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Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation

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Abstract

Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation

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Objectives: To determine the clinical and cost-effectiveness of adding rituximab to the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy regime for adult patients with diffuse large B-cell lymphoma (DLBCL).

Data sources: Electronic bibliographic database.

Review methods: Comparative studies were selected for review if they addressed the clinical or cost-effectiveness of adding rituximab to CHOP in people aged at least 18 years with DLBCL. The internal validity of the study was assessed through the use of the validated Jadad scoring system. Data were abstracted into standardised data extraction forms. Costs were estimated through resource use data taken from the published trial and the unpublished sponsor submission. Unit costs were taken from published sources, where available. An economic evaluation was undertaken to evaluate the cost-effectiveness of R-CHOP compared with CHOP alone for patients with DLBCL using data sources and methodology similar to the manufacturer's submission.

Results: In the systematic review of effectiveness, one randomised controlled trial was identified. The study was, in most respects, methodologically rigorous and well conducted and the statistical evidence favoured the addition of rituximab to CHOP. The total cost of rituximab with CHOP (R-CHOP) and CHOP alone estimated from the model developed by ScHARR was £14,456 and £5773, respectively, for patients aged 60 years and over, and £15,181 and £7311 for patients aged less than 60 years over a 15-year time horizon. The ScHARR model estimated that the addition of rituximab to CHOP generated an additional 0.82 QALY at an extra cost of £8683 compared with CHOP alone therapy over a 15-year time horizon, a cost/quality-adjusted life-year (QALY) ratio of £10,596 for patients aged 60 years or more. For patients aged under 60 years, 1.05 QALY were generated at an additional cost of £7870, a cost/QALY ratio of £7533. Assuming that the societal value of a QALY was £30,000 then R-CHOP is cost-effective compared with CHOP in the treatment of DLBCL.

Conclusions: In the short term, the addition of rituximab to the CHOP regimen increased the likelihood of a complete-response by 20% without a significant rise in the risk of a serious adverse event in people aged 60 years or older. Over a 2-year follow-up period, the intervention reduced the risk of death, progression or relapse by 45% and reduced the risk of death by 47% in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. The cost-effectiveness modelling presented here has shown that rituximab in combination with CHOP chemotherapy regimen is likely to be considered a cost-effective treatment for DLBCL when compared with the current standard treatment, CHOP chemotherapy only. Analysis of quality of life (QoL) in the area of NHL is limited and only one cost–utility analysis for the treatment of CHOP in NHL was identified. Both the SCHARR and the manufacturer's models utilised QoL utility scores from an unpublished data source. Further research within this area would help to improve the robustness of QoL utility analysis within DLBCL and also NHL as a whole.Further clinical trials might also establish whether R-CHOP may replace peripheral blood stem cell transplant in high-risk patients and whether the doses of chemotherapy in the elderly may be reduced if rituximab is added to less intensive regimens.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Antibody An immunoglobulin molecule that has a specific amino acid sequence by virtue of which it interacts only with the antigen that induced its synthesis in cells of the lymphoid series (especially plasma cells) or with antigen closely related to it. Antibodies are classified according to their mode of action as agglutinins, bacteriolysins, haemolysins, opsonins, precipitins, etc.

Antigen A substance that is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibodies or specifically sensitised T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulates, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (epitopes) combines with antibody or a specific receptor on a lymphocyte.

B-cell A type of lymphocyte normally involved in the production of antibodies to combat infection. It is a precursor to a plasma cell. During infections, individual B-cell clones multiply and are transformed into plasma cells, which produce large amounts of antibodies against a particular antigen on a foreign microbe. This transformation occurs through interaction with the appropriate CD4 T-helper cells.

CD20 Unglycosylated phosphoproteins expressed only on B-cells. They are regulators of transmembrane calcium conductance and thought to play a role in B-cell activation and proliferation.

Lymph The almost colourless fluid that bathes body tissues and is found in the lymphatic vessels that drain the tissues of the fluid that filters across the blood vessel walls from blood. Lymph carries lymphocytes that have entered the lymph nodes from the blood.

Lymphoblast Often referred to as a blast cell. Unlike other usages of the suffix blast, a lymphoblast is a further differentiation of a lymphocyte, T or B, occasioned by an antigenic stimulus. The lymphoblast usually develops by enlargement of a lymphocyte, active re-entry to the S phase of the cell cycle, mitogenesis and production of much mRNA and ribosomes.

Lymphocyte White cells of the blood that are derived from stem cells of the lymphoid series. Two main classes are recognised, T and B lymphocytes, the latter responsible (when activated) for production of antibody, the former subdivided into subsets (helper, suppressor, cytotoxic T-cells) and responsible both for cell-mediated immunity and for stimulating B-cells.

Lymphoma Malignant tumour of lymphoid cells. Lymphomas are of either Hodgkin's or non-Hodgkin's type.

Non-Hodgkin's lymphoma A group of lymphomas which differ in important ways from Hodgkin's disease and are classified according to the microscopic appearance of the cancer cells. There are many different subtypes of non-Hodgkin's lymphoma; some of these are fast growing and life threatening, others are slow growing and may not require immediate treatment.

T-cell A class of lymphocytes, so called because they are derived from the thymus and have been through thymic processing. Involved primarily in controlling cell-mediated immune reactions and in the control of B-cell development. The T-cells coordinate the immune system by secreting lymphokine hormones.

List of abbreviations

ABMT	autologous bone marrow transplantation
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisolone
CI	confidence interval
CIC	commercial-in-confidence
CR	complete response/complete responder
CRu	unconfirmed complete response
DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EVI	expected value of information
EVPI	expected value of perfect information
GELA	Groupe d'Etude des Lymphomes de l'Adulte
HDC	high-dose chemotherapy
HIV	human immunodeficiency virus
ILSG	International Lymphoma Study Group
IPI	International Prognostic Index
IWF	International Working Formulation
LDH	lactate dehydrogenase
LY	life years
LYG	life years gained
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Clinical Excellence
NR	non-responder (and relapse from complete responders)
ONS	Office of National Statistics
PR	partial response
QALY	quality-adjusted life-years
QoL	quality of life
QUOROM	Quality of Reporting of Meta-analyses
R-CHOP	rituximab in addition to cyclophosphamide, doxorubicin, vincristine, prednisolone
RCT	randomised controlled trial
REAL	Revised European American Lymphoma
ScHARR	School of Health and Related Research
SIGN	Scottish Intercollegiate Guidelines Network
SNLG	Scottish and Newcastle Lymphoma Group
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Description of proposed service

Rituximab, a novel immunotherapeutic agent, is proposed for first-line use, in its currently licensed indication for stage II–IV diffuse large B-cell lymphoma, in conjunction with the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy regime.

Epidemiology and background

Non-Hodgkin's lymphoma (NHL) is a cancer of the lymphatic tissue, causing enlargement of lymph nodes and generalised symptoms. It is a heterogeneous condition. Diffuse large B-cell lymphoma (DLBCL), a clinical subtype of NHL, behaves in an aggressive fashion, with a short natural history but a long-term survival rate of about 30% with current therapies. In an average pre-2003 health authority covering 500,000 individuals, 22–23 people will present each year with DLBCL. Most will be over 50 years old. The primary objective of current treatments for this condition is to induce cure. First-line therapy is usually CHOP chemotherapy with or without radiotherapy. Second-line treatment is usually high-dose chemotherapy supported by bone marrow or peripheral blood stem cell transplant in fitter patients. For others, palliative chemotherapy is indicated.

Objectives

A systematic review of the literature was commissioned to determine the clinical and cost-effectiveness of adding rituximab to CHOP for adult patients (≥18 years old) with DLBCL. The primary outcome was survival free of progression, relapse or death. Secondary outcomes were overall survival, response rates and toxic effects.

Data sources

Fifteen electronic bibliographic databases were searched to identify all literature relating to the clinical and cost effectiveness of rituximab for the treatment of aggressive NHL.

Review methods

Comparative studies were selected for review if they addressed the clinical or cost-effectiveness of adding rituximab to CHOP in people aged ≥18 years with DLBCL. The internal validity of the study was assessed through the use of the validated Jadad scoring system. Data were abstracted into standardised data extraction forms.

Number and quality of studies and direction of evidence

In the systematic review of effectiveness, one randomised controlled trial (RCT) was identified. No other comparative studies of any design were identified. Although there were minor inadequacies in trial design and reporting, the study was, in most respects, methodologically rigorous and well conducted. The statistical evidence favoured the addition of rituximab to CHOP.

Summary of benefits

In the short term, the addition of rituximab to the CHOP regimen increased the likelihood of a complete-response by 20% ($p = 0.009$), without a significant rise in the risk of a serious adverse event (8%; $p = 0.19$), in people aged ≥60 years. Over a 2-year follow-up period, the intervention reduced the risk of death, progression or relapse by 45% ($p < 0.001$) and reduced the risk of death by 47% ($p = 0.007$) in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. Arguments are presented that clinical effectiveness can be derived for a younger population on the grounds that disease biology is consistent by age and prognosis is inversely correlated with age.

Costs

Costs were estimated through resource use data taken from the published trial and the

unpublished sponsor submission. Unit costs were taken from published sources, where available. The total cost of rituximab with CHOP (R-CHOP) and CHOP alone estimated from the model developed by ScHARR was £14,456 and £5773, respectively, for patients aged ≥60 years and £15,181 and £7311 for patients aged <60 years over a 15-year time horizon. The manufacturer's (Roche) model estimated the total cost of rituximab with CHOP (R-CHOP) and CHOP alone as £11,807 and £2892, respectively, for patients aged ≥60 years and £14,643 and £5920 for patients aged <60 years over a 15-year time horizon.

Cost per quality-adjusted life-year (QALY)

An economic evaluation was undertaken to evaluate the cost-effectiveness of R-CHOP compared with CHOP alone for patients with DLBCL. Although the data sources and methodology employed were similar to the Roche company submission, the interpretation and results were numerically different. However, the overall conclusions regarding the overall cost-effectiveness were the same. The model employed by Roche estimated that treatment with R-CHOP generated 1.45 more QALY at an extra cost of £8915 compared with CHOP treatment over a 15-year time period, a cost/QALY ratio of £6143 for patients aged ≥60 years. For patients aged <60 years, 1.29 QALY were generated at an additional cost of £8723, a cost/QALY ratio of £6770. The ScHARR model estimated that the addition of rituximab to CHOP generated an additional 0.82 QALY at an extra cost of £8683 compared with CHOP alone therapy over a 15-year time horizon, a cost/QALY ratio of £10,596 for patients aged ≥60 years. For patients aged <60 years, 1.05 QALY were generated at an additional cost of £7870, a cost/QALY ratio of £7533. If we were to assume that the societal value of a QALY (the amount that one is prepared to pay to gain 1 QALY) was £30,000 then R-CHOP would be considered cost-effective compared with CHOP in the treatment of DLBCL. Extensive sensitivity analysis including both probabilistic and one-way sensitivity analysis undertaken in both models shows the overall results to be particularly robust and therefore R-CHOP appears to be a cost-effective treatment for DLBCL.

Conclusion

Clinical effectiveness

In the systematic review of effectiveness, one RCT was identified. In the short term, the addition of rituximab to the CHOP regimen significantly increased the likelihood of a complete response, without a significant rise in the risk of a serious adverse event, in people aged ≥60 years with stage II–IV DLBCL. Over a 2-year follow-up period, the intervention significantly prolonged survival without progression or relapse (the primary outcome), and significantly prolonged overall survival in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. Arguments are presented that clinical effectiveness can be derived for a younger population on the grounds that disease biology is consistent by age and prognosis is inversely correlated with age.

Cost-effectiveness

The cost-effectiveness modelling presented here has shown that rituximab when used in combination with the CHOP chemotherapy regimen is likely to be considered a cost-effective treatment for DLBCL when compared with the current standard treatment, CHOP chemotherapy only. Although both the ScHARR and the Roche models are based on the same data and use the same methodology, different interpretations of the clinical outcomes and costs have produced different results. However, the difference in the cost/QALY outcome does not lead to a difference in the overall result that the addition of rituximab to the CHOP regimen is likely to be considered cost-effective. Extensive sensitivity analysis undertaken in both models has shown the results to be particularly robust.

Need for further research

As rituximab is a relatively recent anticancer drug developed for the treatment of malignancies arising from B-lymphocytes, there data are currently available from only one RCT comparing R-CHOP and CHOP treatments in DLBCL. However, as stated by Roche in their submission, there are other relevant trials ongoing.

Analysis of quality of life (QoL) in the area of NHL is limited and only one cost–utility analysis for the treatment of CHOP in NHL was identified. Both the SCHARR and ROCHE models utilised QoL utility scores from an unpublished data source. Further research within this area would help to improve the robustness of QoL utility analysis within DLBCL and also NHL as a whole. One way of achieving this would be for the National Institute for Clinical Excellence to commission certain cancer networks to record stage, International Prognostic Index IPI score, outcome and QoL data for a cohort of patients receiving R-CHOP for DLBCL.

Further clinical trials might also establish whether R-CHOP may replace peripheral blood stem cell transplant in high-risk patients and whether the doses of chemotherapy in the elderly may be reduced if rituximab is added to less intensive regimens.

Chapter 1

Aim of the review

This review aims to determine whether the use of rituximab, a novel immunotherapeutic agent, in conjunction with the cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy regime as first-line therapy for diffuse large B-cell lymphoma (DLBCL) is clinically and cost-effective.

Chapter 2
Background

Description of underlying health problem

Epidemiology

Non-Hodgkin's lymphomas (NHLs) are one of the leading causes of death from cancer, accounting for 3% of cancer deaths.[1] An international collaborative study found DLBCLs to be the most common subcategory (accounting for 30.6%) of all NHLs.[2] The median age at diagnosis was reported to be 64 years in a large international case series[2] and 67 years in a series of 2729 service users in the North of England and Scotland (Proctors, Scottish and Newcastle Lymphoma Group (SNLG): personal communication regarding material from the Vanguard database, 2002). Relevant data are given in *Table 1*.

At the time these most recent figures were collected, the incidence of NHL was still rising.[3] The rate of increase is, generally, reported to be around 3–4% per annum.[4–6] With an annual increase of 4%, an average English health authority of 500,000 would see 28 cases (29 in Wales) during the year 2003. The cause of this increase is unclear, especially as some of the risk factors (see the 'Aetiology' section below) appear to be falling.[7]

Aetiology

The causes of NHL in general, and DLBCL specifically, are unclear. There are a number of well-established risk factors, such as infectious agents (e.g. HIV[8]), immunosuppression (e.g. postorgan transplantation[9]), genetic susceptibility (e.g. ataxia telangeictasia[10]) and environmental factors (e.g. exposure to agrochemicals[11]).

Pathology

Background

NHLs are a heterogeneous group of cancers that are characterised by abnormal growth of tissue in the lymphatic system. The lymphatic system comprises the tissues, organs and vessels that produce, store and deliver cells that fight infection, or 'lymphocytes'. Of these, there are two main classes: T and B lymphocytes. 'T-cells' are responsible both for cell-mediated immunity and for stimulating 'B-cells'. When activated, B-cells produce antibody. Lymphoma may be classified as a B-cell or T-cell NHL, depending on whether it is B or T lymphocytes that are proliferating at an abnormal rate. Approximately 85% of all NHLs are of B-cell origin and the remaining 15% of T-cell origin.[12]

DLBCLs are a pathological subclass of NHLs grouped together for clinical purposes.[13] All are composed of large cells with vesicular nuclei, prominent nucleoli, basophilic cytoplasm and a moderate to high proliferation fraction. They typically present as a nodal or extranodal mass with fast tumour growth associated with systemic symptoms, such as sweats, fatigue and fever. In about 40% of cases, these lymphomas appear in areas outside lymph nodes, including the digestive tract, skin, bone, thyroid and testes.

TABLE 1 *Incidence and prevalence*

	England and Wales	England	Wales
All NHLs: number of cases (1997)[a]	7640	6930	430
All NHLs: crude rate per 100,000[b]	14.7	14.1	14.9
DLBCL: estimated number of cases[c]	2338	2121	132
DLBCL: crude rate per 100,000	4.5	4.3	4.5
DLBCL: projected number of cases, 2003[d]	3076	2790	173
DLBCL: projected crude rate per 100,000, 2003[d]	5.8	5.6	5.9

[a] The Office of National Statistics (ONS) most recent figures are for 1997.[3]
[b] Estimated figures based on ONS figures: England and Wales, 51,411,000; England, 49,284,000; and Wales, 2,927,000.[3]
[c] The Non-Hodgkin's Lymphoma Classification Project identifies 30.6% of all NHLs to be DLBCLs.[2]
[d] Estimated population for 1999 based on ONS figures: England and Wales, 52,689,900; England, 49,752,900; and Wales, 2,937,000.[1]

Surgery is typically carried out for diagnostic purposes and, once the DLBCL is identified, it is staged to find out how far the disease has spread. The standard staging system for non-Hodgkin's lymphomas, described in Appendix 1, reflects both the number of sites of involvement and the presence of disease above or below the diaphragm.[14]

Systems of classification

Classificatory systems for NHLs have developed alongside understanding of the different cellular components of the lymphatic system that the cancer process affects. However, as there is rarely consensus and unity of practice with regard to classification, it is imperative to recognise a number of key taxonomies.

Of the many diagnostic systems proposed before 1982, only the Kiel Classification[15] and the International Working Formulation (IWF)[16] survived in use through until the 1990s, the Kiel Classification mainly in Europe and the IWF mainly in the USA. The Kiel Classification, which introduced the distinction between T and B malignancies, grouped together NHLs into two prognostic groups, based primarily on morphology and cytology. Under this scheme, 'low-grade' lymphomas were recognised to have a long median survival, but to be incurable at advanced stages; 'high-grade' lymphomas, on the other hand, had a shorter natural history but were sometimes curable. DLBCL had no exact corollary under this schema, but many of the 'high-grade' centroblastic and B-immunoblastic lymphomas would now be grouped under that term. The Kiel system suffered from problems of poor reproducibility among pathologists and did not include primary extranodal lymphomas. The IWF divided NHLs into three prognostic groups, based solely on histopathologic criteria: low, intermediate and high grades. Most of the diseases now known as DLBCL would have been known as 'large cell' and included under the heading 'G. Malignant lymphoma, diffuse (DL)', a category of intermediate NHLs.

By the 1990s both the IWF and the Kiel system needed to address immunophenotypic, molecular genetic and clinical information that had emerged since the early 1980s. The International Lymphoma Study Group (ILSG) established the Revised European American Lymphoma (REAL) classification in 1994, based on morphology, immunophenotype, genotype and clinical features. The category DLBCL as used in this report, emerges in the REAL classification ('B cell neoplasms; Type II – Peripheral B cell neoplasms; Type I – Diffuse large B cell lymphoma').[13]

In the USA, the National Cancer Institute (NCI) modified the REAL system, encouraging the descriptors, 'indolent' and 'aggressive' instead of low, intermediate or high grade.[17] Aggressive lymphomas grow quicker than indolent lymphomas, but generally respond better to chemotherapy. Under this system, DLBCL is considered an aggressive lymphoma, and is known simply as 'diffuse large cell lymphoma'.

The ILSG recently agreed to a proposal by the WHO to broaden the consensus of the REAL classification, to incorporate new data and to publish the updated classification as the new WHO lymphoma classification. The International Lymphoma Study showed that pathologists could use the REAL classification, with inter-observer reproducibility better than for other classifications. New entities not specifically recognised in the Working Formulation accounted for 27% of the cases. Diseases that would have been lumped together as 'low grade' or 'intermediate-high grade' in the Working Formulation showed marked differences in survival, confirming that they need to be treated as distinct entities. Clinical features such as the International Prognostic Index (IPI) were also important in determining patient outcome. As a result, the WHO adapted the REAL classification for the WHO-REAL system.[18] The WHO Clinical Advisory Committee concluded that clinical or prognostic groupings of lymphoid neoplasms was neither necessary nor desirable. In part this is because each lymphoma is seen as a separate disease process that may be more or less aggressive in individual patients. Patient treatment is determined by the specific type of lymphoma, with the addition of grade within the tumour type, if applicable, and clinical prognostic factors such as the IPI (see the section 'The International Prognostic Index', p. 5). The REAL-WHO schema classifies 'Diffuse large B-cell lymphoma' under 'Section II. Peripheral B-cell neoplasms'.

To summarise, DLBCL is a classification that derives from the REAL classification system and is perpetuated in the REAL-WHO scheme. The neoplasms which it comprises are named or grouped differently in other classificatory schema. Therefore, this review defines its population inclusion criteria in terms of REAL and REAL-WHO.

Prognosis

Prognostic factors in DLBCL can be categorised as those related primarily to the service user, those related to the tumour and those related to aggressiveness indicators.

Patient-related variables

The most consistent observation among patient-related prognostic variables is the poor outcome found with advanced age.[19,20] Performance status, as defined by the Eastern Cooperative Oncology Group (ECOG),[21] is also important (see Appendix 2).[22] The existence of serious concomitant illness such as lung, heart or kidney disease might greatly limit the drugs that can be used and thus alters the physician's ability to treat the patient effectively. In particular, elderly patients with DLBCL represent a group that is difficult to treat because of comorbidity, diminished organ functions, altered drug metabolism and irregular drug clearance rates.[23]

Tumour-related variables

Tumour-related variables such as high tumour burden[22,24] or proliferating fraction[25] are associated with a poor prognosis. Specific sites of tumour involvement, especially the bone marrow, but also other sites such as the gastrointestinal tract, have been identified as significant adverse prognostic factors.[26] Some extranodal sites, such as brain[27] or testis,[28] require special treatment strategies, and DLBCL which have arisen in those sites constitute particularly aggressive malignancies (see the section 'Aggressiveness indicators', below). Response rate after primary treatment is highly predictive of outcome. More rapidly responding patients (those with high tumour sensitivity) have a better outlook.[29,30]

Aggressiveness indicators

The many subtypes of NHL are broadly divided into two major subgroups: 'indolent' (25–30%) and 'aggressive'. Indolent lymphomas are characterised by a low-grade histological appearance, slow growth but relapsing disease progression. They often have a high initial response rate, remission after relapse is possible and patients have a median survival rate of as long as 10 years. However, they are usually incurable, with final resistance to therapy resulting in death.[31,32]

Aggressive NHLs are defined as tumours that are likely to cause death in a short period if left untreated. Unlike indolent lymphomas, they are potentially curable with current therapies. By definition, aggressive NHLs proliferate faster, which is to say they have more cells in cycle. This factor makes them more sensitive to chemotherapy (which works on the cell cycle), but also more effective at repairing. DLBCL is an aggressive lymphoma.

The level of aggression affects prognosis. The adverse prognosis associated with an elevated serum lactate dehydrogenase (LDH) level reflects a bulky tumour and/or particularly rapid growth.[24] The unfavourable prognostic role of serum level of b2-microglobulin in diffuse large B-cell lymphomas has also been documented.[33]

The International Prognostic Index (IPI)

The International non-Hodgkin's Lymphoma Prognostic Factors Project has analysed the results of more than 3000 patients with aggressive lymphomas and designed an IPI.[34] The IPI incorporates five factors: age (>60/≥60 years); stage (localised/disseminated); LDH level (normal/above normal); ECOG performance status (PS; 0–1/≥2);[21] and, number of extranodal disease sites (0–1/>1). For each negative prognostic factor a score of 1 is assigned, and for each positive factor a score of zero, so that a high score predicts for poor prognosis. In younger patients, an age-adjusted index based on performance status, stage and LDH is used.

Both indices define four prognostic groups: low risk, low-intermediate risk, high-intermediate risk and high risk (*Table 2*). These groupings have a high predictive value for both likelihood of complete response (CR) after initial treatment and overall survival in most types of lymphoma.

Significance in terms of ill-health (burden of disease)

The nature of NHL in general, and DLBCL in particular, and the duration of the disease suggest that both individually and at a population level it is responsible for a considerable amount of morbidity and mortality. In 1998, NHL accounted for 0.7% of all deaths and 2.9% of all cancer deaths in England and Wales, making it the 11th most common cause of cancer mortality,[35] and there is evidence to suggest that its incidence is increasing.

Current service provision

Objectives of treatment and important health outcomes

There are at least five potential objectives in treating DLBCL, or indeed any other cancer:

TABLE 2 *Outcome of patients with aggressive NHL by risk group*[34]

Risk group	Age	No. of risk factors	5-year survival rate (%)
Low	All ages	0 or 1	73
Low-intermediate		2	51
High-intermediate		3	43
High		4 or 5	26
Low	≤60 years (age-adjusted)	0	83
Low-intermediate		1	69
High-intermediate		2	46
High		3	32

- to eradicate the cancer and so effect a long-term cure
- to achieve long-term cancer stasis or regression with the aim of prolonging life
- to treat symptoms, particularly those arising from relapse or recurrence or disease progression, and so improve quality of life (QoL)
- to help patients come to terms with their condition, again improving QoL
- to manage the terminal stages of the disease so allowing dignified death, free of discomfort and distress.

These objectives predict that the following outcomes are likely to be of potential importance:

- absence of cancer at given points in time following diagnosis
- duration of survival
- QoL
- patient and carer satisfaction.

However, because aggressive NHLs are potentially curable (see the section 'Aggressiveness indicators', p. 5), the primary objective of current treatments for DLBCL is to induce cure (absence of any clinical symptoms of disease).

Current service provision

First-line therapy: limited disease (stages I–II)

CHOP chemotherapy is the standard treatment for patients with stage I–II DLBCL.[36] In some cases this may be followed by involved-field radiation therapy.[37,38]

Treatment with eight cycles of CHOP results in 40–50% complete remission, a 3-year survival rate of 30% and a 35–40% overall survival rate.[39] Adverse effects of CHOP may result in fatal toxicity (~1–3%) and around 30% develop life-threatening toxicities (grade 4 on the NCI toxicity scale, for which see Appendix 3).[36,40,41] Adverse events resulting from myelosuppressive agents include neutropenia, thrombocytopenia and anaemia resulting in infections or reactivation of infections. Other common side-effects are neurological problems (vincristine), cardiac symptoms (doxorubicin), alopecia, gastrointestinal irritation, anxiety, skin rash and decreased sexual interest.

Patients treated with an abbreviated aggressive combination chemotherapy followed by involved-field irradiation have been known to achieve a complete response rate of >90% and a 5-year disease-free survival of 80–85%.[38] Combined strategy with three cycles of a CHOP chemotherapy regimen followed by involved-field radiotherapy is less toxic than eight courses of CHOP as exclusive treatment, with life-threatening toxic effects occurring in 30 and 40% of cases, respectively.[37] In summary, combined CHOP–radiotherapy appears to be more effective than CHOP alone for patients with limited disease.

First-line therapy: advanced disease (stages III–IV)

CHOP is the standard chemotherapy regimen for patients with stage III–IV DLBCL, producing a 53% complete remission rate and a 5-year overall survival of near 50%.[36]

Involved field irradiation to initial bulky (>10 cm) or semibulky sites (5–10 cm) of disease is not a standard treatment option. However, non-randomised studies show it to be a reasonable choice for the individual patient with advanced disease who has achieved a complete remission after chemotherapy.[42]

Treatment of relapsed or refractory disease

High-dose chemotherapy (HDC), supported by autologous or allogeneic bone marrow transplantation, or autologous peripheral stem cell transplantation, is standard therapy for patients

with chemosensitive relapsed DLBCLs, where performance status is high.[43–48] Despite a high response rate, studies suggest as few as 10% of relapsed patients achieve long-term survival with conventional salvage chemotherapy, with a median survival after relapse of 4–6 months.[49–51] HDC supported by autologous bone marrow transplantation (ABMT) produces a 30–55% complete remission rate (overall response rate: 84%) in patients with chemosensitive relapse, with a cure rate of 30–50%.[43,52]

Patients with chemoresistant relapse, and also for those with primary refractory lymphoma, are unlikely to benefit from the use of HDC supported by stem cell transplantation.[48] Earlier identification of high-risk patients using the IPI and anticipation of HDC before chemoresistance may allow improved outcome with this treatment modality.

In elderly patients, or those whose medical condition precludes aggressive treatment, palliative care may be offered with relatively low-dose chemotherapy directed at symptom control.

Current service cost

Because treatment of DLBCL is part of general haematological or oncology services, the cost of caring for this group of patients is very difficult to derive from routine financial information available in the NHS. However, consideration of the variety of treatments to which an individual might be exposed during the course of their illness suggests that the costs of caring for DLBCL are likely to be considerable. In this, the support required from both primary and palliative care services in the terminal stages of the disease should not be underestimated.

Variation in services

A position paper released in 2002 by the British Committee for Standards in Haematology concludes that "A CHOP-like regimen plus rituximab is indicated for the treatment of patients over the age of sixty with newly diagnosed CD20 positive [DLBCL]". Although this guidance may encourage some uniformity of treatment, recent practice outside of trials is best understood through retrospective audit.

The database operated by the SNLG (see the section 'Epidemiology', p. 3) has captured population-based data since 1994. They hold treatment and outcome data on more than 95% of the lymphomas presenting in a catchment of 8.5 million.[53] The industrial submission contains data extracted from this database on 2790 patients with a median age of 67 years (range, 20–98 years). These patients were diagnosed as having 'high-grade lymphomas' according to the Kiel classification up to 1995 and DLBCL from then to September 2002. The variations in treatment may be for a variety of treatments, including clinical preference, the age and performance status of the service user and, in the case of second-line and salvage therapies, whether the patient has been identified as refractory to chemotherapy.

Of 2790 patients, 599 (21%) did not receive chemotherapy, of whom 496 were aged ≥60 years; 1359 (49%) received CHOP and 832 (30%) other chemotherapy regimes. CHOP was the most common treatment for those aged ≥60 years, received by 816 out of 1888 (43%) people in this age bracket. Of the 2191 patients receiving first-line chemotherapy, 1349 achieved a CR with their initial therapy, of whom some might be expected to have relapsed. Of these, and the 842 who did not receive a CR, 420 received second-line chemotherapy. Second-line treatment produced a CR rate of 93/420 (22%); 110 out of 420 patients (26%) who received second-line therapy (including nine aged ≥60 years) received high-dose chemotherapy and autologous peripheral blood stem cell transplants as salvage therapy.

Description of new intervention

Identification of patients and important subgroups

Rituximab has been proposed for first-line treatment of patients with DLBCL, in combination with CHOP chemotherapy. CR to first-line treatment is very important in NHL: of those who do not achieve CR, few become long-term survivors.[2,54]

Criteria for treatment

It is proposed that rituximab, in combination with CHOP, be available to all people with stage II–IV DLBCL, in whom it is not contraindicated.

Intervention

Therapeutic classification

Rituximab is a 'monoclonal antibody'. Monoclonal antibodies are produced by fusing single antibody-forming cells (generated in laboratory mice) to tumour cells (grown in culture). The resulting 'hybridoma' cell produces relatively large quantities of identical antibody molecules. By allowing the hybridoma to multiply in culture, it is

possible to produce a population of cells, each of which produces identical antibody molecules. These antibodies are called 'monoclonal antibodies' because they are produced by the identical offspring of a single, cloned antibody-producing cell. Once a monoclonal antibody is made, it can be used as a specific probe to track down and purify the specific protein that induced its formation.

Rituximab uniquely targets only the CD20 surface marker/antigen, which is expressed on B cells in more than 90% of NHLs.[13,55] Rituximab causes 'lysis' (rupture of cell membranes and loss of cytoplasm) of both normal and cancerous B lymphocytes. This halts the proliferation of cancerous cells. The body replaces the normal cells after several months.

Brand and generic name

Rituximab is the generic name, Hoffman-La Roche's brand name being MabThera®. Rituximab is also known as IDEC-C2B8 and Rituxan.[56]

Dosage form and route

Rituximab is sold as a concentrate for solution for infusion. The BNF prescribes intravenous administration intermittent in glucose 5% or sodium chloride 0.9%. It is diluted to 1–4 mg/ml and the bag gently inverted to avoid foaming.[56]

Licensed indications

Rituximab is indicated for the treatment of patients with CD20-positive DLBCL in combination with CHOP chemotherapy. It is also indicated for treatment of patients with stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.[56]

Contraindications

Rituximab is contraindicated in patients with known hypersensitivity to any of its components or to murine proteins.[53]

Warnings

Full resuscitation facilities should be at hand and, as with other cytotoxics, treatment should be undertaken under the close supervision of a specialist.

Rituximab should be avoided during pregnancy unless the potential benefit to the mother outweighs risk of B-lymphocyte depletion in the foetus. It is also contraindicated in women who are breast-feeding. Effective contraception is required during treatment and for 12 months after treatment.

Rituximab should be used with caution in patients receiving cardiotoxic chemotherapy or with a history of cardiovascular disease because exacerbation of angina, arrhythmia and heart failure have been reported. Transient hypotension occurs frequently during infusion and antihypertensives may need to be withheld for 12 hours before infusion.

Infusion-related side-effects (including cytokine release syndrome) are reported commonly with rituximab and occur predominantly during the first infusion; they include fever and chills, nausea and vomiting, allergic reactions (such as rash, pruritus, angioedema, bronchospasm and dyspnoea), flushing and tumour pain. Patients should be given an analgesic and an antihistamine before each dose of rituximab to reduce these effects. Premedication with a corticosteroid should also be considered. The infusion may have to be stopped temporarily and the infusion-related effects treated. Evidence of pulmonary infiltration and features of tumour lysis syndrome should be sought if infusion-related effects occur.

Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab. Patients with a high tumour burden and those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).[56]

Personnel involved

The delivery of rituximab requires no additional personnel to the administration of CHOP, namely a senior clinician (specialist registrar or above), a specialist nurse and a specialist pharmacist.

Setting

Outpatients would receive intravenous transfusion in the same chemotherapy suite as would be used for the administration of CHOP.

Equipment required

The intervention would require no equipment outside of that normally associated with a chemotherapy suite, that is: electrical infusion pumps to deliver drugs; triple lumen; scalp cooling equipment; water cooler; defibrillator and resuscitation trolley; vacuum probes; oxygen flowmeter probes; reclining chairs; and sundry medical items, such as manual monitoring equipment. Some clinics advise that rituximab is infused while the patient is on a bed, rather than in a chair.

Length of treatment

Each service user would expect to receive one treatment, every 3 weeks, for eight cycles; in other words, eight intravenous days (4–6 hours each) at the chemotherapy suite, over the course of 24 weeks.

Follow-up required

Service varies between clinics, but patients might expect to see their clinician perhaps four to six times during the first year and then four to six times over the next 3 years. Thereafter, they might expect to come in once per year.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

This systematic review was carried out according to the recommendations of the Quality of Reporting of Meta-analyses (QUOROM) statement (Appendix 4).[57]

Search strategy

The search aimed to identify all literature relating to the clinical and cost-effectiveness of rituximab (MabThera) for the treatment of aggressive NHL. The main searches were conducted in August and September 2002.

Sources searched

Fifteen electronic bibliographic databases were searched, covering biomedical, science, social science, health economic and grey literature. A list of databases is provided in Appendix 5.

In addition, the reference lists of relevant articles and sponsor submissions were handsearched and various health services research-related resources were consulted via the Internet. These included health economics and health technology assessment organisations, guideline-producing agencies, generic research and trials registers and specialist sites. A list of these additional sources is given in Appendix 6. Citation searches were conducted on the key paper[58] and its author using the Science and Social Science Citation Index facilities, MEDLINE and EMBASE.

Search terms

A combination of free-text and thesaurus terms were used. 'Population' search terms (e.g. lymphoma, lymphocytes, non-Hodgkin's, high-grade, intermediate-grade, large-cell) were combined with 'intervention' terms (e.g. rituximab, MabThera, Rituxan, antineoplastic agents). Copies of the search strategies used in the major databases are included in Appendix 7.

Search restrictions

No language, study/publication or date restrictions were applied to the main searches. The main searches performed in MEDLINE and EMBASE included filters for systematic reviews/meta-analyses, economic/QoL evaluations, controlled trials and guidelines, in order to assist with the identification of these types of articles (all other study types were also saved). The filters that were used in MEDLINE are included in Appendix 8.

Inclusion and exclusion criteria

The structured title was formulated as 'rituximab plus CHOP versus CHOP alone for DLBCL'. Comparative studies were included if: (a) the study population had untreated DLBCL that had been diagnosed according to the REAL, or REAL-WHO classificatory schema; (b) the study intervention was rituximab in combination with CHOP, and the study comparator was CHOP alone (where the cycles of CHOP in each arm were identical); and (c) study end-points included event-free survival (see below for definition). There were no language restrictions and studies reported only in abstract form were reported.

The primary outcome of interest for this study was event-free survival, with events defined as disease progression or relapse, death or initiation of new alterative treatment. Secondary outcomes were overall survival, response rates and toxic effects. Event-free and overall survival were calculated as the time from randomisation to the date of first-reported event or death, respectively. Response rate was defined in the terms laid down by Cheson and colleagues,[59] with patients considered to be responders if they demonstrated a CR or unconfirmed CR (see Appendix 9). Adverse events were defined as any adverse change from the patient's baseline condition, including intercurrent illness, that occurred during the course of the clinical trial after the start of treatment, whether or not considered related to trial treatment.

Reasons for exclusion were (a) a non-comparative study design; (b) populations other than those described above; (c) absence of the interventions and/or comparators described above; and (d) absence of 'event-free survival as the primary outcome of interest'.

The abstracts of potentially relevant citations were reviewed. After examining the full manuscripts of all potentially relevant abstracts, those deemed to be potential randomised controlled trials (RCTs) relating directly to the structured title were obtained.

Data extraction strategy

Data extraction was completed independently by two researchers and disagreement resolved by consensus. The Scottish Intercollegiate Guidelines Network (SIGN) forms were used for data extraction. Data on event-free survival, response rate, survival and safety were abstracted as reported.

Quality assessment strategy

The Jadad checklist[60] was used to determine study quality of RCTs. Two reviewers independently undertook the quality assessment, with any differences resolved by consensus.

Results

Quantity and quality of research available

Number of studies identified

The search retrieved 5273 citations.

Number and type of studies included

One study was included. This was a randomised, open-label, parallel-group, multicentre trial, performed by the French Groupe d'Etude des Lymphomes de l'Adulte (GELA) comparing CHOP and R-CHOP (rituximab in addition to cyclophosphamide, doxorubicin, vincristine, prednisolone) in elderly patients (aged 60–80 years) with newly diagnosed DLBCL.[58,61]

Number and type of studies excluded, with reasons for specific exclusions

Of the 5273 citations retrieved, 5211 were rejected on the basis of their title or abstract as not meeting the inclusion criteria (see the section 'Inclusion and exclusion criteria', p. 11). Of the 62 citations retrieved for more detailed evaluation, 53 were rejected on the same grounds. The remaining nine papers all described aspects of the same phase III RCT.[58,62–69] The literature search retrieved no other comparative studies that met the inclusion criteria. A flow chart is provided in Appendix 10, as recommended by the QUOROM statement.[57]

Quality and characteristics of studies

The GELA study scored 2 out of a possible 5 in the Jadad score (Appendix 11). This score reflects inadequacies in the reporting or the study design itself, which are associated with the potential for bias. The report states that, "Eligible patients were randomly assigned by the study co-ordinating center to treatment…".[58] However, no method of randomisation is reported either in the paper or in the industry submission. 'Blinding' was not addressed in the peer-reviewed paper.[58] The trial was described as open-label in the industry submission, but this aspect of study design and the decision not to blind were not discussed in either the peer-reviewed paper or the industrial submission.[61] Studies have shown that the lower the level of blinding, the greater is the overestimate in treatment effect.[70,71] However, although methodologists have quantified such exaggeration in RCTs from other clinical settings, the review group did not believe that their findings were generalisable to the outcomes of cancer progression trials, and no attempt was made to assess the exaggeration of the clinical effect.

In other regards, the GELA trial may be considered methodologically sound, and it should also be noted that there are serious practical objections to clinician blinding and also ethical objections to patient blinding. Clinician blinding could be achieved, for example, by administering a placebo saline solution to the CHOP-only arm. However, given that the majority of patients require treatment alteration or supportive care because of adverse effects on the first infusion of rituximab, the attendant medical staff and many patients could easily discern the makeup of most of the treatment arm. With this in mind, the ethical questions concern the value of a clinically unnecessary 4-hour placebo infusion for the control group, with the associated discomfort and increased risk of thrombosis.

Further study characteristics are presented in the SIGN methodology checklist in Appendix 12. The study recruited patients aged 60–80 years with previously untreated, stage II–IV DLBCL, with a performance status of 0–2 (good to fair), and no cardiac contraindication to doxorubicin. According to the manufacturer, Hoffman-LaRoche, the decision to carry out this trial in elderly patients was a pragmatic one, "based on the need of the researchers to obtain definitive answers to questions about the role of R-CHOP in DLBCL within an acceptable time-frame, rather than the consequence of any belief that older patients would respond differently to younger ones."[53]

Patients were stratified by centre and age-adjusted prognostic score. None of the clinical or pathological differences between treatment groups were significant. The inclusion criterion allowed only patients with untreated DLBCL who had been diagnosed according to the REAL or REAL-WHO schema. Central pathological review was completed for 97% of patients, and the results

confirmed the diagnoses of DLBCL in 90% of those assessed in the R-CHOP group and 85% in the CHOP group. Inter-observer reproducibility of 85% is consistent with the results of the ILSG's study, which informed the WHO Clinical Advisory Committee on their uptake of the REAL classification system.[18] Therefore, the presence of neoplasms other than DLBCL in this trial should be understood as a reflection of clinical reality in a pragmatic study, not a deviation from protocol. Further details of the GELA study population are presented in Appendix 13.

All patients received CHOP, the combination of 750 mg of cyclophosphamide per square metre of body-surface area on day 1; 50 mg of doxorubicin per square metre on day 1; 1.4 mg of vincristine per square metre, up to a maximum dose of 2 mg, on day 1; and 40 mg of prednisolone per square metre per day for 5 days. They were treated every 3 weeks for eight cycles of CHOP. Patients in the R-CHOP arm also received rituximab, at a dose of 375 mg per square metre, on day 1 of each of the eight cycles of CHOP. The rituximab infusion was interrupted in the event of fever, chills, oedema, congestion of the head and neck mucosa, hypotension or any other serious adverse event and was resumed when such an event was no longer occurring. No radiation therapy was scheduled or recommended at the end of treatment.

Patients who had grade 4 (severe) neutropenia or febrile neutropenia after any cycle of chemotherapy were given granulocyte colony-stimulating factor. If grade 4 neutropenia persisted during the next cycle, the doses of cyclophosphamide and doxorubicin were decreased by 50%. For patients with grade 3 (moderate) or 4 thrombocytopenia, the doses of cyclophosphamide and doxorubicin were decreased by 50%. If the neutrophil count was $<1500/mm^3$ or the platelet count was $<100{,}000/mm^3$ before a scheduled cycle, the cycle was delayed for up to 2 weeks, and then treatment was stopped. The doses of rituximab were not modified, but rituximab was discontinued when CHOP was stopped. The trialists stopped treatment if lymphoma progressed or the patient declined to continue or at the discretion of the investigator in cases of intercurrent illness or adverse events.

The GELA trialists assessed tumour responses after eight cycles of chemotherapy or at the end of treatment in accordance with the International Workshop criteria.[59] CR was defined as the disappearance of all lesions and of radiological or biological abnormalities observed at diagnosis and the absence of new lesions. An unconfirmed CR was defined as a CR with the persistence of some radiological abnormalities, which had to have regressed in size by at least 75%. Partial response was defined as the regression of all measurable lesions by more than 50%, the disappearance of non-measurable lesions and the absence of new lesions. Stable disease was defined as a regression of any measurable lesion by 50% or less or no change for the non-measurable lesions, but without growth of existing lesions or the appearance of new lesions. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25% or growth of any measurable lesion that had regressed during treatment by more than 50% from its smallest dimensions.

An adverse event was defined as any adverse change from the patient's baseline condition, whether it was considered related to treatment or not. Events were graded according to the NCI Common Toxicity Criteria grading system.[40] Grade 3 and 4 events (grades 2–4 for infections) were recorded in detail; grade 1 and 2 adverse events were not described.[58]

Tabulation of results

Results are presented in *Table 3*. More detailed tabulated results are presented in Appendix 14.

For the primary outcome, event-free survival, and for the secondary outcome, overall survival, relative risks and statistical measures of confidence presented are derived from the published report of the GELA trial. The GELA trial fitted a Cox proportional hazards model, adjusting for treatment and the following baseline prognostic factors: stage; number of extranodal sites; bone marrow involvement; ECOG score; albumin value; LDH value; β_2-microglobulin value; and IPI score. Terms for the interaction of each of these covariates with treatment were included in order to assess whether the treatment effect was consistent across different values of the covariates.[61] The number of patients at risk at 2 years after randomisation was 64 for the R-CHOP arm and 58 for the CHOP arm.[58]

Reports of the secondary outcome, response rate, were confused in the published report of the GELA trial. *Table 3* in the journal article reports 152 complete or unconfirmed complete responders in the R-CHOP arm and 124 in the CHOP arm. However, the text translates this as 76% for the R-CHOP arm and 63% for the CHOP arm, which either overstates the R-CHOP responders as a percentage of the intention-to-treat population or understates the CHOP responders as a percentage

TABLE 3 *Results*

	R-CHOP (n = 202)	CHOP (n = 197)	Relative risk (95% CI)	p
Primary outcome				
Two-year event free survival: % (95% confidence interval, CI)	57 (50 to 64)	38 (32 to 45)	0.55 (0.41 to 0.75)[a]	<0.001[a]
Secondary outcomes				
Two-year overall survival: % (95% CI)	70 (63 to 77)	57 (50 to 64)	0.53 (0.37 to 0.77)[a]	0.007[a]
Complete/unconfirmed complete responders: *n* (%)	152 (75)	124 (63)	1.20 (1.05 to 1.37)[b]	0.009[b]
Severe adverse events: *n* (%)	160 (79)	145 (74)	1.08 (0.96 to 1.20)[b]	0.19[b]

[a] Relative risks and statistical measures of confidence derived from the GELA publication.[58]
[b] Relative risks and statistical measures of confidence produced by the review team.

of the number assessed for response to treatment: two participants (1%) in the R-CHOP arm and seven (4%) in the CHOP arm could not be assessed, as treatment was stopped before evaluation of the tumour.[58] The review team used the data from the table, with the Cochrane Collaboration's Review Manager 4.1 software, to generate relative risks and statistical measures of confidence for the intention-to-treat population presented below. A fixed-effects model was used.

For the secondary outcome, toxic events, no aggregate figures, overall relative risks or statistical measures of confidence were available from the published data. Raw data from the industrial submission presented only aggregate percentages for severe adverse events (grade 3 or 4, 2–4 for infections): "Overall, 74% of patients *treated with CHOP* and 79% of those receiving R-CHOP experienced one or more adverse events" [our emphasis].[61] These percentages reflect the numbers treated, not the intention-to-treat population: one participant randomised to the CHOP arm died before treatment was administered.[58] The review team used these data with the Cochrane Collaboration's Review Manager 4.1 software to generate relative risks and statistical measures of confidence for the intention-to-treat population, presented below. A fixed effects model was used.

Discussion of results

The choice of comparators, the choice of outcome measures, the methods for comparing efficacy and the adverse effects reported in the GELA trial are comprehensive and clinically relevant. Despite the inadequacies in trial design and the reporting, with regard to blinding (see the section 'Quality and characteristics of studies', p. 12), the overall approach of the study is methodologically rigorous. Therefore, it seems likely that the direction of the effect is genuine. However, the weakness in trial design (see the section 'Quality and characteristics of studies', p. 12) would probably affect the estimates of the size of the effect, weakening it to an unknown degree.

Assessment of effectiveness

Critical review and synthesis of information

Primary outcome: event-free survival

After 2 years of follow-up, 86 of 202 (43%) patients in the R-CHOP arm had experienced an event: the median time to event had not been reached. In the CHOP group, 120 of 197 (61%) participants had experienced an event and the median time to event was 13 months. Event-free survival was significantly longer where rituximab was added to CHOP ($p < 0.001$). Two-year event-free survival was recorded in 57% (95% CI: 50 to 64) of those receiving R-CHOP and 38% (32 to 45) of those receiving CHOP alone. The relative risk of any event (progression, relapse or death) was 0.58 (0.44 to 0.77). After adjustment for baseline prognostic factors this was reduced to 0.55 (0.41 to 0.75), representing a 45% reduction in the risk of such an event.[58]

Secondary outcome: overall survival

In the R-CHOP arm, 59 (29%) participants were reported to have died after 2 years of follow-up, as opposed to 81 (41%) in the CHOP arm. The median time to death had not been reached in either arm. Overall survival at 2 years was significantly longer ($p = 0.007$) where rituximab was added to CHOP. Two-year survival was recorded in 70% (95% CI: 63 to 77) of those receiving R-CHOP and 57% (95% CI: 50 to 64) of those receiving CHOP alone. The relative risk of death

from any cause was 0.64 (95% CI: 0.45 to 0.89). After adjustment for baseline prognostic factors this was reduced to 0.53 (95% CI: 0.37 to 0.77), representing a 47% reduction in the risk of death.[58]

Secondary outcome: response rates
There were significantly more complete responses or unconfirmed complete responses where rituximab was added to CHOP ($p = 0.009$). The relative increase in the chance of a complete or unconfirmed complete response was 20% (95% CI: 1.05 to 1.37).

Secondary outcome: toxic effects
The increased risk of a severe adverse event (grade 3 or 4, grade 2–4 for infections) was not significant where rituximab was added to CHOP ($p = 0.19$). The relative increase in such events was 8% (95% CI: 0.96–1.20).

Summary and conclusions of the evidence for and against the intervention

In the short term, the addition of rituximab to the CHOP regimen significantly increased the likelihood of a complete or unconfirmed complete response, without a significant rise in the risk of a serious adverse event, in people aged ≥60 years with stage II–IV DLBCL. Over a 2-year follow-up period, the intervention significantly prolonged survival without progression or relapse (the primary outcome), and significantly prolonged overall survival in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting (see the next section).

The principal caveat with regard to the evidence presented in this report is its derivation from a single source, albeit an apparently reliable one (if potentially subject to bias through the absence of blinding). There will be occasion to compare these results with those of two other trials by 2006. In the USA, the ECOG 4494 study has finished recruiting but is not expected to report for some time. Like the GELA trial, its population is of advanced age, but also involves a second randomisation to maintenance treatment. The MabThera International Trial (MInT) aims to recruit 800 patients aged 18–60 years with untreated DLBCL. Recruitment was due to close in the middle of 2003.[72,73]

Subgroup differences: age

Although the review team did not find any subgroups specified in the GELA trial protocol, subgroup analyses were published in a journal article.[58] According to the GELA trialists, there was a significant benefit of the addition of rituximab to CHOP, both among patients with relatively low risk disease, indicated by an IPI score of 0 or 1 ($p < 0.001$), and those with high-risk disease, indicated by a score of 2 or 3 ($p < 0.03$). Patients younger than 70 years and ≥70 years old had the same benefit from the combination of CHOP plus rituximab.

There is no direct evidence for the clinical effectiveness of R-CHOP for populations under the age of 60 years. This being so, the case for the extension of the GELA trial evidence rests on two factors: the consistency in disease biology across age groups and the better prognosis associated with younger populations.

There is no known biological difference between the DLBCL of younger and older patients.[72] The GELA trial's subgroup analysis showed that patients older or younger than 70 years experienced the same benefit with the addition of rituximab to CHOP, suggesting that in an otherwise homogeneous patient group receiving optimum treatment, age does not predict for the likelihood of benefiting from rituximab.[58]

The beneficial effect of adding rituximab to CHOP was at least as great and reached a higher level of statistical significance in good prognosis compared with poor prognosis patients. Generally, younger patients have a better prognosis than older patients; therefore, it would be expected that they would benefit from the addition of rituximab to their chemotherapy by at least as much as older patients. In one randomised phase II study ($n = 54$, of which 70% were <60 years old) of rituximab alone, 100% of patients with an IPI score of 0–1 had an antitumour response to R-CHOP (including 67% who had a complete response).[74] In another phase II study ($n = 33$) designed to establish the safety and efficacy of R-CHOP in patients with newly diagnosed aggressive lymphoma, the response rate to R-CHOP was at least as good in patients under the age of 60 years as in those over the age of 60 years. All younger patients showed at least a partial response to treatment and almost exactly the same proportion (61% versus 60% in the older age group) achieved the complete response.[75]

According to the manufacturer, Hoffman-LaRoche, "treatments that work well in younger patients are also considered to be the best treatments for older patients, since the biological characteristics of their

disease are the same. However, such treatments cannot always be delivered to older patients because of co-morbidities or organ dysfunction. It is the inability to deliver optimum therapy that is thought to underlie the steady decline in prognosis with advancing age at diagnosis."[53]

Although these propositions are well informed and logical, the same logic also provides one argument against extending the treatment to the under-60s without further, direct evidence of clinical effectiveness. It is true that elderly patients typically have a low performance status and therefore receive more 'conservative' treatment, by comparison with the more aggressive interventions available to the under-60s.[76] By the same token, the benefits of R-CHOP may have to be weighed against other CHOP comparators available only to younger patients. For younger patients with a poor prognosis, one such treatment might be sequential high-dose chemotherapy with autologous stem cell transplantation, which is the subject of the British National Lymphoma Investigation-sponsored Mistral trial.

The other, simpler argument is that younger patients tend to respond better to CHOP alone,[23,39,58] and so, although the case made above that rituximab has benefit in this population seems robust, the clinical effect may be more marginal than in older patients.

In summary, although it seems likely that the direction of the clinical effect of the intervention in younger people would be the same, there is insufficient evidence to confirm that the extent of that effect would be as great, relative to comparator therapies, as in older populations.

Adverse effects of intervention

The majority of patients treated with rituximab experience mild to moderate infusion reactions (fever, chills/rigors) with the first infusion. Other infusion reactions include pruritis, nausea, vomiting, asthenia, angioedema, hypotension, bronchospasm, headache, throat irritation, urticaria, rash, myalgia, hypertension, rhinitis and dizziness. Such reactions occur within 30–120 minutes of starting the first infusion and may be resolved with interruption or slowing of the infusion and with supportive care instituted as indicated. The number of intravenous reactions decreases with each subsequent infusion.[74]

Rare, severe and sometimes fatal infusion reactions have occurred with rituximab, which again usually occur within 30–120 minutes into the first infusion. Signs and symptoms may include angioedema, hypoxia or bronchospasm and hypotension. The most severe reactions and outcomes include myocardial infarction, ventricular fibrillation, pulmonary infiltrates, acute respiratory distress syndrome and cardiogenic shock. The infusion should be interrupted for severe reactions. Supportive care should be instituted as indicated. In most cases rituximab infusions can be started at half the previous rate when symptoms have resolved. Patients with high levels of circulating malignant cells should be monitored closely.

Acute tumour lysis has been occasionally reported with rituximab infusions.[77,78] It is characterised by a rapid reduction in tumour followed by acute renal failure, hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalaemia and sometimes death. Tumour lysis syndrome has been reported to occur within 12–24 hours after the first infusion. The risks include high numbers of circulating malignant cells or high tumour burden. Preventative measures should be instituted for those patients at high risk. If tumour lysis occurs, electrolyte imbalances should be corrected while monitoring renal function and fluid balance. Dialysis should be instituted as indicated.[79]

Rarer side-effects include severe mucocutaneous reactions, cardiovascular infectious, pulmonary, immune/autoimmune and haematological events. Rituximab should be stopped in the event of serious arrhythmias and cardiac monitoring implemented during and after future infusions. Patients developing severe mucocutaneous reactions, which have been reported from 1 to 13 weeks after rituximab infusion, should not receive any future rituximab. Infectious events occur in about 30% of people and serious infectious events in 2%, due to reversible B-cell depletion. More serious pulmonary adverse events, of the types described above, mostly occur 1–4 weeks after rituximab infusion. Uveitis, pleuritis, optic neuritis, serum sickness with polyarticular arthritis and vasculitis with rash have been rarely reported. Cytopenias (grade III and IV) have been reported in 12% of patients treated with rituximab and include thrombocytopenia, anaemia, neutropenia and lymphopenia. One occurrence of aplastic anaemia and two of haemolytic anaemia have been reported. There have also been rare postmarketing reports of marrow hypoplasia and prolonged pancytopenia.

Chapter 4
Economic analysis

The model

ScHARR's cost-effectiveness model

The economic model developed by the School of Health and Related Research (ScHARR) uses the framework of the Roche model (see the section 'Assessment of Roche's economic model', p. 28) but it has incorporated different modelling assumptions. The main differences are:

- the interpretation of the number of life years gained (LYG) attributed to treatment with CHOP from survival curves of patients with acute large B-cell NHL.
- the interpretation of the increase in LYG attributed to the inclusion of rituximab to the CHOP treatment
- the inclusion of other treatment costs attributed to patients who fail to respond to CHOP and/or rituximab treatment.

The model evaluates the cost-effectiveness of introducing rituximab to the treatment regimen of R-CHOP compared with a CHOP-only treatment regimen.

The model is a Markov transition model with three health states that split into two age cohorts, those aged ≥60 years and those aged <60 years. The three states are complete responder (CR) to treatment, non-responder and relapse from complete responders (NR) to treatment, and death. The proportion of patients who achieved a CR on receiving CHOP for DLBCL and the duration of overall survival of patients who have received a CHOP regimen have been derived from the SNLG database acquired by Roche and kindly provided to ScHARR. The observed survival data from the SNGL database has been uses to reflect the transitions between the health states over time. The relative effectiveness of R-CHOP compared with a CHOP-only treatment regimen for patients with DLBCL has been derived from the published literature based on the GELA studies.[58,61] The model calculates an incremental cost-effectiveness ratio over a 15-year time horizon. The cost-effectiveness ratio is the additional cost of rituximab with CHOP chemotherapy (R-CHOP) per the additional benefits of R-CHOP therapy. The additional benefits gained are measured as quality-adjusted life-years (QALYs).

Creating survival curves for the CR and NR populations

This section of the report describes how the survival curves for the CR and NR populations who received the CHOP were derived for the model based on data from the SNLG database. The survival curves for CR and NR populations who received R-CHOP were then created by applying the relative improvement in the proportion of CRs and disease-free survival that R-CHOP provides compared with CHOP alone based on evidence reported on the GELA trial.[58,61]

The Kaplan–Meier survival curves derived from the SNLG were the overall survival of all patients receiving CHOP and disease-free survival of patients who were CR to CHOP therapy. Overall survival is normally calculated from the date of randomisation to the date of death, regardless of the cause of death, and any patients who are censored are alive at the time of the analysis. Therefore, summing the area under an overall survival curve gives the total LYG for that particular disease, in our case DLBCL patients receiving CHOP.

Disease-free survival is normally calculated for patients who are CRs from the date of randomisation to the date of the first event, where events are classed as relapses and death from the disease. However, unrelated deaths are not considered to be events and are usually censored at date of death. Therefore, summing the area under the disease-free survival curve does not give the true LYG for patients who are CR. Further review of the disease-free survival curve from the SNLG suggests that this method of creating the disease-free curve was likely as there were only two types of cases occurring, relapses and non-relapses.

The ScHARR model divides the population that received CHOP chemotherapy into two populations or disease states, CR and NR, the latter including those not responding to the initial CHOP therapy and those relapsing after being a CR.

A survival curve for the CR and NR was derived using the following assumptions with regard to the SNLG data:

- The initial proportion of CR and hence NR was taken from the SNLG data.
- A probability distribution was created to determine for every death at time *t* along the overall survival curve, whether it came from the CR or NR populations. No published evidence could be found that compared relative risk of death between a CR and NR. It was assumed that there was a 90% chance that each death at time *t* came from the NR population, as the prognosis for patients who do not respond to initial CHOP chemotherapy is poor (sensitivity around this assumption is addressed later). When all the NR population had died, all further deaths at time *t* from the overall survival curve then came from the CR population.
- Every relapse from the CR population at time *t* on the disease-free survival curve from the SNLG data was added to the NR population.

It should be noted that these 'survival curves' created for the CR and NR health states are not true Kaplan–Meier survival curves as the proportion of patients left alive in the NR health state can increase at a given time *t* if the number of relapses from the CR health state is greater than the deaths from the NR health state.

Monte Carlo simulation was employed to determine the sensitivity on the pseudo-survival curves of assuming that nine in 10 deaths occur in the NR health state. Although each simulation run produced different survival curves for both the CR and NR populations, this method ensured that the total LYG from summing the areas under each of the CR and NR survival curves always equalled the total LYG from the original overall SNLG survival curve. *Figure 1* shows typical survival curves for the CR and NR populations together with the original Kaplan–Meier overall survival curve for DLBCL patients aged >60 years receiving CHOP.

Calculating benefits

The GELA study research report[61] shows that the addition of rituximab to the CHOP regimen increased the CR rate and prolonged disease-free and overall survival.[58] The relative improvement in CR rate between R-CHOP and CHOP was calculated from Coiffier and colleagues[58] (*Table 3*), where complete response was defined as complete responders and unconfirmed complete responders, and showed that there was a relative increase of 19.5% for the R-CHOP group compared with CHOP alone ($p = 0.009$). The relative improvement in disease-free survival for patients treated with R-CHOP was derived from the GELA study research report,[61] which states that R-CHOP reduced the risk of progression by 53% (risk ratio 0.47). The relative improvements in CR rates and disease-free survival were applied to the CR survival curve for patients receiving the CHOP regimen to create CR survival curves for patients receiving R-CHOP. The improved CR rate was used to alter the proportion of the total population

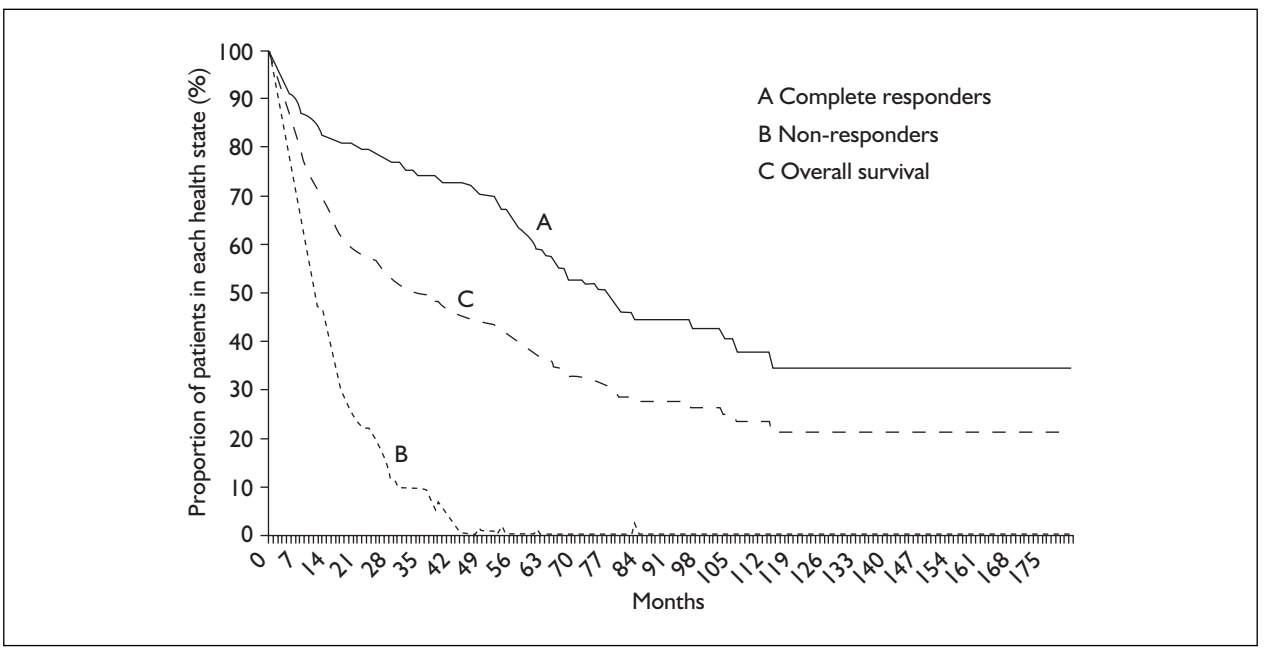

FIGURE 1 *Survival curves: proportion of patients alive in each health state and probability of overall survival*

who after completion of R-CHOP treatment are in the CR disease state and those who are in the NR disease state. The NR survival curve is applicable to patients in the NR disease state following either CHOP or R-CHOP treatment as we assume that patients who fail to respond or relapse from the R-CHOP regimen have the same probability of survival as those who fail to respond or relapse from the CHOP regimen. The model calculates the mean duration of survival by adding together the disease-free survival among patients who achieved a CR to the mean survival among patients who failed to be a CR or relapsed after being a CR. The mean survival for each of the disease states is calculated by summing the area under each curve:

total mean survival = mean survival complete responder × percentage complete responder + mean survival non-responder × percentage non-responder

In the model, the relative survival benefits of R-CHOP are assumed to last for the first 3 years only as the trial on which these assumptions are made had a follow-up period of 3 years. For years 3–15, the survival rate of patients in the CR health state following R-CHOP is assumed to be the same as the survival rate of patients in the CR health state following CHOP.

Quality-adjusted life-years (QALYs)

QoL utility scores are applied to LYG in order to adjust the survival benefits for the QoL that patients experience within a given health state. There are very few published studies measuring the QoL of patients within the disease area of DLBCL. Uyl-de Groot and colleagues[80] in a cost-effectiveness study comparing CHOP with ABMT derived QoL utility scores of 0.78 after 6-months of remission, 0.81 after 1-year of remission and 0.92 after 2-years of remission for patients with DLBCL receiving a CHOP regimen. These utility scores were based on only 5, 11 and 12 patients, respectively. The utility scores employed by the ROCHE model, based on the EuroQol,[81] originally formed part of their commercial-in-confidence (CIC) submission and came from an unpublished data source which had not been seen by the review team at the time the analysis was undertaken and therefore validity and reliability could not be assessed. However, the figures are reproduced here with the kind permission of the authors of the original study (Drs J Doorduijn, I Buijt and M Groot).The utility scores employed by the Roche model have been utilised in the ScHARR model owing to the lack of other data sources. The utility estimates for the CR and NR groups based on information supplied by Roche are 0.83 and 0.38, respectively. The LYG were then turned into QALYs by applying a QoL utility score to the LYG in the CR and NR populations.

Table 4 shows the Qol utility scores for patients with DLBCL in different disease states in different time periods following CHOP treatment. These results are from the analysis undertaken by Drs J Doorduijn, I Buijt and M Groot and were obtained using the EQ5D to describe health-related QoL in a group of patients with NHL. Utility weights for these states were taken from a large UK community sample.[82]

The Roche assumption of using 0.83 as the QoL utility value for CR in their model seems reasonable. However, the assumption that NR should have a QoL utility value of 0.38 appears low. This is also the opinion of Drs J Doorduijn, I Buijt and M Groot, authors of the QoL study.

Sensitivity analysis around the QoL utility scores undertaken in the section 'Sensitivity analysis' (p. 23) shows that there is little effect on the overall results in reducing the difference in QoL utility scores between CR and NR. Hence the apparent low estimate of the QoL utility score assumed for NR has not unduly biased the overall cost-effectiveness results.

TABLE 4 *QoL utility scores*

State	3 months	6 Months	10 months	18 months
Complete responder	0.83 [0.79 to 0.87], *n* = 56	0.79 [0.74 to 0.85], *n* = 51	0.81 [0.74 to 0.88], *n* = 45	0.80 [0.75 to 0.86], *n* = 41
Partial responder	0.67 [0.55 to 0.78], *n* = 35	0.73 [0.63 to 0.83], *n* = 23	0.72 [0.57 to 0.87], *n* = 15	0.79 [0.68 to 0.1], *n* = 9
Progressive disease	0.31 [–0.22 to 0.64], *n* = 35	0.48 [0.27 to 0.70], *n* = 15	0.49 [0.24 to 0.74], *n* = 16	0.75 [0.61 to 0.90], *n* = 9

Calculating costs

The analysis has attempted to include all treatment costs for all patients with DLBCL who receive CHOP or R-CHOP treatment regimens including second-line therapies and palliative care cost.

Treatment cost of CHOP and R-CHOP regimens

The drug cost of CHOP has been derived from papers by Sweetenham and colleagues[83] and Beard and colleagues.[84] The cost per course of CHOP based on Sweetenham and colleagues was £172.50, whereas Beard and colleagues estimated the cost to be £160, ranging to £283 if one assumes a 50% chance of neutropenic sepsis. The default cost for a course of CHOP is assumed to be £172.50. The average number of courses of CHOP, from the GELA study,[61] was 7.1 for patients receiving CHOP only and 7.5 for patients receiving R-CHOP. The difference is due to a greater number of early treatment failures within the CHOP-only arm of the trial. We have attempted to cost in the staff resources used in both the dispensing of the drugs used in CHOP and R-CHOP and the administration of the drugs and care of the patients while they receive their treatment. This estimate of cost for dispensing the drugs used in CHOP and R-CHOP was based on a personal communication from the Chief Pharmacist at the Weston Park Hospital, Sheffield, and the estimate of staff resources used in caring for the patients is based on a personal communication from Dr J Radford, Professor of Medical Oncology, Christie Hospital NHS Trust, Manchester. The methodology of how the staff resource costs were derived is shown in detail in Appendix 15. *Table 5* illustrates the estimated average patient cost for patients receiving CHOP.

The cost of rituximab was derived from using the BNF 44[56] for the unit cost of rituximab combined with the average dosage and infusions given in the ROCHE submission, based on the GELA study,[61] and is illustrated in *Table 6*.

The cost of adverse events has not been included in the model as analysis of the trial results suggests that there was no statistically significant difference in adverse events between patients who received CHOP and those who received R-CHOP (*Table 3*). In costing the treatments of CHOP and R-CHOP, we have attempted to include elements where the costs differ significantly between the two treatments. We accept that this is not comprehensive but further variations in cost between CHOP and R-CHOP treatment have been addressed in the sensitivity analysis.

Second-line therapy and palliative care costs

Patients with DLBCL who fail to respond to CHOP or R-CHOP treatment regimens have limited treatment options. Patients who are aged

TABLE 5 *Cost estimations of CHOP treatment*

	CHOP only	R-CHOP
Average number of courses of CHOP	7.1	7.5
Average cost per cycle of CHOP (£)	172.50	172.50
Average pharmacy cost of dispensing per cycle (£)	25.47	25.47
Average doctor/nursing cost per cycle (£)	74.00	74.00
Average cost per patient of CHOP treatment (£)	1931	2040

TABLE 6 *Cost estimations of rituximab treatment*

mg Vials	No. used	Unit cost (£)	Total cost (£)
500	1	873.15	873.15
100	1.7	174.63	296.87
Average cost per infusion (£)			1170
Average pharmacy cost of dispensing per cycle (£)			8.49
Average doctor/nursing cost per cycle (£)			80.30 (65.60)[a]
Average number of infusions (£)			7.4
Average cost per patient (£)			9269

[a] Average cost for cycles 1–7 (cycle 8).

<60 years have been found to respond to other forms of HDC including stem cell transplantation and ABMT.[80] Trials have shown that patients treated with HDC/ABMT do not respond as well as patients treated with CHOP and hence CHOP is the preferred treatment.[80] The model has assumed that 20% of patients who fail to respond to CHOP or R-CHOP treatment and are aged <60 years receive HDC/ABMT with a 25% success rate. This assumption has been based on a personal communication from Professor B Hancock at the Weston Park NHS Hospital Trust, Sheffield, the cost of which is based on NHS reference costs for bone marrow transplantation. A weighted average of the classification of ABMT was taken to represent the unit cost to the NHS of HDC/ABMT, which is illustrated in *Table 7*. The average cost of £25,028 is the same assumption used in the Roche submission.[53]

For other patients who fail to respond to CHOP or R-CHOP where HDC/ABMT is not an option, palliative chemotherapy and intensive palliative nursing care are provided. This treatment has been costed into the model at an average patient cost of £5200. This cost consists of palliative chemotherapy at £1000 and 2 weeks of intensive nursing at £300 per day. These data are based on a personal communication from Professor B Hancock at the Weston Park NHS Hospital Trust, Sheffield.

The model includes a surveillance cost for monitoring CRs, which can help spot and prevent relapses.[85] This surveillance cost is applicable to CRs who received both CHOP and R-CHOP regimens.

Discounting

All benefits have been discounted at 1.5% per annum with the costs discounted at 6.0% per annum in line with National Institute for Clinical Excellence (NICE) recommendations.[86,87] Sensitivity around these figures is presented. A summary of model assumptions is given in *Table 8*.

TABLE 7 *Estimation of HDC/ABMT costs*

Code	Classification	Number	Average cost (£)	Weighted cost (£)
BMTA1	Autografts (requiring search and live harvesting)	172	18,693	2,021
BMTA2	Other autografts	147	20,712	1,914
BMTA3	Allografts (requiring search and live harvesting)	335	37,270	7,847
BMTA4	Other allografts	151	36,151	3,431
BMTA5	Peripheral blood stem transplantation	669	15,130	6,362
BMTA6	Other bone marrow grafts	117	46,956	3,453
Total		1,591		25,028

TABLE 8 *Summary of model assumptions*

Assumptions	CHOP	R-CHOP	Reference
CR rate aged 60+ (%)	62.1	72.4	SNLG
CR rate aged <60 (%)	71.3	83.0	SNLG
Relative increase in CR (%)		19.5	Coiffier[87]
Relative reduction in disease-free survival (%)		47	GELA study[61]
Duration of risk reduction (years)		2.8	GELA study[61]
Mortality ratio, CR:NR	1:9	1:9	Assumption
Percentage of NR undertaking HDC/ABMT (%)	20	20	Personal communication
QoL utility scores			
CRs	0.83	0.83	Personal communication
NRs/relapses	0.38	0.38	Personal communication
Costs			
CHOP per course (£)	272	272	NHS prices
Rituximab per cycle (£)		1,259	NHS prices
HDC/ABMT per patient (£)	25,028	25,028	NHS prices
Palliative care per patient (£)	5,200	5,200	Personal communication
Surveillance per year (£)	308	308	Edelman *et al.* (1997)[85]

Results

Patients aged over 60 years

The results in *Table 9* show the outputs from the ScHARR model (with 95% CI) for patients aged ≥60 years. This is based on 10,000 runs of the model based on the inputs shown in *Table 7*. The model has assumed that 90% of all deaths based on the overall average survival curve occurs in the NR health state. The small CI ranges show the probabilistic nature of the mortality assumptions on the CR and NR health states has had little effect.

The mean overall survival among patients in the SNLG database who received CHOP was 5.25 years. The estimate from the model of the mean overall survival for patients receiving the R-CHOP regimen is 6.23 years, an increase of 0.98 years. The Roche model estimated that the net increase in mean overall survival between patients receiving CHOP to R-CHOP to be 2.0 years.

The ScHARR model estimated the average difference in patient cost for patients treated with rituximab as £8683. This consists of the average cost of rituximab over the first 6 months of £9209 and additional average CHOP and surveillance costs over the 15-year period of £106 and £76, respectively, offset by reduced average cost of treating patients in the NR health state. Dividing the average additional costs of £8683 by the average additional QALYs gained of 0.82 gives an estimated average cost per QALY ratio of £10,596.

Patients aged under 60 years

The results in *Table 10* show the outputs from the ScHARR model (with 95% CI) for patients aged less than 60 years. This is based on 10,000 runs of the model based on the inputs shown in *Table 8*. The model has assumed that 90% of all deaths based on the overall average survival curve occurs in the NR health state. The small CI ranges show the probabilistic nature of the mortality assumptions on the CR and NR health states has had little effect.

The mean overall survival among patients in the SNLG database who received CHOP was 8.86 years. This differs slightly from the Roche model owing to differences in the survival curves used. The overall survival curve presented to ScHARR included an early death that was not apparent in the overall survival curve used by Roche.

The estimate from the model of the mean overall survival for patients receiving the R-CHOP regimen is 9.77 years, an increase of 0.92 years. The Roche model estimated that the net increase

TABLE 9 *Results: aged ≥60 years*[a]

Parameter	CHOP	R-CHOP	Difference
Response rate (%)	62.1	72.4	10.2
Survival			
Progression-free	4.66 (4.60 to 4.72)	5.83 (5.76 to 5.89)	1.17 (1.14 to 1.20)
Post-progression	0.58 (0.53 to 0.64)	0.40 (0.36 to 0.44)	–0.19 (–0.17 to –0.21)
Overall	**5.25**	6.23 (6.19 to 6.26)	0.98 (0.95 to 1.02)
Discounted survival			
Progression-free	4.28 (4.22 to 4.32)	5.35 (5.28 to 5.40)	1.07 (1.05 to 1.10)
Post-progression	0.57 (0.52 to 0.63)	0.39 (0.35 to 0.43)	–0.18 (–0.17 to –0.20)
Total	**4.85**	5.73 (5.70 to 5.77)	0.89 (0.86 to 0.92)
QALYs	3.77 (3.74 to 3.79)	4.58 (4.54 to 4.62)	0.82 (0.80 to 0.84)
Costs			
Rituximab (£)		**9,209**	**9,209**
CHOP (£)	**1,911**	**2,018**	**106**
Surveillance (£)	1,652 (1,627 to 1,674)	1,728 (1,704 to 1,748)	76 (67 to 86)
Cost of NRs (£)	2,209 (2,165 to 2,250)	1,500 (1,471 to 1,529)	–709 (–722 to –695)
Total (£)	5,773 (5,708 to 5,827)	14,456 (14,406 to 14,498)	8,683 (8,667 to 8,701)
Cost-effectiveness			
Per life-year (LY) gained (£)			9,774 (9,438 to 10,157)
Per QALY gained (£)			10,596 (10,300 to 10,902)

[a] Figures in bold are fixed (not affected by mortality assumptions).

in mean overall survival between patients receiving CHOP to R-CHOP to be 1.85 years.

The ScHARR model estimated the average difference in patient cost for patients treated with rituximab as £7870. This consists of the average cost of rituximab over the first 6 months of £9209 and additional average CHOP and surveillance costs over the 15-year period of £106 and £63, respectively, offset by reduced average cost of treating patients in the NR health state with HDC/ABMT and palliative care. Dividing the average additional costs of £7870 by the average additional QALYs gained of 1.05 gives an estimated average cost/QALY ratio of £7533.

Sensitivity analysis

Probabilistic sensitive analysis

Table 11, illustrates the assumptions for each variable used in the Monte Carlo simulation. A log normal distribution has been assumed for the relative risk reductions and increase in CR rate: let

TABLE 10 *Results: aged <60 years*[a]

Parameter	CHOP	R-CHOP	Difference
Response rate (%)	71.3	85.2	13.9
Survival			
Progression-free	7.49 (7.33 to 7.63)	9.20 (9.01 to 9.36)	1.71 (1.67 to 1.75)
Post-progression	1.36 (1.23 to 1.52)	0.70 (0.63 to 0.78)	–0.66 (–0.60 to –0.74)
Overall	**8.86**	9.90 (9.79 to 10.00)	1.05 (0.94 to 1.14)
Discounted survival			
Progression-free	6.77 (6.63 to 6.89)	8.31 (8.14 to 8.46)	1.54 (1.51 to 1.58)
Post-progression	1.28 (1.16 to 1.42)	0.66 (0.60 to 0.73)	–0.62 (–0.56 to –0.69)
Total	**8.05**	8.97 (8.87 to 9.06)	0.92 (0.82 to 1.01)
QALYs	6.10 (6.04 to 6.16)	7.15 (7.04 to 7.25)	1.05 (0.99 to 1.09)
Costs			
Rituximab (£)		**9,209**	**9,209**
CHOP (£)	**1,911**	**2,018**	**106**
Surveillance (£)	2,303 (2,256 to 2,346)	2,367 (2,320 to 2,409)	63 (57 to 70)
Cost of NRs (£)	3,096 (3,058 to 3,130)	1,595 (1,575 to 1,612)	–1,501 (–1,518 to –1,483)
Total (£)	7,311 (7,232 to 7,381)	15,181 (15,142 to 15,242)	7,870 (7,860 to 7,897)
Cost-effectiveness			
Per life-year (LY) gained (£)			8,532 (7,796 to 9,563)
Per QALY gained (£)			7,533 (7,208 to 7,941)

[a] Figures in bold are fixed (not affected by mortality assumptions).

TABLE 11 *Assumptions used in Monte Carlo simulation*

Variable	Distribution	Parameter	Source
Relative increase in CR rate	Log-normal	μ = ln1.195, σ = 0.07	Coiffier *et al.*[58]
Relative risk reduction of progression-free survival	Log-normal	μ = ln0.47, σ = 0.21	GELA[61]
Utilities	Uniform	Progression-free: range 0.664–0.996 Progression: range 0.304–0.456	Assumption same as Roche
Surveillance costs	Normal	μ = £308, σ = £50	Assumption same as Roche
Cost of CHOP	Normal	μ = £256, σ = £50	Assumption
Cost of rituximab	Normal	μ = £1,253, σ = £200	Assumption
Percentage of NRs undertaking HDC/ABMT	Uniform	10–30%, μ = 20%	Assumption
Cost of palliative care per patient	Normal	μ = £25,028, σ = £2,500	Assumption
Cost of HDC/ABMT per patient	Normal	μ = £5,200, σ = £750	Assumption

relative risk $rr = p_1/p_2$. Assuming $\ln(rr)$ is normally distributed, with mean $\mu = \ln(rr)$, as $\ln(p_1/p_2) = \ln(p_1) - \ln(p_2)$, then $\text{Var}[\ln(p_1/p_2)] = \text{Var}[\ln(p_1)] + \text{Var}[\ln(p_2)]$.

Figures 2 and *3* illustrate the result from the probabilistic sensitivity analysis represented as a cumulative distribution function of cost–utility.

These cost-effectiveness acceptability curves (CEACs) show the risk that the addition of rituximab to CHOP regimen may exceed a certain threshold of acceptable affordability. For patients aged ≥60 years the 5th and 95th percentiles of the CEAC were £5728 and £23,413, respectively. In other words, if the societal value of a QALY (the amount that one is prepared to pay

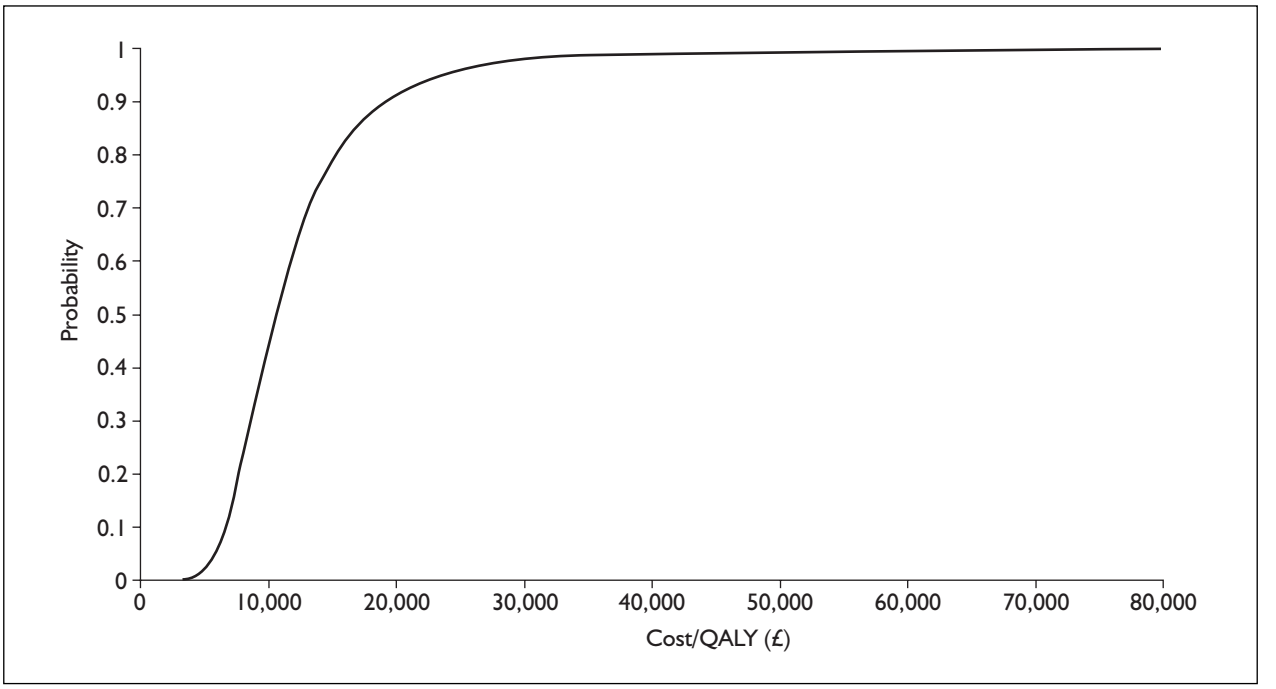

FIGURE 2 *CEAC patients aged ≥60 years. Cumulative distribution – C/E per QALY.*

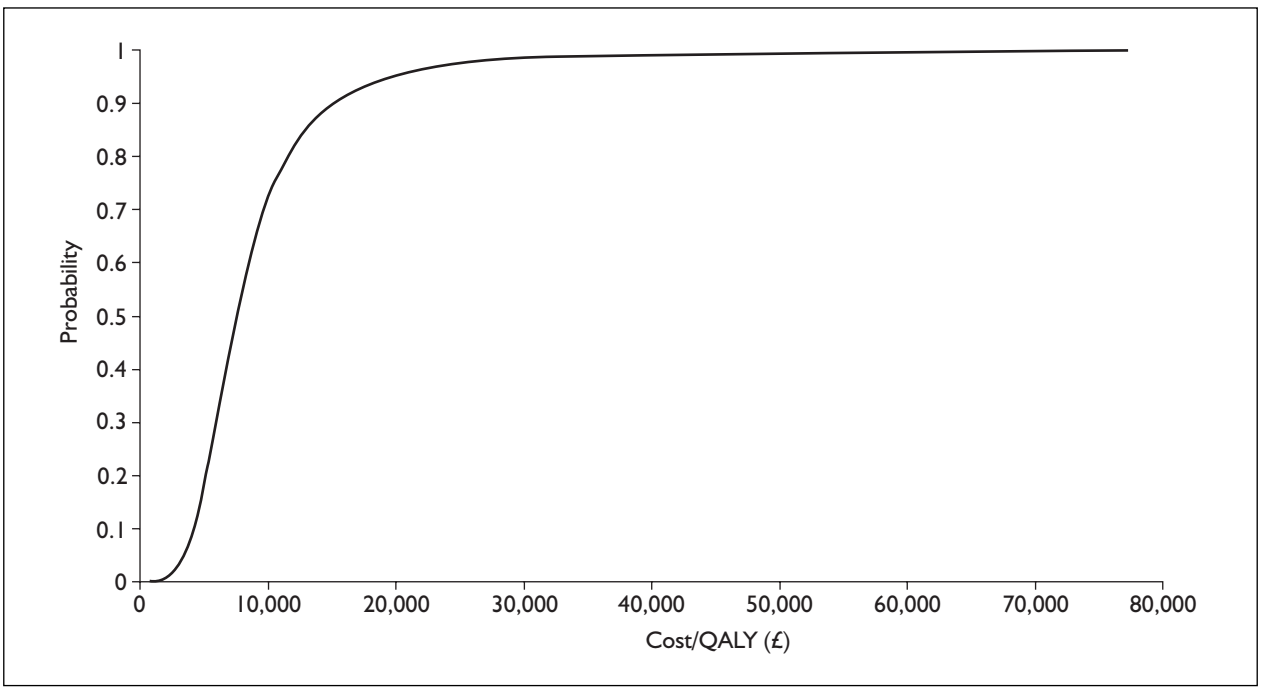

FIGURE 3 *CEAC patients aged <60 years. Cumulative distribution – C/E per QALY.*

to gain one QALY) is £30,000, then for patients aged ≥60 years there is a 2.2% chance that the cost would exceed this theoretical limit.

For patients aged <60 years, the 5th and 95th percentiles of the CEAC were £3523 and £18,969, respectively. Put another way, if we were to assume that a 'willingness to pay' to gain one QALY was £30,000, then for patients aged <60 years there is a 1.4% chance that the cost would exceed this theoretical limit.

Expected value of information (EVI)
The EVI approach uses a decision analytic structure to prioritise further areas of research by analysing the uncertainty that exists around parameters on the net benefit of alternative interventions.[88,89]

When making the decision on whether to fund a new technology over an existing one, we want to be certain that we are making the correct decision. The CEACs above show that with the uncertainty around the mean value of each parameter there is a small chance that R-CHOP is not the cost-effective option and that CHOP could be the technology (or intervention) of choice. The EVI approach describes the potential combined extra QALY and cost consequences that will be missed out on if the 'wrong' decision is made, that is, the lost opportunity to have the incremental net benefit. However, if we could reduce the uncertainty, by obtaining more data on the uncertain elements of the decision problem, we could then make the decision with more confidence. The value of further information (i.e. research) is in its ability to reduce the uncertainty in the problem and in particular reduce the chances of us making the wrong decision, and reduces the expected opportunity loss. If we had perfect information about all the parameters in the decision problem, then we would have eliminated all the uncertainty and reduce the expected opportunity cost to zero.

This method of expected value of perfect information (EVPI) allows us to quantify the value of having 'perfect information' about certain parameters in pounds and pence and to assess the importance of different uncertain parameters to the overall decision.

To calculate the EVPI, we varied the parameters around their uncertainty range, as listed in *Table 11*, and conducted a Monte Carlo simulation of 10,000 iterations as we did to create the CEACs. For each individual iteration of the model we calculate the mean net benefit for both the CHOP and R-CHOP treatments and identify the strategy with the highest mean net benefits. We record the optimal strategy and calculate the opportunity cost for each iteration as follows:

opportunity cost = (net benefits for the optimal strategy) – (net benefit for the R-CHOP treatment)

Note: net benefit = $\lambda \times$ benefits (QALY) – cost, where λ is the willingness to pay for a unit of health benefit and is assumed to be £30,000. When the R-CHOP treatment is the optimal strategy for an individual iteration, then the opportunity cost is zero.

The mean value of the opportunity loss over all the iterations is equivalent to the expected cost of uncertainty and provides an estimate of the 'per patient EVPI'.

The result of the EVPI gave us a mean value of opportunity loss or, put another way, the value of perfect information is £53 per patient. With the cost of giving R-CHOP therapy at around £9300 per patient, this represents a very small level of uncertainty. The number of people with DLBCL in England and Wales in 2003 has been estimated at around 3000[4–6] (see *Table 14*). Multiplying the 3000 people with DLBCL by the £53 gives £159,000, which is the maximum value society would be prepared to pay into further research to give us perfect information. This is likely to be substantially smaller than the cost of undertaking further trials and reflects the small level of uncertainty in the results produced by the model.

The EVI for single parameters or sets of parameters is called 'partial EVPI' and can be used to highlight the parameters in which further research would be best spent to reduce the uncertainty in the overall decision. As the overall EVPI in this case is so small, no partial EVI was deemed necessary.

One-way sensitivity analysis
Table 12 shows the results of conducting an extensive one-way sensitivity analysis on the main variables within the model. The sensitivity around the QALY assumptions multiplies the average utility scores for elderly patients (aged ≥70 years) in the UK[90] by the default QALY values. This has the effect of standardising the default utility scores to the average utility scores of patients aged ≥70 years and changes the definition of the upper utility value of 1, which did reflect perfect health,

TABLE 12 *One-way sensitivity analyses*

Variable	Assumption	Differences			
		LY	QALY	Cost (£)	Cost per (£) QALY
Base case		0.89	0.82	8,683	10,596
Relative increase in CR rate					
Low	Lower by 10%	0.53	0.48	9,045	18,709
High	Higher by 10%	1.24	1.16	8,308	7,200
Relative risk reduction disease-free					
Low	Lower by 15%	0.82	0.76	8,661	11,344
High	Higher by 15%	0.96	0.88	8,696	9,939
Mortality assumptions, ratio 1:9 (CR:NR) 11,203	Ratio 1:4 (CR:NR)	0.80	0.78	8,715	11,203
Duration of treatment effect					
Low	2	0.80	0.75	8,654	11,602
High	5	0.99	0.90	8,714	9,686
Chemotherapy costs					
CHOP					
Low	Lower by 20%	0.89	0.82	8,662	10,569
High	Higher by 20%	0.89	0.82	8,704	10,625
Rituximab					
Low	Lower by 20%	0.89	0.82	6,841	8,349
High	Higher by 20%	0.89	0.82	10,525	12,843
Surveillance costs					
Low	Lower by 20%	0.89	0.82	8,668	10,579
High	Higher by 20%	0.89	0.82	8,698	10,617
Utilities					
Lower multiplied by age related QoL utility[90]	CR = 0.62, NR = 0.28	0.89	0.61	8,683	14,180
Discount rate (benefits)					
6% cost, 0% benefits		0.98	0.90	8,683	9,658
6% cost, 6% benefits		0.68	0.64	8,683	13,601

to representing average health for the UK population in that age group.

Altering the relative risk in the complete responder rate by 10 percentage points (i.e. from 19.5 to 9.5%) had a large effect on the incremental cost per QALY ratio as the number of QALYs gained for the average R-CHOP patient compared with the average CHOP patient is reduced. Altering the mortality ratio assumption between the CR and NR health states from the default assumption that 90% of deaths occur in the NR health state to only 80% appeared to only have a marginal effect on the cost/QALY value.

Threshold analysis

Threshold analysis, shown in *Table 13*, was undertaken on the main assumptions used in the model to ascertain what level each variable would have to achieve to ensure that R-CHOP is not the preferred strategy of treatment compared with CHOP for patients with DLBCL. We have assumed that the societal value (the amount that one is prepared to pay to gain one unit of health benefit) of a QALY is £30,000.

For CHOP to become the preferred treatment for DLBCL patients compared with R-CHOP, assuming a £30,000 threshold, there have to be large alterations in the main variables. The relative increase in the CR rate has to fall to <4% or the cost of rituximab needs to increase threefold. The utilities attributed to each of the health states also need to fall and there should be no apparent gain in health status between the two health states. The mortality assumption also appears to be a robust

TABLE 13 *Threshold analysis (patients aged ≥60 years)*

Variable	Baseline value	Threshold value	Direction of effect
Relative increase in CR rate (%)	19.5	<4.5	Reducing the relative increase in CR rate increases the cost per QALY
Relative risk in disease-free survival (%)	47	>197	(i.e. a 97% reduction in disease-free survival for R-CHOP patients)
Cost of rituximab (£)	1398 per treatment	>£3400	Increasing the cost of rituximab increases the cost/QALY
QoL utilities	CR = 0.83, NR = 0.38	<0.33 <0.33	Decreasing the utility of patients in CR to the same as NR patients cannot force R-CHOP to cross the threshold unless the utility of NR patients also decreases
Mortality	CR 10%, NR 90% (ratio 1:9)	CR >46.5%, NR >53.5%	Reducing the death rate ratio between the CR and NR decreases the LY and the QALY gained and hence increases the cost/QALY

assumption. For CHOP to become the preferred treatment option compared with R-CHOP, the mortality ratio needs to approach 50:50. If this were indeed the case, then it would mean that a patient who became a CR by treatment with either CHOP or R-CHOP would still have the same chance of dying at any given time as a patient who had failed to respond to treatment. In other words, it would mean that both CHOP and R-CHOP treatments would have no beneficial clinical effect on patients with DLBCL.

Conclusion

The cost-effective modelling conducted here has shown that rituximab when used in combination with CHOP chemotherapy regimen is a cost-effective treatment for DLBCL when compared with the current standard treatment with CHOP chemotherapy only. For the population aged ≥60 years R-CHOP therapy costs an additional £8638 while generating 0.82 QALYs over a 15-year period. This equates to a cost per QALY of £10,540, which compares favourably if we assume that the societal value of one QALY is £30,000. For the population aged <60 years, R-CHOP treatment cost an extra £7831 while generating an extra 1.05 QALY. This equates to a cost per QALY of £7485.

The analysis is primarily based on two major sources of data, the GELA study and a UK database of treatment patterns among patients with DLBCL. The QoL utility scores are based on an unpublished trial and could be viewed as being high when compared with the average utility scores for elderly patients.[90] The GELA study is currently the only trial to have reported that has directly compared R-CHOP and CHOP treatments for DLBCL. However, extensive sensitivity analysis, including probabilistic sensitivity analysis, one-way sensitivity analysis and EVI, has shown the results presented by the model to be particularly robust and therefore R-CHOP appears to be a cost-effective treatment for DLBCL.

Budget impact for rituximab

The addition of rituximab to the standard treatment of CHOP for the treatment of DLBCL increases the overall cost of treatment. In this section we have attempted to show the likely impact to the NHS of adopting R-CHOP as the standard treatment for DLBCL at the expense of CHOP therapy, although we accept that there is a high degree of uncertainty. First, we attempted to estimate the future number of people who will be diagnosed with DLBCL in the next few years (*Table 14*). Second, we estimated the likely number of DLBCL patients who will be treated with R-CHOP and multiplied this by the additional cost of adding rituximab to CHOP, having first estimated how the uptake rate of patients moving from CHOP to R-CHOP treatment will develop year on year.

In 1997 there were 7640 people (4110 men and 3530 women) diagnosed with NHL in England and Wales.[1] Of these patients, 30.6%[2] would be expected to have DLBCL. This equates to 2338

TABLE 14 *Estimate of DLBCL population in England and Wales*

Year	Incidence rate (per 100,000)	Annual increase (%)	DLBCL population
1997	4.4	–	2338
1998	4.6	4	2431
1999	4.8	4	2529
2000	5.0	4	2630
2001	5.2	4	2735
2002	5.4	4	2844
2003	5.6	4	2958
2004	5.8	4	3076
2005	6.1	4	3199
2006	6.3	4	3327
2007	6.6	4	3461

TABLE 15 *Budget impact for rituximab*

	Year 1: 2003	Year 2: 2004	Year 3: 2005	Year 4: 2006	Year 5: 2007
DLBCL population	2958	3076	3199	3327	3461
% treated with CHOP or R-CHOP	50	50	50	50	50
No. of CHOP/R-CHOP patients	1479	1538	1600	1664	1731
R-CHOP uptake (%)	5	50	95	95	95
R-CHOP patients	74	769	1,520	1581	1644
Total budget impact (£)	685,906	7,127,861	14,088,880	14,654,289	15,238,236

people being diagnosed with DLBCL in 1997, an incidence rate of 4.4 per 100,000 population (estimated England and Wales population for 1999 based on ONS figures: 52,689,900).

The incidence of NHL appears to be increasing at a rate of 3–4% per annum.[4-6] Therefore, it is assumed that this annual increase will continue to 2007 and the proportion of NHL that is diagnosed as DLBCL remains at 30.6%.

The additional cost of adding rituximab to the CHOP regimen was illustrated in *Table 6* as £9269 for an average of 7.4 cycles.

Data from the SNLG database suggests that 50% of DLBCL patients receive CHOP chemotherapy and 50% other drug regimens. Therefore, it is assumed that R-CHOP therapy will only replace the current CHOP regimen in the treatment of DLBCL (i.e. 50%). Following consultation with our internal and external reviewers, with regard to the uptake rate of adding rituximab to CHOP therapy for DLBCL patients following a positive NICE recommendation for the addition of rituximab to CHOP therapy for DLBCL patients, it was felt that by the end of 2005 all patients who are not contraindicated for the use of rituximab should be receiving R-CHOP for DLBCL. Therefore, we have assumed that changes in clinical practice will be rapid and that the proportion of patients treated with the R-CHOP regimen at the expense of CHOP alone will increase by 45% in year 2, from a baseline of 5%, and 45% in year 3, so that there will be 95% coverage by year 3.

The result of these assumptions is shown in *Table 15*. The estimated impact on the NHS will be in the region of £14 million by 2005 and £15 million by 2007.

Assessment of Roche's economic model

A combination of the *BMJ* checklist for economic evaluations[91] together with the Eddy checklist (1985)[92] on mathematical models employed in technology assessments was used to assess the quality of the submitted model, the questions of which are duplicated below. The reviewer's comments on the methodology are produced together with discussions on the likely impact of the different assumptions used. Where the questions have been answered appropriately and sufficiently, the term 'OK' has been used.

1. A statement of the problem.
2. A discussion of the need for modelling versus alternative methodologies.

3. A description of the relevant factors and outcomes.
4. A description of the model, including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. Note: n = number of health states within submodel.
5. A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence.
6. A list of assumptions pertaining to the structure of the model (e.g. factors included, relationships and distributions) and the data.
7. A list of parameter values that will be used for a base case analysis and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis.
8. The results derived from applying the model for the base case.
9. The results of the sensitivity analyses: unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.
10. A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect.
11. A description of the validation undertaken including:
    (a) concurrence of experts
    (b) internal consistency
    (c) external consistency
    (d) predictive validity.
12. A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results.
13. A description of research in progress that could yield new data that could alter the results of the analysis.

Comments are as follows:

1. OK.
2. OK. A modelling methodology is justified owing to the lack of any previous economic analysis being undertaken alongside any clinical trial. Currently there is no other cost-effectiveness analyses evaluating rituximab with CHOP chemotherapy compared with CHOP only in the treatment of DLBCL.
3. OK.
4. OK. The model submitted is a three-state Markov model evaluated over a 15-year time horizon. The standard comparator to rituximab and CHOP is CHOP therapy only. The modelling approach adopted here is based on a UK-specific data set, which follows patients over a much longer time horizon than previous clinical trials and is used to calculate survival, while incorporating clinical outcomes and relative risk ratios resultant from a recent French clinical trial (GELA) comparing CHOP versus R-CHOP. The model is split by age with the younger patients, aged <60 years, having a better response rate to treatment, based on clinical evidence, and a secondary cost attributed equally to both arms for patients who fail to respond to CHOP or R-CHOP treatment and undertake ABMT. The model excludes any benefits that may be gained by responding to ABMT. The benefits measured are LYG and QALYs gained. The costs include the drug costs and follow-up costs for patients who are CRs to treatment. No costs for the treatment of patients who fail to respond to initial therapy have been included for patients aged ≥60 years. The costs and benefits have been discounted at 6% and 1.5%, respectively.
5. OK. The model is based on two main data sources, the French GELA clinical trial, which is the only clinical trial comparing CHOP with R-CHOP that has reported results, and the SNLG database, which has been utilised to obtain UK-specific survival rates. Results from the GELA trial are used to derive the relative increase in CR rate, relative risk reduction in survival and disease-free survival from the addition of rituximab to the CHOP regimen. The improvement in CR rate was calculated on differences resulting from the GELA trial that included complete and unconfirmed CRs. The SNLG database contains information on around 2800 patients with DLBCL/high-grade lymphoma. Cost data were ascertained from published literature and NHS list prices. QALY assumptions were originally marked as CIC in the company submission but have been reproduced here with kind permission of the authors of the original study.
6. The relative risk difference from adding rituximab to a CHOP regimen has been applied to the increase in CRs, reduction in disease-free survival and reduction in overall survival. In the reviewer's opinion, including all three improvements to the inclusion of rituximab in the CHOP regimen is overestimating the effect. Coiffier and colleagues[58] stated in reporting on the GELA study that the longer survival in the R-CHOP

group was due to a higher response rate during therapy and fewer relapses among patients who had a CR. Applying an improvement in CR rate and an increase in disease-free survival (reduction in relapse) by implication will bring about an improvement in overall survival. Therefore, adding a further improvement to overall survival overstates the effect and, owing to the model methodology employed, introduces an assumption that patients who fail to respond to R-CHOP therapy achieve an improvement in survival over patients who fail to respond to CHOP-only therapy. However, any improvement in survival of patients who fail to respond to treatment was not reported by Coiffier and colleagues.[58] The survival curves derived from the SNLG data relate to disease-free and overall survival. However, the method by which the disease-free survival curve is derived seems unsuitable to be used to measure LYG. There is evidence to suggest that the disease-free survival curve has excluded deaths from any cause other than lymphoma and hence using this survival curve as a source of measuring LYG for the total population seems inappropriate. The relative risk improvements of R-CHOP over CHOP have only been applied for the 2.8 years for which patients on the GELA trial were followed. However, some of the relative risks are reported after only 2 years and not from the end of the trial.

7. Roche undertook a probabilistic sensitivity analysis in addition to one-way sensitivity analysis. The parameters listed in *Table 16* illustrate the assumptions used in the Monte Carlo simulation. The CEAC was derived from this analysis.

   The variable values used in the one-way sensitivity analysis and their confidence intervals are presented in *Tables 17* and *18*.
8. Model results: these are presented in *Tables 19* and *20*.
9. Results of the sensitivity analysis: the results from the Monte Carlo simulation were

TABLE 16 *Assumptions used in Monte Carlo simulation*

Variable	Distribution	Parameter
Relative increase in CR rate	Log-normal	$\mu = \ln 1.21$, $\sigma = 0.08$
Relative risk reduction of progression-free survival	Log-normal	$\mu = \ln 0.52$, $\sigma = 0.23$
Relative risk reduction of overall survival	Log-normal	$\mu = \ln 0.47$, $\sigma = 0.21$
Utilities	Uniform	Progression-free: range 0.664–0.996 Progression: range 0.304–0.456
Surveillance costs	Normal	$\mu = 308$, $\sigma = 50$

TABLE 17 *One-way sensitivity analysis assumptions: aged ≥60 years*

Parameter	CHOP	R-CHOP
Percentage of CR	61.6 (fixed)	
Efficacy assumptions		
Relative increase in CR (%)		21 (±10%)
Relative reduction in overall survival (%)		52 (±15%)
Relative reduction in disease-free survival (%)		47 (±15%)
Duration of risk reduction (years)		2.8 (2 to 5)
Utilities		
Disease-free	0.83 (±15%)	0.83 (±15%)
No CR or progression	0.38 (±15%)	0.38 (±15%)
Costs		
CHOP (£)	173 (±15%)	173 (±15%)
Rituximab (£)		1,170 (±15%)
Surveillance (£)	308 (±15%)	308 (±15%)
Time horizon (years)	15 (5 to 20)	15 (5 to 20)

presented as a CEAC. The 5th and 95th percentiles of the cost-effectiveness distribution were £3793 and £10,332, respectively. In other words, there is only a 5% chance that the cost-effectiveness calculation (cost per QALY) would exceed £10,332 based on the assumptions used in the model.

The results of the one-way sensitivity analysis undertaken on the patients aged ≥60 years model are presented in *Table 21*. No sensitivity analysis on the patients aged <60 years was presented by Roche.

10. The method by which the disease-free survival curve was employed in this model has already been discussed, as has the application of the relative increase in CR rate and relative risk reductions in disease-free and overall survival to the R-CHOP population. These assumptions all benefit the R-CHOP population and increase the number of LYG

TABLE 18 *One-way sensitivity analysis assumptions: aged <60 years*

Parameter	CHOP	R-CHOP
Percentage of CR	71.3 (fixed)	
Efficacy assumptions		
Relative increase in CR (%)		21 (±10%)
Relative reduction in overall survival (%)		52 (±15%)
Relative reduction in disease-free survival (%)		47 (±15%)
Duration of risk reduction (years)		2.8 (2 to 5)
Percentage of patients who receive ABMT	11 (Fixed)	11 (fixed)
Utilities		
Disease-free	0.83 (±15%)	0.83 (±15%)
No CR or progression	0.38 (±15%)	0.38 (±15%)
Costs		
CHOP (£)	173 (±15%)	173 (±15%)
Rituximab (£)		1,170 (±15%)
ABMT per treatment (£)	25,028 (fixed)	25,028 (fixed)
Surveillance (£)	308 (±15%)	308 (±15%)
Time horizon (years)	15 (5 to 20)	15 (5 to 20)

TABLE 19 *Results: aged ≥60 years*

Parameter	CHOP	R-CHOP	Difference
Response rate (%)	62.1	75.4	13.3
Survival			
Progression-free	4.53	6.36	1.83
Overall	5.25	7.25	2.00
Discounted survival			
Progression-free	4.20	5.89	1.69
Post-progression	0.64	0.77	0.13
Total	4.85	6.67	1.82
QALYs	3.73	5.18	1.45
Costs			
Rituximab (£)		8,576	8,576
CHOP (£)	1,213	1,282	69
Surveillance (£)	1,679	1,950	270
Total (£)	2,892	11,807	8,915
C/E			
Per LY gained (£)			4,459
Per QALY gained (£)			6,143

TABLE 20 *Results aged <60 years*

Parameter	CHOP	R-CHOP	Difference
Response rate (%)	71.3	86.5	15.2
Probability of ABMT (%)	11	11	0.0
Survival			
Progression-free	6.51	8.10	1.59
Overall	8.91	10.75	1.85
Discounted survival			
Progression-free	5.98	7.44	1.46
Post-progression	2.12	0.77	0.13
Total	8.09	6.67	1.82
QALYs	5.77	7.05	1.29
Costs			
Rituximab (£)		8,576	8,576
CHOP (£)	1,213	1,282	69
Surveillance (£)	2,018	2,096	78
ABMT (£)	2,689	2,689	0
Total (£)	5,920	14,643	8,723
C/E			
Per LY gained (£)			4,718
Per QALY gained (£)			6,770

for these patients. The QoL utility score applied to the CR health state based on an unpublished study appears high and does not differ between patients who are aged ≥60 years to patients who are aged ≤ 60 years. Kind and colleagues[90] showed that the QoL of an individual is related to age and diminishes as age increases. Their study on the general UK population showed that people aged ≥60 years had an average QoL utility score lower than people age <60 years. Kind and colleagues average QoL utility score for the general population was also lower than that attributed to patients in the CR health state. The higher the utility score for the CR health state, the greater is the number of QALYs gained by the R-CHOP population. A 10% increase in the utility score for the CR health state equates to about a 9% reduction in the cost-effectiveness calculation.

11. As such, no validation has been undertaken as this is the first such model in the field of cost-effectiveness of R-CHOP over CHOP. The assumptions are based on published/prepublished literature and utilise a powerful survival data source (SNLG), and the model structure is clear and results are consistent with parameter variation. However, there is no other model or available data against which to validate the answers.
12. There is no explicit description of the settings to which the results of the analysis can be applied or any list of factors that could limit the applicability of the results. However, this question is not really applicable to this model as the results of the analysis are clearly applicable to all patients with acute DLBCL.
13. OK. There is a clear list of the current trials involving rituximab in the treatment of aggressive NHL including DLBCL, although it is stated that none of these studies are intended to replicate the GELA study.[60]

TABLE 21 *One-way sensitivity analysis results*

Variable	Assumption	Differences			
		LY	QALY	Cost (£)	Cost per (£) QALY
Base case		1.8	1.5	8,915	6,143
Relative increase in CR rate					
Low	Lower by 10%	1.8	1.4	8,915	6,347
High	Higher by 10%	1.8	1.5	8,915	5,951
Relative risk reduction disease-free and overall					
Low	Lower by 15%	1.5	1.3	8,915	6,961
High	Higher by 15%	2.2	1.6	8,915	5,476
Duration of treatment effect					
Low	2	1.5	1.2	8,866	7,124
High	5	2.4	1.8	8,992	5,071
Chemotherapy costs					
CHOP					
Low	Lower by 15%	1.8	1.5	8,905	6,136
High	Higher by 15%	1.8	1.5	8,926	6,150
Rituximab					
Low	Lower by 15%	1.8	1.5	7,629	5,257
High	Higher by 15%	1.8	1.5	10,200	7,029
Surveillance costs					
Low	Lower by 15%	1.8	1.5	9,167	6,316
High	Higher by 15%	1.8	1.5	8,663	5,969
Utilities					
Low	Lower by 15%	1.8	1.2	8,915	7,227
High	Higher by 15%	1.8	1.7	8,915	5,342
Discount rate (benefits)					
Low	0%	2.0	1.6	8,953	4,478
High	4%	1.6	1.3	8,845	6,980
Time horizon (years)					
Low	5	0.8	0.7	8,778	12,615
High	20	2.1	1.6	8,915	5,689

Chapter 5

Implications for other parties

Given that the context for care and the mode of delivery is identical with the comparator therapy, there are no implications for other parties that do not also apply to CHOP.

Chapter 6

Factors relevant to the NHS

The government white paper *Our Healthier Nation* set a target that there should be 100,000 fewer cancer deaths in people under the age of 75 years by 2010: 60,000 by the use of more preventive measures; 20,000 by early detection and screening; and 20,000 by improvements in survival. The National Cancer Plan has four broad aims, two of which are to save more lives and to ensure that people with cancer get the right professional support and care, in addition to the best treatments.

Chapter 7
Discussion

In the short term, the addition of rituximab to the CHOP regimen significantly increased the likelihood of a CR, without a significant rise in the risk of a serious adverse event, in people aged ≥60 years. Over a 2-year follow-up period, the intervention significantly prolonged survival without progression or relapse (the primary outcome), and significantly prolonged overall survival in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. Arguments are presented that clinical effectiveness can be derived for a younger population on the grounds that disease biology is consistent by age and prognosis is inversely correlated with age.

Adding rituximab involves the administration of an additional intravenous infusion of rituximab to three of the four CHOP regimen drugs administered in this way. No additional hospital visits are required and treatment remains on an outpatient basis.

Adverse effects associated with R-CHOP, beyond those associated with CHOP alone, are mostly limited to reactions during, and immediately after, rituximab administration, especially the first infusion of each course. Although these may occasionally be severe or life threatening, most may be quickly resolved by slowing or pausing the infusion and by the institution of supportive care.

Comprehensiveness of the review

Our own searches of the randomised evidence were exhaustive and we are confident that we have not missed any published reports of RCTs or other systematic reviews of R-CHOP in the treatment of DLBCL.

Needs for further research

As rituximab is a relatively recent anticancer drug developed for the treatment of malignancies arising from B-lymphocytes, there are currently available only data from one RCT comparing R-CHOP and CHOP treatments in DLBCL. However, as stated by Roche in their submission,[53] there are other relevant trials ongoing.

Analysis of QoL in the area of NHL is limited and only one cost–utility analysis for the treatment of CHOP in NHL was identified.[2] Both the ScHARR and Roche models utilised QoL utility scores from an unpublished data source. Further research within this area would help to improve the robustness of QoL utility analysis within DLBCL and also NHL as a whole. One way of achieving this would be for NICE to commission certain cancer networks to record stage, IPI score, outcome and QoL data for a cohort of patients receiving R-CHOP for DLBCL.

Further clinical trials might also establish whether peripheral blood stem cell transplant can improve on R-CHOP in high risk patients and whether the doses of chemotherapy in the elderly may be reduced if rituximab is added to less intensive regimens

Chapter 8
Conclusions

Clinical effectiveness

In the systematic review of effectiveness, one RCT was identified. In the short term, the addition of rituximab to the CHOP regimen significantly increased the likelihood of a CR, without a significant rise in the risk of a serious adverse event, in people aged ≥60 years suffering from stage II–IV DLBCL. Over a 2-year follow-up period, the intervention significantly prolonged survival without progression or relapse (the primary outcome), and significantly prolonged overall survival in this population. There is no direct evidence for the clinical effectiveness of adding rituximab to CHOP in the treatment of DLBCL in those aged 18–59 years, although data from phase I and II trials confirm its safety and efficacy in a preclinical setting. Arguments are presented that clinical effectiveness can be derived for a younger population on the grounds that disease biology is consistent by age and prognosis is inversely correlated with age.

Cost-effectiveness

The cost-effective modelling presented here has shown that rituximab when used in combination with CHOP chemotherapy regimen is a cost-effective treatment for DLBCL when compared with the current standard treatment with CHOP chemotherapy only. Although both the ScHARR model and the Roche model are based on the same data and use the same methodology, different interpretations of the clinical outcomes and costs have resulted in different results. However, the difference in the cost per QALY answers does not lead to a difference in the overall result that the addition of rituximab to the CHOP regimen is a cost-effective treatment. Extensive sensitivity analysis undertaken in both models has shown the results to be particularly robust.

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About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the effectiveness and cost-effectiveness of healthcare interventions for the NHS R&D Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute of Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are: Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration (WMHTAC), University of Birmingham.

Contributions of authors

Daniel Hind (Research Associate) and Vicky Abbott (Placement Student) carried out the review of the background information and the clinical effectiveness review. Chris Knight (Senior Operational Analyst) carried out the cost-effectiveness review. Naomi Brewer (Information Officer) undertook the electronic literature searches.

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Appendix 1

Ann Arbor staging system[17]

The standard staging system used for DLBCL is the same as that proposed for Hodgkin's disease at the Ann Arbor Conference in 1971. It classifies four stages of disease (*Table 22*).

Each stage of disease is divided into two subsets of patients according to the presence (A) or absence (B) of systematic symptoms. Fever of not evident cause, night sweats and weight loss of more than 10% of body weight are considered systemic symptoms.

TABLE 22 *Ann Arbor staging system*

Stage	Description
I	Involvement of a single lymph node region (I) or a single extranodal site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extralymphatic site (IIIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localised involvement of an extralymphatic site (IIIE) or spleen (IIIs) or both (IIIEs)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Localised involvement of liver or bone marrow is also considered stage IV

Appendix 2

ECOG performance status

TABLE 23 *ECOG performance status*

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3

NCI common toxicity criteria

0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event
4	Life-threatening or disabling adverse event
5	Death related to adverse event

Appendix 4

QUOROM checklist

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis [or systematic review] of RCTs	Y	iii
Abstract		Use a structured format	Y	iii
		Describe:		
	Objectives	The clinical question explicitly	Y	iii
	Data sources	The databases (i.e. list) and other information sources	N	
	Review methods	The selection criteria (i.e. population, intervention, outcome and study design): methods for validity assessment, data abstraction and study characteristics, and quantitative data synthesis in sufficient detail to permit replication	Y	iii
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and CIs); subgroup analyses	Y	iii
	Conclusions	The main results	Y	iii
		Describe:		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review	Y	3
Methods	Searching	The information sources, in detail (e.g. databases, registers, personal files, expert informants, agencies, handsearching) and any restrictions (years considered, publication status, language of publication)	Y	11
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, study design)	Y	11
	Validity assessment	The criteria and process used (e.g., masked conditions, quality assessment and their findings)	Y	12
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)	Y	12
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, etc., and how clinical heterogeneity was assessed	Y	12–13
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), method of combining results (statistical testing and CIs), handling of missing data; how statistical heterogeneity was assessed; a rationale for any *a priori* sensitivity and subgroup analyses; and any assessment of publication bias	Y	14–16

continued

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Results	Trial flow	Provide a meta-analysis profile summarising trial flow	Y	Appendix 10
	Study characteristic	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)	Y	Appendices 11–14
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary	Y	14–16
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in the light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda	Y	15–16, Chapter 7

Appendix 5

Electronic bibliographic databases searched

1. BIOSIS previews
2. CANCERLIT
3. CCTR (Cochrane Controlled Trials Register)
4. CDSR (Cochrane Database of Systematic Reviews)
5. CINAHL
6. EBM Reviews – ACP Journal Club
7. EMBASE
8. HEED (Health Economic Evaluations Database)
9. MEDLINE
10. NHS DARE (Database of Assessments of Reviews of Effectiveness)
11. NHS EED (Economic Evaluations Database)
12. NHS HTA (Health Technology Assessment)
13. PreMedline
14. Science Citation Index
15. Social Sciences Citation Index

Appendix 6

Other sources searched

1. Adverse Event Reporting System, USA
2. AHRQ (Agency for Healthcare Research and Quality), USA
3. Association of Cancer Physicians
4. Bandolier
5. British National Lymphoma Investigation
6. British Oncological Association
7. British Oncology Pharmacy Association
8. British Psychosocial Oncology Society
9. British Society for Haematology
10. Cancer BACUP
11. Cancer Research UK
12. CCOHTA (Canadian Coordinating Office for Health Technology Assessment)
13. CenterWatch
14. Cheltenham and Tewkesbury Primary Care Trust
15. CHE (Centre for Health Economics), York
16. Clinical Evidence
17. CliniWeb
18. CMA (Canadian Medical Association) InfoBase
19. COIN (Department of Health)
20. Current Controlled Trials
21. Community of Science databases
22. Drug Safety Research Unit
23. DES Reports (West Midlands Health Technology Assessment Collaboration)
24. Department of Health
25. eBNF (electronic British National Formulary)
26. eGuidelines
27. EMEA (European Agency for the Evaluation of Medicinal Products)
28. eMedicines Compendium
29. European Society for Medical Oncology
30. GOOGLE
31. Health Evidence Bulletin, Wales
32. Health Technology Board for Scotland
33. HSRU (Health Services Research Unit), Aberdeen
34. INAHTA (International Network of Agencies for Health Technology Assessment) Clearinghouse
35. Index to Theses (Sheffield University)
36. ISI Proceedings (Web of Science)
37. Leukaemia Research Fund
38. Leukaemia Care Society
39. Long Term Medical Conditions Alliance
40. Lymphoma Association
41. Macmillan Cancer Relief
42. Marie Curie Cancer Care
43. MEDLINEplus Drug Information
44. MeRec Publications – the National Prescribing Centre (NPC)
45. MRC Trials Register
46. National Assembly for Wales
47. National Cancer Alliance
48. National Cancer Research Institute
49. National Cancer Steering Group
50. National Council for Hospice and Specialist Palliative Care Services
51. National Guidelines Clearinghouse
52. National Research Register (2002, Issue 4, Update Software/Department of Health, CD ROM)
53. NCCHTA (National Coordinating Centre for Health Technology Assessment)
54. NHS CRD (Centre for Reviews and Dissemination), University of York
55. OMNI
56. POINT (Department of Health)
57. ReFeR (Research Findings Register)
58. Roche
59. Royal College of Nursing
60. Royal College of Pathologists
61. Royal College of Physicians
62. Royal College of Surgeons
63. Royal Pharmaceutical Society
64. ScHARR Library catalogue
65. SIGN (Scottish Intercollegiate Guidelines Network)
66. SEEK (Sheffield Evidence for Effectiveness and Knowledge)
67. Toxline
68. Trafford South Primary Care Trust
69. Trent Working Group on Acute Purchasing Reports
70. TRIP (Turning Research into Practice) database
71. Wessex DEC (Development and Evaluation Committee) Reports
72. WHO
73. Welsh Assembly Government
74. Welsh Cancer Network

Appendix 7

Search strategies used

BIOSIS

1985–2002
SilverPlatter WebSPIRS
Search undertaken September 2002

#1 'Lymphoma-' / disease-management, drug therapy, therapy
#2 'Large-cell-lymphoma' / disease-management, drug therapy, therapy
#3 'B-cell-lymphoma' / disease-management, drug therapy, therapy
#4 'B-lymphocyte' / disease-management, drug therapy, therapy
#5 ((Lymphoma*) near5 (non Hodgkin*))
#6 ((B) near5 (lymphocyte* or lymphoma*))
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 Rituximab* or MabThera* or Rituxan*
#9 LO1X X20
#10 'Antineoplastic-drug' in TP
#11 #8 or #9 or #10
#12 #7 and #11

CancerLit

1960s–2002

National Cancer Institute, USA

http://www.cancer.gov/search/cancer_literature/
Search undertaken September 2002

Database limits:
All languages; All fields; All publication types except letter; All years; Human only.

Rituximab AND non-hodgkin
Rituxan AND non-hodgkin
MabThera AND non-hodgkin

CDSR and CCTR

2002, Issue 3
The Cochrane Library, Update Software (CD-ROM version)
Search undertaken September 2002

#1 LYMPHOMA:ME
#2 LYMPHOMA-B-CELL:ME
#3 LYMPHOMA-DIFFUSE:ME
#4 LYMPHOMA-HIGH-GRADE:ME
#5 LYMPHOMA-INTERMEDIATE-GRADE:ME
#6 LYMPHOMA-LARGE-CELL:ME
#7 LYMPHOMA-NON-HODGKIN*:ME
#8 B-LYMPHOCYTES*:ME
#9 (LYMPHOMA* near NON-HODGKIN*)
#10 B NEAR LYMPHOCYTE*
#11 (LYMPHOCYTE* or LYMPHOMA*)
#12 ANTIGENS-CD20:ME
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 ANTIBODIES-MONOCLONAL:ME
#15 ANTINEOPLASTIC-AGENTS:ME
#16 (RITUXIMAB* OR MABTHERA* OR RITUXAN*)
#17 (LO1X AND X20)
#18 #14 OR #15 OR #16 OR #17
#19 #13 AND #18

CINAHL

1982–2002
Ovid Biomed
Search undertaken September 2002

#1 Lymphoma/ or *lymphoma, b-cell/ or *lymphoma, diffuse/ or *lymphoma, high-grade/ or *lymphoma, intermediate-grade/ or *lymphoma, large-cell/
#2 *Lymphoma, non-hodgkin/
#3 *B-Lymphocytes/
#4 ((Lymphoma$) adj5 (non-hodgkin$)).tw
#5 ((B) adj5 (lymphocyte$ or lymphoma$)).tw
#6 *Antigens, CD20/
#7 Or/1-6
#8 *Antibodies, Monoclonal/tu
#9 *Antineoplastic agents/tu
#10 (Rituximab$ or MabThera$ or Rituxan$).af
#11 LO1X X20.tw
#12 Or/8-11
#13 7 and 12

Citation Indexes (Science and Social Sciences)

1981–2002
Web of Science
Search undertaken September 2002

Database limits:
DocType=All document types; Language=all languages; Databases=SCI-EXPANDED, SSCI; Timespan=All years.

((rituximab* or mabthera* or rituxan*) and (non-hodgkin* or non hodgkin* or nonhodgkin* or B) and (lymphoma* or lymphocyte*))

CRD Databases (NHS DARE, EED, HTA)

CRD Website – complete databases
Search undertaken September 2002

rituximab/all fields or
mabthera/all fields or
rituxan/all fields

EBM Reviews – ACP Journal Club

1991–March/April 2002
Ovid Biomed
Search undertaken September 2002

#1 Lymphoma$.tw
#2 ((Lymphoma$) adj5 (b-cell or b cell or diffuse or high-grade or high grade or intermediate-grade or intermediate grade or large-cell or large cell)).tw
#3 ((Lymphoma$) adj5 (non-hodgkin$ or non hodgkin$)).tw
#4 ((B) adj5 (lymphocyte$ or lymphoma$)).tw
#5 ((antigen$) adj5 (CD20)).tw
#6 Or/1-5
#7 ((Antibod$) adj5 (monoclonal$)).tw
#8 ((Antineoplastic$) adj5 (agent$)).tw
#9 (Rituximab$ or MabThera$ or Rituxan$).af
#10 LO1X X20.tw
#11 Or/7-10
#12 6 and 11

EMBASE

1980–2002
SilverPlatter WebSPIRS
Search undertaken September 2002

#1 'Nonhodgkin-lymphoma' / all subheadings
#2 'Lymphoma-' / disease management, drug-therapy, therapy
#3 'Large-cell-lymphoma' / disease-management, drug therapy, therapy
#4 'B-cell-lymphoma' / disease-management, drug therapy, therapy
#5 'B-lymphocyte' / disease-management, drug therapy, therapy
#6 ((Lymphoma*) near5 (non Hodgkin*))
#7 ((B) near5 (lymphocyte* or lymphoma*))
#8 'CD20-antigen' / drug therapy
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 'Monoclonal-antibody' / drug-therapy
#11 'Antineoplastic-agent' / drug-therapy
#12 Rituximab* or MabThera* or Rituxan*
#13 LO1X X20
#14 #10 or #11 or #12 or #13
#15 #9 and #14

HEED (Office of Health Economics Health Economic Evaluation Database)

CD-ROM version
Search undertaken September 2002

Search terms:
Rituximab
MabThera
Rituxan

Fields searched:
Quick Search – All Data

MEDLINE

1966–2002
Ovid Biomed
Search undertaken August 2002

#1 Lymphoma/ or *lymphoma, b-cell/ or *lymphoma, diffuse/ or *lymphoma, high-grade/ or *lymphoma, intermediate-grade/ or *lymphoma, large-cell/
#2 *Lymphoma, non-hodgkin/
#3 *B-Lymphocytes/
#4 ((Lymphoma$) adj5 (non-hodgkin$)).tw
#5 ((B) adj5 (lymphocyte$ or lymphoma$)).tw
#6 *Antigens, CD20/
#7 Or/1-6
#8 *Antibodies, Monoclonal/tu
#9 *Antineoplastic agents/tu
#10 (Rituximab$ or MabThera$ or Rituxan$).af

#11 LO1X X20.tw
#12 Or/8-11
#13 7 and 12

PreMedline

27 August 2002
Ovid Biomed
Search undertaken September 2002

#1 Lymphoma$.tw
#2 ((Lymphoma$) adj5 (b-cell or b cell or diffuse or high-grade or high grade or intermediate-grade or intermediate grade or large-cell or large cell)).tw
#3 ((Lymphoma$) adj5 (non-hodgkin$ or non hodgkin$)).tw
#4 ((B) adj5 (lymphocyte$ or lymphoma$)).tw
#5 ((antigen$) adj5 (CD20)).tw
#6 Or/1-5
#7 ((Antibod$) adj5 (monoclonal$)).tw
#8 ((Antineoplastic$) adj5 (agent$)).tw
#9 (Rituximab$ or MabThera$ or Rituxan$).af
#10 LO1X X20.tw
#11 Or/7-10
#12 6 and 11

Appendix 8

Methodological search filters used in Ovid MEDLINE

Economic/QoL evaluations

#1. Economics/
#2. Exp "costs and cost analysis"/
#3. Economic value of life/
#4. Exp economics, hospital/
#5. Exp economics, medical/
#6. Economics, nursing/
#7. Exp models, economic/
#8. Economics, pharmaceutical/
#9. Exp "fees and charges"/
#10. Exp budgets/
#11. Ec.fs
#12. (Cost or costs or costed or costly or costing$).tw
#13. (Economic$ or pharmacoeconomic$ or price$ or pricing$).tw
#14. Quality-adjusted life years/
#15. "Economic burden".tw
#16. Cost of illness/
#17. Exp quality of life/
#18. Quality of life.tw
#19. Life quality.tw
#20. Hql.tw
#21. (Sf 36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short form thirty six or short form thirtysix or shortform 36).tw
#22. Qol.tw
#23. (Euroqol or eq5d or eq 5d).tw
#24. Qaly$.tw
#25. Quality adjusted life year$.tw
#26. Hye$.tw
#27. Health$ year$ equivalent$.tw
#28. Health utilit$.tw
#29. Hui.tw
#30. Quality of wellbeing$.tw
#31. Quality of well being.tw
#32. Qwb.tw
#33. (Qald$ or qale$ or Qtime$).tw
#34. Or/1-34

Guidelines

#1. Guideline.pt
#2. Practice guideline.pt
#3. Exp guidelines/
#4. Health planning guidelines/
#5. Or/1-4

Randomised controlled trials

#1. Randomized controlled trial.pt
#2. Controlled clinical trial.pt
#3. Randomized controlled trials/
#4. Random allocation/
#5. Double blind method/
#6. Single blind method/
#7. Or/1-6
#8. Clinical trial.pt
#9. Exp clinical trials/
#10. ((Clin$) adj25 (trial$)).ti,ab
#11. ((Singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
#12. Placebos/
#13. Placebos.ti,ab
#14. Random.ti,ab
#15. Research design/
#16. Or/8-15
#17. Comparative study/
#18. Exp evaluation studies/
#19. Follow up studies/
#20. (Control$ or prospective$ or volunteer$).ti,ab
#21. Prospective studies/
#22. Or/17-21
#23. 7 or 16 or 22

Systematic reviews/meta-analyses

#1. Meta-analysis/
#2. Exp review literature/
#3. (Meta-analy$ or meta analy$ or metaanaly$).tw
#4. Meta analysis.pt
#5. Review academic.pt
#6. Review literature.pt
#7. Letter.pt
#8. Review of reported cases.pt
#9. Historical article.pt
#10. Review multicase.pt
#11. Or/1-6
#12. Or/7-10
#13. 11 not 12

Appendix 9

Response criteria

Responses were defined as follows.

Complete response (CR)

Disappearance of any lesion or radiological or biological abnormality seen at diagnosis, and no new lesion.

Unconfirmed complete response (CRu)

Disappearance of nearly all lesions and all clinical symptoms but persistence of some clinical or radiological abnormalities that had regressed by more than 75%, and normalisation of all biological abnormalities and performance status; if persisting lymphoma cells are found in any biopsy, then the patient was considered to have a partial response.

Partial response (PR)

Regression by more than 50% of all measurable lesions, disappearance of unmeasurable lesions, and no new lesion; persisting lymphoma cells in any biopsy, in patients who otherwise met the criteria for CRu.

Stable disease

No response to treatment; regression by less than 50% of any measurable lesion or regression by more than 50% but with persistence of clinical symptoms, no change in the unmeasurable lesions, no growth of existing lesions or growth by less than 50% and no new lesion.

Progressive disease

Appearance of a new lesion, growth of more than 25% of the initial diameter of any lesion or regrowth by more than 50% from nadir for any measurable lesion that had regressed during treatment.

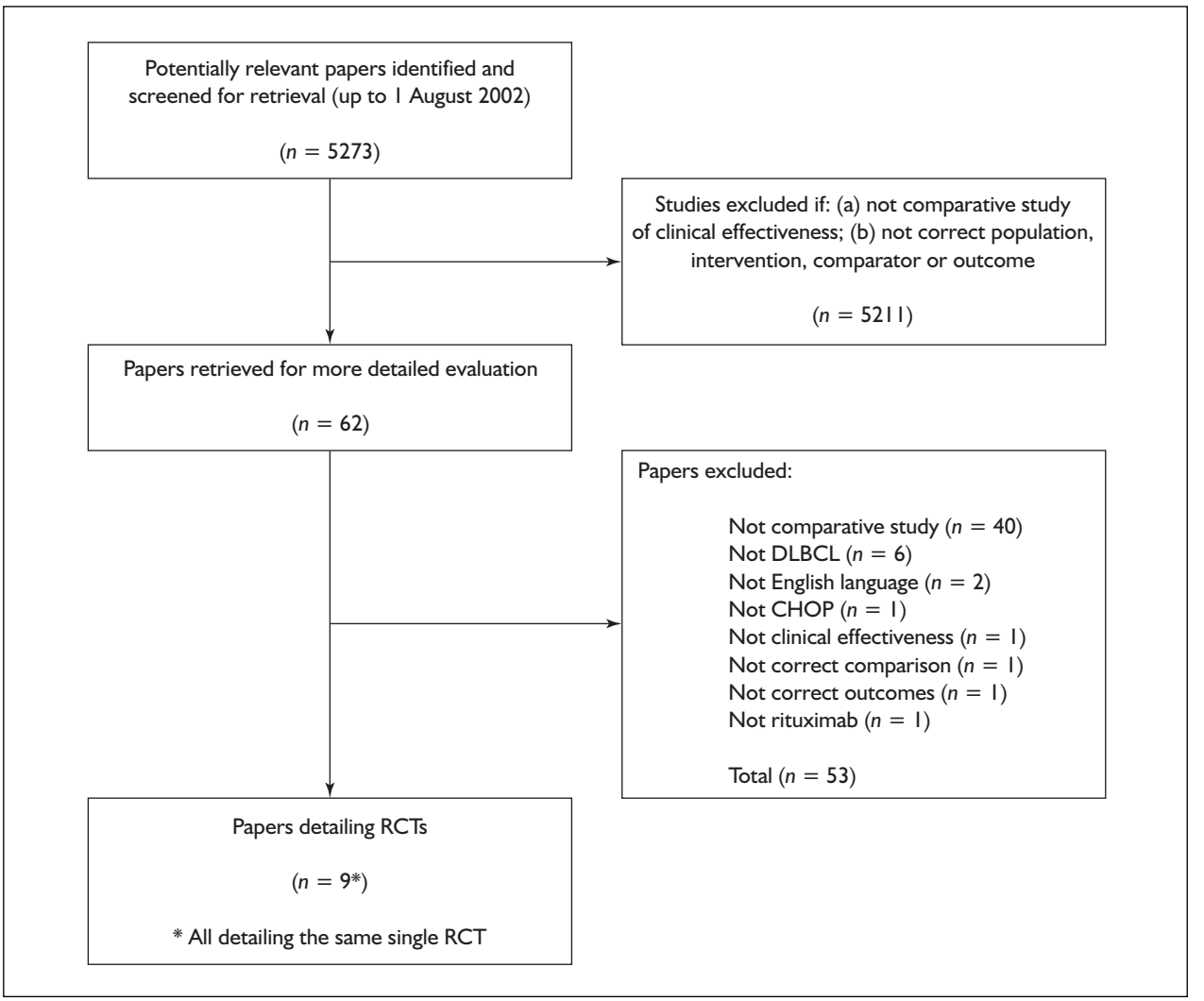
Patients were considered to be responders if they had CR or CRu.

The investigator determined the response category.

The site and dimensions of the largest tumour mass only were recorded.

Appendix 10

QUOROM flow chart



Appendix 11

JADAD quality checklist

Trial

GELA trial (Coiffier *et al.*[58])

Randomisation

	☑ Yes	☐ No
(extra point)	☐ Yes	☑ No
(deduct point)	☐ Yes	☑ No

Randomisation – trials that report using the following methods are to receive a point: reporting that the trial was a 'randomised' one. Trials that describe an appropriate method of randomisation, such as table of random numbers, computer generated, receive an additional point. However, if the report described the trial as randomised and it was inappropriate, such as date of birth, hospital numbers, a point is deducted.

Double-blinding

	☐ Yes	☑ No
(extra point)	☐ Yes	☑ No
(deduct point)	☐ Yes	☑ No

Double-blinding – trials that report using the following methods are to receive a point: reporting that a trial was 'double-blind'. Trials that describe appropriate method of double-blinding, such as identical placebo, active placebo, receive an additional point. However, if the report described the trial as double-blind and it was inappropriate, such as comparison of tablets versus injection with no double dummy, a point is deducted.

Withdrawals and dropouts

	☑ Yes	☐ No

Withdrawals and dropouts – trials that report using the following methods are to receive a point: the number and reasons for dropouts and withdrawals in each group must be stated. However, if there is no statement on withdrawals, this item must be given no point.

Jadad score

2 out of a possible 5

Appendix 12

SIGN methodology checklist

Study identification:

Checklist completed by:

SECTION 1: INTERNAL VALIDITY

	Evaluation criterion	How well is this criterion addressed?
1.1	Does the study address an appropriate and clearly focused question?	**Well covered.** Phase III (clinical effectiveness) trial "…to compare CHOP chemotherapy plus rituximab with CHOP alone in elderly patients with diffuse large-B cell lymphoma."[58]
1.2	Was the assignment of subjects to treatment groups randomised?	Poorly addressed. Report states that, "Eligible patients were randomly assigned by the study co-ordinating center to treatment…".[58] However, no method of randomisation is reported either in the paper or in the industry submission.[61] The review team contacted the study team, who confirmed that random number tables were used, an adequate method for sequence generation.
1.3	Was an adequate concealment method used?	**Well addressed.** Allocation concealment was not addressed in the industry submission: "Patients were randomly assigned to a treatment group, stratified by age-adjusted IPI score and study center A centralized randomization procedure was used. The investigators completed a randomization form for each consenting eligible patient and faxed this to the Randomization center located at Hôpital St Louis in Paris… Randomization numbers, which were generated by the GELA secretariat, were allocated sequentially in the order in which the patients were enrolled."[61]
1.4	Were subjects and investigators kept 'blind' about treatment allocation?	**Not addressed.** 'Blinding' was not addressed in the peer-reviewed paper.[58] The trial was described as open-label in the industry submission, but this aspect of study design, and the decision not to blind, was ignored. [61]
1.5	Were the treatment and control groups similar at the start of the trial?	**Well covered.** "There was no significant difference between the two groups in any clinical or pathological characteristic."[58]
1.6	Apart from the treatment under investigation, were the groups treated equally?	**Not addressed.** Not mentioned.
1.7	Are all relevant outcomes measured in a standard, valid and reliable way?	**Well covered.** All relevant outcomes are measured in a standard, valid and reliable way.[58]
1.8	What percentage of the clusters recruited into the study are included in the analysis?	**Well covered.** 100% of patients were included in the analysis, despite one having died before receiving their first treatment (from the CHOP only arm).[58]

1.9	Were all the subjects analysed in the groups to which they were randomly allocated?	**Well covered.** "Analyses of efficacy and safety included all randomised patients and followed the intention-to-treat principle."[58]
1.10	Are the results homogeneous between sites?	**Not addressed.** Not mentioned.
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code + +, +, or –*	+
2.2	If coded as +, or –, what is the likely direction in which bias might affect the study results?	Studies have also shown that the lower the level of blinding, the greater is the overestimate in treatment effect. Whether or not double-blinding is practically possible or not, Schulz and colleagues have demonstrated such trials to yield significantly larger estimates of effects ($p = 0.01$), with odds ratios exaggerated by 17%.[70,71]
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Despite the inadequacies in trial design and the reporting, with regard to blinding, the overall approach of the study is methodologically rigorous. Therefore, it seems likely that the direction, if not the size of the effect, is genuine.
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes. The trial demonstrates that CHOP plus rituximab is clinically effective for DLBCL in 60–80-year-olds, the age group associated with poor prognosis.[19,20] Therefore, younger patients would expect to benefit still more.
If the study reports an evaluation or comparison of diagnostic tests, please complete a diagnostic studies checklist before completing the next section.		
SECTION 3: DESCRIPTION OF THE STUDY		
3.1	What interventions are evaluated in this study?	The clinical effectiveness of CHOP chemotherapy plus rituximab is evaluated against CHOP alone in elderly patients with DLBCL.
3.2	What outcome measures are used? *i.e. benefits and harms*	"Primary outcomes were event-free survival, with events defined as disease progression or relapse, death or initiation of new alterative treatment. Secondary endpoints were response rate, survival and safety."[58]
3.3	How many patients participated in the study?	399
3.4	What was the scale and direction of the measured effect?	"The risk ratio associated with treatment with CHOP plus rituximab as compared with CHOP alone was 0.55 (95% confidence interval, 0.41 to 0.75) for death, disease progression, or another event and 0.53 (0.37 to 0.77) for death from any cause, as compared with the unadjusted values of 0.58 (0.44 to 0.77) and 0.64 (0.45 to 0.89), respectively."[58] The adjustments referred to were for two negative prognostic factors: β_2-microglobulin and the presence of more than one extranodal site of disease.
3.5	Is any statistical measure of uncertainty given? *e.g. confidence intervals; p values*	Both confidence intervals (see 3.4) and *p*-values were provided.
3.6	What are the characteristics of the study population? *e.g. age, sex, disease characteristics of the population, disease prevalence.*	See *Table 24*, Appendix 13.

3.7	What are the characteristics of the study setting? *e.g. rural, urban, hospital inpatient or outpatient, general practice, community.*	Multi-centre trial: urban hospitals, outpatient settings.
3.8	How many groups/sites are there in the study? *If the study is carried out on more than one group of patients, or at more than one site, indicate how many are involved.*	Patients were recruited at 86 centres – 72 in France, 1 in Switzerland and 13 in Belgium.
3.9	Are there any specific issues raised by this study? *Make any general comments on the study results and their implications*	No.

Appendix 13

GELA trial patient characteristics

TABLE 24 *GELA trial: patient characteristics*

Characteristic	No. (%)	
	CHOP plus rituximab (*n* = 202)	**CHOP (*n* = 197)**
Age (years)		
<65	44 (22)	48 (24)
65–69	57 (28)	62 (24)
70–74	52 (26)	56 (28)
≥75	49 (24)	31 (16)
Male sex	92 (46)	107 (54)
Performance status[a]		
0	37 (33)	70 (36)
1	90 (45)	94 (48)
>1	45 (22)	33 (17)
Stage		
I	0	1 (1)
II	41 (20)	39 (20)
III	33 (16)	29 (15)
IV	128 (63)	128 (65)
B symptoms[b]	78 (39)	70 (36)
No. of extranodal sites		
0	46 (23)	44 (22)
1	95 (47)	102 (52)
>2	61 (30)	51 (26)
Bulky tumour (>10 cm)	60 (30)	64 (32)
Bone marrow involvement	56 (28)	55 (28)
Elevated lactate dehydrogenase	131 (65)	132 (67)
Histological findings		
Not reviewed	6 (3)	8 (4)
Reviewed	196 (97)	189 (96)
DLBCL	176 (87)	160 (81)
Not DLBCL	20 (10)	29 (15)
Age-adjusted IPI scores[c]		
0	20 (10)	21 (11)
1	61 (30)	56 (28)
2	87 (43)	94 (48)
3	34 (17)	26 (13)
Standard IPI scores[c]		
0–1	29 (14)	23 (12)
2	64 (32)	69 (35)
3	78 (39)	82 (42)
4–5	31 (15)	23 (12)

[a] Performance status was defined according to ECOG criteria (with an increasing score indicating declining performance).
[b] B symptoms were defined as weight loss, fever and night sweats.
[c] Higher scores indicate a higher risk of death.

Appendix 14

GELA trial results

Data abstracted as reported in published paper: all available *p*-values reported.[58]

TABLE 25 *GELA trial: results of the intention-to-treat analysis of end-points*

End-point	CHOP plus rituximab (*n* = 202)	CHOP (*n* = 197)	*p*-Value
Event[a] – No. (%)[b]	86 (43)	120 (61)	0.002
Progression during treatment	19 (9)	44 (22)	
New alternative treatment	11 (5)	9 (5)	
Progression after stable disease	1 (<1)	1 (1)	
Progression after partial	5 (2)	4 (2)	
Response	29 (14)	49 (25)	
Relapse	21 (10)	13 (7)	
Death without progression	12 (6)	11 (6)	
During treatment	9 (4)	2 (1)	
After treatment	3 (2)	9 (5)	
Median time to event (months)	Not reached	13	<0.001
Relative risk event[c]	0.58	(0.44-0.77)	
2-Year event-free survival (%)[b]	57 (50 to 64)	38 (32 to 45)	
Median survival (months)	Not reached	Not reached	0.007
Relative risk of death[c]	0.64	(0.45-0.89)	
Death – No. (%)	59 (29)	81 (41)	
2-Year survival (%)[b]	70 (63 to 77)	57 (50 to 64)	

[a] Data from patients with no reported event were censored as of the most recent assessment or at the cutoff date for the analysis (30 June 2001).
[b] Because of rounding, not all percentages total 100.
[c] Values in parentheses are 95% CIs.

TABLE 26 *GELA trial: response to treatment (data abstracted as reported)*[58]

Response[a]	No. (%)	
	CHOP plus rituximab (*n* = 202)	CHOP (*n* = 197)
Complete response	106 (52)	72 (37)
Unconfirmed complete response	46 (23)	52 (26)
Partial response	15 (7)	11 (6)
Stable disease	2 (1)	1 (1)
Progressive disease	19 (9)	43 (22)
Death without progression	12 (6)	11 (6)
Could not be assessed[b]	2 (1)	7 (4)

[a] Tumour responses were classified as complete response, unconfirmed complete response, partial response and stable disease according to the International Workshop criteria.
[b] Treatment was stopped because of toxic effects, the patient's decision or the investigator's decision before evaluation of the tumour.

TABLE 27 *GELA trial: non-haematological adverse events (data abstracted as reported)*[58]

Event[a]	Patients with an event in at least 1 cycle (%)			
	Any grade		Grade 3 or 4	
	CHOP plus rituximab	CHOP	CHOP plus rituximab	CHOP
Fever	64	59	2	5
Infection	65	65	12	20
Mucositis	27	31	3	2
Liver toxicity	46	46	3	5
Cardiac toxicity	47	35	8	8
Neurological toxicity	51	54	5	9
Renal toxicity	11	14	1	2
Lung toxicity	33	30	8	11
Nausea or vomiting	42	48	4	8
Constipation	38	41	2	5
Alopecia	97	97	39	45
Other toxicities	84	80	20	25

[a] All adverse events reported by the patient or observed by the investigator were recorded. An adverse event was defined as any adverse change from the patient's baseline condition, whether it was considered related to treatment or not. Each event was graded according to the NCI Common Toxicity Criteria grading system; higher numbers denote more severe toxicity.

Appendix 15

Calculating staff resource use

The estimated staff costs for CHOP and R-CHOP are based on personal communications with the Chief Pharmacist at the Weston Park Hospital, Sheffield, and Dr J Radford, Professor of Medical Oncology, Christie Hospital NHS Trust, Manchester.

Pharmacy costs

Table 27 shows the average cost of preparing one pharmacy item based on the average preparation time for each grade, their annual wage, and also assuming that they all work 8 hours per day for 211 days per year (after accounting for weekends, 10 statutory leave days, 25 days' leave, 5 study/training days and 10 days sickness leave).[93]

Staff treatment costs

The assumptions used in estimating the staff cost for administering and monitoring patients receiving CHOP and R-CHOP are based on a personal communication from Professor J Radford and estimates of adverse event data from a phase III trial of the administration of rituximab alone in a clinical setting.[58]

For the administration of CHOP it has been assumed that the staff resources involved are 2 hours clinician time (Registrar) and 1 hour nurse time (Grade G). The cost per hour has been estimated at £27 for a registrar and £20 for a grade G nurse.[93] Therefore, the estimated cost of administrating CHOP is (£27 × 2) + (£20 × 1) = £74.

For the administration of rituximab it has been assumed that the first infusion takes 4 hours and subsequent infusions take 3 hours. However, 77% of cases experience mild/moderate infusion reactions on the first infusion within 30–120 minutes of starting. This is resolved by halving the speed of the infusion. A nurse must be present throughout to take readings every 15 minutes. The incidence of infusion reactions decreased with each subsequent infusion to 30% on the fourth infusion and 14% on the eighth infusion.

Table 28 shows the average nurse cost for administrating rituximab for each infusion. This

TABLE 28 *Average cost of preparing one pharmacy item*

Grade	Preparation time (minutes)	Annual wage (£)	Cost (£)	Therapy	No. of items	Cost per item (£)	Total cost (£)
Pharmacist	10	35,000	3.46	CHOP	3	8.49	25.47
Technician	20	20,000	3.95	R-CHOP	4	8.49	33.97
Assistant technician	10	11,000	1.09				
Average per item	40		8.49				

TABLE 29 *Cost of administering rituximab*

Infusion No.	Percentage of infusion reaction	Average time for infusion (hours)	Cost of nurse time per Infusion (£)
1	77	6.31	126.20
2	55	4.09	81.83
3	42	3.84	76.83
4	30	3.60	72.00
5	26	3.53	70.54
6	21	3.41	68.29
7	16	3.32	66.39
8	14	3.28	65.60
Average			78.46

TABLE 30 *Total estimated cost of staff resource use*

Therapy	Pharmacy (£)	Administration (£)		Total per cycle (£)
		CHOP	Rituximab	
CHOP	25.47	74.00	–	99.47
R-CHOP	33.97	74.00	78.46	186.43

estimate assumes that the average adverse reaction occurs after 1 hour. Therefore, if a patient experiences a mild/moderate infusion reaction during the first infusion, the total time of the infusion will be 7 hours. For subsequent infusions if a patient experiences a mild/moderate infusion reaction, the total time of the infusion will be 5 hours. The percentage number of infusion reactions for the first, fourth and eighth infusions was derived from McLaughlin *et al.* (1998).[94]

Fitting a logarithmic curve through the three known points derived an estimate of the percentage of infusion reactions for all other infusions. The 'goodness of fit' gave an R^2 of 0.995, although it is acknowledged that many curves could easily fit through three data points and give an excellent goodness of fit.

Table 29 shows the total estimated administration costs for CHOP and R-CHOP.

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We look forward to hearing from you.

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