference costs 2013/14 – Daycase and Regular Day/Night (SB14Z)
Outpatient delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£265.85	Gamma (SE= 88.17, α =9, β = 29)	NHS Reference costs 2013/14 – Outpatient (SB14Z)
Outpatient delivery of subsequent elements of a chemotherapy cycle	£313.80	Gamma (SE= 265.61, α =1, β = 225)	NHS Reference costs 2013/14 – Outpatient (SB15Z)
Day case delivery of complex chemotherapy, including prolonged infusional treatment, at first attendance	£401.48	Gamma (SE= 161.26, α =6, β = 65)	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB14Z)
Day case delivery of subsequent elements of a chemotherapy cycle	£327.75	Gamma (SE= 137.17, α =6, β = 57)	NHS Reference costs 2013/14 - Daycase and Regular Day/Night (SB15Z)
Inpatient chemotherapy delivery cost (per day)	£384.88	Gamma (SE= 148.49, α =7, β = 57)	NHS Reference costs 2013/14 - Weighted average cost of "Malignant Lymphoma, including Hodgkin's and non-

Chemotherapy cost element	Cost	PSA distribution‡	Source
			Hodgkin's" (SA31) in elective Inpatients - Excess Bed Days
Rituximab			
375mg/m^2 Rituximab given as an IV on day 1 of each cycle, plus additional doses where the number of cycles is less than 4 (4 doses in total)	£1,222.41	Gamma (SE= 906.16, α =2, β = 672)	Unit costs from eMIT.
R-CHOP (outpatient)			
Total cost for 6 cycles of R-CHOP	£12,274.27	See sections above for PSA and reference details	
R-CVP (outpatient)			
Total cost for 6 cycles of CVP	£11,932.05	See sections above for PSA and reference details	
R-Bendamustine (outpatient)			
Total cost for 6 cycles of R-Bendamustine	£14,212.38	See sections above for PSA and reference details	
R-ESHAP (inpatient)			
Total cost for 3 cycles of R-ESHAP	£11,380.19	See sections above for PSA and reference details	
R-DHAP (inpatient)			
Total cost for 3 cycles of R-DHAP	£9,161.62	See sections above for PSA and reference details	
R-GDP (outpatient)			
Total cost for 3 cycles of R-GDP	£7,763.82	See sections above for PSA and reference details	
R-ICE (outpatient)			
Total cost for 3 cycles of R-ICE	£9,338.43	See sections above for PSA and reference details	
R-GEMP (outpatient)			
Gemcitabine (1000mg/m^2 IV Day 1, 8, 15)†	£94.08	Gamma (SE= 71.53, α =2, β =54)	Unit costs from eMIT.
Cisplatin (100mg/m^2 IV Day 15)†	£34.51	Gamma (SE= 14.48, α =6, β =6)	Unit costs from eMIT.
Methylprednisolone (1000mg IV Days 1 to 5)	£40.85	Gamma (SE=10.25, α =16, β =3)	Unit costs from eMIT.
GEMP cost per cycle	£869.25		
Total cost for 4 cycles of R-GEMP	£8,366.64		
R-FC (outpatient)			
Fludarabine (30mg/m^2 per day for 3 days)†	£76.69	Gamma (SE=28.31, α =7, β =10)	Unit costs from eMIT.
Cyclophosphamide (300mg/m^2 per day for 3 days)†	£26.61	Gamma (SE=2.76, α =93, β =0)	Unit costs from eMIT.
FC cost per cycle	£803.11		
Total cost for 4 cycles of R-FC	£8,102.06		
R-GCVP (outpatient)			
Gemcitabine (1000mg/m^2 IV Days 1 and 8)†	£62.72	Gamma (SE=47.69, α =2, β =36)	Unit costs from eMIT.
Cyclophosphamide (750mg/m^2 IV	£25.36	Gamma (SE=1.92, α	Unit costs from eMIT.

Chemotherapy cost element	Cost	PSA distribution‡	Source
Day 1)†		=174, β =0)	
Vincristine (1.4mg/m^2 [max 2mg] IV Day 1)†	£6.16	Gamma (SE=1.78, α =12, β =1)	Unit costs from eMIT.
Prednisolone or prednisone (100mg Days 1 to 5 oral)	£83.15	Gamma (SE=61.64, α =2, β =46)	Unit costs from BNF.
GCVP cost per cycle	£877.20		
Total cost for 3 cycles of R-GCVP	£7,896.05		
R-Mini-BEAM (inpatient)			
BCNU carmustine (60 mg/m^2 IV Day 1)†	£358.80	Uniform (200,1000)	GC Correspondence
Cytarabine (100 mg/m^2 twice daily IV Days 2 to 5)†	£35.31	Gamma (SE=6.63, α =28, β =1)	Unit costs from eMIT.
Etoposide (75 mg/m^2 IV Days 2 to 5)†	£39.69	Gamma (SE=64.84, α =0, β =106)	Unit costs from eMIT.
Melphalan (30 mg/m^2 IV Day 6)†	£129.81	Gamma (SE=96.23, α =2, β =71)	Unit costs from BNF.
Total cost of R-Mini-BEAM inpatient	£2,872.87		
Total cost for 2 cycles of R-mini-BEAM inpatient	£11,384.98		
R-Mini-BEAM (outpatient)			
BCNU carmustine (60 mg/m^2 IV Day 1)†	£358.80	Uniform (200,1000)	GC Correspondence
Cytarabine (150 mg/m^2 twice daily IV Days 2 to 4)†	£39.73	Gamma (SE=64.84, α =0, β =106)	Unit costs from eMIT.
Etoposide (100 mg/m^2 IV Days 2 to 4)†	£21.39	Gamma (SE=28.42, α =1, β =38)	Unit costs from eMIT.
Melphalan (30 mg/m^2 IV Day 5)†	£129.81	Gamma (SE=96.23, α =2, β =71)	Unit costs from BNF.
Total cost of R-Mini-BEAM outpatient	£1,249.54		
Total cost for 2 cycles of R-mini-BEAM outpatient	£8,138.32		
Average cost for basket of immunochemotherapy regimens	**£9,995.90**		
† Based on average body surface area for cancer patients from Sacco et al. (2010) (1.91m^2 for males and 1.71m^2 for females)			
‡ PSA values for delivery costs were estimated using upper and lower estimates from NHS reference costs 2013/14. PSA values for proportions delivered as outpatient and day case were estimated by multiplying base case values by 100. PSA values for drug costs sourced from eMIT were based on reported SDs. In the absence of uncertainty data from the BNF, PSA values for Rituximab, bendamustine and ifosfamide were based on upper and lower estimates of ± 50. Carmustine cost was varied using a uniform distribution with upper and lower values based on GC correspondence.			

B.2.2.7 GCSF costs

Based on the advice of the guideline committee, it was assumed that granulocyte-colony stimulating factor (GCSF) would be used in 50% of patients receiving chemotherapy. The unit costs associated with GCSF agents (lenograstim or filgrastim, including biosimilars) were sourced from the BNF as unit costs were not available from eMIT (Tab;e 26). It was assumed that GCSFs would be administered for seven days based on guidelines for the use of GCSF from St Luke's Cancer Alliance.

Table 26: GCSF costs

GCSF cost element	Cost	PSA distribution‡	Source
Lenograstim 263mcg	£62.54	Gamma (SE=46.36, α =2, β =34)	Unit costs from BNF
Filgrastim† 300mcg	£55.78	Gamma (SE=41.35, α =2, β =31)	Unit costs from BNF
Number of days that GCSF is administered	7.00	Gamma (SE=5.19, α =2, β 4 =4)	Guidelines for the Use of G-CSF Following Chemotherapy. St Luke's Cancer Alliance, Royal Surrey County Hospital
Average GCSF cost	£414.10		Unit costs from eMIT.
†Average of Neupogen®, Nivestim®, Ratiograstim® and Zarzio®			
‡ PSA values estimated using upper and lower estimates of ± 50%.			

B.2.2.8 Palliative care costs

The cost of palliative care was estimated using estimates from a costing report by the Nuffield Trust (Georghiou et al. 2014, 'Exploring the cost of care at the end of life'). A cost of £7,287 was applied based on the average resource use of patients with cancer in the last three months of life (Table 27).

Table 27: Palliative care costs

Type of care	Average cost per cancer patient	PSA distribution‡	Source
Cost of all hospital contacts	£5,890	Gamma (SE =4366.20, alpha =2, beta =3237)	Exploring the cost of care at the end of life (Nuffield Trust, Georghiou 2014)
Local authority-funded care	£444	Gamma (SE =329.13, alpha =2, beta =244)	
District nursing care	£588	Gamma (SE =435.88, alpha =2, beta =323)	
GP contacts	£365	Gamma (SE =270.57, alpha =2, beta =201)	
Average palliative care cost per patient	**£7,287**		
‡ PSA values estimated using upper and lower estimates of ± 50%.			

It should be noted that this cost is generic to all cancers and is not specifically related to follicular lymphoma. However, in the absence of more robust data, it has been assumed that the costs in follicular lymphoma would not differ substantially. The influence of changing the cost of palliative care was explored in sensitivity analysis.

It should also be noted that the costs of local authority-funded care may be an overestimate of the true cost because the data may include some patients that have made private contributions to partly cover the cost of care. However, since this aspect only makes up a

small proportion of the overall average cost, the effect of this overestimate was thought to be negligible.

B.2.3 Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs) so that both the quantity and quality of life are taken into account. QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. For the purposes of this economic evaluation, the QoL data shown in Table 28 were utilised.

Table 28: Quality of life values applied in the economic model

Health state	Utility score	PSA distribution‡	Source
Asymptomatic follicular lymphoma	0.8800	Beta (α = 24, β = 3)	Unpublished data from Wild et al. 2005 for "disease free" patients from ScHARR
Symptomatic follicular lymphoma	0.8050	Beta (α = 106, β = 26)	Unpublished data from Wild et al. 2005 for "progression free" patients from ScHARR
Progressive disease	0.7363	Beta (α = 62, β = 22)	Unpublished data from Wild et al. 2005 for "disease progression" from ScHARR
‡ PSA values estimated using patient numbers from Wild et al. 2005.			

The QoL data were sourced from an unpublished Oxford Outcomes study (Wild et al. 2005) that was utilised in the NICE technology appraisal for Rituximab in the first-line treatment of stage III-IV follicular lymphoma. Further details of the study were subsequently published in the accompanying technology assessment report by ScHARR.

There was no suitable QoL data that was directly applicable to the asymptomatic follicular lymphoma health state. Therefore, it was assumed that the QoL value associated with this health state would be equivalent to ‘disease free’ patients from the Wild et al. 2005 study (utility value of 0.880 based on 27 patients).

The QoL values associated with symptomatic follicular lymphoma and progressive disease were estimated to be 0.8050 and 0.7363, respectively. This was based upon the Wild et al. (2005) QoL study, using the approach adopted in the ScHARR technology assessment report whereby aggregated utility values for a ‘progression free’ (n=84) and ‘disease progression’ (n=132) health state were used.

It should be noted that this study has limitations. Most notably, as the study is unpublished, full details of the study are unavailable. Furthermore, the patient numbers are relatively small (particularly for the disease free health state) and in some cases it is not clear how values have been estimated. However, as there is no better alternative data available, the use of this QoL data was thought to be appropriate. This study has also been used in numerous previous economic evaluations making this analysis consistent with the existing economic literature. The effect of using alternative QoL values was explored in sensitivity analysis.

Note that QoL decrements associated with treatment-related morbidity were not incorporated in the base case analysis. This was mostly because there was no high quality data available in this area. This was illustrated by previous economic studies in this area, which have generally relied upon author assumptions or estimates from clinicians. Under NICE methodology, these methods would not be preferable as QoL values should be based on estimations obtained directly from patients and ideally using the EQ-5D survey. In addition, there were also concerns that the QoL impact associated with treatment related morbidity may already be captured in the QoL data from Wild et al. 2005. Thus, if separate morbidity

decrements were to be applied then this could lead to double counting the QoL impact of morbidity decrements.

Particularly noteworthy is the assumption that first-line treatment with rituximab induction (± maintenance) does not have an associated QoL decrement (i.e. QoL value is equivalent to patients managed with watchful waiting). This assumption was based on the results of the QoL aspect of Ardeshna et al. (2014), which showed that overall there was no QoL detriment associated with rituximab (in comparison to watchful waiting). This assumption was tested in sensitivity analysis where a lower QoL was applied in patients receiving rituximab induction with and without maintenance.

B.2.4 Base Case Results

The model was run over a 40 year time horizon with total costs and QALYs estimated for each treatment strategy with future costs and benefits discounted at a rate of 3.5% per year as recommended by NICE.

The base case results of the analysis for are presented in Tables 29 and 30. It can be seen that, in comparison to watchful waiting, both rituximab induction and rituximab maintenance were found to be cost-effective and indeed dominant (i.e. more effective and cost saving). Using dominance rank to ascertain the optimal strategy overall, it can be seen that rituximab induction is the most cost-effective strategy with rituximab maintenance found to be more effective but at a substantially increased cost that means it's not cost-effective with an ICER of £69,406 well above the NICE threshold.

Table 29: Deterministic base case cost-effectiveness results against common baseline (watchful waiting)

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Watchful waiting	£48,147	-	10.98	-	-
Rituximab induction	£38,355	-£9,793	11.31	0.33	**Dominant**
Rituximab induction + maintenance	£47,969	-£179	11.45	0.47	**Dominant**

Table 30: Deterministic base case cost-effectiveness results using dominance rank

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Rituximab induction	£38,355		11.31		-
Rituximab induction + maintenance	£47,969	£9,614	11.45	0.14	**£69,406**
Watchful waiting	£48,147	£9,793	10.98	-0.33	**Dominated**

In addition to the deterministic results above, the base case results were also generated probabilistically. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis (sufficient for stability in the ICER). The probabilistic base case results are presented in Tables 31 and 32.

Table 31: Probabilistic base case cost-effectiveness results against common baseline (watchful waiting)

	Cost		QALYs		ICER (cost per QALY)
Initial treatment	Total	Incremental	Total	Incremental	
Watchful waiting	£47,568	-	10.37	-	-
Rituximab induction	£37,525	-£10,043	10.67	0.31	**Dominant**

Initial treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Watchful waiting	£47,568	-	10.37	-	-
Rituximab induction + maintenance	£47,178	-£390	10.80	0.43	**Dominant**

Table 32: Probabilistic base case cost-effectiveness results using dominance rank

Initial treatment	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Rituximab induction	£37,525	-	10.67	-	
Rituximab induction + maintenance	£47,178	£9,652	10.80	0.12	**£77,289**
Watchful waiting	£47,568	£10,043	10.37	-0.31	**Dominated**

It can be seen that the mean results of the probabilistic results do not differ substantially from the deterministic analysis. Both rituximab strategies were again found to be cheaper and more effective than the watchful waiting strategy. Using dominance rank, it can be seen that rituximab induction is the most cost-effective strategy with the addition of maintenance rituximab found to be more effective but at a substantially increased cost meaning that it was not found to be cost-effective with an ICER of £77,289, which is well above the NICE threshold.

B.2.5 Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in Table 33.

Table 33: One-way sensitivity analysis results

Change made	Optimal strategy
Lower hazard ratio (0.14) for starting new treatment after R-maintenance	**R-maintenance**
Upper hazard ratio (0.31) for starting new treatment after R-maintenance	R-induction
Lower hazard ratio (0.22) for starting new treatment after R-induction	R-induction
Upper hazard ratio (0.56) for starting new treatment after R-induction	**R-maintenance**
Average age = 50 years old	R-induction
Average age = 70 years old	R-induction
Subsequent relapse rates = 4.8% (rate after R-maintenance in first line)	R-induction
Subsequent relapse rates = 0%	R-induction
Time horizon = 3 years	R-induction
BCNU Carmustine cost = £1,000 per 100mg	R-induction
NHS Reference cost used for autologous transplant	R-induction
Subsequent treatment costs = £0	R-induction
Subsequent treatment costs + 50%	R-induction
Asymptomatic QoL value = progression free QoL value	R-induction
QoL on WW 0.01 higher than QoL with rituximab	R-Induction

Change made	Optimal strategy
QoL on WW 0.05 higher than QoL with rituximab	R-Induction
No differences in QoL values	R-Induction
R-resistance – (relapse rate 50% higher in subsequent lines after R in first line)	R-induction
R-resistance – (relapse rate 100% higher in subsequent lines after R in first line)	R-Induction

It can be seen that the conclusion of the analysis is unchanged in most modelled scenarios i.e. rituximab induction was found to be the optimal strategy in most analyses (at a threshold of £20,000 per QALY). The notable exceptions were the upper hazard ratio for starting new treatment after rituximab induction (making it less effective) and the lower hazard ratio for starting new treatment after rituximab induction plus maintenance (making it more effective). In these scenarios, it was found that rituximab maintenance became the optimal strategy as its relative effectiveness in comparison to rituximab induction was improved.

B.2.6 Threshold analysis

One of the distinguishing features of this analysis in comparison to previous economic evaluations of watchful waiting and active treatment in other disease areas, was that there was assumed to be no QoL benefit for patients on watchful waiting (in comparison to active treatment). While there is fairly strong evidence for this assumption from Ardeshna et al. 2014, it was thought to be an area worthy of further exploration.

Therefore, a threshold analysis was conducted to ascertain the QoL improvement required in patients on watchful waiting, over and above active treatment with a rituximab strategy, for watchful waiting to become cost-effective at a threshold of £20,000 per QALY.

It was found that watchful waiting becomes cost-effective when it was assumed that QoL is 0.105 lower for patients on receiving rituxiumab in comparison to watchful waiting strategies.

B.2.7 Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values.

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using ICER scatterplots and a cost-effectiveness acceptability curve (CEAC) in Figures 6, 7 and 8. The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

Figure 6: ICER scatteplot for rituximab induction in comparison to watchful waiting

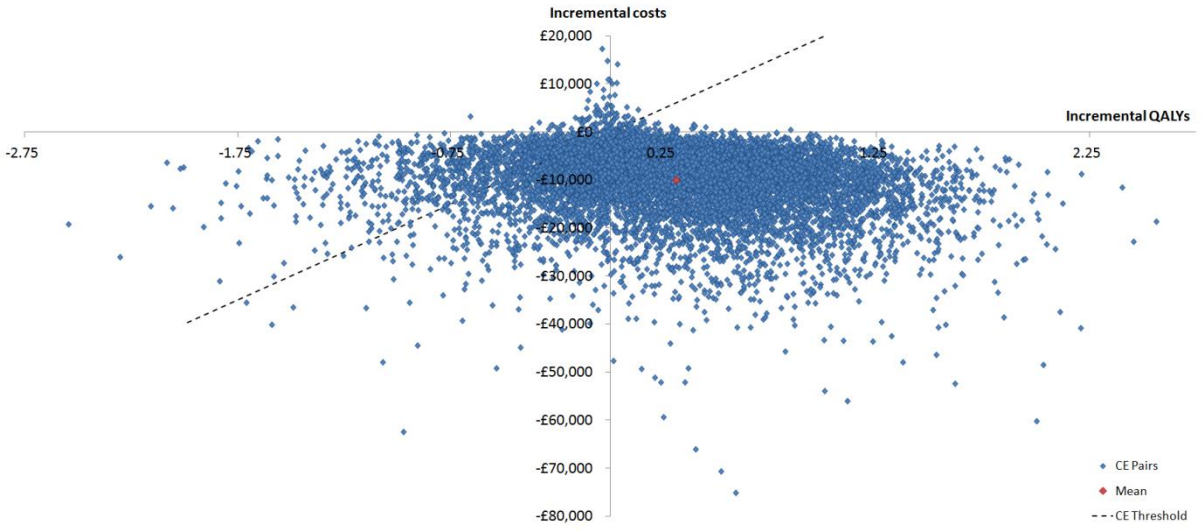


Figure 7: ICER scatteplot for rituximab induction in comparison to rituximab maintenance

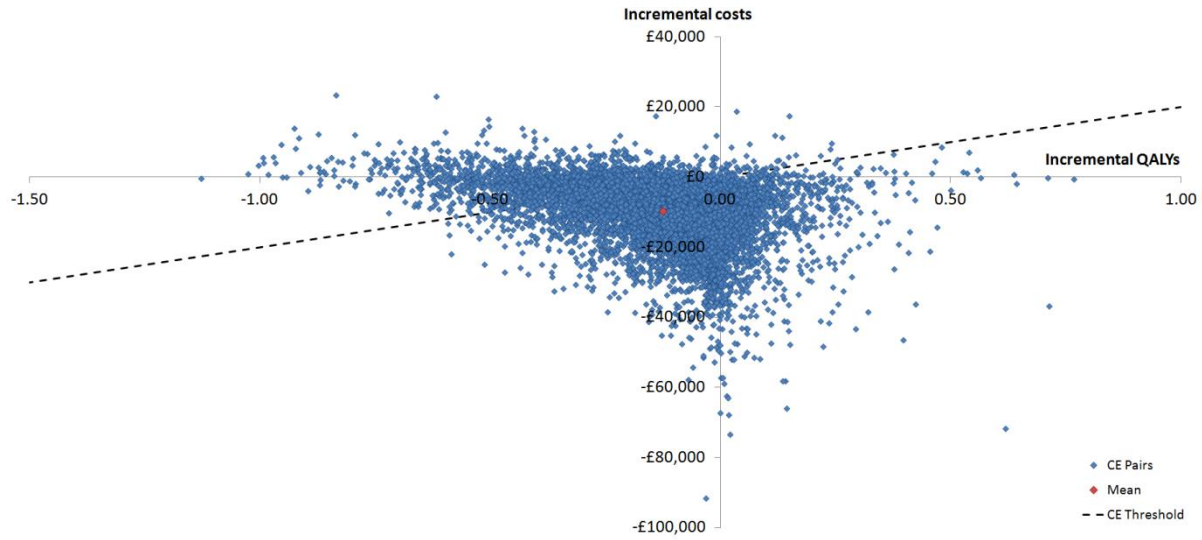
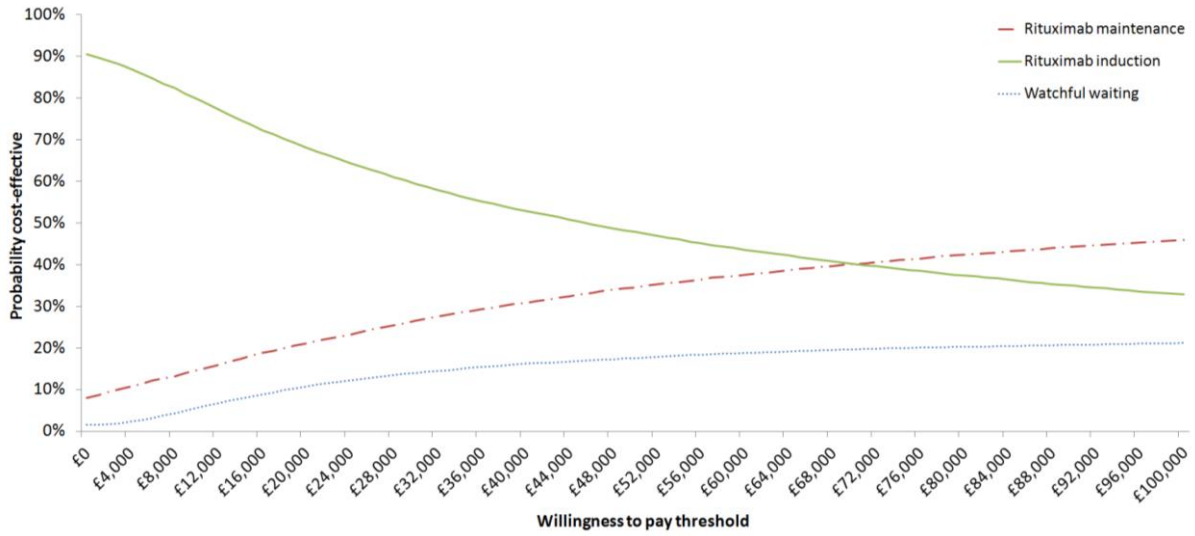


Figure 8: Cost-effectiveness acceptability curve (CEAC) for management strategies for asymptomatic follicular lymphoma



The ICER scatterplot depicted in Figure 6 shows the incremental cost-effectiveness pairs for a comparison between rituximab induction and watchful waiting. It can be seen that the majority of the results reside in the South East quadrant showing that rituximab induction was found to be more effective and less expensive than watchful waiting (i.e. rituximab induction is dominant). It can also be seen that the majority of the cost-effectiveness pairs reside below the cost-effectiveness threshold line (£20,000 per QALY) meaning that in the majority of cases, rituximab induction was found to be cost-effective.

The ICER scatterplot depicted in Figure 7 shows the incremental cost-effectiveness pairs for a comparison between rituximab induction and rituximab maintenance. It can be seen that the majority of the results reside in the South West quadrant showing that rituximab induction was found to be less effective and less expensive than watchful waiting. It can also be seen that the majority of the cost-effectiveness pairs reside below the cost-effectiveness threshold line (£20,000 per QALY) meaning that in the majority of cases, rituximab induction was found to be cost-effective.

In the CEAC presented in Figure 8 where all interventions are considered, it can be seen that, at a willingness to pay threshold of £20,000 per QALY, rituximab induction has a 68% probability of being cost-effective, while rituximab maintenance has a 21% probability of being cost-effective and watchful waiting has 11% probability of being cost-effective.

B.2.8 Discussion

This analysis aimed to estimate the cost-effectiveness of management strategies for patients with newly diagnosed asymptomatic advanced (stage II-IV) follicular lymphoma. In particular, whether an active treatment strategy with rituximab should be adopted or a watchful waiting approach. To our knowledge, this is the first model that has investigated these treatment approaches in the UK context. One previous analysis (Prica et al. 2015) was identified that conducted a similar analysis but this analysis considered the Canadian health care system and was therefore not directly applicable to the UK context.

The results of the base case analysis suggest that using an active treatment strategy with rituximab induction ± maintenance is cost-effective in comparison to a watchful waiting approach. Indeed, the results suggest that these strategies would be cost saving as well as more effective (i.e. dominant). Rituximab induction alone was found to be the preferred strategy overall. It was found that the addition of rituximab maintenance to rituximab induction was not cost-effective as the marginally greater effectiveness with the strategy

(0.12 QALYs) was not enough to justify its higher cost (£9,652). This is reflected in the ICER value of ICER of £69,406 per QALY in comparison to rituximab induction alone, which is well above the NICE cost-effectiveness threshold of £20,000 per QALY.

In the deterministic sensitivity analysis, these findings were found to be robust with the conclusion of the analysis remaining unchanged in the vast majority of modelled scenarios. Furthermore, in probabilistic sensitivity analysis, rituximab induction was found to have the highest probability of being cost-effective (68%) at the £20,000 per QALY threshold.

There were a few limitations to the analysis that should be noted. As with most economic analyses, the analysis is, to a large extent, dependent on the clinical data upon which it is based. While a systematic review was undertaken to ensure that the model inputs reflect the best clinical evidence currently available, the evidence base was found to have limitations. The key clinical study utilised in the analysis was the study by Ardeshna et al. (2014) and while the study was a randomised trial, it was adjudged to be of very low quality in the appraisal for this guideline (using GRADE methodology). This was primarily because it was an open label study and the number of events was low (see clinical evidence review for more details). As such, the clinical evidence identified in both disease groups was considered to be of very low quality in the appraisal for this guideline. Therefore, there is a clear need for higher quality evidence in this area.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The key QoL values applied in this model were sourced from an unpublished QoL study by Wild et al. 2005. As mentioned in the previous section on QoL, there were limitations with this study. Most notably, since the study was unpublished, it was difficult to fully appraise its quality. However, while there is uncertainty around the veracity of the QoL inputs, it should be noted that the quantity of QALY benefits was not found to be a crucial determinant of the model result. The key QoL aspect of the model relates to the reduction in QoL associated with relapses and progression that would necessitate treatments that carry a QoL burden (e.g. immunochemotherapy or autologous transplant). However, in terms of the comparison between the rituximab strategies and the watchful waiting approach, it is merely the direction of this effect that is important not that the magnitude.

A further limitation is the uncertainty around treatment in subsequent therapy lines. For simplicity and practicality, it has been assumed in the model that patients receive a maximum of five treatment lines. In reality, some patients may receive more than this. Furthermore, the treatment received in lines four and five was assumed to be an average of commonly used immunochemotherapy regimens. Some patients may receive alternative immunochemotherapy regimens or another form of treatment (such as further transplants or radiotherapy). However, the guideline committee felt that the modelled pathway was representative of the most likely pathway followed by patients (with an estimated 90% of patients treated using immunochemotherapy in subsequent treatment lines). Furthermore, this aspect of the model was not found to be very influential on the conclusions of the analysis (even when subsequent treatment costs were set to zero, rituximab was still found to be cost-effective).

B.2.9 Conclusion

The results of the base case analysis suggest that rituximab induction alone is the optimal strategy to adopt in patients with asymptomatic follicular lymphoma. This result was shown to be robust in one-way sensitivity analysis, where rituximab induction remained cost-effective in the vast majority of scenarios. The result was further strengthened in probabilistic sensitivity analysis (PSA) where the strategy was found to have a 68% probability of being cost-effective at a threshold of £20,000 per QALY. Furthermore, rituximab maintenance was shown to have the next highest probability of being cost-effective with a 21% probability of being cost-effective at the £20,000 per QALY threshold, suggesting that there is a strong

case for active treatment (i.e. 89% probability of active treatment being cost-effective) rather than a watchful waiting approach

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Appendix C: Abbreviations

ABC	Activated B-cell
AITL	Angioimmunoblastic T-cell lymphoma
non-ALCL	Non-anaplastic large cell lymphoma
ASCT	Autologous stem cell transplantation
BCL2	B-cell lymphoma 2
BL	Burkitt's lymphoma
BNF	British National Formulary
Ca	Cancer antigen
CEAC	Cost effectiveness acceptability curve
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisolone
CHVPi	Cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α
CNS	Central nervous system
CT	Computed Tomogrpahy
CVP	Cyclophosphamide, vincristine and prednisolone
DA-EPOCH-R	Rituximab, etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin
DFS	Disease free survival
DLBCL	Diffuse large B-cell lymphoma
DNA	Deoxyribonucleic acid
EFS	Event-free survival
FDG	Flurodeoxyglucose
FDG-PET	Flurodeoxyglucose Positron Emission Tomography
FISH	Fluorescence in situ hybridisation
FL	Follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
GC	Guideline Committee
GCSF	Granulocyte-colony stimulating factor
GEP	Gene expression profiling
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GVHD	Graft versus host disease
Gy	Gray
alloHCT	Allogeneic transplantation
HDCT	High dose chemotherapy
HIV	Human Immunodeficiency Virus
HMRN	Haematological Malignancies Research Network
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health related quality of life
autoHCT	Autologous transplantation
ICER	Incremental cost-effectiveness ratio

IHC	Immunohistochemistry
IHC-FISH	Immunohistochemistry - fluorescence in situ hybridisation
IPI	International Prognostic Index
LDH	Lactate dehydrogenase
LFT	Liver function test
MALT	Mucosal associated lymphoid tissue
MCP	Mitoxantrone, chlorambucil and prednisolone
eMIT	Electronic Market Information Tool
MCL	Mantle cell lymphoma
MIPI-B	Mantle cell lymphoma international prognostic index-biological
MZL	Marginal zone lymphoma
NCAT	National Cancer Action Team
NHL	Non-Hodgkin's lymphomaActiv
NHS	National Health Service
NPV	Negative predictive value
NRM	Non-relapsed mortality
ONS	Office of National Statistics
OS	Overall survival
PCR	Polymerase chain reaction
PET-CT	Positron Emission Tomography – Computed Tomogrpahy
PFS	Progression free survival
PICO	Population, Intervention, Comparison, Outcome
PMBCL	Primary mediastinal B-cell lymphoma
PPV	Positive predictive value
PSA	Probability sensitivity analysis
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma not otherwise specified
QALY	Quality adjusted life year
QOL	Quality of life
QUADAS2	Quality Assessment of Diagnostic Accuracy Studies 2
R-BFM	Rituximab plus Berlin–Frankfurt–Münster regimen
R-CHEOP	Rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine and prednisolone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
R-CODOX-M	Rituximab, cyclophosphamide, doxorubicin, vincristine, cytarabine and methotrexate
RCT	Randomised control trial
R-GDP	Rituximab, gemcitabine, dexamethasone and cisplatin
R-HyperCVAD (HDMTX)	Rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone, (methotrexate and cytarabine)

R-LMB	Rituximab plus Lymphome Malin B regimen
RNA	Ribonucleic acid
allo-SCT	Allogeneic stem cell transplant
auto-SCT	Autologous stem cell transplant
SEER	Surveillance, Epidemiology and End Results
TBI	Total body irradiation
TRM	Treatment related mortality
U&E	Urea and electrolytes
WHO	World Health Organisation

Appendix D: Glossary

Allogeneic stem cell transplantation (AlloSCT)

A complex procedure involving administration of high-dose cytotoxic therapy (chemotherapy with or without radiotherapy) followed by transplant of peripheral blood or bone marrow stem cells (and rarely cord blood) from a sibling or unrelated donor. This is usually followed by immunosuppression.

Asymptomatic

Without obvious signs or symptoms of disease. Cancer may cause symptoms and warning signs, but, especially in its early stages, cancer may develop and grow without producing any symptoms.

Autologous stem cell transplantation (ASCT)

A procedure involving administration of high-dose chemotherapy followed by transplant of peripheral blood or bone marrow stem cells previously harvested from the patient

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis or inform the choice of treatment of a disease.

Blood and marrow transplantation (BMT)

Another term for allogeneic and autologous HSCT. The term 'Bone Marrow Transplantation' is now obsolete as most transplants use haematopoietic stem cells collected from peripheral blood as opposed to bone marrow.

Chemotherapy

The use of medication (drugs) that is toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Cohort studies

Research studies in which groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it, or patients within the cohort are compared with each other.

Computed tomography (CT)

Imaging technique in which the person lies on a table within a x-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3-D views.

Cost effectiveness analysis

A type of economic evaluation that compares the costs and benefits of different treatments. In cost-effectiveness analysis benefits are measured in clinical outcome units, for example, additional heart attack prevented, life years gained, etc. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio.

False negative

An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.

False positive

An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease

Fluorescence in situ hybridisation (FISH)

A molecular test carried out on biopsy or cytology samples to show whether extra or abnormal copies of specific genes or genetic material are present or absent.

GRADE

The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Graft versus host disease (GVHD)

A common complication following an allogeneic stem cell transplant. Immune white blood cells in the transplant (graft) recognize the recipient (the host) as "foreign." The transplanted immune cells then attack the host's body cells.

Granulocyte Colony Stimulating Factor (GCSF)

A type of protein that stimulates the bone marrow to make white blood cells (granulocytes).

Health economics

The study of the allocation of scarce resources among alternative health care treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.

High dose therapy

Previous term used interchangeably with Bone Marrow Transplantation. Now both terms have been replaced with either Haematopoietic Stem Cell Transplantation (HSCT) and Blood and Marrow Transplantation (BMT) in order to reflect current clinical and scientific practice.

High grade lymphomas

Faster growing, clinically aggressive lymphomas.

Immunohistochemistry

The process of detecting antigens (e.g., proteins) in the cells of a tissue section, by using antibodies binding specifically to antigens in biological tissues.

Immunophenotyping

A technique used to study the protein expressed by cells. It is usually done on liquid specimens and involves the labelling of white blood cells with antibodies directed against surface proteins on their membrane. The labelled cells are processed in a flow cytometer, a

laser-based instrument capable of analyzing thousands of cells per second. The whole procedure can be performed on cells from the blood, bone marrow or spinal fluid in a matter of a few hours.

Indolent lymphomas

Lymphomas that grow and spread slowly (also called low grade lymphomas).

Induction chemotherapy

The first phase of chemotherapy treatment designed to induce remission.

Lymph nodes or glands

Small bean-shaped organs located along the lymphatic system. Nodes filter bacteria or cancer cells that might spread through the lymphatic system and to other parts of the body.

Magnetic resonance imaging (MRI)

A type of scan which uses a magnetic field and radio waves to produce images of sections of the body.

Meta analysis

Results from a collection of independent studies (investigating the same issue) are pooled, using statistical techniques to synthesise their findings into a single estimate of an effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to pool statistically results in this way.

Morbidity

Detrimental effects on health.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1,000, 10,000 or 100,000 people.

Multi disciplinary team (MDT)

A team with members from different health care professions and specialties (e.g. urology, oncology, pathology, radiology, nursing). Cancer care in the NHS uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.

Myelodysplasia

Another term for Myelodysplastic Syndrome.

Myelodysplastic syndromes (MDS)

A group of diseases in which the bone marrow functions abnormally and fails to produce enough normal blood cells. It may progress to acute myeloid leukaemia. Sometimes referred to as myelodysplasia.

Neuropathy

Damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

Neutropenia

An abnormally low number of neutrophils, the most important type of white blood cell to fight off bacterial infections.

Non-Hodgkin's lymphoma (NHL)

Any cancer of lymphocytes other than Hodgkin lymphoma. There are two main groups – high grade which are aggressive and fast growing and low grade which are slow growing (also known as indolent lymphomas). High grade lymphomas include: diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma, Burkitt lymphoma, and AIDS-related lymphoma. Low grade or indolent lymphomas include: follicular lymphomas, mantle cell lymphoma, lymphoplasmacytic lymphoma and marginal zone lymphomas. Extra-nodal lymphomas are those that develop outside lymph nodes such as those affecting the skin or intestine.

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Platelets

The small blood cells involved in stopping bleeding

Polymerase chain reaction techniques

A technology in molecular biology used to amplify a single copy or a few copies of a piece of DNA, generating thousands to millions of copies of a particular DNA sequence.

Positron emission tomography CT (PET-CT)

A medical imaging technique using a device which combines a positron emission tomography (PET) scanner (which utilises a radioactive tracer to show functional activity) with an x-ray computed tomography (CT) scanner. Images acquired from both devices can be taken sequentially, in the same session, and combined into a single superposed image.

Prevalence

The proportion of a population found to have a condition

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Specific characteristics of a cancer or the person who has it which might affect the patient's prognosis.

Prospective study

A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen.

Psychosocial support

A general term for any non-therapeutic intervention that helps a person cope with stressors in the home or at work.

Qualitative research

Research in which the outcomes are usually recorded in words, rather than with numbers. Often used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)

A measure of health outcome, which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0-1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research

Research which uses numerical measurement techniques (e.g. measuring survival times after treatment).

Radiotherapy

The use of radiation, usually high energy x-rays to control the growth of cancer cells.

Randomised controlled trial (RCT)

An experimental clinical trial (study) investigating the effectiveness of different treatments in which participants are assigned at random to different groups which receive the intervention being assessed or a 'control' treatment. RCTs give the most reliable (i.e. least biased) form of evidence on clinical effectiveness.

Relapse

Where cancer starts to grow again after treatment.

Remission

A period when cancer has responded to treatment and there are no signs of cancer or cancer-related symptoms. In haematological cancers, there are specific criteria for remission depending on the condition, depending on blood and bone marrow and/or radiological assessments.

Sensitivity

In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all

those who get a negative test result do not have the disease. To judge fully the accuracy of a test, its Specificity must also be considered.

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other setting. The analysis is repeated using different assumptions to examine the effect on the results.

Specificity

In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To judge fully the accuracy of a test, its Sensitivity must also be considered.

Survival

Survival is the time alive after diagnosis of a disease

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Appendix E: Guideline Scope

E.1 Guideline title

Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma

E.1.1 Short title

Non-Hodgkin's lymphoma

E.2 The remit

The Department of Health has asked NICE: 'to develop a guideline on the diagnosis and management of non-Hodgkin's lymphoma'.

E.3 Need for the guideline

E.3.1 Epidemiology

- Non-Hodgkin's lymphomas are a diverse group of conditions that are categorised according to the cell type affected (B cell or T cell), as well as the clinical features and rate of progression of the disease. Most people with a diagnosis of non-Hodgkin's lymphoma (approximately 90%) have a B-cell lymphoma. The most common B-cell lymphomas are diffuse large B-cell and follicular lymphoma. Other less common types of B-cell lymphoma include mantle cell lymphoma, MALT lymphoma and Burkitt's lymphoma.
- According to data published by Cancer Research UK (CRUK), non-Hodgkin's lymphoma accounts for 4% of cancers in men and women in the UK, with 12,180 new cases and 4436 deaths recorded in 2010. The incidence of non-Hodgkin's lymphoma increases with age. It is the fourth most commonly diagnosed cancer in adults aged 25–49 years and the fifth most commonly diagnosed cancer in adults aged 50–74 years. The incidence rises sharply in people over 50 years and more than 70% of all cases of non-Hodgkin's lymphoma are diagnosed in people over 60 years.
- The age-standardised relative survival rates for non-Hodgkin's lymphoma (all subtypes combined) in England over the period 2005–2009 show that 76% of men are expected to survive for at least 1 year, with 61% surviving 5 years or more. The survival rates for women are slightly higher, with 79% expected to survive for 1 year or more and 66% surviving for at least 5 years.
- Data from HMRN (Haematological Malignancy Research Network) show that 1-year survival rates are significantly higher for follicular lymphoma (96%) than for diffuse large B-cell lymphoma (65%) and mantle cell lymphoma (71%). Five-year survival rates follow a similar pattern, with rates significantly higher for follicular lymphoma (87%) and significantly lower for mantle cell lymphoma (27%) compared with the other lymphoma subtypes.
- Relative survival for non-Hodgkin's lymphoma is improving. In men, 1- and 5-year age-standardised relative survival rates (all subtypes combined) in England increased by 26 and 34% respectively between 1971–1975 and 2005–2009. In women, 1- and 5-year age-standardised relative survival rates increased by 27 and 34% during the same time period.
- Using HMRN data for 2004–2011, it is estimated that 48% of all non-Hodgkin's lymphoma cases diagnosed in the UK are diffuse large B-cell lymphoma. This is an aggressive cancer that needs immediate treatment. The aim of treatment in most patients is a complete remission and cure.

- Follicular lymphoma is the second most common type of non-Hodgkin's lymphoma (19%). It frequently demonstrates an indolent behaviour and responds to initial therapy, but has a tendency to relapse after treatment.
- MALT lymphoma is the third most common type of non-Hodgkin's lymphoma with a median age at presentation of 61 years. The stomach is the most frequently involved organ, and in many cases there is a strong association between gastric MALT lymphoma and chronic Helicobacter pylori infection. Other sites that may be involved include the salivary glands, eyes, lung, intestinal tract, skin and thyroid gland. It is generally regarded as an indolent or low-grade lymphoma, but high-grade histological transformation can occur.
- Mantle cell lymphoma accounts for less than 10% of all non-Hodgkin's lymphoma and is characterised by the chromosomal translocation t(11;14)(q13:32). This results in over-expression of the cell cycle regulator protein cyclin D1. The median age at onset is 60–65 years. Mantle cell lymphoma has an unusual clinical phenotype because it is an aggressive cancer in most patients, but a few patients will be cured with chemo-immunotherapy regimens used for aggressive lymphomas.

E.3.2 Current practice

- The non-specific clinical presentation of non-Hodgkin's lymphoma (such as enlarged lymph glands, anaemia or other abnormal blood tests) often results in delays and inconsistencies in diagnosis.
- Diagnosis of non-Hodgkin's lymphoma is made on tissue biopsy using immunohistochemistry and often flow cytometry and molecular studies. Diagnosis can be complex and the 2008 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues lists over 25 subtypes of B-cell non-Hodgkin's lymphoma alone.
- Significant improvements in the understanding of the biology of non-Hodgkin’s lymphoma have led to more specific and targeted treatment for the different subtypes.
- Staging is an integral part of the initial work-up in every patient with non-Hodgkin’s lymphoma, and includes laboratory assessment, different types of imaging (for example, CT scan, MRI and positron emission tomography [PET]), and nuclear medicine techniques.
- A wide range of treatments are used for managing non-Hodgkin's lymphoma. Management also includes observation for some patients with certain disease subtypes. For those patients who need treatment, there can be several phases: induction therapy, assessment of disease response to treatment, maintenance treatment, treatment at the point of first relapse, consolidation after relapse and palliative treatment.
- Radiotherapy and immunotherapy have established roles in the treatment of non-Hodgkin's lymphoma.
- Several novel chemotherapy agents have been licensed for treating non-Hodgkin’s lymphoma in the past 10 years and there is variation in the use of chemotherapy regimens particularly for second and third-line treatment.
- High-dose chemotherapy with bone marrow transplantation is frequently used for relapsed non-Hodgkin's lymphoma.

E.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

1 The areas that will be addressed by the guideline are described in the following sections.

E.4.1 Population

E.4.1.1 Groups that will be covered

2 • Adults and young people (16 years and older) referred to secondary care with suspected
3 non-Hodgkin's lymphoma.
4 • Adults and young people (16 years and older) with newly diagnosed or relapsed non-
5 Hodgkin's lymphoma.

E.4.1.2 Groups that will not be covered

6 • Children and young people under 16 years.
7 • Adults and young people (16 years and older) with chronic lymphocytic leukaemia or small
8 lymphocytic lymphoma.
9 • Adults and young people (16 years and older) with lymphoblastic lymphoma.
10 • Adults and young people (16 years and older) with rare T-cell lymphomas, such as, NK T-
11 cell lymphoma, mycosis fungoides, Sezary syndrome, anaplastic large-cell lymphoma of
12 T/null type ALK-, anaplastic large-cell lymphoma of T/null type, anaplastic large cell
13 lymphoma of T/null type ALK+, enteropathy-type T-cell lymphoma, primary cutaneous
14 CD30-positive T-cell lymphoproliferative disorder, extranodal NK/T-cell lymphoma, nasal
15 type, adult T-cell lymphoma/leukaemia (HTLV-1 positive).
16 • Adults and young people (16 years and older) with post-transplant lymphoproliferative
17 disease.
18 • Adults and young people (16 years and older) with skin lymphoma.
19 • Adults and young people (16 years and older) with central nervous system lymphoma.

E.4.2 Setting

20 • All settings in which NHS care is received.

E.4.3 Management

E.4.3.1 Key issues that will be covered

21 a) The specific information and support needs of people with non-Hodgkin’s lymphoma and
22 their carers at the time of diagnosis and treatment planning, as well as during and after
23 treatment.
24 b) The role of image-guided core biopsy compared with excision biopsy in the diagnosis of
25 non-Hodgkin’s lymphoma.
26 c) The role of centralised specialist laboratories offering integrated diagnostic reporting in the
27 diagnosis of non-Hodgkin’s lymphoma.
28 d) The role of genetic and molecular testing in the diagnosis and prognosis of non-Hodgkin’s
29 lymphoma (for example, FISH [fluorescence in situ hybridisation] and gene expression
30 profiling).
31 e) The role of PET-CT in initial staging, evaluating interim response to treatment and post-
32 treatment assessment for people with non-Hodgkin's lymphoma.
33 f) The frequency and nature of follow-up for people with non-Hodgkin's lymphoma after
34 attaining remission.
35 g) The most effective first-line treatment for early-stage follicular lymphoma.
36 h) The role of autologous and allogeneic transplantation in people with follicular lymphoma.

i) The role of immediate compared with deferred chemotherapy (watch and wait) in treating advanced asymptomatic follicular lymphoma.
j) The most effective first-line treatment for people with MALT lymphoma, including the role of antibiotic therapy, radiotherapy and chemo-immunotherapy.
k) The most effective first-line treatment for people with mantle cell lymphoma, including the choice of first-line treatment, the role of consolidation of high-dose therapy with stem cell support and the role of maintenance treatment.
l) The most effective first-line treatment for peripheral T-cell lymphoma.
m) The most effective first-line treatment for Burkitt's lymphoma.
n) The role of consolidation radiotherapy in first-line treatment of diffuse large B-cell lymphoma.
o) The initial treatment of composite/discordant and transformed follicular lymphoma.
p) The most appropriate salvage strategies, including indication for autologous and allogeneic transplantation, for people with diffuse large B-cell lymphoma.
q) Indications and methods for central nervous system prophylaxis for people with diffuse large B-cell lymphoma.
r) The survivorship issues for people treated for non-Hodgkin's lymphoma.

E.4.3.2 Issues that will not be covered

- Referral of people from primary care with suspected non-Hodgkin's lymphoma (this will be covered by 'Suspected cancer', the update of Referral guidelines for suspected cancer [NICE clinical guideline 27]).

E.4.4 Main outcomes

- Overall survival.
- Progression-free survival.
- Disease-related morbidity.
- Disease-related mortality.
- Treatment-related morbidity and mortality.
- Diagnostic accuracy.
- Health-related quality of life.
- Cost effectiveness.

E.4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

a) What are the information and support needs of patients with a diagnosis of non-Hodgkin's lymphoma and their carers:
    - at the point of first diagnosis
    - during treatment
    - after treatment
    - for those considering palliative care? [4.3.1a]
b) Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of non-Hodgkin's lymphoma? [4.3.1b]

c) Is integrated diagnostic reporting (via Specialist Integrated Haematological Malignancy Diagnostic Services [SIHMDS]) or local reporting more accurate in the diagnosis of non-Hodgkin's lymphoma? [4.3.1c]

d) What is the diagnostic value of genetic/molecular testing in diffuse large B-cell non-Hodgkin’s lymphoma? [4.3.1d]

e) What is the prognostic value of genetic/molecular testing in diffuse large B-cell non-Hodgkin’s lymphoma? [4.3.1d]

f) What is the diagnostic value of pre-treatment functional imaging with PET-CT compared with other initial assessments (for example, CT, bone marrow biopsy, clinical assessment) for people with different subtypes of non-Hodgkin’s lymphoma? [4.3.1e]

g) What is the prognostic value of an interim assessment using functional imaging with PET-CT during the treatment of non-Hodgkin’s lymphoma? [4.3.1e]

h) What is the prognostic value of functional imaging with PET-CT performed after the various types of treatment for non-Hodgkin's lymphoma are completed (for example, chemotherapy)? [4.3.1e]

i) In asymptomatic patients who have undergone treatment with curative intent for non-Hodgkin’s lymphoma, what are the optimal method(s), frequency and duration of follow-up? [4.3.1f]

j) What is the most effective first-line treatment for people with early-stage follicular lymphoma (for example, radiotherapy [at various dose levels, types of field radiation therapy], chemotherapy, interferon and observation)? [4.3.1g]

k) Is autologous transplantation, allogeneic transplantation or no transplantation the most effective treatment for people with follicular lymphoma at various time points (for example, first remission, first relapse, second remission, third relapse)? [4.3.1h]

l) Is immediate chemotherapy or deferred chemotherapy (watch and wait) the more effective treatment for people with advanced asymptomatic follicular lymphoma? [4.3.1i)

m) What is the most effective first-line treatment for people with MALT lymphoma (for example, antibiotic therapy, radiotherapy and chemo-immunotherapy)? [4.3.1j]

n) What is the most effective first-line treatment for people with mantle-cell lymphoma (for example, chemo-immunotherapy, radiotherapy)? [4.3.1k]

o) What is the effectiveness of first-line consolidation of high-dose therapy with autologous and allogeneic transplantation in people with mantle-cell lymphoma? [4.3.1k]

p) What is the most effective first-line maintenance strategy for people with mantle-cell lymphoma (for example, rituximab, interferon alfa, observation)? [4.3.1k]

q) What is the most effective first-line treatment for people with peripheral T-cell lymphoma (for example, chemotherapy, radiotherapy)? [4.3.1l]

r) What is the effectiveness of first-line consolidation of high-dose therapy with autologous and allogeneic transplantation in people with peripheral T-cell lymphoma? [4.3.1l]

s) What is the most effective first-line treatment for people with Burkitt’s lymphoma (for example, chemo-immunotherapy)? [4.3.1m]

t) What is the effectiveness of radiotherapy (at various dose levels) when added to chemotherapy compared with observation as first-line treatment for people with diffuse large B-cell lymphoma? [4.3.1n]

u) What is the most effective first-line treatment for people with histological transformation of follicular lymphoma to diffuse large B-cell lymphoma as well as composite/discordant lymphomas (for example, chemo-immunotherapy, radiotherapy)? [4.3.1o]

v) What is the effectiveness of first-line consolidation of high-dose therapy with autologous and allogeneic transplantation in people with histological transformation of follicular lymphoma to diffuse large B-cell lymphoma as well as composite/discordant lymphomas? [4.3.o]

w) What is the most appropriate salvage strategy for people with diffuse large B-cell lymphoma (for example, high-dose chemotherapy with autologous or allogeneic transplantation or chemo-immunotherapy)? [4.3.1p]

x) What is the most effective method of central nervous system prophylaxis for people with diffuse large B-cell lymphoma? [4.3.1q]

y) In which patients with diffuse large B-cell lymphoma does central nervous system prophylaxis improve outcomes? [4.3.1q]

z) What are the survivorship issues for people treated for non-Hodgkin's lymphoma? [4.3.1r]

aa) What is the most effective surveillance protocol for late adverse effects of treatment (for example, secondary cancers, cardiac disease or pulmonary disease) in people treated for non-Hodgkin's lymphoma? [4.3.1r]

E.4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

E.4.7 Status

E.4.7.1 Scope

This is the final scope.

E.4.7.2 Timing

The development of the guideline recommendations will begin in January 2014.

E.5 Related NICE guidance

E.5.1 Published guidance

E.5.1.1 NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

E.5.1.2 NICE guidance to be incorporated

This guideline will incorporate the following NICE guidance:

- Rituximab for the first-line treatment of stage III-IV follicular lymphoma: (review of NICE technology appraisal guidance 110). NICE technology appraisal guidance 243 (2012).
- Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma: Review of technology appraisal guidance 37. NICE technology appraisal guidance 137 (2008).
- Rituximab for aggressive non-Hodgkin's lymphoma. NICE technology appraisal guidance 65 (2003).

E.5.1.3 Other related NICE guidance

- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Opioids in palliative care. NICE clinical guideline 140 (2012).

- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Coeliac disease. NICE clinical guideline 86 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Erythropoetin (alfa and beta) and darbepoetin for the treatment of cancer-treatment induced anaemia. NICE technology appraisal guidance 142 (2008).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Laparo-endogastric surgery. NICE interventional procedure guidance 25 (2003).
- Haemato-oncology. NICE cancer service guidance (2003).

E.5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. NICE technology appraisal. Publication expected February 2014.
- Bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma. NICE technology appraisal. Publication expected July 2014.
- Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. NICE technology appraisal. Publication date to be confirmed.
- Suspected cancer: recognition and management of suspected cancer in children, young people and adults (update). NICE clinical guideline. Publication date to be confirmed.

E.6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix F:People and organisations involved in production of the guideline

F.1 Members of the Guideline Committee

GC Chair	
Prof. David Linch	Head of Department of Haematology, University College London
GC Lead Clinician	
Dr Christopher McNamara	Consultant Haematologist, University College London Hospital
Committee members	
Dr Ian Chau	Consultant in Medical Oncology, Departement of Medicine, The Royal Marsden Hospital, London & Surrey
Dr Graham Collins	Consultant Haematologist, Oxford University Hospitals Foundation NHS Trust
Morag Day	Patient and Carer Member
Jacqueline Green	Nurse Consultant – Haematology and Oncology, Croydon Health Services
Professor Peter Hoskin	Consultant Clinical Oncology, Mount Vernon Cancer Centre, Rickmansworth Road, North Wood, Middlesex
Gilly Howard-Jones	Lymphoma Clinical Nurse Specialist, University Hospital Southampton NHS Foundation Trust
Dr Andrew Jack	Consultant Haematopathologist, Head of Haematological Malignancy Diagnostic Service, St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust
Dr Kim M Linton	Senior Lecturer and Honorary Consultant Medical Oncologist, The Christie NHS Foundation Trust, The University of Manchester
Dr Karl Peggs	Reader in Stem Cell Transplantation/Honorary Consultant , UCL Cancer Institute, University College London
Katharine Robinson	Patient and Carer Member
Dr Bhuey Sharma	Consultant Radiologist, The Royal Marsden Hospital,
Tessa Somerville	Patient and Carer Member
Dr Jennifer Wimperis	Consultant Haematologist, Norfolk and Norwich University Hospital NHS Trust

F.1.1 Declarations of interest

Member	Interest declared	Type of interest	Decision taken
David Linch	Received honoraria from Roche for attending advisory boards and giving lectures at sponsored meetings covering the treatment of Lymphoma and the development of monoclonal antibody treatments.	Personal Pecuniary, Non-specific	
David Linch	Received honoraria from	Personal	Declare and participate in

Member	Interest declared	Type of interest	Decision taken
	Chugai for attending advisory boards and giving lectures at sponsored meetings covering the treatments of neutropenia and therapy induced neutropenia and rheumatoid arthritis.	Pecuniary, Non-specific	discussions on all topics as guideline is not covering treatments of neutropenia and therapy induced neutropenia and rheumatoid arthritis.
David Linch	Medical Advisor to Cellectsis.	Personal Pecuniary, Non-specific	Declare and participate in discussions on all topics. Email received from JG conforming from Andrew Dillon that DL can continue as a medical advisor to Cellectsis whilst chairing the guideline.
David Linch	Chair of Safety Committee for Cell Medica. Safety oversight of two early phase clinical trials of anti-CMV specific T-cell lymphocytes.	Personal non-pecuniary	Declare and participate in discussions on all topics as guideline is not covering anti-CMV specific T-cell lymphocytes.
David Linch	Member of the safety/oversight committee for Cellgene. Safety trial of lenalidomide in relapsed lymphoma.	Personal non-pecuniary	Declare and participate in discussions on all topics as lenalidomide is being investigated by TA's and therefore will not be investigated by the guideline. Note: 28.02.14 David Linch has resigned from committee.
David Linch	President of the Lymphoma Association.	Personal non-pecuniary	Declare and participate in discussions on all topics as interest is not specific to the content of the guideline.
David Linch	Department receives funding from Astra Zeneca for PHD studentships. No direct involvement.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as does not have supervisory responsibility for PHD student.
David Linch	Department receives funding from Chugai for of PHD studentships. Is co-supervisor.	Non-personal pecuniary	
David Linch	Received reimbursement of travelling expenses and conference registration fee from Gilead for attending the American Society of Haematology in San Francisco	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics expenses were not beyond reasonable amounts
Chris McNamara	Principle investigator for the GALLIUM trial on rituximab versus GA101 in combination with chemotherapy in first-line follicular and marginal zone lymphoma. Funded by	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as individual has only provided advice on laboratory diagnostics components of the trial

Member	Interest declared	Type of interest	Decision taken
	NCR and Roche. Advised on setting up the laboratory diagnostics for patients participating in the trial, when the trial protocol was being determined		protocol.
Chris McNamara	Local principle investigator for the PACIFICO trial (Alkylator Combination In Follicular lymphoma Immuno-Chemotherapy for Older patients: a phase III comparison of first-line R-CVP (rituximab, cyclophosphamide, vincristine and prednisone) versus R-FC (rituximab, fludarabine and cyclophosphamide). Funded by CTAAC	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as individual has no supervisory responsibility for the trial.
Chris McNamara	Local principle investigator for the REMoDLB trial (A randomised evaluation to see whether adding bortezomib to standard combination chemotherapy and rituximab (RCHOP) can improve progression free survival in diffuse large B-cell lymphoma with Bortezomib). Funded by Janssen Cilag Ltd	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as individual has no supervisory responsibility for the trial.
Chris McNamara	Local principle investigator for the RATHL trial (a multicentre randomised phase II study to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin's lymphoma). Funded by CRUK	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma is not being covered by the guideline.
Chris McNamara	Local principle investigator for the RAPID trial (A randomised Phase III trial to determine the role of FDG-PET Imaging in Clinical Stages IA/IIA Hodgkin's Disease). Funded by Leukaemia and Lymphoma Research	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma is not being covered by the guideline.
Chris McNamara	Medical advisor to the Lymphoma Association	Personal non-pecuniary	Declare and participate in discussions on all topics as interest is not specific to the content of the guideline.
Ian Chau	Attended an advisory board for factors to consider for patients with metastatic	Personal non-pecuniary interest	Declare and participate in discussions on all topics as colorectal cancer is not

Member	Interest declared	Type of interest	Decision taken
	colorectal cancer. Hosted by Sanofi Oncology no payment was received.		being covered by the guideline.
Ian Chau	Attended an advisory board for GI cancers. Hosted by Eli Lily, no payment was received.	Personal non-pecuniary interest	Declare and participate in discussions on all topics as GI cancer is not being covered by the guideline.
Ian Chau	Attended an advisory board for Anti-CD30 antibody drug conjugate therapy in Hodgkins and CD30+ and oral discussion on JSPAC01 and SOFT studies. Hosted by Taiho, no payment was received.	Personal non-pecuniary interest	Declare and participate in discussions on all topics as Hodgkins lymphoma is not being covered by the guideline.
Ian Chau	Attended an advisory board for GI cancers. Hosted by Gilead, no payment was received.	Personal non-pecuniary interest	Declare and participate in discussions on all topics as GI cancer is not being covered by the guideline.
Ian Chau	Received reimbursement of travelling expenses and subsistence from Sanofi Oncology for attending the World Congress on GI cancers.	Personal pecuniary, Specific	Declare and participate in discussions on all topics as expenses not beyond reasonable amounts.
Ian Chau	Received reimbursement of travelling expenses and subsistence from Sanofi Oncology for attending the European Society of Medical Oncology (ESMO) meeting.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond reasonable amounts.
Ian Chau	Chief investigator and involved in developing the trial protocol for the PERU trial. A multi-centre randomised phase II clinical study of UFT, radiotherapy with or without cetuximab following induction gemcitabine plus capecitabine in patients with locally advanced pancreatic cancer. Funded by Merck Serono	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as locally advanced pancreatic cancer is not being covered by the guideline.
Ian Chau	Chief investigator and involved in developing the trial protocol for the CALIVER trial. A multi-centre randomised phase II clinical study of aflibercept plus chemotherapy in patients with colorectal liver-only metastases deemed to be inoperable or unsuitable for upfront liver resection. Funded by Sanofi Oncology.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as colorectal liver-only metastases are not being covered by the guideline.
Ian Chau	Co-investigator on a mulitcentre randomised	Non-personal pecuniary,	Declare and participate in discussions on all topics

Member	Interest declared	Type of interest	Decision taken
	phase II study of CHEMO-T, Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) versus gemcitabine, cisplatin and methyl prednisolone (GEM-P) in the first line treatment of T-cell lymphoma. Funded by Leukaemia and Lymphoma Research.	Specific	as no supervisory responsibility on trials.
Ian Chau	Member of the UK primary CNS lymphoma group.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Ian Chau	Received honorarium from Bayer for attending an advisory board meeting on anti-coagulates.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as anti-coagulates drugs are not being investigates by the guideline.
Graham Collins	Received honoraria from Takeda for attending an advisory board on Brentuximab in the treatment of Hodgkin's lymphoma and anaplastic large T-Cell lymphoma.	Personal pecuniary, Specific	Declare and withdraw from discussion on any topic on Brentuximab until October 2014.
Graham Collins	Received honoraria from Mundipharma for attending an specialist nurses educational forum to present to lymphoma nurses indolent non-Hodgkin's lymphoma, covering first and second line chemotherapy and antibody options.	Personal pecuniary, Specific	Declare and withdraw from discussion on any topic covering the first and second line treatment of indolent lymphoma until October 2014.
Graham Collins	Received honoraria from Takeda for attending the American Society of Haematologists meeting and giving a presentation on Brentuixmab in ALCL and Hodgkin's.	Personal pecuniary, Specific	Declare and withdraw from discussion on any topic on Brentuximab until December 2014.
Graham Collins	Received honoraria from Roche for attending a local nurse specialist group and giving a presentation on the updates in lymphoma, covering Ibrutinib and other targeted therapies.	Personal pecuniary, Non-specific	Declare and withdraw from discussion on any topic where ibrutinib is an intervention until Ocotber 2014.
Graham Collins	Received reimbursement of travelling expenses, subsistence and conference registration from Roche for attending the American Society of Haematologists meeting.	Personal pecuniary, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Graham Collins	Received reimbursement of travelling expenses and	Personal pecuniary,	Declare and participate in discussions on all topics

Member	Interest declared	Type of interest	Decision taken
	subsistence from Takeda for attending the International lymphoma meeting in Lugano.	Specific	as expenses not beyond a reasonable amount.
Graham Collins	Principal investigator on the GALLIUM trial on rituximab versus GA101 in combination with chemotherapy in first-line follicular and marginal zone lymphoma. Funded by NCR, Roche, and the German low study group.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Principal investigator on the REMoDL_B: R-Chop versus R-Chop+ bortezomib in first line treatment of diffuse large B-cell lymphoma. Funded by Janssen-Cilag.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Principal investigator on the Mabcute: 2 year rituximab maintenance versus ongoing until progression, in relapsed indolent non-Hodgkin's lymphoma. Funded by Roche.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Principal investigator on the Chemo T-CHOP versus GEM-P for first line treatment of peripheral T-cell lymphoma. Funded by NIHR.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Principal investigator on the AZD1152, a phase IIa trial on an aurora kinase B inhibitor in relapsed/refractory diffuse large B-cell lymphoma. Funded by Oxford University Hospitals NHS trust, Christie Hospital NHS foundation trust, University of Manchester Early Phase Cancer Research Hub, Oxford.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Principal investigator on the GS-US-313-0125, phase III trial of rituximab + bendamustine with either idelalisib or placebo in relapsed/refractory indolent non-Hodgkin's lymphoma. Funded by Gilead.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Graham Collins	Chief investigator and involved in developing the trial protocol for the ECHALON-1 study, an international randomised trial of ABVD verses AVD + brentuximab vedotin in the first line treatment of	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkins lymphoma is not being investigated by the guideline.

Member	Interest declared	Type of interest	Decision taken
	advanced classic Hodgkin lymphoma. Funded by Takeda.		
Graham Collins	Chief investigator and involved in developing the trial protocol for the RomiCar trial, phase I/II trial investigating a novel drug combination in relapsed/refractory peripheral T-cell lymphoma with assessment of HR23B as predictive biomarker of response. This has been accepted onto the LLR Trials Acceleration Programme portfolio and is due to open Q4 2013. Funded by Leukaemia and Lymphoma Research, Onyx Therapeutics	Non-personal pecuniary, Specific	Declare and withdraw from discussion on any topic on novel drug combinations in relapsed/refractory peripheral T-cell lymphoma.
Graham Collins	Chief investigator and involved in developing the trial protocol for the PimTor phase I/II trial of a PIM inhibitor (AZD1208) and mTOR inhibitor (AZD2014) as single agents in combination, in relapsed/refractory B-cell non-Hodgkin's lymphoma. This is currently being prepared for funding submission to Astra Zeneca.	Non-personal pecuniary, Specific	Declare and withdraw from discussion on any topic on PIM inhibitor (AZD1208) and mTOR inhibitor (AZD2014) in relapsed/refractory B-cell non-Hodgkin's lymphoma.
Graham Collins	Member of the NCRI study group.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Graham Collins	Member of the lymphoma association.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Graham Collins	Received reimbursement of travelling expenses and hotel accommodation from Napp pharmaceuticals to attend the American Society of Haematologists.	Personal pecuniary interest, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Graham Collins	Received reimbursement of travelling expenses and hotel accommodation from Sandoz to attend the European Haematology Association meeting	Personal pecuniary interest, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Graham Collins	Received honoraria from Gilead for attending an advisory board on Idelalisib in	Personal pecuniary interest, Specific	Declare and participate in discussions on all topics as Idelalisib is being

Member	Interest declared	Type of interest	Decision taken
	the treatment of indolent non-Hodgkin lymphoma		investigated by TA's and therefore will not be investigated by the guideline.
Graham Collins	Received honoraria from Takeda for giving a talk on Hodgkin's Lymphoma at the British Society of Haematology meeting.	Personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma is not being covered by the guideline.
Graham Collins	Received reimbursement of travelling expenses and hotel accommodation from Napp pharmaceuticals to attend the American Society of Haematologists.	Personal pecuniary interest, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Graham Collins	Received an honorarium from Takeda to attend an educational meeting to discuss suitable case studies when using brentuximab Meeting was focused on Hodgkin's lymphoma and anaplastic large cell lymphoma	Personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma and anaplastic large cell lymphoma are not being investigated by the guideline.
Graham Collins	Received an honorarium from Takeda for giving a talk to the East of England Blood club on Hodgkin's lymphoma.	Personal Pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma is not being covered by the guideline.
Graham Collins	Received an honorarium from Gilead for giving a talk on the use of idelalisib in double refractory follicular lymphoma	Personal pecuniary, Specific	Declare and participate in discussions on all topics as idelalisib is being investigated by NICE TA's and therefore will not be included as an intervention in this topic in the guideline
Graham Collins	Received an honorarium from Celgene for attending an advisory board on the use of lenlaidomide in relapsed / refractory mantle cell lymphoma	Personal pecuniary, Specific	Declare and participate in discussions on all topics as lenalidomide is being investigated by NICE TA's and therefore will not be included as an intervention in this topic in the guideline
Graham Collins	Received an honorarium from Takeda for giving a talk to the Scottish Lymphoma Group on the use of brentuximab in Hodgkin's lymphoma	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as the guideline does not included Hodgkin's lymphoma.
Graham Collins	Received honorarium from Takeda for attending an advisory board meeting on Brentuximab Vedotin in Hodgkins Lymphoma and	Personal pecuniary, Specific	Declare and participate in discussions on all topics as Hodgkins Lymphoma and Aplastic large cell lymphoma is not the focus

Member	Interest declared	Type of interest	Decision taken
	Aplastic large cell lymphoma.		of the guideline.
Graham Collins	Received honorarium from Takeda for attending an advisory board meeting on Brentuximab Vedotin in Hodgkins Lymphoma and Aplastic large cell lymphoma.	Personal pecuniary, Specific	Declare and participate in discussions on all topics as Hodgkins Lymphoma and Aplastic large cell lymphoma is not the focus of the guideline.
Jackie Green	Explains the MDSBio Study of Molecular and functional characterisation of bone marrow function in normal subjects, myelodysplastic syndromes (MDS), acute myeloid leukaemia (AML) and secondary disorders of haematopoiesis to haematology patients with abnormal blood count.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as myelodysplastic syndromes (MDS), acute myeloid leukaemia (AML) and secondary disorders of haematopoiesis is not the focus of the guideline.
Jackie Green	Member of the London Cancer Alliance, haematology pathway lead nurse group.	Personal non-pecuniary interest	Chair person's action to declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Received reimbursement of travelling expenses and conference registration fee for attending the European Society for Radiation and Oncology (ESTRO) in December 2013.	Personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics expenses were not beyond reasonable amounts
Peter Hoskin	Chief investigator for a trial investigating brachytherapy +/- external beam radiotherapy, which received funding from Dept of Health and CRUK. Continues to follow those patients up and publish data from the study.	Non personal pecuniary, Non-specific	Declare and participate in discussions on all topics as brachytherapy +/- external beam radiotherapy is not being covered by the guideline.
Peter Hoskin	Holds a research grant from Varian which pays the salary for a data manager working on HDR boost, for Brachytherapy in prostate cancer.	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as brachytherapy and prostate cancer is not being covered by the guideline.
Peter Hoskin	Department reimbursed for studies on abiraterone by Cougar	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as abiraterone for prostate cancer is not being covered by the guideline.
Peter Hoskin	Department reimbursed for studies on alpharadin by Astellas	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as alpharadin for prostate cancer is not being covered by the guideline.
Peter Hoskin	Department reimbursed for studies on MDV 3100 by Medivation	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as MDV 3100 for prostate

Member	Interest declared	Type of interest	Decision taken
			cancer is not being covered by the guideline.
Peter Hoskin	Department reimbursed for studies on Denosumab for prostate cancer. Funded by Amgen	Non personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Denosumab for prostate cancer is not being covered by the guideline.
Peter Hoskin	Trustee for funding research within the unit/department. Funded by Donations/Legacies. No Non-Hodgkins lymphoma research has been funded in the last 12 months.	Personal non-pecuniary interest	Declare and participate in discussions on all topics as no Non-Hodgkins lymphoma research has been funded in the last 12 months.
Peter Hoskin	Chairs Steering Group for the National Cancer Intelligence Network (NCIN)	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Member of the committee for Medical Aspects of Radiation Exposure (COMARE)	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Chair of the executive committee of GEC ESTRO Brachytherapy Group	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline..
Peter Hoskin	Member of the faculty board of the Royal College of Radiologists.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Member of the specialist training committee for the Royal College of Radiologists.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Member of the specialist training advisory committee (STAC) for the Royal College of Radiologists	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Editorial board member for the Journal of Clinical Oncology.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Editorial board member for the Journal of Bone Oncology.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Editorial board member for the Journal of Contemporary Brachytherapy.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Member of the East of England senate.	Personal non-pecuniary interest	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Member on the NICE	Personal non-	Declare and participate in

Member	Interest declared	Type of interest	Decision taken
	standing committee for rapid updates.	pecuniary interest	discussions on all topics is not specific to the content of the guideline.
Peter Hoskin	Department receives grants from Astellas for trials in prostate cancer.	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as prostate cancer is not being covered by the guideline.
Peter Hoskin	Department receives grants from Bayer for trials in prostate cancer.	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as prostate cancer is not being covered by the guideline.
Peter Hoskin	Department receives grants from Millennium for trials in prostate cancer.	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as prostate cancer is not being covered by the guideline.
Peter Hoskin	Department receives grants from Varian for trials in prostate cancer.	Non personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as prostate cancer is not being covered by the guideline.
Gillian Howard Jones	Received honoraria from Roche for presenting preparing for patient triggered follow-up at the CNS lymphoma forum.	Personal Pecuniary, Specific	Declare and withdraw from discussion on any topic on patient triggered follow-up until November 2014.
Gillian Howard Jones	Received travel expenses from Brighton team and Janssen to talk about the new follow up service at Southampton.	Personal pecuniary	Declare and participate in discussions on all topics expenses were not beyond reasonable amounts
Andrew Jack	Received reimbursement of travelling and subsistence expenses from Roche for attending the American Society of Haematologists (ASH) meeting in December 2013.	Personal pecuniary interest, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Andrew Jack	Member of a the trial management group for a Phase III randomised clinical trial comparing rituximab given every 14 days with CHOP given every 21 days (R-CHOP 14 vs21) for patients with newly diagnosed diffuse large B Cell non Hodgkins Lymphoma. Funded by Cancer Research UK and Chugai Pharma Europe Ltd.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Andrew Jack	Principal investigator for a randomised evaluation of molecular targeted therapy with bortezomib in diffuse	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.

Member	Interest declared	Type of interest	Decision taken
	large B-cell lymphoma (REMoDL-B). Funded by Janssen-Cilag.		
Andrew Jack	Principal investigator for biomarker development and monoclonal antibodies for the treatment of lymphoma. Funded by Genentech Ltd.	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Andrew Jack	Principal investigator on a trial to compare remission rates of low grade non Hodgkin's lymphoma with GA101 vrs rituximab. Funded by Experimental Cancer Medicine (ECMC), Genentech Ltd, NCRN and Roche.	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Andrew Jack	Principal investigator on the stratification of treatment by molecular and genetic sub-typing for diffuse large B-cell lymphoma. Funded by Leukaemia and lymphoma research.	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Andrew Jack	Represents the NCRI on the Lunenburg lymphoma biomarker consortium, the European and North American initiative for the development of biomarkers in clinical trials.	Personal non-pecuniary interest	Chair person's action to declare and participate in discussions on all topics as the interest is not specific to the content of the guideline.
Andrew Jack	Host Trust is contracted to provide diagnostic services for the GALLIUM trial to Roche. Responsible for supervising staff and ensuring the work is carried out to the required quality in line with the contract.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as individual has no responsibility for the contract and does not provide any advice or opinion to Roche.
Andrew Jack	Has supervisory responsibility for a collaborative research project to identify targets for therapeutic antibody development. Funded by Genetech.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as therapeutic antibody development is not the focus of the guideline.
Kim Linton	Received honoraria for attending an advisory board on the role of pixantrone in the treatment of relapsed/refractory B-cell non-Hodgkins lymphoma. Payment was received from Cell therapeutics life sciences.	Personal pecuniary, Specific	Declare and participate in discussions on all topics as Pixantrone is being investigated by TA's and therefore will not be investigated by the guideline.
Kim Linton	Received honoraria for attending an advisory board on Brentuximab vedotin in T-	Personal pecuniary,	Declare and withdraw from discussion on any topic on Brentuximab vedotin until

Member	Interest declared	Type of interest	Decision taken
	cell lymphoma and Hodgkin's disease.	Specific	October 2014.
Kim Linton	Received honoraria, travel and subsistence expenses from Pfizer for attending conference and being on panel discussing engaging with the NHS.	Personal pecuniary, Non-specific	Declare and participate in discussion on all topics as engaging with the NHS is not being investigated by the guideline.
Kim Linton	Received reimbursement of travelling expenses and conference fee for attending the International malignant lymphoma meeting in June 2013.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Kim Linton	Principal investigator and involved in developing the trial protocol on the development of a molecular test for Diffuse large B-cell lymphoma molecular sub-type. Funded by Almac diagnostics, Affymetrix and MRC confidence in concept funding.	Non-personal pecuniary, Specific	Declare and withdraw from discussion on developing molecular tests for Diffuse large B-cell lymphoma.
Kim Linton	Local Principal investigator on the CAL 101-09; Calistoga Phase II study investigating the efficacy and safety of PI3K delta inhibitor (CAL101) in patients with indolent B-cell non-Hodgkins lymphoma refractory to rituximab and alkylating agents. Funded by Gilead Science.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Kim Linton	Local Principal investigator on the DLC001; Phase II/III study comparing lenalidomide with conventional single agent chemotherapy in patients with relapsed diffuse large b-cell lymphoma. Funded by Celgene	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as lenalidomide is being investigated by TA's and therefore will not be investigated by the guideline.
Kim Linton	Local Principal investigator on the IELSG-32; investigator-led randomised phase 3 trial on primary chemotherapy with high dose methotrexate and high dose cytarabine with or without thiotepa, and with or without rituximab, followed by whole brain irradiation vs. high dose chemotherapy supported by autologous stem cell transplantation for immunocompetent patients with newly diagnosed primary	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials and newly diagnosed primary CNS lymphoma is not being investigated by the guideline.

Member	Interest declared	Type of interest	Decision taken
	CNS lymphoma.		
Kim Linton	Principal investigator on the Bayer 16349; Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent or aggressive Non-Hodgkin's. Funded by Bayer.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Kim Linton	Local Principal investigator on the ARROVEN, Takeda sponsored post authorisation safety assessment of Brentuximab Vedotin treatment in relapsed Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma. Funded by Takeda.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials and Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma are excluded from the scope of the guideline.
Kim Linton	Local Principal investigator on the Gilead 0125 trial, a randomised phase lll trial investigating the addition of Idelalisib to the Rituximab - Bendamustine combination in relapsed/refractory indolent B cell NHL	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Kim Linton	Principal investigator on the ReBel trial; International phase 1/2 study investigating the combination of rituximab and lenalidomide +/- bendamustine in patients with relapsed follicular lymphoma, expected to start recruiting in Q1 2014. Funded by Hovon, GLSG & Celgene.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Kim Linton	Co- investigator on the INCA trial, a multicentre randomised phase II clinical trial of Inotuzumab Ozogamicin plus Rituximab and CVP (IORCVP) versus Gemcitabine plus Rituximab and CVP (GemRCVP) for the first line treatment of patients with diffuse large B cell lymphoma who are not suitable for anthracycline containing chemotherapy. Funded by Pfizer.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Kim Linton	Co- investigator on the RomiCar study. A phase I/II study to determine the maximum tolerated dose and activity of the combination of romidepsin and carfilzomib in relapsed or refractory	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.

Member	Interest declared	Type of interest	Decision taken
	peripheral T-cell lymphoma. Funded by Leukaemia and Lymphoma Research, and Onyx Therapeutics.		
Kim Linton	Co investigator on the BREVITY study. A phase II study of brentuximab vedotin (SGN-35) using a response adapted design in patients with Hodgkin lymphoma unsuitable for chemotherapy. Funded by Millennium.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as relapsed Hodgkin Lymphoma is not being investigated by the guideline.
Kim Linton	Co- investigator on the Relapsed primary CNS lymphoma trial. Funded by LLR TAP.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as newly diagnosed primary CNS lymphoma is not being investigated by the guideline.
Kim Linton	Chair of the Lymphoma Translational Research Group, Manchester.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Chair of the Bioinformatics Steering Committee.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Lymphoma DG representative on MCRC Biobank Management Board.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Member of the National NCRI Lymphoma Biology Subgroup.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Advisor for the Clinical Outcomes Group (Lymphoma DG)	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Member of BCSH writing group – DLBCL guidelines.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Member of NCRN low grade lymphoma sub group and biological studies sub group	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Kim Linton	Department received a medical education grant from Pfizer for £2,000 to commission the development of a patient held diary including design, printing and material costs.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics the use of patient held diaries is not being covered by the guideline.
Kim Linton	Received an honorarium from Pfizer for attending an	Personal Pecuniary,	Declare and withdraw from discussion on any topics

Member	Interest declared	Type of interest	Decision taken
	Advisory Board in on 'Input on our strategies and materials for educating stakeholders about Pfizer's potential biosimilars and the related development pathways'	Specific	which include Pfizer potential biosimilars until October 2015
Kim Linton	Member of the Gilead Oncology faculty to provide haematology-oncology expert and speaker training and slide resource on Idelalisib.	Personal non-pecuniary	Declare and participate in discussions on all topics as Idelalisib is being investigated by TA's and therefore will not be investigated by the guideline.
Karl Peggs	Received honoraria for attending the European Millennium Takeda Advisory Board on the role of transplantation in Hodgkin Lymphoma.	Non-personal pecuniary interest, Non-specific	Declare and participate in discussions on all topics as Hodgkin lymphoma is not being covered by the guideline.
Karl Peggs	Received honoraria for attending the MSD global advisory board to discuss the trial design for their phase II study of letermovir (an anti-CMV drug).	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as cytomeagalovirus infections are not being covered by the guideline.
Karl Peggs	Received honoraria for attending the MSD advisory board that covered the role of oral antifungal in bone marrow transplant patients and acute myeloid leukaemia.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as bone marrow transplant patients and acute myeloid leukaemia is not being covered by the guideline.
Karl Peggs	Received travel and subsistence for acting as an advisor to Selectis who make genetically modified cells for treating infection.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Karl Peggs	Received reimbursement of travelling expenses and subsistence for attending the international Society for Hodgkin's lymphoma debate on the role of transplantation in patients with Hodgkin's lymphoma.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Karl Peggs	Received reimbursement of travelling expenses and subsistence for attending the Controversies in stem cell transplantation debate on the role of allegeneic transplantation in patients with Hodgkin's lymphoma.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Karl Peggs	Received reimbursement of travelling expenses and subsistence for attending the Cellular therapy meeting	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as expenses not beyond a

Member	Interest declared	Type of interest	Decision taken
	where cell therapy for oral infections was discussed.		reasonable amount.
Karl Peggs	Principal investigator on the ProT4, NCRN phase II study of prophylactic CD8-depleted DLI following T-cell depleted reduced intensity allogeneic transplantation. Funded by Leukaemia and Lymphoma research.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Karl Peggs	Principal investigator on the LenaRIC, NCRB phase II study of allogeneic transplantation with post transplant lenalidomide and donor-lymphocytes in multiple myeloma. Funded by CTAAC	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Karl Peggs	Chief investigator and involved in developing the trial protocol for the PAIReD, a national joint NCRN/BSBMT phase II study of reduced intensity allogeneic transplantation in primary resistant and relapsed refractory patients with Hodgkin's lymphoma. Funded by CRUK, Chugai, Pharma UK Ltd, ECMC, NCRN and UCL.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkin lymphoma is not being covered by the guideline.
Karl Peggs	Chief investigator and involved in developing the trial protocol for the CMV-ACE/ASPECT, a multi centre phase II study of pre-emptive CMV specific T –cell lymphocytes in related donor allogeneic transplantation (Relating to the use of anti-viral immune cells to treat viral infections). Funded by Leukaemia and Lymphoma Research Cell Medica Ltd.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as anti-viral immune cells to treat viral infections is not being covered by the guideline.
Karl Peggs	Chief investigator and involved in developing the trial protocol for the CMV IMPACT a multi centre randomised confirmatory national study of prophylactic CMV-specific T-cell lymphocytes depleted sibling allogeneic transplantation. (Relating to the use of anti-viral immune cells to treat viral infections). Funded by Cell Medica Ltd, ECMC, and the Wellcome trust.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as anti-viral immune cells to treat viral infections is not being covered by the guideline.

Member	Interest declared	Type of interest	Decision taken
Karl Peggs	Member of the NCRI lymphoma clinical studies group.	Personal non-pecuniary	Declare and participate in discussions on all topics is not specific to the content of the guideline.
Bhuey Sharma	Received an honorarium from Roche Products Ltd for giving a lecture on “Metastatic breast cancer: future positive. Navigating the HER 2+ journey: Targeting and imaging invasion and metastases”.	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics as breast cancer is not being investigated by the guideline.
Bhuey Sharma	Co-investigator on a multicentre randomised phase II study on CHEMO-T, Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) versus gemcitabine, cisplatin and methyl prednisolone (GEM-P) in the first line treatment of T-cell lymphoma. Funded by Royal Marsden NHS Foundation trust.	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Bhuey Sharma	Co-investigator on a multicentre randomised phase II study on LEGEND comparing Lenalidonmide plus rituximab, gemcitabine, methylprednisolone and cisplatin (RG-EMP) in second line treatment of diffuse large B-cell lymphoma. Funded by Celgene Europe Ltd.	Non-personal pecuniary interest, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Tessa Somerville	Receive travel expenses from Haemo-Onc for volunteer work on the ward	Personal pecuniary, Non-specific	Declare and participate in discussions on all topics expenses were not beyond reasonable amounts
Jennie Wimperis	Received reimbursement of travelling expenses and subsistence from Boehringer Ingelheim for attending the European Haematology Association meeting.	Personal pecuniary, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Jennie Wimperis	Principal investigator on a multicentre randomised phase II study on CHEMO-T, Cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) versus gemcitabine, cisplatin and methyl prednisolone (GEM-P) in the first line treatment of T-cell lymphoma. Funded by NIHR.	Non-personal pecuniary, Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Jennie Wimperis	Principal investigator on the bright light survey, a quality assessment of all cancers of	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as quality assessment of

Member	Interest declared	Type of interest	Decision taken
	teenagers and young adults. Funded by NIHR		all cancers of teenagers and young adults is not being covered by the guideline.
Jennie Wimperis	Principal investigator and local administrator on a multicentre randomised phase II study on RATHL, to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin's lymphoma.	Non-personal pecuniary, Non-specific	Declare and participate in discussions on all topics as Hodgkin's lymphoma is not being covered by the guideline.
Jennie Wimperis	Gatekeeper for three endowment funds used for research projects within department. If requests are above £1000 then the request is referred to the trust committee. No non-Hodgkins lymphoma related research has been funded in the last 12 months.	Personal non-pecuniary	Declare and participate in discussions on all topics as no non-Hodgkins lymphoma related research has been funded in the last 12 months.
Jennie Wimperis	Trustee for the Big C cancer charity. Helps direct the activities of the charity, signs off allocation of grants and general governance. No non-Hodgkins lymphoma related research has been funded in the last 12 months.	Personal non-pecuniary	Declare and participate in discussions on all topics as no non-Hodgkins lymphoma related research has been funded in the last 12 months.
Jennie Wimperis	Chair of the BCSH guideline committee.	Personal non-pecuniary interest.	Declare and participate in discussions on all topics.

F.2 Organisations invited to comment on the guideline development

1 The following stakeholders registered with NICE and were invited to comment on the scope
2 and the draft version of this guideline.

5 Boroughs Partnership NHS Foundation Trust	Abbott Molecular
Addenbrookes Hospital	Alliance Pharmaceuticals
Allocate Software PLC	Amgen UK
Anglia community leisure	Association for Palliative Medicine of Great Britain
Association of Anaesthetists of Great Britain and Ireland	Association of Chartered Physiotherapists in Oncology and Palliative Care
Barnsley Hospital NHS Foundation Trust	Baxalta UK Ltd
Bayer plc	Belfast Health and Social Care Trust
Blood & Marrow Transplantation Clinical reference Group NHS England	Bloodwise
Boehringer Ingelheim	Boehringer Ingelheim Ltd
Boots	British Dietetic Association
British HIV Association	British Infection Association

British Lymphoma Pathology Group	British Medical Association
British Medical Journal	British National Formulary
British Nuclear Cardiology Society	British Nuclear Medicine Society
British Psychological Society	British Red Cross
British Society of Gastrointestinal and Abdominal Radiology	British Society of Paediatric Gastroenterology Hepatology and Nutrition
BSPGHAN	Cancer Commissioning Team
Cancer Research UK	Caplond Services
Care Not Killing Alliance	Care Quality Commission
Celgene UK Ltd	Children's Cancer and Leukaemia Group
CLEAR Cannabis Law Reform	College of Paramedics
County Durham and Darlington NHS Foundation Trust	Croydon Clinical Commissioning Group
Croydon Council	Croydon University Hospital
CTI Life Sciences	Cumbria Partnership NHS Foundation Trust
CWHHE Collaborative CCGs	Cytori Therapeutics Inc
Department of Health	Department of Health, Social Services and Public Safety - Northern Ireland
East and North Hertfordshire NHS Trust	East Kent Hospitals University NHS Foundation Trust
East of England Strategic Clinical Network	Ethical Medicines Industry Group
Faculty of Dental Surgery	Five Boroughs Partnership NHS Trust
Gilead Sciences Ltd	Gloucestershire Hospitals NHS Foundation Trust
GP update / Red Whale	Greater Manchester & Beyond Coalition of PLW & HIV
Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network	Health and Care Professions Council
Health and Social Care Information Centre	Healthcare Improvement Scotland
Healthcare Infection Society	Healthcare Quality Improvement Partnership
Healthwatch East Sussex	Herts Valleys Clinical Commissioning Group
Hywel Dda University Health Board	Joint Royal Colleges Ambulance Liaison Committee
Lancashire Care NHS Foundation Trust	Leukaemia CARE
Local Government Association	London cancer alliance
London North West Healthcare NHS Trust	Lymphoma Association
Macmillan Cancer Support	Mastercall Healthcare
Medical Directorate Services	Medicines and Healthcare Products Regulatory Agency
Milton Keynes Hospital NHS Foundation Trust	Milton Keynes NHS Foundation
Ministry of Defence	Muslim Doctors and Dentists Association
Napp Pharmaceuticals Ltd	National Clinical Guideline Centre
National Collaborating Centre for Cancer	National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health	National Deaf Children's Society
National Institute for Health Research	National Institute for Health Research Health Technology Assessment Programme
National Patient Safety Agency	Newcastle upon Tyne Hospitals NHS Foundation Trust
NHS Barnsley Clinical Commissioning Group	NHS Choices

NHS Chorley and South Ribble CCG	NHS Cumbria Clinical Commissioning Group
NHS England	NHS Gloucestershire CCG
NHS Hardwick CCG	NHS Health at Work
NHS Medway Clinical Commissioning Group	NHS North East Lincolnshire CCG
NHS Plus	NHS Sheffield
NHS Somerset CCG	NHS South Cheshire CCG
NHS Wakefield CCG	NHS Warwickshire North CCG
NHS West Cheshire CCG	NIHR CCRN ENT Specialty Group
North of England Commissioning Support	Northern Health and Social Care Trust
Nottingham City Council	Nursing and Midwifery Council
Older People's Advocacy Alliance	Oxfordshire Clinical Commissioning Group
Pfizer	Primary Care Pharmacists Association
Primrose Bank Medical Centre	Public Health Agency for Northern Ireland
Public Health England	Queen Elizabeth Hospital King's Lynn NHS Trust
Roche Products	Royal College of Anaesthetists
Royal College of General Practitioners	Royal College of General Practitioners in Wales
Royal College of Midwives	Royal College of Nursing
Royal College of Obstetricians and Gynaecologists	Royal College of Paediatrics and Child Health
Royal College of Pathologists	Royal College of Physicians
Royal College of Physicians and Surgeons of Glasgow	Royal College of Psychiatrists
Royal College of Radiologists	Royal College of Speech and Language Therapists
Royal College of Surgeons of England	Royal Cornwall Hospitals NHS Trust
Royal Pharmaceutical Society	Royal Surrey County Hospital NHS Trust
Sandoz Ltd	Scottish Clinical Virology Consultants Group
Scottish Intercollegiate Guidelines Network	Serious Hazards of Transfusion
Sheffield Children's NHS Trust	Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence	Somerset, Wiltshire, Avon and Gloucestershire Cancer Services Operational Group
Society and College of Radiographers	South London & Maudsley NHSFT
South Eastern Health and Social Care Trust	South West Yorkshire Partnership NHS Foundation Trust
South Wales Cancer Network	St Helens and Knowsley Teaching Hospitals NHS Trust
Southern Health & Social Care Trust	Stockport Clinical Commissioning Group
Staffordshire and Stoke on Trent Partnership NHS Trust	Teenage Cancer Trust
Takeda UK Ltd	Teva UK
Teenagers and Young Adults with Cancer	The Institute of Cancer Research
The British Society for Haematology	uMotif Digital Health
The Patients Association	University Hospitals Birmingham
University Hospital Birmingham NHS Foundation Trust	Welsh Government
Velindre NHS Trust	Western Health and Social Care Trust
Welsh Scientific Advisory Committee	Wicked Minds
Western Sussex Hospitals NHS Trust	WMUK

Wigan Borough Clinical Commissioning Group	Yorkshire and Humber Strategic Clinical Network
York Hospitals NHS Foundation Trust	

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F.3 Individuals carrying our literature reviews and complementary work

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Manager	
Coral McCarthy[i]	National Collaborating Centre for Cancer, Cardiff
Lianne Gwillim	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Dr Laura Bunting[ii]	National Collaborating Centre for Cancer, Cardiff
Dr Mia Schmidt Hansen	National Collaborating Centre for Cancer, Cardiff
Senior Health Economist	
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Health Economists	
Professor Deborah Fitzsimmons	Academic Director, Swansea Centre for Health Economics, Swansea University
Dr Bernadette Sewell	Health Economist, Swansea Centre for Health Economics, Swansea University
Dr Kateryna Onishchenko[iii]	Health Economist, Swansea Centre for Health Economics, Swansea University
Dr Mari Jones	Research Fellow, Swansea Centre for Health Economics, Swansea University
Professor Ceri Phillips	Professor of Health Economics and Head of College, Swansea Centre for Health Economics, Swansea University
Information Specialists	
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Elise Hasler	National Collaborating Centre for Cancer, Cardiff

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[i] February 2014 – March 2015
[ii] Until August 2015
[iii] Until June 2015