RITUXIMAB as THIRD LINE TREATMENT for REFRACTORY or RECURRENT STAGE III or IV FOLLICULAR NON-HODGKINS LYMPHOMA

Report commissioned by: NHS R&D HTA Programme
On behalf of: The National Institute for Clinical Excellence
Produced by: Department of Public Health and Epidemiology
University of Birmingham*
The Health Economics Facility
Health Services Management Centre
University of Birmingham**

Authors: Beverley Wake, Research Associate*
Stirling Bryan, Senior Lecturer in Health Economics**
Pelham Barton, Lecturer in Mathematical Modelling**
Anne Fry-Smith, Information Scientist*
Clare Davenport, Specialist Registrar in Public Health*
Fujian Song, Senior Research Fellow*
Chris Hyde, Senior Lecturer in Public Health*

Correspondence to: Dr C.J.Hyde
Dept. Public Health and Epidemiology
University of Birmingham
Edgbaston
Birmingham
B15 2TT
E-mail ; C.J.Hyde@bham.ac.uk

Date completed: 9/1/2001
Expiry Date: 1/1/2004
HOW TO CITE THIS REPORT

WEST MIDLANDS DEVELOPMENT AND EVALUATION SERVICE
The West Midlands Development and Evaluation Service produces rapid systematic reviews about the effectiveness of health care interventions and technologies, in response to requests from West Midlands Health Authorities. Each review takes 3-6 months and aims to give a timely and accurate analysis of the available evidence, generating an economic analysis (usually a cost-utility analysis) of the intervention accompanied by a statement of the quality of the evidence.

CONTRIBUTIONS OF AUTHORS
Beverley Wake : Main project worker, developed protocol, systematic review of effectiveness
Stirling Bryan : Systematic review of cost-effectiveness
Pelham Barton : Systematic review of cost-effectiveness
Anne Fry-Smith : Searches, proof-reading
Claire Davenport : Data extraction, quality assessment, proof-reading
Fujian Song : General support and assessment of evidence on natural history
Chris Hyde: Development of protocol, advice on conduct of systematic reviews of effectiveness, searches for ongoing trials and initial drafting of final report.

All the named authors commented on, and agreed the final version of this report.

CONFLICTS OF INTEREST
Source of funding
This report was commissioned by the NHS R&D HTA programme.

Relationship of reviewer(s) with sponsor
No members of the review team or the units to which they belong at the University of Birmingham have any pecuniary relationship with sponsors, specific and non-specific.

ACKNOWLEDGEMENTS
Prof. A.K.Burnett: Peer review and general advice
Dr. C. Fegan : Peer review and general advice
Dr. A. Jacob : Peer review and general advice
Dr .S. Johnson : Peer review and general advice
Dr. T. A .Lister : Peer review and general advice
Dr. P. Revell : Peer review and general advice
Ann Massey : Minute taking and arrangement of meetings
CONTENTS

AIM OF THE REVIEW ........................................................................................................................................ 9

1. BACKGROUND ............................................................................................................................................... 10
   1.1 Description of underlying health problem ................................................................................................. 10
      1.1.1 Nature of the condition ......................................................................................................................... 10
      1.1.2 Epidemiology ......................................................................................................................................... 12
      1.1.3 Aetiology and prognosis ....................................................................................................................... 13
      1.1.4 Prognostic factors ................................................................................................................................... 13
      1.1.5 Significance in terms of ill-health (burden of disease) ......................................................................... 15
   1.2 Current service provision .......................................................................................................................... 15
      1.2.1 Objectives of treatment and important health outcomes ........................................................................ 15
      1.2.2 Current treatment options ................................................................................................................... 15
      1.2.3 Evidence on the effectiveness of existing treatments for follicular NHL ............................................. 16
      1.2.4 Current service cost ................................................................................................................................ 17
      1.2.5 Variation in services ............................................................................................................................. 17
   1.3 Description of new intervention ................................................................................................................ 18
   1.4 Summary of key points from background .................................................................................................. 18

2. EFFECTIVENESS ............................................................................................................................................ 19
   2.1 Objective ..................................................................................................................................................... 19
   2.2 Methods for reviewing effectiveness .......................................................................................................... 20
      2.2.1 Protocol .................................................................................................................................................. 20
      2.2.2 Search strategy ....................................................................................................................................... 20
      2.2.3 Inclusion and exclusion criteria ........................................................................................................... 20
      2.2.4 Data extraction strategy ....................................................................................................................... 21
      2.2.5 Quality assessment strategy ............................................................................................................... 21
      2.2.6 Analysis ................................................................................................................................................ 21
   2.3 Results ........................................................................................................................................................... 21
      2.3.1 Quantity and quality of research available ............................................................................................ 21
      2.3.2 Assessment of effectiveness ............................................................................................................... 32
   2.4 Summary of effectiveness .......................................................................................................................... 36

3. ECONOMIC ANALYSIS ................................................................................................................................ 37
   3.1 Objectives ..................................................................................................................................................... 37
   3.2 Methods for economic analysis .................................................................................................................. 37
      3.2.1 Search strategy ....................................................................................................................................... 37
      3.2.2 Handling information identified ........................................................................................................... 38
   3.3 Results ........................................................................................................................................................... 38
      3.3.1 Estimation of net benefits (i.e. taking account of disbenefits) .............................................................. 38
      3.3.2 Estimation of net costs ........................................................................................................................... 38
      3.3.3 Cost impact of rituximab ...................................................................................................................... 39
      3.3.4 Critique of other attempts to assess cost-effectiveness ........................................................................ 40
      3.3.5 Further exploration of assumptions in other attempts to assess cost-effectiveness .......................... 43
   3.4 Summary of economic analysis .................................................................................................................. 45

4. IMPLICATIONS FOR OTHER PARTIES ........................................................................................................ 46

5. RESEARCH IN PROGRESS ............................................................................................................................. 46
   5.1 Method ......................................................................................................................................................... 46
   5.2 Results ........................................................................................................................................................... 46

3
5.3 Key points arising ........................................................................................................ 51
6. DISCUSSION ................................................................................................................ 51
   6.1 Main results of report informing conclusions .......................................................... 51
   6.2 Assumptions, limitations and uncertainties ............................................................... 52
   6.3 Need for further research ........................................................................................ 53
7. CONCLUSIONS ............................................................................................................ 54
8. APPENDICES ............................................................................................................... 55
9. REFERENCES .............................................................................................................. 71

APPENDICES
Appendix 1 The Revised European American Classification of Lymphoid Neoplasms (REAL) system ........................................................................................................... 55
Appendix 2 US National Cancer Institute modification of REAL classification system .... 57
Appendix 3 Search strategies to identify prospective cohort studies on the natural history of NHL ......................................................................................................................... 58
Appendix 4 Search strategy to identify effectiveness of any treatments for NHL ............ 59
Appendix 5 Protocol ......................................................................................................... 60
Appendix 6 Search strategies to identify studies on effectiveness of rituximab in NHL .... 65
Appendix 7 List of experts contacted as part of search ..................................................... 66
Appendix 8 Search strategy and methods to identify on-going trials of rituximab .......... 66
Appendix 9 Details of bibliographic database search employed to identify ongoing trials involving rituximab .......................................................... 68
Appendix 10 Details of excluded studies and reasons for exclusion .................................. 69
Appendix 11 Search strategies to identify cost and quality of life studies ....................... 70

TABLES
Table 1 International Working Formulation (IWF) classification of NHL ...................... 11
Table 2 Ann Arbor staging system for NHL ........................................................................ 12
Table 3 Factors associated with length of survival in NHL .............................................. 14
Table 4 Population characteristics of total cohorts ......................................................... 23
Table 5 Population characteristics of most directly relevant subsets of patients .......... 24
Table 6 Details of interventions and outcomes for total cohorts .................................... 25
Table 7 Quality assessment, threats to validity and relevance .......................................... 26
Table 8 Results of rituximab case series ........................................................................... 27
Table 9 Resolution of symptoms in study by McLaughlin 1999 ...................................... 29
Table 10 Detailed table of adverse events (by % patients affected where possible) ........... 30
Table 11 Comparison of adverse events as reported in original publication and economic analysis derived from the same study ............................................................ 39
Table 12 Assessment of cost-effectiveness analyses: study characteristics and results .... 41
Table 13 Assessment of cost-effectiveness analyses: effectiveness and cost data .......... 41
Table 14 Assessment of cost-effectiveness analyses: sensitivity analyses .................... 42
Table 15 Incidences of adverse events used in sensitivity analysis ................................. 44
Table 16 Effect of equal incidence of adverse events ..................................................... 44
Table 17 Costs of adverse events used in sensitivity analysis .......................................... 44
Table 18 Effect of equal cost of adverse events ............................................................. 44
Table 19 On-going and completed but unpublished trials of rituximab ......................... 49

SUMMARY
Description of proposed service

Rituximab is a novel immunotherapeutic agent. What is under debate is whether wider use should be made of it in its currently licensed indication. This is for stage III or IV follicular non-Hodgkin’s lymphoma (NHL) which is chemoresistant or in its second or subsequent relapse after chemotherapy i.e. as a third line of treatment.

Epidemiology and background

NHL is a cancer of lymphatic tissue causing enlargement of lymph nodes and generalised symptoms. It is a heterogeneous condition. Follicular lymphoma behaves in an indolent fashion, with a median survival of 8-12 years. However, it is incurable and most patients with the disease will die from it. An average Health Authority of 500,000 persons may have between 13 and 24 stage III/IV follicular NHL patients presenting each year. Most will be over 50 years of age.

Management consists of intermittent treatment when the disease relapses and causes symptoms. Its aim is to maximise quality of life by inducing remission, abolishing symptoms associated with relapse, with minimal treatment side-effects. Cancer-specific treatment is not usually instituted while the patient is asymptomatic (“watchful waiting”). First line therapy is usually oral chlorambucil (or an equivalent alkylating agent). Second line treatment is usually an anthracycline containing chemotherapy containing regime such as CHOP, or fludarabine.

Number and quality of studies, and direction of evidence

The systematic review of effectiveness undertaken identified no RCTs or comparative studies. 4 prospective case-series were included, incorporating information on 387 patients. All were open to substantial bias and considerable caution was applied in interpreting the results.

No information was available on overall survival, nor were there direct measurements of impact on quality of life. Rituximab did achieve clinical responses in some patients, but most of these were partial (generally defined as ≥50% decrease in size of lesions and no new lesions). The duration of responses appeared to be of a length that would be clinically useful. Symptoms at baseline were abolished completely in responders and to some extent in “non-responders” too. However prior to treatment, symptoms only appeared to be present in a minority of patients. Mild to moderate adverse events occurred in most patients; severe adverse events occurred in a minority of patients; fatal adverse events were very rare, but did occur. Some non-responders experienced the adverse effects of rituximab, without great benefit.

Summary of benefits

The extent to which beneficial effects are outweighed by adverse events is impossible to quantify. Qualitatively rituximab is probably effective. Any impression of a poor ratio of benefit to disbenefit needs to be tempered by the observation that incomplete response rates and severe adverse events are common to all currently used third line treatments in this condition. The absence of direct comparative data makes it very difficult to assess whether
the ratio of benefits to disbenefits with rituximab is better, worse or the same as currently used alternatives.

- **Costs**

The drug cost of rituximab is high at approximately £4,900 per treatment cycle. However, the cost of administering rituximab is at worst similar to other commonly used treatments, because adverse events are less. Arguably the cost per course of treatment for rituximab is actually less, but this depends on the degree to which the incidence of adverse events is lower for rituximab. Even if lower cost per treatment course for rituximab is accepted, this will not convert into cost savings for the NHS unless rituximab replaces existing treatments. This seems unlikely; rituximab is more likely to be regarded as an additional treatment option rather than an alternative. A crude upper estimate of the budget impact on the NHS in England and Wales is £17.4 m per annum.

- **Cost/QALY**

Reliable estimates of the relative cost-effectiveness and cost-utility of rituximab cannot currently be provided given the uncertainties surrounding the level of net benefits.

- **Other important issues regarding implications**

The acceptability of rituximab to patients is likely to be high because of the reduced number of times it needs to be administered and the shorter period over which the treatment is completed.

- **Need for further research**

Further research on the effectiveness of rituximab and indeed all currently used therapies for NHL should be as great a priority for NHS resources, as making new treatments available. A trial of alternative treatment strategies over the whole course of disease, though difficult to design, could be a powerful way of taking this issue forward. Direct measurement of impact on quality of life is essential in future RCTs.
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>Acute myeloblastic leukaemia</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>CCST</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide, doxorubicin, vincristine, prednisolone</td>
</tr>
<tr>
<td>CLL</td>
<td>Chronic lymphocytic leukaemia</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response/remission</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised tomography</td>
</tr>
<tr>
<td>CVP</td>
<td>Cyclophosphamide, vincristine, prednisolone</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Co-operative Oncology Group</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>HA</td>
<td>Health Authority</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ILSG</td>
<td>International Lymphoma Study Group</td>
</tr>
<tr>
<td>iv</td>
<td>Intravenous</td>
</tr>
<tr>
<td>IWF</td>
<td>International Working Formulation</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>NEED</td>
<td>NHS Economic Evaluations Database</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response/remission</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>REAL</td>
<td>Revised European-American Lymphoma Classification</td>
</tr>
<tr>
<td>RR</td>
<td>Response/remission rate (overall)</td>
</tr>
<tr>
<td>SCT</td>
<td>Stem-cell transplant</td>
</tr>
<tr>
<td>TLS</td>
<td>Tumour lysis syndrome</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
DEFINITIONS OF TERMS

As used by the authors in the specific context of this report.

Advanced Synonymous with Ann Arbor stage III/IV – see stage
Aggressive Types of NHL where the cancer cells divide quickly
Chemoresistant Generally synonymous with refractory – see below. In the context of the UK licence for rituximab we have taken chemoresistant to mean that the follicular NHL is refractory to both first and second line treatment options
First line Treatment options applied when patients with follicular NHL first becomes symptomatic ie after any period of “watchful waiting”
High grade Synonymous with aggressive – see above
Indolent Types of NHL where the cancer cells divide slowly
Low grade Synonymous with indolent – see above
Recurrence Resurgence of follicular NHL following a response to treatment, usually marked by onset of new symptoms or return of previously experienced symptoms. The first appearance of symptoms, following a period during which the follicular NHL is asymptomatic, is not a recurrence or relapse
Refractory Where treatment fails to bring about any response – see below
Relapse Synonymous with recurrence – see above
Remission Improvement in disease. However, as spontaneous remission is very rare, remission is generally synonymous with response (to treatment) – see below. Periods where follicular NHL does not progress are common, but these are not remissions as defined
Response Improvement brought about by treatment following a recurrence. In research, remission is usually defined on the basis of serial CT or MRI scans. Degrees of response are recognised, particularly complete and partial, but their definitions vary slightly. Complete response is not synonymous with cure.
Second line Treatment options applied when patients have relapsed/recurred following, or proved refractory/chemoresistant to, first line treatment options – see above
Stage In NHL the degree of dispersion of affected lymph nodes and lymphoid tissue around the body. In the Ann Arbor system stage III/IV indicates that affected tissues are widely dispersed around the body
Third line Treatment options applied when patients have relapsed/recurred following, or proved refractory/chemoresistant to, both first and then second line treatment options – see above
AIM OF THE REVIEW

Despite undoubted improvements in the treatment of haematological malignancies, a number of conditions remain difficult to treat. Non-Hodgkin’s lymphoma (NHL) is such a condition and consequently the search continues for therapeutic agents which might improve its management. Rituximab is a novel immunotherapeutic agent that has been licensed in recent years.

The research question addressed by this report is, “What is the clinical effectiveness and cost-effectiveness of rituximab in stage III or IV follicular NHL which is chemoresistant or in its second or subsequent relapse after chemotherapy?” these being the circumstances for which rituximab is currently licensed.
1. BACKGROUND

1.1 Description of underlying health problem

1.1.1 Nature of the condition

Non-Hodgkin’s lymphomas (NHLs) are a heterogeneous group of cancers affecting the lymphatic system and are usually manifest by enlargement of lymph nodes, which occur throughout the body. The enlarged lymph nodes may give rise to cosmetic disfigurement, pain and restricted movement. The disease also gives rise to generalised symptoms such as malaise, weight loss, fevers and night sweats and in 15-20% the disease occurs in other lymphoid tissue including the spleen. The NHLs have been traditionally divided into 2 prognostic groups:

- Indolent or low grade lymphomas to which the follicular types generally belong. These have a long median survival, but are currently incurable at advanced stages. Most patients present with these types.
- Aggressive or high grade lymphomas. These have a shorter natural history, but 30-60% may be cured.

The lymphatic system has a number of different components and the cancer process may affect any of these. This in turn gives rise to different specific types of cancer within the broad category of NHL. Classification systems have evolved to capture these different specific types of NHL. However, as we have gained greater understanding about the diversity of cells making up the human immune system and how disease affects them, so the classification system has had to be up-dated.

One of the main classification systems is the International Working Formulation (IWF) shown in Table 1. The main distinction made in this classification is between how quickly the cancer cells divide. In low grade (indolent) NHL the cells divide relatively slowly; in high grade (aggressive) NHL they divide quickly.

The IWF classification further distinguishes on the basis of the cell types that can be identified when an affected lymph node taken from someone with NHL is examined microscopically. In the IWF classification the types of NHL constituting “follicular lymphoma” are types B, C and D. Although not stated in the classification all these types are derived from B-cells (as opposed to the other main type of cell making up the lymphatic system, T-cells). That is IWF B-D are B-cell NHL. It should however be noted that there are other types of NHL derived from B-cells eg type J, Burkitt’s lymphoma. In contrast to IWF B-D, which are indolent, this type of B-cell NHL is aggressive.
Table 1 International Working Formulation (IWF) classification of NHL 3

Low-grade
A. Small lymphocytic, consistent with CLL (SL)
B. Follicular, predominantly small cleaved cell (FSC)
C. Follicular, mixed small cleaved and large cell (FM)

Intermediate-grade
D. Follicular, predominantly large cell (FL)
E. Diffuse, small cleaved cell (DSC)
F. Diffuse mixed, small and large cell (DM)
G. Diffuse, large cell cleaved or noncleaved cell (DL)

High-grade
H. Immunoblastic, large cell (IBL)
I. Lymphoblastic, convuluted or nonconvuluted cell (LL)
J. Small noncleaved cell, Burkitt’s or non-Burkitt’s (SNC)

Unfortunately as yet there is not complete agreement on the ideal classification system for NHL and lymphomas/leukaemias in general. Consequently it is necessary to understand other commonly used classification systems. The Revised European American Classification of Lymphoid Neoplasms (REAL) system 4 and the US National Cancer Institute (NCI) modification of the REAL classification system 2 are presented in Appendices 1 & 2. The key points to note are that:

- Using the REAL system, “follicular lymphoma” corresponds to - II. Peripheral B cell neoplasms D. Follicle centre lymphoma, follicular
- Using the NCI modification, “follicular lymphoma” corresponds to - III. Indolent lymphoma/leukaemia A. Follicular centre cell lymphoma, follicular. Grades I, II & III

The most up-to-date classification is the WHO-REAL system. This is not used in any of the studies considered in this technology appraisal and is not described further. It is however similar to the REAL classification.

In addition to classifying NHL by the type of cell involved, it is also common to describe its stage. This gives an indication of how widely dispersed affected lymph nodes are around the body. Its intention is similar to staging in other cancers, in that it provides an indication of the prognosis of the particular type of NHL. The Ann Arbor Staging System 5 is still the most commonly used – see Table 2. In this report, stage III/IV follicular lymphoma is the severity of particular interest.
Table 2 Ann Arbor staging system for NHL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of single lymph node region or localized involvement (I) of single extralymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions (II) or localized involvement of a single associated extralymphatic organ or site at its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III) that may be accompanied by localized involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E)</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.</td>
</tr>
</tbody>
</table>

B is added to the stage if there is:
- Unexplained loss of more than 10% of body weight in the 6 months before diagnosis
- Unexplained fever with temperatures above 38°C
- Drenching night sweats

These are often referred to as “B symptoms”

1.1.2 Epidemiology

NHL accounts for around 2% of all cancers in the UK making it around the 10th commonest malignancy with around 2500 new cases reported each year. NHL is an important cause of mortality. In England and Wales in 1998 there were 3966 deaths from NHL accounting for 0.7% of all deaths and 2.9% of all cancer deaths, making it the 11th most common cause of cancer mortality.

We estimated the overall incidence rates in England and Wales by applying averaged age-specific incidence data from 1991 to 1991 census population data in 5 year age bands. The overall incidence was estimated to be 14.6 and 12.1 per 100,000 population in males and females respectively. If we make an assumption drawn from a study by the International Lymphoma Study Group (ILSG) that average overall survival for NHL patients is 5 years, prevalence rates in England and Wales would be approximately 73 and 61 per 100,000 population for males and females respectively.

NHL is rare in the under 50’s. At age 40 in 1991 the incidence rate was approximately 7 and 3 per 100,000 population in men and women respectively. This rises to approximately 47 and 75 per 100,000 at age 75 and above. The increasing longevity of the population alone suggests that the number of cases of NHL will grow. Independently of this there is some evidence that the incidence of NHL is increasing at a rate too great to be accounted for by improved diagnostic techniques alone. In Yorkshire there was an upward trend between 1978 and 1991 of 5-6% per annum.

Changing classification systems have meant there is uncertainty over the proportion of NHLs that are follicular in origin. The Working Classification Project classified 40% as follicular; whereas the ILSG using the REAL system classified 22% as follicular lymphoma. Up to 90% of follicular lymphomas present as stage III/IV disease.

Using the epidemiological data above suggests that the approximate number of new cases per year of stage III/IV follicular NHL in the average HA (Health Authority) of 500,000 persons...
would be 13 if 22% NHL is follicular in origin. If 40% of NHL is follicular in origin, this figure rises to approximately 24. Assuming a median survival of 10 years (see below for justification) in turn suggests prevalent cases in the average HA will be 130 to 240, again depending on whether the proportion of NHL which is follicular is 22% or 40%.

1.1.3 Aetiology and prognosis

The causes of NHL in general, and follicular lymphoma specifically, are unclear. There are a number of well-established risk factors such as infectious agents eg HIV 11, immunosuppression eg post organ transplantation 12, genetic susceptibility eg ataxia telangiectasia 13, and environmental factors eg exposure to agrichemicals 8.

There is some debate over median survival of low grade or indolent NHL, including follicular lymphomas, due to its heterogeneous nature. However typical values are 8 to 12 years 14, 15. Current treatments appear to make little difference to the overall survival, and virtually never bring about a permanent cure 2. They are diseases of sequential episodes of relapse and remission. Relapse generally results from periods of more rapid growth of the cancer cells, leading in turn to resurgence of lymph node enlargement and generalised symptoms. Consequently, during relapses, treatment is given to achieve remission, abolish the generalised symptoms and restore quality of life. If achieved, the periods of remission may last several years. However, with each relapse, remission as a result of treatment becomes harder to achieve (that is the disease is more likely to become refractory to treatment) and the period of remission shorter. Indolent lymphoma may also convert to an aggressive form which may sustain a complete remission with intensive chemotherapy 2. The majority of patients will eventually die as a direct result of their lymphoma. However, since patients are generally elderly and disease duration long, patients may die of unrelated illnesses too.

High grade or aggressive types of NHL require immediate therapy, often combination chemotherapy, in keeping with their rapidly progressive nature. However, paradoxically the outlook may be better for those responding to currently available treatment, since long-term disease free survival is achieved in approximately 50% of patients 1.

1.1.4 Prognostic factors

A systematic search was undertaken of cohort studies that might provide accurate information on the natural history of NHL, particularly follicular lymphoma. The search strategy used is given in Appendix 3.

The factors which may be associated with length of survival of patients with NHL in four of the studies identified 16, 17, 18, 19 are outlined in Table 3. The median follow up was from 51 months to 9 years. The number of patients included ranged from 157 18 to 987 17.

Using univariate analysis, a number of factors were found to be statistically significantly associated with the survival of NHL patients. Multivariate analysis identified fewer significant factors and the important prognostic factors identified were different across different studies. According to the results of multivariate analysis, the following prognostic factors may be important: age >60 years, B symptoms, extranodal sites, large tumour size, elevated serum lactate dehydrogenase (LDH), poor Eastern Co-operative Oncology Group (ECOG) performance status, erythrocyte sedimentation rate (ESR) and haemoglobin levels.
Table 3 Factors associated with length of survival in NHL

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Gender</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Stage</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>B symptoms</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Tumour bulk</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>ESR</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Substantial splenomegaly</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Serous effusion</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Orbital/epidural involvement</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>International Prognostic Indicator score</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Cell type</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

In the one study of direct relevance 16 484 patients with low grade stage III/IV follicular lymphoma were included, and 3 prognostic factors were identified: B symptoms, at least 3 nodal sites >3 cm, and age >60 years. For patients with 0, 1, and 2/3 factors, the overall survival at 5 years was 74%, 66%, and 45% respectively.

The results of these recent studies are generally consistent with previous studies. For example, the International Non-Hodgkin’s Lymphoma Prognostic Factors Project 20 identified five pre-treatment features that were independently associated with 5-year survival in patients with aggressive NHL: age (≤60 vs >60), tumour stage (I/II vs III,IV), number of extranodal sites (≤1 vs >1), performance status (0/1 vs >1) and serum LDH levels (≤1 vs >1). These five patient characteristics were used to develop a model for predicting outcome in patients with aggressive NHL and although initially constructed for these patients it has now been applied to other subtypes of NHL, where it has similar predictive value 1.

The key point arising from investigations of prognostic factors in NHL, is that they are numerous and that they interact. The corollary of this is that where uncontrolled case-series are used to assess effectiveness, minor differences in the prognostic factors of those entering the case-series, may themselves cause major differences in patient outcome. Thus without detailed information on prognostic factors, comparing case-series treated with one agent with case-series treated by another agent and attempting to impute differences in outcomes to the different treatments is highly dubious. Even if the prognostic factors are defined in detail, our ability to accurately adjust the outcomes for imbalances in prognostic factors has been questioned. This uncertainty must be even greater where the number of potentially important prognostic factors is large and the nature of the interaction between them uncertain, as is clearly the case for NHL.
1.1.5 **Significance in terms of ill-health (burden of disease)**

The nature of NHL in general and follicular lymphoma in particular, and the duration of the diseases, suggests that individually and at a population level it is responsible for a considerable amount of morbidity and mortality. 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 and there is evidence that it’s incidence is increasing.

1.2 **Current service provision**

1.2.1 **Objectives of treatment and important health outcomes**

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

- Eradicating the cancer, and so effecting a long-term cure
- Achieving long term cancer stasis or regression, with the aim of prolonging life
- Treating symptoms, particularly those arising from relapse or recurrence or disease progression, and so improving quality of life
- Helping patients come to terms with their condition, again improving quality of life
- Managing the terminal stages of the disease, so allowing dignified death, free of discomfort and distress

This predicts that the following health outcomes are likely to be of potential importance:

- Absence of cancer at given points in time following diagnosis
- Mortality, particularly cancer specific mortality
- Duration of survival
- Quality of life
- Patient and carer satisfaction

However in NHL, because the prospect of cure with current treatments is acknowledged to be rare (and there has been no claim that rituximab substantially alters this), the main focus of specific cancer therapy is on treating symptoms arising from relapse and recurrence, so maximising quality of life during the period of survival.

Specific events that contribute to this end, and so might act as proxies for the main objective, can thus be identified as:

- Number of relapses/recurrences
- Duration of relapses/recurrences
- Severity of symptoms associated with the relapses/recurrences
- Ability to bring about a remission
- Speed of induction of remission
- Reduction of symptoms associated with the remission
- Adverse events associated with induction of the remission
- Duration of remission

1.2.2 **Current treatment options**

For patients presenting with stage III/IV follicular NHL several treatment options are available. However, patients will probably receive all treatments in the course of their disease. The order in which they are offered is based on the degree to which the chances of
achieving a remission are off-set by the number and severity of adverse events suffered to achieve remission. A further consideration, particularly in younger patients, is the need to use the available treatment options in an order that does not compromise treatment options at later relapse points.

**First line**: Management may initially include “watch and wait” (no specific anti-cancer therapy). During this time the disease may remain stable, and the period of watchful waiting may be as long as 72 months. Single agent therapy with an oral alkylating agent such as chlorambucil (with or without oral steroids) is usually the first specific chemotherapy used.

**Second line**: Following first relapse/recurrence or failure to respond to first line therapy, combination intravenous (iv) chemotherapy containing alkylating agents (eg cyclophosphamide) in combination with anthracyclines (eg doxorubicin) and other cytotoxic drugs, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and CVP (cyclophosphamide, vincristine and prednisolone) is usually given until a “best response” is obtained. After further relapse the patient may be retreated with the same therapy. Fludarabine, although unlicensed for this indication, may be given as an alternative and indeed is being used increasingly as a first line therapy. This agent may also be used before or after combination chemotherapy, as a single agent or in combination.

**Third line**: At a point where the cancer has relapsed following all usually applied first and second line therapies, or where it has proved chemoresistant/refractory to these therapies, newer therapies may then be used including rituximab, cladribine (2-chlorodeoxyadenosine), interferon-α or high dose therapy with stem cell support.

1.2.3 Evidence on the effectiveness of existing treatments for follicular NHL

A search was carried out for systematic reviews of randomised controlled trials (RCT) and other rigorous research on the effectiveness of existing treatments for NHL, using a strategy outlined in Appendix 4. Unfortunately there appear to have been few systematic reviews of the effectiveness of existing agents, particularly as applied to stage III/IV follicular lymphoma. The two most rigorous and relevant reviews identified are discussed below.

**Gustafsson 1996** 21: This review concluded that for advanced disease (stage III/IV low grade NHL):

1. Two studies of limited tumours at stage III reported greatly prolonged remission after extensive radiotherapy or combination therapy. However, only a small number of patients are appropriate for such extensive irradiation.
2. Two RCTs trials compared chemotherapy and combination therapy at stage III/IV and arrived at different results: one showed no difference between chemotherapy alone or in combination with total body irradiation; while one found that combination therapy yielded significant longer relapse-free and overall survival. Clinical observation is that total body irradiation is little used in the UK.
3. The value of adjuvant radiotherapy in advanced disease has not been confirmed.

**Cheson 1998** 22: This review presented some quantitative results about several ‘new’ treatment approaches.

1. Fludarabine. According to several case series, responses to fludarabine occur in about 50% of patients with an indolent NHL who have relapsed following an initial response or who are refractory to prior therapies, including 10% to 15% complete remissions.
Complete remissions are more common in patients who receive fludarabine as initial treatment for an indolent NHL, with a frequency of almost 40%, and an overall response rate of about 70%. Major side effects of fludarabine include moderate myelosuppression, profound immunosuppression, and neurotoxicity.

2. Cladribine. Response rate to cladribine in several case series ranged from 43% to 77% in patients with indolent NHL who received prior therapy, and from 71% to 100% among patients with no prior therapy. Side-effects are similar to those for fludarabine.

3. Interferon $\alpha$. There are more than 10 RCTs in which interferon has been used during induction, as maintenance, or as both. When incorporated into induction programs, the effect on response rates has been inconsistent. Of the studies combining interferon with chemotherapy agents there was a longer time-to-treatment failure with interferon in most, but with an inconsistent effect on survival.

4. Stem-cell transplantation (SCT). There is limited data available on the use of allogeneic bone marrow transplant in indolent NHL. The experience with autologous stem-cell transplantation for low grade NHL is larger than bone marrow transplantation. Short-term and long-range complications of autologous stem-cell transplantation include treatment-related mortality, prolonged anaemia or thrombocytopenia, a markedly increased rate of secondary myelodysplasia, and acute myeloblastic leukaemia (AML) which ranges from 6.8% to 19%.

Identified reviews overall were predominantly narrative, with little information about quantitative results of primary studies. Some reviews focused on intermediate/high grade NHL. One review presented some quantitative data on fludarabine for indolent NHL and another suggested CHOP as a treatment option, with a reference describing long term follow-up of patients with low grade malignant lymphomas treated with doxorubicin based chemotherapy or chemoimmunotherapy.

An obvious issue arising is that gauging the relative effectiveness of a new treatment is problematic, because the effectiveness of existing treatments has not been clearly quantified in RCTs.

1.2.4 Current service cost

Because treatment of follicular lymphoma 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 long duration of disease and the variety of treatments to which an individual might be exposed over the course of their illness, suggests that the costs of caring for follicular lymphoma are likely to be considerable. In this, the support required from primary care and palliative care services in the terminal stages of the disease should not be underestimated.

1.2.5 Variation in services

There appears to be debate about the order in which the available treatment options described in 1.2.2 are delivered. This suggests that there will be variation in the treatments offered by different clinicians. However, guidelines are being developed by the clinical group of the British Committee for Standards in Haematology.
1.3 Description of new intervention

Rituximab (MabThera®) is manufactured by Roche Products Limited. A genetically engineered chimeric mouse/human monoclonal antibody against the CD20 antigen found on the surface of most mature and malignant B lymphocytes, it binds to the CD20 antigen, inducing lysis probably by antibody-dependent toxicity and complement-dependent cytotoxicity.

Rituximab was licensed for the use in the UK and Europe in June 1998 for the “treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy” ie third line therapy. It had been previously licensed in the US by the Food and Drug Administration in November 1997 from Genentech Inc. and IDEC Pharmaceutical Corporation under the trade name Rituxan (IDEC-C2B8) for patients with relapsed or refractory, low grade or follicular CD20-positive, B-cell NHL.

The British National Formulary (BNF) states the following regarding rituximab: “Rituximab…… has recently been introduced for the treatment of chemotherapy resistant advanced follicular lymphoma… Full resuscitation facilities should be on hand…treatment should be undertaken under the close supervision of a specialist since fatalities following severe cytokine release syndrome (Tumour Lysis Syndrome – TLS) have occurred 1-2 hours following rituximab”. Patients with a high tumour burden are most at risk. Also rituximab should be used with caution in patients with cardiovascular disease. Infusion-related side effects are said to be common particularly during the first infusion and that prophylaxis with an analgesic and an antihistamine should be administered. Rituximab is contraindicated during pregnancy and in nursing mothers.

The recommended dosage is 375 mg/m² given as an iv infusion once weekly for four doses (days 1, 8, 15 and 22). The average net drug cost of a 4 dose treatment for an average adult (surface area 1.7m²) is approximately £ 4,900. This is based on the cost of 1x500mg vial £873.15, and 2x100mg vials £174.63 for each of four cycles.

Currently many clinicians appear to use rituximab as a treatment of last resort. That is they use rituximab only when other non-contraindicated currently available treatments have failed, particularly where the disease does not respond to other treatment options ie is chemoresistant/refractory. This would generally involve giving rituximab as the fourth or fifth treatment option, as opposed to the third. This implies that the new model of treatment is the addition of rituximab to the existing range of treatments available, and that it is envisaged that it would be applied at some stage of the disease provided it was not contra-indicated.

What does not seem to be under consideration is the wholesale replacement of a currently used treatment options with rituximab.

1.4 Summary of key points from background

Disease:
- NHL is a cancer of lymphatic tissue causing enlargement of lymph nodes and generalised symptoms
- Indolent NHL is widely acknowledged to be incurable and most patients with the disease will die as a direct consequence of their condition
- NHL is a heterogeneous condition; the types behave differently
• Follicular lymphomas make up 22 - 40% and generally behave in an indolent fashion
• Up to 90% of follicular lymphomas present with stage III/IV disease
• The average HA may have between 13 and 24 stage III/IV follicular NHL patients presenting each year
• Most will be over the age of 50 years
• The median survival for indolent NHL is 8 to 12 years
• Several prognostic factors have been identified and they probably interact in a complex manner

Existing treatments:
• Management consists of intermittent treatment when the disease relapses and causes symptoms
• The aim of treatment is thus to maximise quality of life by inducing remission, abolishing symptoms associated with relapse, with minimal treatment side-effects
• Cancer-specific treatment is not usually instituted while the patient is asymptomatic (“watchful waiting”)
• First line therapy is usually oral chlorambucil (or an equivalent alkylating agent), with or without steroids
• Second line treatment is usually an anthracycline containing chemotherapy containing regime such as CHOP, or fludarabine
• The effectiveness of most existing treatments has been poorly quantified using RCTs

New treatment:
• Rituximab is a novel type of treatment, termed immunotherapy – the drug is directed against a marker found on B-cells
• It is currently licensed for “treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy” ie as third line therapy
• It is administered as a course of 4 injections over 1 month
• Care must be taken on first infusion, as severe reactions have been identified
• The cost of the drug is approximately £5,000 for a course of four injections
• Many clinicians in the UK currently use rituximab as a treatment of last resort
• In this model of use, rituximab is an additional treatment option to currently established treatments
• Used in this way rituximab is unlikely to wholly replace any of the existing treatment options

2. EFFECTIVENESS

2.1 Objective
To systematically review the evidence of the effectiveness of rituximab for stage III/IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy.
2.2  Methods for reviewing effectiveness

2.2.1  Protocol
The review was undertaken in accordance with a pre-defined protocol (see Appendix 5).

2.2.2  Search strategy
A broad comprehensive search for studies assessing the effectiveness of rituximab was undertaken involving:

- Electronic bibliographic database searches; MEDLINE (Ovid) 1966-Sept 2000; Embase (Ovid) 1980-Sept 2000; Science Citation Index (Web of Science) 1981- Oct 2000; Cochrane Library 2000 Issue 3 (see Appendix 6 for detail on search terms used)
- Citation checking of studies and reviews obtained
- Citation checking of the reference list of the single industry submission
- Contact with experts in the field (see Appendix 7 for list)
- Internet search engines

This search strategy was amplified by identification of potentially relevant citations in the systematic searches conducted for:

- Evidence on the effectiveness of treatments other than rituximab for NHL (see Appendix 4 for further details)
- Identification of on-going and unpublished trials involving rituximab (Appendices 8 and 9 for further details). This included further extensive interrogation of relevant Internet web-sites which as listed in Appendix 8 and a search of the National Research Register (2000, Issue 4)

In the initial protocol we indicated that we would attempt to search conference abstracts. This however was not feasible in the time available.

2.2.3  Inclusion and exclusion criteria

Intervention: Rituximab at the dose given on the product information sheet ie 375mg/m² given as an iv infusion once weekly for four doses.

Population: Stage III/IV follicular lymphoma which is chemoresistant or in its second or subsequent relapse after chemotherapy, as indicated in the UK licensing information.

Comparator: Any, which also includes no treatment and any of the current recommended treatments.

Outcomes: No restriction was made according to the outcomes measured. However, survival, quality of life and adverse events were the outcomes designated a priori as those of greatest interest.

Design: The initial inclusion criteria specified RCTs. As stated in our protocol, in the absence of RCTs we extended our inclusion criteria to include non-randomized controlled trials and studies with no parallel control arm ie case-series. In the latter case, by definition, the inclusion criterion relating to presence of a comparator was dropped. With respect to case-series, studies containing fewer than 10 patients were excluded.
Application of inclusion/exclusion criteria was undertaken by two reviewers (BW & CD). Decisions were be made independently of the data extraction and prior to the scrutiny of results.

2.2.4 Data extraction strategy

Data concerning study characteristics, study quality and results were extracted independently by two reviewers (BW and CD) using a series of proforma. Any differences were resolved by consensus.

2.2.5 Quality assessment strategy

A generic framework, as suggested by the Cochrane Collaboration assessing selection, performance, detection and attrition biases, was employed to describe the strengths and weaknesses of the included studies. If RCTs had been identified they would have been assessed using the Jadad checklist.

In relation to case-series the strengths and weaknesses of the included studies were assessed using a pre-specified framework incorporating:
- Need to indicate that they were conducted prospectively
- Ideally present the results of a consecutive series
- Give clear indications of the patient characteristics particularly with regard to stage of disease and previous treatments
- That losses to follow-up with respect to particular outcomes of interest are <10%

These had been developed by two of the authors in a previous systematic review on a different topic. The quality assessment was performed independently by two reviewers (BW and CD) and any differences resolved by consensus.

2.2.6 Analysis

As pre-stated the main method of analysis was qualitative. Meta-analysis was not employed and no sub-group analysis was performed.

2.3 Results

2.3.1 Quantity and quality of research available

- Number of studies identified
  269 studies were identified. By applying the inclusion criteria documented above 13 studies were selected as potentially relevant on the strength of their abstract. These 13 provisionally included studies were considered in detail on the basis of the full text of the article, where this was available.

- Number and type of studies included
Rituximab for NHL

No RCTs or comparative studies of any description were identified and included. * 4 (5/13 papers as one provided more information on the same study) studies were finally included for review 31, 32, 33, 34, 35. These were all prospective case series.

- **Number and type of studies excluded, with reasons for specific exclusions**
  8 of the potentially included 13 studies were excluded. The main reasons for exclusion were suspicion of duplication, papers were reviews only or that they did not meet our inclusion criteria. Full details of excluded studies and reasons for exclusion are available in Appendix 10.

- **Included study characteristics**
  Population characteristics of the complete cohorts from the included studies are recorded in Table 4.

The four included case-series were small to moderate in size ranging from 31 included 31 to 166 35. In some respects the patients in each of these were similar particularly with respect to age and sex. However given the importance of age as a prognostic factor, it may be that even the small differences in median age observed (55y; 50y and 58y – median age not given for Ghielmini) are important. With respect to stage all studies were inclusive, not prescribing stage of disease with the result that as well as including stage III/IV, stage I/II were also present. However, again considering the importance of stage as a prognostic factor, variation in the proportions of stage III/IV which might inevitably arise from failure to restrict by stage, may present problems in comparing the results. All studies excluded patients with lymphoma which were not positive for the CD20 marker.

There were further important differences. In particular, with respect to condition Foran 32 included follicular lymphoma, Davis 31 and McLaughlin 35 IWF type A in addition, and Ghielmini 33 mantle cell lymphoma in addition. There was also variation in the inclusion/exclusion criteria relating to prior treatment. Ghielmini 33 made no stipulation about

* Late in the review, as part of the search for on-going studies, one RCT directly comparing rituximab versus rituximab and IDEC-Y2B8 in approximately 150 patients with relapsed or refractory low grade NHL, was identified. This appears to have finished recruiting but has not yet reported in full. An interim analysis reported in abstract only appears to indicate greatly improved response in the rituximab + IDEC-Y2B8 arm. This trial is also of great interest because it collected information on impact on QOL. The limited reporting of the final results for practical purposes led to the exclusion of this study from our systematic review, but clearly the statement about absence of comparative research needed to be qualified by acknowledgement that the study had been conducted.
Table 4 Population characteristics of total cohorts

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Davis 1999</th>
<th>Foran 2000</th>
<th>Ghielmini 2000</th>
<th>M'Laughlin 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim of study</td>
<td>To evaluate the safety and efficacy of rituximab in bulky relapsed or refractory low-grade follicular NHL</td>
<td>To confirm the activity of rituximab follicular lymphoma including monitoring of blood and BM for Bcl-2/Ig gene rearrangement</td>
<td>Interim report of efficacy and toxicity of induction Rx of ongoing randomised trial rituximab vs extended rituximab in follicular &amp; mantle cell lymphomas.</td>
<td>Pivotal trial on the safety and clinical efficacy of rituximab in relapsed indolent lymphoma</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>31</td>
<td>70</td>
<td>120</td>
<td>166</td>
</tr>
<tr>
<td>Demographics</td>
<td>Age: Median age 55 (range 33-79) 52% male 48% female</td>
<td>Median age 50 (range 35-77) 54% male 46% female</td>
<td>Not given overall</td>
<td>Median age 58 57% male 43% female</td>
</tr>
<tr>
<td></td>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria given :</td>
<td>Yes – low grade or follicular B cell NHL, IWF types A-D</td>
<td>Yes – follicular lymphoma</td>
<td>Yes – follicular and mantle cell lymphoma</td>
<td>Yes – low grade or follicular B cell lymphoma (only 130 are follicular NHL)</td>
</tr>
<tr>
<td>Condition</td>
<td>No – all stages included</td>
<td>No – stage not given</td>
<td>No – all stages included</td>
<td>No – all stages included</td>
</tr>
<tr>
<td>Stage</td>
<td>Yes – primary therapy failure/ relapsed</td>
<td>Yes – patients must be previously treated</td>
<td>No – treated and untreated included</td>
<td>Yes – patients must be relapsed (&lt;4 times)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Yes – ≥18 years</td>
<td>No – but all patients &gt;18 yrs</td>
<td>Yes – &gt;18 years</td>
<td>Yes – adult</td>
</tr>
<tr>
<td>Age</td>
<td>No – male and female included</td>
<td>No – male and female included</td>
<td>No – male and female included</td>
<td>No – male and female included</td>
</tr>
<tr>
<td>Sex</td>
<td>Yes – CD20+ only</td>
<td>Yes – CD20+ only</td>
<td>Yes – CD20+ only</td>
<td>Yes – CD20+ only</td>
</tr>
<tr>
<td>Sex</td>
<td>Yes – WHO status 0-2 only</td>
<td>No – but all patients PS 0-2</td>
<td>No</td>
<td>Yes – Zubrod performance status 0-2</td>
</tr>
<tr>
<td>CD20 status</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Performance status</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pregnancy/lactation</td>
<td>Yes – must be not pregnant or lactating &amp; using birth control</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Other serious disease/infection</td>
<td>No</td>
<td>No</td>
<td>Yes – excluded</td>
<td>Yes – excluded</td>
</tr>
<tr>
<td>HIV/Hepatitis</td>
<td>No</td>
<td>Yes – excluded</td>
<td>Yes – excluded</td>
<td>Yes – excluded</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes – excluded</td>
</tr>
<tr>
<td>Other anti-cancer therapy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes – excluded</td>
</tr>
<tr>
<td>Other criteria</td>
<td>Blood counts, must have bidimensionally measurable disease, at least 1 lesion &gt;10cm, life expectancy ≥ 4 months</td>
<td>Transformation to diffuse large B cell lymphoma excluded</td>
<td>Must have measurable disease</td>
<td>Must have progressive measurable disease, patients with lesions ≥10 cm, recent major surgery excluded</td>
</tr>
</tbody>
</table>

prior treatment whereas the other three included studies did. In Foran it the number of prior treatments was not specified; in Davis it was at least one; in McLaughlin it was one to three. This and other variation between inclusion/exclusion criteria in the four included studies strongly predicts that the case-mix varies between the studies, particularly in respect of factors which have a strong influence on prognosis, especially diagnosis and amount of prior treatment. This would not be a problem, if homogenous subsets of included patients could be identified corresponding as closely as possible to the current licensed indications for use of rituximab.

Table 5 records our attempts to identify patient subsets directly relevant to assessing the effectiveness of rituximab in its licensed indications within the total cohorts of the included case-series. In all of these it was clear that they did include substantial numbers of patients with the condition/stage/prior treatment characteristics of interest. However, it was impossible, despite further enquiry of lead authors and/or the company sponsoring the studies, to quantify the exact proportion of the total cohort which had stage III or IV follicular lymphoma which was chemoresistant or was in its second or subsequent relapse.
Rituximab for NHL after chemotherapy †. Table 5 expands on the nature of the uncertainty for each of the included case-series. The sub-sets of most relevance for which results were reported was with the exception of McLaughlin, follicular lymphoma. For McLaughlin results were only available for the whole cohort of 166, of which 130 (78%) were follicular B-cell NHL. In all four included case-series although the numbers with follicular lymphoma were clear, the numbers of these that were stage III/IV and chemoresistant or in second or subsequent relapse after chemotherapy were not. Other demographic details of the most relevant sub-sets were also generally absent.

### Table 5 Population characteristics of most directly relevant subsets of patients

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number in study</td>
<td>31</td>
<td>70</td>
<td>120</td>
<td>166</td>
</tr>
<tr>
<td>% patients relevant to review i.e. meeting current licensing indications</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Reasons for uncertainty</td>
<td>71% have follicular B cell NHL but only 68% of 31 are stage III/IV. % patients having 2 or more relapses is unknown.</td>
<td>Only 55/70 had 2 or more previous treatments and the stage for all patients is not given.</td>
<td>78/120 have follicular lymphoma but only 84% have stage III/IV disease and only 76% have had 2 or more relapses</td>
<td>Of 130/166 patients with follicular B cell NHL % with stage III/IV disease not known (overall 147/166). Patients with ≥2 relapses not known (overall 73/166)</td>
</tr>
<tr>
<td>Nearest relevant subset of cohort for which results are given</td>
<td>22 patients with follicular B cell NHL</td>
<td>55 follicular lymphoma patients with 2 or more previous Rx</td>
<td>78 patients with follicular lymphoma</td>
<td>No other cohort available</td>
</tr>
<tr>
<td>Information not known about this subset</td>
<td>% who are stage III/IV with 2 or more relapses</td>
<td>% who are stage III/IV</td>
<td>% who are stage III/IV with 2 or more relapses</td>
<td>N/A</td>
</tr>
<tr>
<td>Demographics of this subset</td>
<td>Age: Not known</td>
<td>Not known</td>
<td>Median 57 (range 31-78)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Sex: 41% male 59% female</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Details of the interventions and outcomes for the total cohort in the included studies are given in Table 6. The interventions used in all the case-series were consistent. By definition all the case-series were subjected to rituximab delivered at a dose of 375mg/m² weekly x 4. There was some variation in the pre-treatment tests employed. All included physical examination and some means to assess severity of disease, particularly computerised tomography (CT) or magnetic resonance imaging (MRI) or X-rays. With respect to target outcomes, all included studies measured clinical response and adverse events. There were important differences in the assessment methods used and the definitions of response. Only the study by McLaughlin 35 appeared to have made any attempts to improve the objectivity of the response outcome.

† During peer review, several comments were received that of the current licenced indications, it is the effectiveness of rituximab in chemoresistance (as opposed to relapse) which is of greatest interest. As stated in the protocol, we did not intend to attempt any sub-group analysis according to either of the two main groups of indications. However, our observations about the difficulty in identifying from the included case-series, sub-groups which are wholly relevant to the to the licensed indications as a whole, inevitably means that examining the effectiveness of rituximab for the indication of chemoresistance, as opposed to relapse, would have been impossible.
### Table 6 Details of interventions and outcomes for total cohorts

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>375mg/m² iv infusion once weekly for 4 doses, initial dose 50mg/h for first hour then up to maximum 400mg/h</td>
<td>375mg/m² iv once weekly for 4 weeks iv in 1L normal saline</td>
<td>375mg/m² iv over 3-5 hours on weeks 1-4 on the same day of the week.</td>
</tr>
<tr>
<td><strong>Concomitant Rx:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids banned</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Other Rx allowed</td>
<td>Prophylactic allopurinol (4 patients)</td>
<td>Antipyrexics, antihistamines, allopurinol and hydration for those at risk of TLS</td>
<td>Antihistamines, paracetamol, allopurinol and hydration</td>
</tr>
<tr>
<td><strong>Pre-treatment tests stated:</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CT/MRI scans/X-rays</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Serum chemistries</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Blood counts</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Physical examination</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pathology specimen</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bone Marrow tests</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Outcome Measures:</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Survival analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Time to progression</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of response</td>
<td>Mortality</td>
<td>Mortality, molecular response</td>
<td>Mortality, molecular response</td>
</tr>
<tr>
<td>Other</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clinical Response assessment methods:</strong></td>
<td>Serial physical exam, CT/MRI scans; investigator and sponsor assessments only</td>
<td>Not detailed; no mention of assessment by independent assessment panel</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>Clinical Response definitions:</strong></td>
<td>All visible lymph nodes on CT scans of neck, chest, abdomen, pelvis &lt; 1cm², any previously palpable node no longer palpable or negative on biopsy/fine needle aspirate. Bone marrow negative, liver and spleen returned to normal size; confirmed at ≥ 28 d</td>
<td>Disappearance of all clinically detectable disease (incl. bone marrow), nodes ≤ 1cm² on 2 occasions ≥ 4 weeks apart</td>
<td>Not stated</td>
</tr>
<tr>
<td>Complete response (CR)*</td>
<td>≥50% decrease lesion size/ no new lesions; confirmed at ≥ 28 days</td>
<td>≥50% decrease lesion size on 2 occasions 1 month apart or estimated ≥ 50% decrease of unmeasurable disease; no new lesions &lt; 50% decrease lesion size or &lt;25% increase in lesion size and/or unmeasurable disease ≥ 25% increase size one or more lesions or any new lesions</td>
<td>Not stated</td>
</tr>
<tr>
<td>Partial response (PR)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>Did not show at least 50% increase or decrease in size lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥50% increase lesion size/ new lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* CR + PR often combined into overall response rate (RR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
measure through use of an independent assessment panel. This is an issue of particular concern given the inevitable openness to detection bias resulting from not having a comparator arm. Most studies measured time to progression and duration of response. Although most measured numbers of deaths, none did a formal survival analysis. None of the included studies directly measured impact on quality of life.

Table 7 Quality assessment, threats to validity and relevance

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in case series</td>
<td>31</td>
<td>70</td>
<td>120</td>
<td>166</td>
</tr>
<tr>
<td>Source of case series</td>
<td>No information given</td>
<td>70 eligible patients from 8 UK institutions over 12 month period included – no other information given</td>
<td>Reports on first 120 patients entered into the trial – no other information given</td>
<td>166 eligible patients enrolled at 31 centres in US and Canada in a 12 month period included – no other information available</td>
</tr>
<tr>
<td>Characteristics well defined:</td>
<td>Yes</td>
<td>No – stage not given</td>
<td>No – sex not given</td>
<td>Yes</td>
</tr>
<tr>
<td>Whole cohort</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Parent population</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>% of cohort relevant to review</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
<td>Not known</td>
</tr>
<tr>
<td>Follow-up:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate (&lt;10% unreported) Length</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate (&lt;10% unreported) Length</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Could analysis be done according to possible prognostic factors?:</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No (Yes*)</td>
</tr>
<tr>
<td>Stage</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No (Yes*)</td>
</tr>
<tr>
<td>Performance status</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sex</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Previous Rx / relapses</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Resistance</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Blood Counts/serum chemistries</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence B symptoms</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes (Yes*)</td>
</tr>
<tr>
<td>Other</td>
<td>Bone marrow infiltration, extranodal disease, splenomegaly</td>
<td>Bone marrow infiltration, extranodal disease, splenomegaly</td>
<td>Bone marrow infiltration, extranodal disease, splenomegaly</td>
<td>Positive bone marrow tests</td>
</tr>
<tr>
<td>Threats to validity</td>
<td>Selection bias</td>
<td>Not enough information on prognostic factors</td>
<td>Not enough information on prognostic factors</td>
<td>Selection bias</td>
</tr>
<tr>
<td></td>
<td>No comparator</td>
<td>No comparator</td>
<td>No comparator</td>
<td>No comparator</td>
</tr>
<tr>
<td>Small cohort</td>
<td>Inadequate follow-up time</td>
<td>Inadequate follow-up time</td>
<td>Inadequate follow-up time</td>
<td>Inadequate follow-up time</td>
</tr>
<tr>
<td>Not enough information on follow-up</td>
<td>Not enough information on follow-up</td>
<td>Not enough information on follow-up</td>
<td>Not enough information on follow-up</td>
<td>Not enough information on follow-up</td>
</tr>
<tr>
<td>Threats to relevance</td>
<td>71% have follicular B cell NHL but only 68% of 31 are stage III/IV. % patients having 2 or more relapses is unknown.</td>
<td>Only 55/70 had 2 or more previous treatments and the stage for all patients is not given.</td>
<td>78/120 have follicular lymphoma but only 84% have stage III/IV disease and only 76% have had 2 or more relapses</td>
<td>Of 130/166 patients with follicular B cell NHL % with stage III/IV disease not known (overall 132/166). Patients with ≥2 relapses not known (overall 73/166)</td>
</tr>
</tbody>
</table>

* Additional information obtained from commercial in confidence data submitted

- **Included study quality**

Table 7 details quality assessment and summarises threats to validity and threats to relevance of included studies. These were assessed in relation to information available for the whole cohort in the case-series, not the subset of greatest relevance. Although obvious, the absence of comparison groups deserves emphasising as a threat to validity. This not only causes difficulties with respect to comparing the outcomes observed with what would have occurred if no treatment or other commonly used treatments had been applied to similar patients at the
same stage of disease, but also makes the possibility of detection bias much more likely. Detailed information on all important prognostic factors was sometimes lacking. In none of the case-series was it stated how the patients actually included in the case-series related to the total population who might have been eligible for inclusion at the institutions undertaking the study. This leaves open the possibility of selection bias. The simplest way of conveying that this was unlikely is to state that consecutive patients presenting with the inclusion criteria were included, unless they refused to give informed consent, but in no case was this stated for the included studies. Attrition bias or loss to follow-up did not seem to be a problem, as for most reported outcomes, the majority of the patients entering the case-series appear to have been accounted for in the results.

Concerning threats to relevance to the stated object of the review, it should be reiterated that the reported results, even when for the most relevant subset, refer to patient groups who do not completely correspond to the current licensed indications for the use of rituximab.

- **Results (see Tables 8, 9 and 10)**

  **Clinical response - overall response rates (RR)**
  Results for the total cohorts were available for three of the included studies. These were 39%; 46%; & 48%. For the most relevant subsets the results for the three studies where overall RR was available, these were 55%; 36%; & 52%.

  **Clinical response – complete responses (CR)**
  Rates of complete response, contributing to overall response were very low. For the total cohorts they were 3%; 3%; & 6%. The pattern was repeated in the two studies providing complete response data for the most relevant subsets 5%; & 3%.

  **Clinical response – partial responses (PR)**
  As a corollary of the low CR rates, PR constituted most the overall RR. For the total cohorts the PR for the three studies where this information was available were 35%; 43%; 42%.

  **Duration of response (in those with PR or CR)**
  For the three studies reporting data on this outcome the median durations were 5.9 months (range: 2.8 to >12.1); 11 months; 11.2 months (approximate 95% CI read from graph in paper: 9 to 16.5). It should be noted that these figures are not mean or median durations of response for the cohort as a whole. They refer to responders alone. No data on duration of response were available for the most relevant subsets in the included case-series.

  **Time to progression (in those with PR or CR)**
  This is generally slightly longer than duration of response. Two of the included studies report median times to progression as medians of 8.1 months (range: 4.5 to >18.6); and 13 months. A third included study reported time to progression as 15/32 as having progressed at median follow-up of 1.5 years. In approximate terms this equates to a median time to progression of at least 18 months. Again it should be clearly noted that these results do not refer to the whole cohort, just those who responded. An indication of the true median time to progression of all patients (as opposed to responders only) is given in the study by

**Table 8 Results of rituximab case series**
Foran 2000

<table>
<thead>
<tr>
<th>Total number in study</th>
<th>31</th>
<th>70</th>
<th>120</th>
<th>166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up period</td>
<td>At least 1 year</td>
<td>Median 1.5 years</td>
<td>12 wks assessment, no further follow-up</td>
<td>Median 36 months</td>
</tr>
<tr>
<td>Losses to follow-up and reasons</td>
<td>N/S</td>
<td>N/S</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td>Drop-outs/exclusions before assessment and reasons</td>
<td>3 excluded (1 treated with CCST, 2 with incomplete response evaluations)</td>
<td>3 patients didn’t complete Rx due to adverse events</td>
<td>2/78 excluded as not follicular lymphoma, 1/78 excluded as had previous treatment &lt; 28 days before Others unknown</td>
<td>15 (1 didn’t start Rx, 8 had CCST, 1 had surgery, 1 lacked measurable lesions, 4 dropped out due to adverse events)</td>
</tr>
<tr>
<td>Deaths</td>
<td>None during Rx, 1 during follow-up at 10 months</td>
<td>N/S</td>
<td>5/120 before or during Rx</td>
<td>27 during follow-up – progressive disease</td>
</tr>
<tr>
<td>Patients evaluated for response</td>
<td>28</td>
<td>70</td>
<td>74/78 follicular lymphoma patients and 5 are missing, 36/42 mantle cell lymphoma</td>
<td>166</td>
</tr>
<tr>
<td>Evaluated as intention-to-treat</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical response rates</td>
<td>RR 39% (95% CI 22-56)</td>
<td>RR 46% (95% CI 33-59)</td>
<td>Not given overall</td>
<td>RR 48% (95% CI 41-56)</td>
</tr>
<tr>
<td>Number of patients evaluated for adverse events</td>
<td>Not stated</td>
<td>70</td>
<td>Not stated</td>
<td>165</td>
</tr>
<tr>
<td>Total adverse events (further detail Table 9)</td>
<td>93% of patients</td>
<td>189 events</td>
<td>N/S</td>
<td>733 events + 68 infections in 1 year after Rx</td>
</tr>
<tr>
<td>Mild-moderate events</td>
<td>Fever (61%), chills (36%), leucopenia (23%), nausea (19%), dizziness (19%), throat infection (19%), infections (6 cases)</td>
<td>177 events of which 12 were infections, pain/lethargy/fever in 39% patients</td>
<td>Fever (36% patients at 1st infusion, 9-11% in following infusions), rigors in 18% at 1st inf. (3-6% in following infusions), 20% asthenia, 17 cases hypotension</td>
<td>23% patients</td>
</tr>
<tr>
<td>Severe Events</td>
<td>4 events</td>
<td>12 events of which 2 were infections</td>
<td>N/S</td>
<td>None</td>
</tr>
<tr>
<td>Fatal events incl. TLS</td>
<td>None</td>
<td>4 events</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other outcomes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to progression (in responders)</td>
<td>Median 8.1 months (range 4.5 - &gt;18.6)</td>
<td>Median 5.9 months (range 2.8 - &gt;12.1)</td>
<td>Not given</td>
<td>Median 13 months</td>
</tr>
<tr>
<td>Duration of response (in responders)</td>
<td></td>
<td></td>
<td></td>
<td>Median remission duration 11.2 months.</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td>Not given</td>
</tr>
<tr>
<td>Survival analysis</td>
<td></td>
<td></td>
<td></td>
<td>Not given</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td>Values of lymphocyte subsets – B cell counts reduced during Rx.</td>
</tr>
<tr>
<td>Nearest subset of relevant patients i.e. meeting licensing indications</td>
<td>Patients with follicular B cell NHL (n=22)</td>
<td>Patients with follicular B cell NHL in 2nd or subsequent relapse (n=55)</td>
<td>Patients with follicular B cell NHL</td>
<td>No other subsets given</td>
</tr>
<tr>
<td>Response rates for subset</td>
<td>RR 55%</td>
<td>RR 52%</td>
<td>RR 36%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>CR 5%</td>
<td>CR 3%</td>
<td>PR 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PR 50%</td>
<td>PD 28%</td>
<td>75% responders female</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Molecular response – gene rearrangement in 33/37 follicular lymphoma patients.</td>
<td></td>
</tr>
<tr>
<td>Other outcomes for subset</td>
<td>None given</td>
<td>None given</td>
<td>Molecular response – gene rearrangement in 33/37 follicular lymphoma patients.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

McLaughlin 35. In this a median time to progression for 151 assessable patients out of 166 patients in total is given as 9.0 months (95% CI: 6.7 to 11.4).
Rituximab for NHL

No data on time to progression were available for the most relevant subsets in the included case-series.

**Overall survival**
No data were provided by any of the included studies on overall survival.

**Quality of life**
No direct measure of impact on quality of life was provided by any of the included studies.

A little information was provided on impact on symptoms. In the study by McLaughlin 34 26% of patients had constitutional or disease-related symptoms at baseline. The nature of the symptoms and the degree to which they resolved are tabulated in Table 9.

**Table 9 Resolution of symptoms in study by McLaughlin 1999 34**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Responders (N=80)</th>
<th>Non-responders (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No at baseline</td>
<td>No resolving</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>6</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Pain</td>
<td>13</td>
<td>12 (92%)</td>
</tr>
</tbody>
</table>

These results confirm that the symptoms did resolve, not only in responders, but to a large degree in non-responders too. As notable a feature however, is the low proportion of patients apparently suffering symptoms.

These findings are confirmed in the study by Davis 31 which reported, “Of 10 [N=31] patients with “B” symptoms or other disease-related signs and symptoms at baseline, 8 experienced complete resolution or transient relief. Two patients with continuing symptoms did not respond to rituximab therapy”.

**Adverse events and toxicity**
Adverse events as reported were frequent. 93% of patients experienced adverse events in the study by Davis 31; 199 events were reported in 70 patients in the study by Foran 32; 733 events and 68 infections were reported in 165 patients in the study by McLaughlin 34. Ghielmini 33 did not report overall adverse event rates. The majority of adverse events were categorised as mild to moderate in severity. Where different types of adverse events were enumerated, fever and rigors/chills were the most common. Ghielmini 33 gave a break-down of whether these occurred in relation to first or subsequent infusions. For fever 36% of patients suffered this adverse event during the first infusion and 9-11% in subsequent infusions. For rigors the corresponding figures were 18% and 3-6%. Other specified mild to moderate adverse events included infections, leucopenia, asthenia, nausea, dizziness and hypotension.
## Table 10 Detailed table of adverse events (by % patients affected where possible)

<table>
<thead>
<tr>
<th></th>
<th>Davis 1999</th>
<th>Foran 2000</th>
<th>Ghielmini 2000</th>
<th>M’Laughlin 34, 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number in study</td>
<td>31</td>
<td>70</td>
<td>120</td>
<td>166</td>
</tr>
<tr>
<td>Evaluated for toxicity</td>
<td>Not stated</td>
<td>70</td>
<td>Not stated</td>
<td>165</td>
</tr>
<tr>
<td>Time scale of adverse events</td>
<td>Events observed during Rx period and up to 30 days after. Incidence of events declined after first infusion</td>
<td>All events are stated as infusional except for infections</td>
<td>All adverse events are during Rx (14 serious adverse events overall reported in study)</td>
<td>During Rx or up to 30 days after Rx (infections up to 1 year after Rx). Most seen in 1st infusion and 55% patients had no toxicity for rest of Rx.</td>
</tr>
<tr>
<td>Deaths</td>
<td>No deaths during Rx</td>
<td>None stated</td>
<td>4 deaths (1 infection, 3 cardiovascular)</td>
<td>3 were MCL patients</td>
</tr>
<tr>
<td>Number of events (treatment related in parentheses)</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Total</td>
<td>Mild/mod</td>
</tr>
<tr>
<td></td>
<td>289 events (173)</td>
<td>* 36 events (20)</td>
<td>* 326 events (193)</td>
<td>* 166/84 events</td>
</tr>
<tr>
<td>Any events (treatment related in parentheses) (bold confirms that figure as reported)</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Total</td>
<td>* 58% (58%)</td>
</tr>
<tr>
<td>Haematological events:</td>
<td>Anaemia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Leucopenia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>23% (all grades)</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td>Non-haematological events:</td>
<td>Pain</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>61% (all grades)</td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>19% (all grades)</td>
</tr>
<tr>
<td></td>
<td>Rigors</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>(all grades)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Rash and pruritis</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>19% (all grades)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
<tr>
<td></td>
<td>Infected</td>
<td>Mild/mod</td>
<td>Severe</td>
<td>Not given</td>
</tr>
</tbody>
</table>

* Additional information obtained from commercial in confidence data submitted

Mild/moderate adverse events are taken to be WHO scale grades 1-2; severe events are grades 3-5.
Severe adverse events were not infrequent. In the study by McLaughlin\textsuperscript{34,38} of the 166 patients (23\%) experienced 44 serious adverse events. The numbers of serious adverse events in the other three included studies\textsuperscript{31,32,33} were 4, 12 and 10 respectively. 4 fatal events (possibly related to rituximab) were reported over all four of the included studies, giving an approximate fatal adverse event rate of 10 per 1000 patients treated (95\% CI: 3 to 26 – assuming a Poisson distribution). However 3 of these deaths occurred in mantle cell NHL which is not a currently licensed indication for rituximab.

Table 10 provides further detail on the nature of adverse events. Of importance it gives additional data on adverse events, supplied commercially in confidence. There is considerable inconsistency between the numbers presented in the published reports and those presented in the full trial reports provided by Roche. However, critically there is consistency about the pattern of adverse events. Most patients experience some adverse events; the majority of these are mild to moderate; the number of patients affected by severe adverse events is not insubstantial. These statements remain true even if the adverse events considered are restricted to those considered as possibly, probably or of unknown relationship to the study treatment in the case of two studies\textsuperscript{31,35} or probably related in one study\textsuperscript{32}.

**Discussion of results**

The key issue highlighted by this systematic review of the evidence on the effectiveness of rituximab in stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy, is the frailty of the evidence base. Major concerns include:

- There is no comparative trial data
- There is no data wholly relating to the target population with the condition/severity/and prior treatment record of interest
- There is no data on key outcomes such as overall survival and impact on quality of life
- The number of patients examined is limited, particularly for the purposes of establishing relatively rare, but influential fatal adverse events
- Allowing for the fact that the study design thought most acceptable to demonstrate effectiveness was non-comparative, the case-series as executed do not minimise bias to the greatest extent possible. Reporting of how the cases in the series were drawn from the total populations who might have been eligible is universally absent, and the definition and measurement of clinical response is such as to make detection bias, the likelihood of which is raised by not having a control arm, even higher.
- Data on key prognostic variables in the included case-series were frequently absent, reducing the likelihood of valid indirect comparison with case-series conducted on the effects of alternative treatments.

With respect to openness to bias, consistency, which undeniably exists for the response rates, should not be confused with accuracy. Unfortunately all the included case-series suffer from the same problems in relation to openness to bias and the possibility that they all give inaccurate estimates of the effects and effectiveness of rituximab must be seriously considered.

Given all these concerns the degree of caution needing to be exercised in interpreting the results of the included studies is at a level where very little can be categorically stated on the
basis of the reported results from the four included effectiveness studies. The next section attempts to do this.

2.3.2 Assessment of effectiveness

Overall effectiveness can only be assessed if accurate information on all the main areas of expected impact have been assessed. In the introduction we highlighted the importance of impact on quality of life. That quality of life has not been measured directly, must therefore be considered a major handicap to assessing the effectiveness of rituximab. Absence of information on overall survival is also problematic, although the difficulty of obtaining such information in NHL needs to be acknowledged.

In lieu of this we do have information which purports to accurately indicate resolution of baseline symptoms, clinical response rates, duration of response and time to progression. However, to reiterate all of these are proxies for the main objective of treatment, maximising quality of life in the remaining period of life of patients with follicular NHL.

Baseline symptoms are present, but in the reported research, in only approximately a quarter to a third of patients. They appear to resolve in all patients making CR and PR to rituximab, and to some extent in “non-responders” too. This observation needs however to be tempered by the fact that assessment of this outcome, like all others reported below is open to bias.

Concerning response rates the best estimates we can give for overall response rates, taken from the most relevant subsets in the included total cohorts, is a range of 36% to 55%. However great caution needs to be exercised in relying on these numerical values, principally because of the likelihood of detection bias in uncontrolled studies. Further it must also be noted that these overall response rates do not relate directly to the population of particular interest. Concerning how good an indication of impact on quality of life the response achieved might be, consideration needs to be given to the observation that most of the responses fall into the partial response category, generally defined as ≥50% decrease in size of lesions and no new lesions. Conversely it should also be recognised that failure to achieve a partial response, does not exclude the possibility that some benefit to the patient has occurred. Indeed the fact that symptoms resolve in some “non-responders” supports this.

For duration of response, figures are only available for the total cohorts of the included studies. Thus, the proportion of directly relevant patients is likely to be even smaller than for response rates. With this proviso the range of duration of response ranges from medians of 5.9 months (range: 2.8 to 12.1) to 11.2 months (approximate 95% CI: 9 to 16.5). However, again great caution is required in taking these values literally. First they are likely to be open to similar levels of detection bias discussed for response rates and second careful consideration needs to be given to the fact that these are median durations of response for responders. From the fact that non-response rates were generally over 50% for the total cohorts, and we can reasonably assume that the response duration in these is 0, one can firmly predict, although not stated in the reports, that the median response durations for the total cohort, the metric by which effectiveness results would be judged for most cancer therapies, is 0 months.

For time to progression, again figures are only available for the total cohorts, not the most relevant sub-sets of the included studies, with similar implications concerning relevance as
Rituximab for NHL

for duration of remission. The range of times to progression was 8.1 months (range: 4.5 to >18.6) to approximately 18 months (no range given). However once again all the reasons for caution in interpreting these figures mentioned for duration of response apply. That, the only time to progression figure available for both responders and “non-responders” in the study by McLaughlin, 9.0 months (95%CI: 6.7 to 11.4) is not dramatically different from times to progression in responders alone, could lend further support to the likelihood that some “non-responders” do get benefit.

The only other outcome on which information is provided by the included studies is adverse events. As for beneficial effects care needs to be taken in interpreting the numerical values. Experience from placebo-controlled trials, clearly indicates that patients may misattribute symptoms stemming from the disease itself to the new treatment to which they are self-evidently being exposed. Even with this in mind it seems clear that the vast majority of patients experience adverse events of mild-moderate severity. More significantly in terms of impact on overall effectiveness severe adverse events are not infrequent. The most easily comprehensible figure is provided by the study by McLaughlin in which 38/166 (23%) of patients suffered severe adverse events. However, this rate appears high when compared to other included studies where the maximum % of patients affected (assuming only one severe event was experienced by any one patient) was 13%, 17% and 8%. Consideration of data supplied commercially in confidence however suggest that the figure reported in McLaughlin actually appears to be the more typical figure for the proportion of patients affected by a severe adverse event.

Finally from the total series of 387, 4 fatal adverse events were recorded. The fact that deaths were noted does alert to the possibility that rituximab related deaths can occur, and that great care is required in administering the drug and avoiding patients where TLS is most likely to occur.

Concerning adverse events in general, aside from the problems of the numerical accuracy of the reported figures, some account needs to be taken of the likelihood that the adverse events reported in trials undertaken when experience with rituximab was less advanced, may to some extent be avoidable. Careful attention to method of administration, optimal use of prophylactic agents to counteract known side-effects and restricting administration to personnel/units with greatest experience in the use of rituximab could mean that the adverse events reported in trials overstate the best adverse event rates which could be achieved in current practice. Unfortunately the degree to which this might be true is unquantifiable, and so for the purposes of this technology appraisal we can only rely on reported rates, acknowledging their imperfections.

In summary we would present the main likely benefits and disbenefits of rituximab as:

a) That rituximab does achieve clinical responses in some patients with stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy
b) That most of these clinical responses are partial (generally defined as ≥50% decrease in size of lesions and no new lesions)
c) That the duration of such responses in responders appears to be of a length which would be clinically useful
d) This assumes that partial response brings about abolition of symptoms associated with relapse/recurrence and that the increase in quality of life is sufficient to off-set the impairment of quality of life associated with the treatment.

e) That prior to treatment symptoms appear to be present in a minority of patients, but that these symptoms are abolished completely in responders and to some extent in “non-responders” too

f) That mild to moderate adverse events occur in most patients; that severe adverse events occur in a minority of patients; and that fatal adverse events are very rare, but do occur

g) That some non-responders will experience the adverse effects of rituximab, without great benefit.

In our view none of these outcomes has been quantified with sufficient accuracy to allow a reliable judgement to be made on whether the benefits outweigh the disbenefits, particularly in the absence of any direct measures of impact on quality of life.

A further major problem in interpreting the available research stems again from an absence of any comparative trials. Without these there is no direct information to compare how the balance of benefits and disbenefits compares with alternative treatments which might be considered in stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy. This is important in a disease where it is widely acknowledged that other treatment options such a CHOP, and newer (although unlicensed) agents such as fludarabine, suffer similarly from incomplete response rates and significant rates of adverse events, which are often as severe if not more severe in nature. Thus viewed in isolation the results for rituximab may appear unpromising, but in relation to alternatives that are currently used, rituximab may represent an improvement. A more unequivocal answer would arise if direct comparisons were made, particularly if they included measurement of impact on quality of life. However, at present there seems to be little impetus for such RCTs.

In such a situation it is tempting to attempt indirect comparison of the results of case-series on rituximab with results of research on the effectiveness of alternatives. Many researchers believe that such an approach is intrinsically unsound. However, accepting that such an approach might be considered expedient we offer the following specific reasons why indirect comparison of the results of separately conducted research is highly likely to yield erroneous results in this review:

- Information on all potentially important outcomes is not available for rituximab studies
- For rituximab, the information on response rate, duration of response, time to progression and adverse events are likely to be subject to bias, and hence inaccuracy
- The information on the effects and effectiveness of the alternative regimes are either absent or as open to as much bias as those for rituximab
- Given the large number of potentially important prognostic factors in NHL and stage III/IV follicular lymphoma, it appears highly unlikely that sufficient data on these factors has been collected to even begin to attempt to correct the estimates of effects and effectiveness for small but potentially extremely influential differences in prognostic factors, which alone might account for or obscure differences in outcomes observed

Finally, with respect to comparators, it should be noted that in the situation where rituximab is being used as a treatment of last resort ie fourth, fifth line of therapy the comparator of interest is likely to be supportive treatment only. This appears to be particularly true where
patients are chemoresistant or refractory to earlier treatment options. In this circumstance, although the absence of any direct comparisons of effectiveness still presents problems, these are possibly less because the natural history at this stage of the disease is clearer ie it is safer to assume that any clinical response observed is likely to be associated with useful improvements in quality of life. Controlled trials would still be the ideal evidence base for assessing effectiveness in this situation, but uncontrolled trials may provide an acceptable alternative.

One included study did provide brief information on RR in “highly-chemoresistant disease”, defined as never having achieved any response to previously attempted treatment. In this very small sub-group, on which we have no definite information about stage, type of prior treatment or diagnosis, 6/21 (29% 95%CI: 9 to 48) achieved a response with rituximab in a situation where no clinical response might have been expected. However, there is no further information on what the impact on the patients of such responses might have been. The Roche submission to NICE (Volume 1, page 28) does provide further unpublished information on sub-group analyses from the McLaughlin study by other categories of “patients without satisfactory treatment options”, representing 118 patients out of the whole cohort of 166. This included the following categories: ≥3 prior chemotherapy treatments (74 patients); resistant to last chemotherapy treatment (44); resistant to all chemotherapy treatments (16); failing prior autologous bone marrow transplantation (23); relapsed and ≥70 years of age (25); ≥60 years of age with concomitant disease (22). The response rates and median times to progression are reported as being similar to those achieved overall. Again this provides some support to the likelihood that at points in disease process where other currently available treatment options would be rejected, use of rituximab does bring about clinical responses in sufficient numbers of patients and of durations that are likely to be clinically useful. However the provisos concerning the accuracy of the numerical data provided through openness to bias, the degree to which the sub-groups map onto the licensed indications, and whether the clinical responses observed are translated into useful improvement in quality of life outweighing the adverse events associated with treatment must be vigorously reiterated.

Concerning the degree to which our conclusions confirm or differ from other systematic reviews of effectiveness, we encountered no other systematic review of the effectiveness of rituximab in stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy, other than that conducted in this report. Good summaries of the existing evidence were encountered in two reports in particular, the Roche submission to NICE and the Cancer Care Ontario Practice Guideline Initiative Evidence Summary on Rituximab in Lymphoma. Although the search strategies employed in each of these reports were rigorous, both lacked detailed critical assessment of the quality of included studies, and formal consideration of the potential impact of bias on how the results should be interpreted. Comparing the review of effectiveness in this technology appraisal with the other summaries identified revealed little disagreement about the studies that should be included, nor the main details of the results that these studies contained. In comparison with the Roche submission there were differences concerning abstracted data on adverse events and the interpretation of the research results generally. (It should also be noted that Roche were no better able than ourselves at isolating the results of those patients in the included case-series that were directly relevant to the current licensed indications for rituximab). The implications

---

1 We would like to seek Roche’s permission to reproduce this data in the final HTA report as an appendix. It does not appear to have been submitted as “commercial in confidence”.
of these differences are considered in more detail on the next section on economic analysis. However, in essence the main difference concerned the certainty with which the observed results of research were translated into firm conclusions. Taking the nature of the available research evidence fully into account, we believe that considerable circumspection is required in concluding that rituximab is effective. Such caution is not evident in the Roche submission to NICE. In contrast in the Cancer Care Ontario Practice Guideline Initiative Evidence Summary on Rituximab in Lymphoma it is clear that although not formally assessed, they did recognise the bias to which the available evidence on effectiveness was open. Consequently they felt unable to issue a formal practice guideline without high quality effectiveness data provided by RCTs.

2.4 Summary of effectiveness

- A systematic review of effectiveness was undertaken
- The review question was, what is the effectiveness of rituximab for stage III – IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy.
- The comprehensive search for studies assessing the effectiveness of rituximab was based around interrogation of four large bibliographic databases (MEDLINE, EMBASE, Science Citation Index and the Cochrane Library)
- The initial inclusion criteria on study design and population had to be relaxed in order to include any studies assessing effectiveness at all
- No comparative studies were identified
- 4 case-series were finally included, incorporating information on 387 patients
- All were open to substantial bias, which suggests a high level of caution is required in interpreting results, particularly their numerical values
- No information was available on overall survival or direct measurement of impact on quality of life
- Rituximab does achieve clinical responses in some patients with stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy
- Most of these clinical responses are partial (generally defined as ≥50% decrease in size of lesions and no new lesions)
- Duration of responses in responders appear to be of a length which would be clinically useful
- This assumes that partial response brings about abolition of symptoms associated with relapse/recurrence and that the increase in quality of life is sufficient to off-set the impairment of quality of life associated with the treatment
- Prior to treatment, symptoms appear to be present in a minority of patients. These symptoms are abolished completely in responders and to some extent in “non-responders” too
- Mild to moderate adverse events occur in most patients; severe adverse events occur in a minority of patients; fatal adverse events are very rare, but do occur
- Some non-responders will experience the adverse effects of rituximab, without great benefit
- The extent to which beneficial effects are outweighed by adverse events is impossible to quantify
• Any impression of a poor ratio of benefit to disbenefit needs to be tempered by the observation that incomplete response rates and severe adverse events are common to all currently used treatments in this condition
• Absence of direct comparative data makes it very difficult to assess whether the ratio of benefits to disbenefits with rituximab is better, worse or the same as currently used alternatives
• There are strong arguments that indirect comparison, which might be considered expedient in the absence of direct comparisons, would yield highly erroneous estimates of relative effectiveness
• The need for direct comparisons may be least where rituximab is being used as a treatment of last resort ie fourth or fifth line of treatment, especially where the lymphoma is chemoresistant or refractory
• The need for circumspection about concluding that the rituximab is definitely effective was shared by one of the two other good recent summaries of research identified

3. ECONOMIC ANALYSIS

3.1 Objectives
The original objectives defined in the protocol were re-stated slightly:
• To systematically review the evidence on costs and health economic impact of rituximab in stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy
• To identify strengths and weaknesses of available cost-effectiveness studies and identify areas that might be revised or extended
• To selectively undertake some further analysis using published data

3.2 Methods for economic analysis
A priori we anticipated that the quality of evidence on effectiveness would be the main limiting factor to an accurate assessment of health economic impact. The pre-specified method was designed on this basis. Following confirmation from the systematic review of effectiveness that the prior assumption about quality of evidence on effectiveness was confirmed, no amendments to the protocol concerning economic analysis were made.

3.2.1 Search strategy
A specific search strategy for information on costs, cost-effectiveness and quality of life involved searches of:
• Bibliographic databases – Medline (Ovid) 1966-September 2000 and the NHS Economic Evaluation Database (NEED)
• Internet sites of UK health economics units

Details of the search terms used are given in Appendix 11. The search for economic information on rituximab and the intervention in the accompanying report, fludarabine, was conducted jointly. The industry submission from Roche to NICE in support of rituximab, was considered as one of the included existing economic evaluations considered in our economic analysis. In addition to the specific search strategy for economic evaluation above, all studies
encountered in the searches for effectiveness referring in any way to cost, were also considered.

3.2.2 Handling information identified

The inclusion criteria allowed all information on costs, quality of life or previous health economic evaluations of rituximab in the treatment of NHL to be included. The quality of all included studies was assessed. In the case of full economic evaluations the criteria used were based on the BMJ guidelines for economic appraisals. All the data in the included studies was abstracted into tables for presentation in this report and for consideration of conclusions.

3.3 Results

3.3.1 Estimation of net benefits (i.e. taking account of disbenefits)

We identified no further information to challenge our assessment of net benefits expressed in section 2. We emphasise that the nature of the evidence precludes accurate quantitative estimates of net effect, although qualitatively we acknowledge that net benefit is likely to accrue, despite the considerable uncertainties. We believe the uncertainties make it impossible to assess reliably whether the net benefit associated with rituximab is the same, less or more than alternatives. The implications of this are greatest in attempting to decide whether rituximab should be used at the earliest stage allowed by the current licence (i.e. as a third line treatment option, and least when it is being used as a treatment of last resort.

3.3.2 Estimation of net costs

Availability of information on costs was limited. The best information on costs, particularly the wider costs of rituximab has been conducted by Sweetenham 37, updated in the Roche submission to NICE. This also provides information on costs of alternative treatment options, CHOP and fludarabine, which again feed into the economic assessment presented in the Roche submission to NICE. These latter components will be discussed further in the critique of others attempts to assess cost-effectiveness.

The method employed by Sweetenham 37 to assess costs involved collecting information on adverse events and resource use covering a 6 month period in parallel with one of the effectiveness case-series included in the systematic review of effectiveness 32. Data was obtained for 64 of the 70 included patients. Data was unavailable on the remaining 6. Unit costs were applied to resource use identified in the following areas: tests; adverse event treatment; drug acquisition; drug administration in inpatient setting; drug administration in outpatient setting. Unit costs in the updated costing in the Roche NICE submission were derived from a variety of specified sources eg Personal Social Services Research Unit, Pharmaceutical Information Costs Assessment System and the BNF.

On this basis the costs per patient of a full course of rituximab were identified as:

- Cost of administration while an in-patient £ 371
- Cost of administration while an out-patient £ 424
- Drug acquisition cost £ 4,890
- Cost adverse events £ 119
• Cost of tests £ 741
• Total £ 6,544

In relation to the cost of other second-line therapies (CHOP £8,744, fludarabine £11,808) the high acquisition cost for rituximab is off-set by greatly reduced costs of adverse events. Thus overall it appears to be the cheapest option. However in respect of the costs attributable to adverse events a note of concern needs to be raised, as the adverse event profile stated as being derived from 64/70 patients from the study by Foran seems to underestimate the published adverse events rates. The two are compared in Table 11.

Table 11 Comparison of adverse events as reported in original publication and economic analysis derived from the same study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Foran 2000</th>
<th>Sweetenham 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=70</td>
<td>N=64</td>
</tr>
<tr>
<td></td>
<td>Number of patients affected</td>
<td>Number of treated adverse events</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>Severe</td>
<td>All grades</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Fever</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Anaemia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>Not calculable</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>58 (mild)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>37 (moderate)</td>
<td></td>
</tr>
</tbody>
</table>

Even allowing for the fact that all observed adverse events in the case-series may not have required treatment and taking into account the fact that the adverse events reported in the published paper are for patients (many of whom may have suffered more than one adverse event), the disparity between the number of treated adverse events in the costing study by Sweetenham and the original study, warns that the cost figure of £6,544 may be an underestimate. Concerning comparison of costs of administration of rituximab with CHOP and fludarabine, further concerns result from the population and manner used to derive resource use in CHOP and fludarabine. These concerns are discussed further below. Despite these concerns it seems likely that the costs of administering rituximab, are at worst similar to those of administering two commonly used alternative treatment regimes for NHL.

3.3.3 Cost impact of rituximab

Concerning NHS savings from the use of rituximab, this seems unlikely based on the consideration that rituximab seems to represent an additional treatment option for stage III/IV relapsed/refractory follicular NHL. That is because it is being used in a condition with a prolonged course during which as many available treatments as seem to offer some hope of achieving response will be applied, it seems highly unlikely to completely displace any existing currently available treatment options. On this basis overall NHS costs can only increase. The size of this increase will be dependent on the number of patients with stage III or IV follicular lymphoma who receive rituximab at some stage in their disease. On this basis a crude worst estimate of the total budget impact can be derived based on annual incidence. This assumes that annual incidence acts as a rough proxy of the number of patients who in
any year will be entering a defined period of their disease where rituximab may be considered the most appropriate treatment option. The calculation is as follows:

- Approx annual overall incidence of NHL: 13.4/100,000
- Incident cases of NHL in E&W (pop 55x10^6): 7,370
- Incident cases of stage III/IV follicular lymphoma: 2,653
  [Assumes 40%, not 22% of NHL is follicular]
- Cost of administering one course of rituximab: £6,544
- Total cost per annum: £17.4 m

This represents a steady state assessment, and in the short term the budget impact may be higher as cases in the prevalent pool receive treatment. However the fact that a number of patients will already be receiving rituximab argues that the effect of this will not be overwhelming and points to the fact a proportion of the £17.4 m may already have been accounted for in the NHS budget. Other considerations which suggest the £17.4 m figure is an overestimate is the likelihood that not all patients will receive rituximab at some stage in the management of their condition; considerations suggesting that this is an underestimate are that the suggested cost of administration of rituximab at £6,544 is too low and that some patients may receive repeated courses of rituximab. Finally it should be noted that this estimate is unlikely to change greatly whether rituximab is used as early in the course of disease as is currently allowed (second relapse/third line treatment option), or as a treatment of last resort. Clearly the estimate will be somewhat less if rituximab is used as a treatment of last resort, because inevitably some patients will die between third and fourth/fifth line treatment options being offered. However the size of the reduction will be small relative to the high proportion of patients we believe would be offered rituximab at some stage of their disease if it was freely available.

Irrespective of the observations above about the potential for inaccuracy, the overall comment would be that the total budget impact is relatively modest. For an average HA, population of 500,000 the worst case estimate of annual additional cost would be £160,000.

### 3.3.4 Critique of other attempts to assess cost-effectiveness

Only one relevant published paper was found, Sweetenham et al. This paper formed the basis of the economic analyses reported in the NICE submission from Roche and so the critique below focuses solely on the NICE submission. Tables 12 to 14 describe some of the key study characteristics and report the results for the base-case cost-effectiveness analyses.
Rituximab for NHL

Table 12 Assessment of cost-effectiveness analyses: study characteristics and results

<table>
<thead>
<tr>
<th>Roche submission to NICE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparators</td>
<td>Two alternative comparators (to rituximab) are used: CHOP and fludarabine</td>
</tr>
<tr>
<td>Perspective</td>
<td>Health sector</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td></td>
</tr>
<tr>
<td>▪ Main analysis:</td>
<td>cost-minimisation analysis</td>
</tr>
<tr>
<td>▪ Further analysis:</td>
<td>cost-utility analysis (referred to as an “illustrative analysis”)</td>
</tr>
<tr>
<td>Base-case effectiveness result</td>
<td></td>
</tr>
<tr>
<td>▪ Response rates:</td>
<td>no difference between treatments</td>
</tr>
<tr>
<td>▪ Response durations:</td>
<td>rituximab assumed to be “at least as good as the alternatives considered in terms of response duration”</td>
</tr>
<tr>
<td>▪ Adverse events:</td>
<td>rituximab associated with fewer serious adverse events</td>
</tr>
<tr>
<td>Base-case cost result</td>
<td></td>
</tr>
<tr>
<td>▪ CHOP:</td>
<td>£8,744</td>
</tr>
<tr>
<td>▪ Fludarabine:</td>
<td>£11,808</td>
</tr>
<tr>
<td>▪ Rituximab:</td>
<td>£6,544</td>
</tr>
<tr>
<td>Base-case ICER</td>
<td>Not estimated. Dominance observed for rituximab (ie lower cost, similar clinical effectiveness and fewer adverse events).</td>
</tr>
</tbody>
</table>

Table 13 Assessment of cost-effectiveness analyses: effectiveness and cost data

<table>
<thead>
<tr>
<th>Roche submission to NICE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source(s) for effectiveness data</td>
<td>Phase II trials for rituximab (section 4.2.6 of NICE submission) and observational studies for CHOP and fludarabine (Hochester 1992; Redman 1992)*</td>
</tr>
<tr>
<td>Analysis of effectiveness data</td>
<td>No further analysis reported in cost-effectiveness section of report</td>
</tr>
<tr>
<td>Quality of life data</td>
<td>Time in treatment and remission states: based on assumptions Utility scores associated with treatment and remission states: derived from data relating to women with early stage breast cancer (Jansen 1998)*</td>
</tr>
<tr>
<td>Resource use data</td>
<td></td>
</tr>
<tr>
<td>▪ For rituximab, most of the data used in the analysis taken from Phase II trial 32 (n=64), except for data on use of tests / investigations which were assumed to be the mean across CHOP and fludarabine.</td>
<td></td>
</tr>
<tr>
<td>▪ For CHOP (n=48) and fludarabine (n=50), taken from observational study.</td>
<td></td>
</tr>
<tr>
<td>Source(s) for cost data</td>
<td>Taken from a range of national and local sources, e.g. University of Kent annual survey, BNF, and local hospital trusts.</td>
</tr>
<tr>
<td>Analysis of cost data</td>
<td>No statistical analysis reported – cost data simply compared.</td>
</tr>
<tr>
<td>Price year</td>
<td>2000</td>
</tr>
<tr>
<td>Discounting</td>
<td>Not relevant – data related to a 6 month time period only.</td>
</tr>
</tbody>
</table>

* Citations as provided in Roche submission:

The economic analysis reported in the Roche submission considers the use of rituximab in patients with stage III-IV follicular lymphoma who are chemoresistant or in their second or subsequent relapse after chemotherapy. The comparators used in the incremental analysis are two alternative forms of chemotherapy, which represent "standard clinical practice in the NHS" (Roche, 2000, p40): fludarabine and CHOP. The central assumption is that there are equivalent clinical outcomes for the three interventions of interest (rituximab, CHOP and fludarabine). This is held to be the case both for the response rate to therapy and, for those patients who do respond, the duration of the response. On the basis of this assumption, a cost-
minimisation analysis is undertaken where the focus is solely upon the costs associated with the alternative treatments. The perspective is that of the NHS and the main result is that, overall, rituximab is associated with a lower cost, because of its favourable side effects profile, and is therefore defined as the 'dominant' alternative.

Table 14 Assessment of cost-effectiveness analyses: sensitivity analyses

<table>
<thead>
<tr>
<th>Roche submission to NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach</td>
</tr>
<tr>
<td>One-way sensitivity analysis only</td>
</tr>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>▪ Incidence of adverse events (arbitrarily varied by +/- 25%)</td>
</tr>
<tr>
<td>▪ Administration of chemotherapy (arbitrarily varied by +/- 25%)</td>
</tr>
<tr>
<td>▪ Tests (i.e. explored impact of removing variation across treatments in use of tests and investigations)</td>
</tr>
<tr>
<td>▪ Variation in setting for treatment of adverse events (i.e. oncology and general clinics / wards)</td>
</tr>
<tr>
<td>Results</td>
</tr>
<tr>
<td>Incremental results not highly sensitive to variation in parameters within the ranges explored.</td>
</tr>
</tbody>
</table>

As discussed above, the evidence supporting the assumption of equivalent clinical outcomes is very weak. However, given that the results indicate that rituximab is associated with a lower cost, the strengths and weaknesses of the cost analysis need also to be explored. Much of the data on resource use associated with the use of rituximab were drawn from the Phase II clinical trial, whereas similar data for CHOP and fludarabine were taken from a separate observational study. Similar patient numbers were in each group (i.e. rituximab n=64; CHOP n=48; fludarabine n=50). These resource data were then converted into costs through the use of unit costs taken from a variety of appropriate sources.

One of the principal concerns for the cost analysis relates to the lack of comparability of the resource use data from the three patient groups. It is clear that the approaches to data collection were not common across the three groups. For example,

- The source of data (and hence the data collection mechanisms) were different for rituximab since these data were collected within the context of the Phase II trial;
- Not all the resource use data used in the analysis was observed, for example,
  - For rituximab, no data were collected on the use of tests / investigations and so the analysts used the average for the resource use data seen across both the CHOP and fludarabine groups,
  - Data collection for the CHOP and fludarabine groups related to a single cycle which was then extrapolated to give a cost for 6 cycles;
- The sample selection process by which patients were included in the studies is not clear and may have been different across the resource utilisation studies.

This final point is borne out by the data on sample characteristics reported in Table 22 of the Roche submission. These data reveal that the three patient groups are not similar, particularly in terms of their mean age and median number of relapses. Patients in the CHOP study had a smaller number of relapses, on average, compared to the other two groups. As part of the submission, the analysts argue that the data they report, therefore, represents a "conservative comparison" with regards to rituximab since the costs of CHOP are likely to be
underestimated and so the incremental cost of rituximab will be overstated. Whilst this line of argument is intuitively appealing, some further data on the side effect profile for patients with a larger number of relapses receiving CHOP would have been helpful.

A further point of concern relates to the comprehensiveness of the resource use data reported in this analysis. The data collection was retrospective for the CHOP and fludarabine groups and therefore relied on routine data sources. Neither the NICE submission nor the paper by Sweetenham 37 indicates whether the data collection for rituximab patients was prospective or retrospective.

The results of the cost analysis are reported as point estimates for a course of treatment. There is clearly some level of uncertainty around these point estimates but this information is not provided. Given that the estimates are based on individual patient resource use data, it would have been possible for confidence intervals (either conventional or bootstrap) to have been estimated. A sensitivity analysis was conducted that allowed some of the uncertainty in the point estimates to be explored. However, the analysis was very limited: single parameters were varied independently through one-way sensitivity analyses, and the values on selected resource use data were varied by an arbitrary figure of +/- 25%. No justification for the range was provided.

In section 5.5.5 of the NICE submission an "illustrative analysis" is reported where quality of life issues are explicitly considered. This represents an attempt to extend the earlier analysis using a cost-utility framework. The argument is made that all treatments considered in the analysis are associated with some level of toxicity and so the quality of life experienced during the treatment period is poorer than that experienced during remission. This is clearly an advantage for rituximab since the duration of the treatment period is shorter. Whilst the logic of the argument is sound, there are some weaknesses in the analysis reported.

- The utility data used in the analysis are taken from patients with early breast cancer. The relevance of such data to a patient group with NHL has to be questioned.
- The estimates of time in treatment and remission health states are given without any indication of the uncertainty in these point estimates. The results of the utility analysis are clearly sensitive to variation in these time intervals and we know from other sources that not all patients receiving CHOP or fludarabine undergo a full course of 6 cycles.

### 3.3.5 Further exploration of assumptions in other attempts to assess cost-effectiveness

We carried out two further sensitivity analyses using the data from Tables 23, 25 and 27 in the Roche submission.

1. We equalised the incidence of adverse events in the CHOP and rituximab groups as far as possible. We applied two methods. For the first method, we simply combined the two groups. For example, from Table 23 in the Roche submission, a total of 37 out of 112 patients (33%) had nausea or vomiting. We adjusted all the incidences to the common value except for neutropenia and anaemia in the rituximab group, as no costs for these were available from Table 27 in the Roche submission. For the second method, we adjusted to allow for the different size of the two samples. The incidences used are shown in Table 15, and the results are shown in Table 16 (discrepancies between the base case values shown and those from Table 30 in the Roche submission result from rounding.)
Table 15 Incidences of adverse events used in sensitivity analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>First method</th>
<th>Second method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>36%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>Fever/infection</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>Other</td>
<td>56%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Table 16 Effect of equal incidence of adverse events

<table>
<thead>
<tr>
<th>Total costs per patient per course</th>
<th>CHOP</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>£8,743</td>
<td>£6,545</td>
</tr>
<tr>
<td>First method</td>
<td>£6,909</td>
<td>£6,596</td>
</tr>
<tr>
<td>Second method</td>
<td>£7,138</td>
<td>£6,605</td>
</tr>
</tbody>
</table>

2. We equalised the cost of adverse events. Again we used a simple weighted average of the costs in the two arms, and a weighted average adjusted for the sample sizes. Since the incidences were returned to those from Table 23 in the Roche submission, the costs for neutropenia and anaemia applied only to the CHOP group. The costs used are shown in Table 17 and the results in Table 18.

Table 17 Costs of adverse events used in sensitivity analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>First method</th>
<th>Second method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>£353</td>
<td>£373</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>£3,396</td>
<td>£3,396</td>
</tr>
<tr>
<td>Fever/infection</td>
<td>£3,203</td>
<td>£3,694</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>£1,456</td>
<td>£1,471</td>
</tr>
<tr>
<td>Anaemia</td>
<td>£2,844</td>
<td>£2,844</td>
</tr>
<tr>
<td>Other</td>
<td>£441</td>
<td>£508</td>
</tr>
</tbody>
</table>

Table 18 Effect of equal cost of adverse events

<table>
<thead>
<tr>
<th>Total costs per patient per course</th>
<th>CHOP</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>£8,743</td>
<td>£6,545</td>
</tr>
<tr>
<td>First method</td>
<td>£7,350</td>
<td>£7,590</td>
</tr>
<tr>
<td>Second method</td>
<td>£7,528</td>
<td>£7,760</td>
</tr>
</tbody>
</table>

These analyses should be regarded as purely illustrative. There are difficulties in dealing with the fact that neutropenia and anaemia occurred only in the CHOP group, and that costs for adverse events listed as Chest, Pain related, and Skin were given only for the rituximab group. Equalising incidence or costs between the two groups may be thought of as an unrealistic extreme.
Subject to our concerns about the appropriateness of using a cost-minimisation analysis, the sensitivity analysis given here supports the robustness of the claim that rituximab is associated with a lower cost per treatment course. However, this should not be interpreted as rituximab being cost-saving. This would only be true if rituximab treatment replaces existing treatment options. If it merely displaces them, any cost will be in addition.

3.4 Summary of economic analysis

- The nature of the evidence on effectiveness precludes accurate quantitative estimates of net effect
- Despite considerable uncertainties, we acknowledge that net benefit is likely to accrue with rituximab treatment in stage III or IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy.
- The uncertainties however make it impossible to assess reliably whether the net benefit associated with rituximab is the same, less or more than alternatives.
- The implications of this are greatest in attempting to decide whether rituximab should be used at the earliest stage allowed by the current licence i.e. second relapse/ third line treatment option, and least when it is being used as a treatment of least resort.
- The net costs to the NHS of administering a course of rituximab are estimated to be approximately £6,500, the majority of this cost is drug acquisition (i.e. £5,000)
- This estimate assumes a very low level of adverse events; the level used is open to challenge
- The net costs to the NHS of administering a course of rituximab appear to be considerably less than administering CHOP and fludarabine
- Much higher drug acquisition costs for rituximab, particularly relative to CHOP, are claimed to be completely off-set by lower costs associated with administration and treating adverse events
- The possibility that the costs associated with administering rituximab have been underestimated must be considered in accepting this claim
- A crude upper estimate of the total annual cost to the NHS in England and Wales of making rituximab available is approximately £17.4 m
- Only two related assessments of health economic impact were identified
- Both approaches, which included the Roche submission to NICE, relied on cost-minimisation analysis, comparing rituximab with CHOP and fludarabine; cost-minimisation assumes that effectiveness is equal
- The invalidity of the main assumption by virtue of absence of accurate relative effectiveness data, together with concerns about the conduct of the cost-minimisation exercises suggests the need for caution in interpreting their results
- Even if claims that the cost per treatment course for rituximab are lower than CHOP or fludarabine are accepted, this should not be interpreted as rituximab being cost saving. Rituximab would need to replace existing treatment options for this to occur, and this seems unlikely
- Little guidance can be provided on whether cost relative to net benefit for investment of NHS resources in rituximab would be the same, better or worse than investment in other areas of health activity, particularly new treatments for other cancers
4. IMPLICATIONS FOR OTHER PARTIES

The findings of this rapid technology have wide implications for all parties involved in the health care process. However one aspect was identified which does deserve special emphasis.

This involves the implication of the simpler administration schedule for use of rituximab for patients, their families and their carers. The two key points are:

- Each course of rituximab is delivered over one month as opposed to six in the case of CHOP and fludarabine
- The number of administrations is four, again less than CHOP and fludarabine

This strongly suggests that rituximab is likely to be less disruptive with attendant impact on quality of life and patient borne costs.

The only currently used treatment which is less disruptive is probably oral alkylating agent therapy such as chlorambucil, commonly used as first line therapy. Consideration however, needs to be given to the advent of an oral preparation of fludarabine, which might considerably reduce the inconvenience to patients of this treatment option.

5. RESEARCH IN PROGRESS

5.1 Method

Early in the course of the appraisal we identified that severe limitations on the quality of the evidence on effectiveness were likely to be a key issue, suggesting at least the need for further research. Consequently, we felt it was essential to provide as rigorous an inventory as possible of on-going research.

The objective was to identify all randomised trials planned, on-going and completed involving rituximab, and to indicate key information about the nature of these trials (intervention, comparison groups, outcomes and size) and when they were likely to complete recruiting or be published. No restriction was placed on the condition of interest, although the main studies we focus on in the results in this section are for NHL. The search strategy used incorporated interrogation of bibliographic databases, particularly MEDLINE, EMBASE and the Cochrane library, and a wide range of Internet web sites of organisations involved in or providing listings of trials in progress. Further details on the search strategy, inclusion criteria and data abstraction process are provided in Appendices 8 and 9.

5.2 Results

The on-going trials are listed in Table 19 sub-divided by the condition of interest, and whether patients are treated or untreated.

- **Current licensed indications for rituximab – previously treated low grade NHL**

There are no directly relevant randomised trials in progress. In particular there are no trials directly comparing rituximab to the most commonly considered alternatives eg CHOP or fludarabine.
There is a randomised comparison between rituximab and a novel radioimmunotherapy agent in relapsed/refractory low-grade NHL. This appears to have been completed but has not been fully published. It is of particular interest because it appears to have directly measured impact on quality of life. If available, this could have been of value in this report, enhancing our estimates of the impact of rituximab – further enquiries on availability of the analysed quality of life data to Roche via NICE are pending. The fact that this is the only trial of all those ongoing which appears to be directly measuring impact on quality of life is an issue of major concern for future NICE assessments on the role of rituximab, which we believe are inevitable.

Other randomised trials in progress in previously treated NHL compare:
- CHOP + rituximab vs. CHOP alone
- High dose therapy + autologous bone marrow transplantation + rituximab vs. high dose therapy + bone marrow transplantation alone
- Rituximab maintenance vs. no rituximab maintenance, both arms having received rituximab for induction of response

It is possible that the results of these trials might provide further important insights into the value of rituximab in its currently licensed indications, and that it would be worth revisiting the role of rituximab in relapsed/refractory stage III/IV follicular lymphoma when the results are available.

**On-going randomised trials of rituximab in previously untreated low grade NHL**

There appears to be considerable interest in exploring the value of rituximab as a first-line therapy in low-grade NHL, including follicular lymphoma. The three identified on-going randomised trials compare:
- Rituximab maintenance vs. no rituximab maintenance in patients who have already received induction therapy with either cyclophosphamide and fludarabine or cyclophosphamide and vincristine and prednisone
- CHOP + rituximab vs. CHOP alone
- Rituximab maintenance vs. no rituximab maintenance, both arms having received rituximab for induction of response

Although these comparisons will undoubtedly provide valuable information in assessing the value of rituximab in first-line therapy for low-grade NHL, the startling omission is a randomised trial making the obvious comparison of the current well-established first-line treatment for low-grade NHL, oral chlorambucil, with rituximab. Again the absence of direct measurement of impact on quality of life as an outcome in any of the trials is a major cause for concern.

**Ongoing randomised trials of rituximab in other types of NHL – intermediate and high grade**

Like use of rituximab in low-grade NHL this is clearly an area of major interest. Without listing the trials in detail it is clear that two major concerns raised above, apply to this body of on-going work too:
- That simple direct comparisons between rituximab and the obvious currently employed alternatives do not seem to be made
- That no on-going trial intends to make a direct measurement of impact on quality of life.
Rituximab for NHL.
<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Condition</th>
<th>Population</th>
<th>Outcomes</th>
<th>Design &amp; Size</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDEC-106-04 36-39</td>
<td>RITUXIMAB</td>
<td>RITUXIMAB + IDEC-Y2BB (radio-immunotherapy)</td>
<td>LG-NHL (IWF types A-D)</td>
<td>Recurrent or refractory</td>
<td>Unclear: probably • Disease response • Toxicity • Quality of life</td>
<td>RCT; target total 150</td>
<td>Completed; no publication</td>
</tr>
<tr>
<td>EORTC 20981 40</td>
<td>CHOP + RITUXIMAB a) induction (x6) AND/OR b) maintenance (max 2y)</td>
<td>CHOP [in both arms induction can be stopped after x3 if no response]</td>
<td>LG-NHL (REAL follicle centre lymphoma, follicular, grades I-III) Stage III/IV</td>
<td>Relapse following chemotherapy with ≤2 non-anthracycline containing regimens</td>
<td>• Disease response • Progression-free survival • Overall survival • Toxicity</td>
<td>RCT; target total 600</td>
<td>Recruiting ends 2003</td>
</tr>
<tr>
<td>EBMT- LYM1 41</td>
<td>HDT + ABMT + RITUXIMAB a) purging AND/OR b) maintenance</td>
<td>HDT + ABMT [HDT = high dose therapy; ABMT = autologous bone marrow transplantation]</td>
<td>LG-NHL (IWF types B-D or REAL follicle centre lymphoma, follicular) Stage not stated</td>
<td>Second or third remission – must have complete response or very good partial response</td>
<td>• Disease response • Progression-free survival (1y) • Overall survival • Toxicity &amp; safety</td>
<td>RCT; target total 460</td>
<td>Recruiting ends 2003</td>
</tr>
<tr>
<td>Swiss IACR 42</td>
<td>RITUXIMAB consolidation</td>
<td>NO</td>
<td>Mixed LG-NHL &amp; intermediate grade NHL (follicular and mantle cell)</td>
<td>Mixed relapsed/refractory and untreated</td>
<td>• Disease response • Progression-free survival • Toxicity</td>
<td>RCT; target total 240</td>
<td>Recruiting ends 2001 or 2002</td>
</tr>
<tr>
<td>E-1496 42</td>
<td>RITUXIMAB maintenance</td>
<td>NO maintenance</td>
<td>LG-NHL (Small lymphocytic, follicular small cleaved cell, follicular mixed cleaved cell, follicular large cell)Stage III/IV</td>
<td>Untreated</td>
<td>• Progression-free survival • Overall survival</td>
<td>RCT; target total 400</td>
<td>Temporarily closed</td>
</tr>
<tr>
<td>Swiss IACR 42</td>
<td>RITUXIMAB consolidation</td>
<td>NO consolidation</td>
<td>Mixed LG-NHL &amp; intermediate grade NHL (follicular and mantle cell)</td>
<td>Mixed untreated and relapsed/refractory</td>
<td>• Disease response • Progression-free survival • Toxicity</td>
<td>RCT; target total 240</td>
<td>Recruiting ends 2001 or 2002</td>
</tr>
<tr>
<td>SWOG-0016 44</td>
<td>RITUXIMAB + CHOP</td>
<td>CHOP or CHOP + I 131 TOSITUMOMAB</td>
<td>LG-NHL (follicular) Bulky stage II, stage III or IV</td>
<td>Untreated</td>
<td>• Disease response • Progression-free survival • Overall survival • Toxicity</td>
<td>RCT; target total 775</td>
<td>Recruiting not yet commenced</td>
</tr>
</tbody>
</table>
### HAEMATOLOGICAL MALIGNANCIES – INTERMEDIATE OR HIGH GRADE NON-HODGKIN’S LYMPHOMA

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Condition</th>
<th>Population</th>
<th>Outcomes</th>
<th>Design &amp; Size</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swiss IACR 42</td>
<td>RITUXIMAB consolidation</td>
<td>NO consolidation</td>
<td>Mixed inter-mediate &amp; LG-NHL (follicular and mantle cell)</td>
<td>Mixed untreated and relapsed/refractory</td>
<td>Disease response, Progression-free survival, Toxicity</td>
<td>RCT; target total 240</td>
<td>Recruiting ends 2001 or 2002</td>
</tr>
<tr>
<td>Coiffier 1998 43</td>
<td>RITUXIMAB (higher dose - one infusion of 375 mg/m² followed by 7 weekly infusions of 500 mg/m²)</td>
<td>RITUXIMAB (lower dose – 8 weekly infusions of 375 mg/m²)</td>
<td>Intermediate or high grade NHL (especially diffuse large B-cell lymphoma and mantle cell lymphoma)</td>
<td>In relapse 1 or 2, if they were refractory to initial therapy, if they progressed after a partial response to initial therapy or if they were elderly (age &gt;60 years) and not previously treated</td>
<td>Disease response, Progression-free survival</td>
<td>RCT; 28+ 26</td>
<td>Completed &amp; published</td>
</tr>
<tr>
<td>E-4494 (Phase I) 46</td>
<td>RITUXIMAB + CHOP</td>
<td>CHOP</td>
<td>Intermediate or high grade NHL (diffuse mixed, diffuse large, immunoblastic large cell B NHL mantle cell lymphoma excluded)</td>
<td>Untreated, Age over 60 y</td>
<td>Disease response, Progression-free survival, Overall survival, Toxicity</td>
<td>RCT; target total 630</td>
<td>Recruiting ends 2002</td>
</tr>
<tr>
<td>E-4494 (Phase II) 46</td>
<td>RITUXIMAB maintenance</td>
<td>NO maintenance</td>
<td>Intermediate or high grade NHL (details as above)</td>
<td>Complete or partial response to CHOP ± RITUXIMAB in phase I of E-4494 Age over 60 y</td>
<td>Disease response, Progression-free survival, Overall survival, Toxicity</td>
<td>RCT; target total 630</td>
<td>Recruiting ends 2002</td>
</tr>
<tr>
<td>NCI-G99-1601 47</td>
<td>RITUXIMAB + CHOP</td>
<td>CHOP</td>
<td>Aggressive B-cell NHL (especially mantle cell, diffuse large/ mixed/small cleaved cell, anaplastic large cell [B-cell type], marginal zone lymphoma/Stage II-IV</td>
<td>Untreated</td>
<td>Disease response, Progression-free survival, Toxicity</td>
<td>RCT; target total 270</td>
<td>Recruiting ends 2002</td>
</tr>
<tr>
<td>SWOG-0019 48</td>
<td>RITUXIMAB + IFOSFAMIDE + CARBOPLATIN + ETOPOSIDE</td>
<td>IFOSFAMIDE + CARBOPLATIN + ETOPOSIDE</td>
<td>Aggressive B-cell NHL (diffuse large cell, small non-cleaved cell/Burkitt’s lymphoma)</td>
<td>Relapsed/refractory to combination chemotherapy with anthracycline containing regime</td>
<td>Disease response, Progression-free survival, Overall survival, Toxicity</td>
<td>RCT; target total 376</td>
<td>Recruiting not yet commenced</td>
</tr>
</tbody>
</table>

### HAEMATOLOGICAL MALIGNANCIES – HIV ASSOCIATED NON-HODGKIN’S LYMPHOMA

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Condition</th>
<th>Population</th>
<th>Outcomes</th>
<th>Design &amp; Size</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC 010 49</td>
<td>RITUXIMAB (induction and maintenance) + CHOP + FILGRASTIM</td>
<td>CHOP + FILGRASTIM</td>
<td>HIV-associated NHL Stages I-IV</td>
<td>Untreated</td>
<td>Unclear, probably Disease response</td>
<td>RCT; target total 120</td>
<td>Recruiting ends 2001</td>
</tr>
</tbody>
</table>

### HAEMATOLOGICAL MALIGNANCIES – CHRONIC LYMPHOCYTIC LEUKAEMIA

<table>
<thead>
<tr>
<th>Study (Ref)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Condition</th>
<th>Population</th>
<th>Outcomes</th>
<th>Design &amp; Size</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLB-9712 50</td>
<td>RITUXIMAB + FLUDARABINE</td>
<td>FLUDARABINE</td>
<td>B cell - CLL</td>
<td>Untreated</td>
<td>Disease response, Progression-free survival, Overall survival, Toxicity</td>
<td>RCT; target total 100</td>
<td>Completed; no publication</td>
</tr>
</tbody>
</table>
5.3 **Key points arising**

- There appears to be information on the impact on quality of life, collected in the course of a recently completed randomised trial which might amplify the assessment of impact of rituximab on quality of life in this technology appraisal.
- There are no other on-going randomised trials which will provide rigorous assessments of effectiveness for the indication of rituximab considered in this report.
- There is clear interest in use of rituximab as a first line treatment for low-grade NHL and for intermediate and high-grade NHL. NICE needs to anticipate that decisions will be required on use of rituximab in these circumstances over the next few years.
- In this respect it is of considerable concern that direct measurement of impact on quality of life does not feature in the outcomes of on-going trials in these areas and that trials making simple direct comparisons of rituximab, alone or combination, with the main current standard treatments do not seem to have been instituted.
- There is no evidence of intent to embark on large scale trials to address the key, but extremely difficult question of which treatment strategy employing all the currently recognised standard treatments for follicular lymphoma in particular, are optimal in terms of overall survival and impact on quality of life during the course of the disease.

6. **DISCUSSION**

6.1 **Main results of report informing conclusions**

This rapid technology appraisal has generated many important findings. These are highlighted at the end of each of the sections 2, 3, 4 and 5. Here we discuss those results that have been most influential in informing our conclusions.

The dominant observation is the poor quality and openness to bias of the evidence on effectiveness. This applies not just to that on rituximab, but to all other standard current therapies applied in the treatment of NHL, particularly stage III or IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy. There are no published RCTs and few comparative studies of any kind. Research in progress will not substantially alter this situation.

The invidious consequence of this is that the only evidence on effectiveness available is uncontrolled prospective case-series. Critical appraisal of these confirms them to be highly susceptible to bias, consequently we have been extremely circumspect about taking the numerical values of clinical response rates, duration of response and time to progression at face-value. Data on adverse events show important discrepancies depending on where the results are reported. No directly measured evidence at all was available on the key outcomes of impact on quality of life and overall survival. There was no directly measured comparison of the impact of rituximab with other currently used standard treatments for relapsed/refractory stage III/IV follicular lymphoma.

Despite these considerable uncertainties, qualitatively there is evidence that rituximab produces clinical responses of a duration which are likely to be useful clinically. Arguably, the situation where this observation appears least susceptible to the uncertainties identified, is
where rituximab is used as a treatment of last resort ie fourth or fifth line treatment, especially where the disease is chemoresistant or refractory. This should not be taken as a definite indication that rituximab should not be applied at the earliest stage allowed by the current licence, following second relapse ie third line treatment. There is no rigorous evidence one way or the other - we do not know.

Other key observations concerning whether rituximab should be made available are that its cost is at worst similar to those of other currently used treatments such as CHOP and fludarabine. Claims that the cost is considerably less need to be subject to close scrutiny, because of the uncertainties about the true incidence and nature of adverse events. More certain is that the acceptability to patients of rituximab treatment is likely to be greater than for CHOP, because of the shorter duration of treatment (1 month as opposed to 6).

The difficulty of accurately quantifying the net benefit of rituximab, let alone its alternatives, means that it is impossible to provide valid estimates of cost-effectiveness and cost-utility, even using economic modelling techniques that were actively considered. Great circumspection needs to be applied to those economic evaluations that have been attempted.

Consideration of research in progress suggests that future decisions on the use of rituximab in other circumstances may face exactly the same difficulties as for its use in stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy. Only new, directly relevant randomised controlled trials instituted in the near future will change this situation.

6.2 Assumptions, limitations and uncertainties

There can be little disagreement about most of the main findings we report. The systematic review employed an extremely comprehensive search and we employed explicit inclusion/exclusion procedures and defined methods of quality assessment, data abstraction and analysis. The absence of RCTs or other comparative studies is undeniable and widely acknowledged. There was no disagreement about the studies that offered the best available evidence on effectiveness of rituximab. Nor was there disagreement about the numerical results of these studies. The only exception was discrepancy in portrayal of adverse event profiles between published reports and the data used to make assessments of the implications of adverse events on cost of administration. We have generally assumed that the data available in the published reports give the most accurate portrayal of adverse events, as it was these that were most consistent with the full study data supplied commercially in confidence.

The issue which we anticipate will cause most debate is the handling of the uncertainties identified in the effectiveness data, particularly the biases to which uncontrolled studies are open. Many researchers working on assessment of effectiveness and reviewing it, would undoubtedly reject the evidence we identified as so biased, that the only available option would be to insist that further primary research on effectiveness, particularly RCTs, was undertaken before a decision on use of rituximab could be made. At the other extreme, many would play down the uncertainties identified and proceed with a decision taking the numerical values of the effectiveness research at face value. We have tried to take a middle course between these, recognising that the evidence is highly subject to bias, but accepting that there is evidence concerning direction of effect. In such circumstances it may sometimes be possible to incorporate uncertainty concerning key parameters into models. This was not open to us in this technology appraisal as we felt wholly unable, given the very high degree
of uncertainty, to hazard plausible ranges for estimates of say clinical response. In the case of this outcome the uncertainty was emphasised still further by the degree that clinical response, generally measured by serial CT or MRI scans, was acting as an accurate proxy of improved or maintained quality of life, the outcome of greatest interest.

6.3 Need for further research

The previous section already indicates specific areas where further research is required. It is debatable whether it is reasonable or practically feasible to reduce the uncertainties concerning the effectiveness of use of rituximab in the circumstances considered in this technology appraisal. However, what is certain is that the decision on rituximab in stage III or IV follicular lymphoma which is chemo-resistant or is in its second or subsequent relapse after chemotherapy should be reconsidered in the light of further evidence on the general use of rituximab as it becomes available.

We strongly recommend that the forthcoming decisions on the use of rituximab in other areas should be anticipated, and that it is recognised that the RCTs as currently planned will not completely answer the obvious effectiveness and cost-effectiveness questions that will be posed. RCTs comparing rituximab with current standard treatments for NHL are urgently required. Further as well as clinical response and survival outcomes, these trials must address impact on patient quality of life, as the prospects for improving longevity remain distant.

Finally the general need for research on effectiveness and cost-effectiveness in the treatment of NHL is highlighted. The difficulties of assessing the effectiveness of rituximab lie as much in the generally poor evidence base under-pinning the use of all treatments for NHL as lack of rigorous comparative research on rituximab itself. Although ambitious, and long-term the key research question which remains unaddressed is the effectiveness of treatment strategies comparing different ways of deploying all the currently available standard treatments for NHL on overall survival and quality of life.
7. CONCLUSIONS

- Rituximab is probably effective, but what is known about the extent of its effectiveness is limited.
- If it is used, clinicians should be clear and patients should be aware of this.
- We would suggest the following as the extent of our knowledge:
  - There is no evidence that rituximab improves survival.
  - Rituximab does achieve clinical responses in some patients with stage III or IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy.
  - Most of these clinical responses are partial (generally defined as ≥50% decrease in size of lesions and no new lesions).
  - Duration of responses in responders appear to be of a length which would be clinically useful.
  - This assumes that partial response brings about abolition of symptoms associated with relapse/recurrence and that the increase in quality of life is sufficient to off-set the impairment of quality of life associated with the treatment.
  - In the available research, prior to treatment, symptoms were only present in a minority of patients. These symptoms were abolished completely in responders and to some extent in “non-responders” too.
  - Mild to moderate adverse events occur in most patients; severe adverse events occur in a minority of patients; fatal adverse events are very rare, but do occur.
  - Some non-responders will experience the adverse effects of rituximab, without great benefit.
  - Whether rituximab is more, less or equally effective as other commonly used treatments in relapsed/refractory stage III/IV follicular lymphoma is unknown.
  - The drug cost of rituximab is high at approximately £4,900 per treatment cycle.
  - However, the cost of administering rituximab is at worst similar to other commonly used treatments, because adverse events are less.
  - Arguably the cost per course of treatment for rituximab is actually less, but this depends on the degree to which the incidence of adverse events is lower.
  - Even if lower cost per treatment course for rituximab is accepted, this will not convert into cost-savings for the NHS unless rituximab replaces the use of existing treatments.
  - A crude upper estimate of the budget impact on the NHS in England and Wales of using rituximab in relapsed/refractory stage III/IV follicular lymphoma is £17.4 m per annum.
  - Reliable estimates of the relative cost-effectiveness and cost-utility of rituximab cannot be provided given the uncertainties surrounding the level of net benefit.
  - The acceptability of rituximab to patients is likely to be high because of the reduced number of times it needs to be administered and the shorter period over which the treatment is completed.
  - Further research on the effectiveness of rituximab and indeed all currently used therapies for NHL should be as great a priority for NHS resources, as making new treatments available.
  - A trial of alternative treatment strategies over the whole course of disease, though difficult to design, could be a powerful way of taking this issue forward.
  - Direct measurement of impact on quality of life is essential in future RCTs.
8. APPENDICES

Appendix 1 The Revised European American Classification of Lymphoid Neoplasms (REAL) system

B-Cell Neoplasms

I. Precursor B cell neoplasm: B-lymphoblastic leukemia/lymphoma

II. Peripheral B cell neoplasms

A. B cell chronic lymphocytic leukemia/ prolymphocytic leukemia / small lymphocytic lymphoma
B. Lymphoplasmacytoid lymphoma/immunocytoma
C. Mantle cell lymphoma
D. Follicle center lymphoma, follicular,
   1. Provisional cytological grades:
      (i) small cell,
      (ii) mixed small and large cell,
      (iii) large cell
   2. Provisional subtype: diffuse, predominantly small cell type
E. Marginal zone B cell lymphoma
   1. Extranodal (MALT type +/- monocytoid B cells)
   2. Provisional subtype: Nodal (+/- monocytoid B cells)
F. Provisional entity: Splenic marginal zone lymphoma(+/- villous lymphocytes)
G. Hairy cell leukemia
H. Plasmacytoma/plasma cell myeloma
I. Diffuse large cell B-cell lymphoma
   1. Subtype: primary mediastinal (thymic) B cell lymphoma
J. Burkitt's lymphoma
K. Provisional entity: high grade B-cell lymphoma, Burkitt's-like

T-Cell and Putative Natural Killer Cell Neoplasms

I. Precursor T cell neoplasm:
   1. T precursor lymphoblastic lymphoma/leukemia

II. Peripheral T cell and NK-cell neoplasms

A. T cell chronic lymphocytic leukemia / prolymphocytic leukemia
B. Large granular lymphoproliferative (LGL) disorder
   1. T-cell type
   2. NK-cell type
C. Mycosis fungoides/Sezary's syndrome
D. Peripheral T cell lymphoma, unspecified
   1. Provisional cytologic categories: medium sized cell, mixed medium and large cell, large cell, lymphoepithelioid cell
   2. Provisional subtype: hepatosplenic gamma/delta T-cell lymphoma
   3. Provisional subtype: subcutaneous panniculitic T-cell lymphoma
E. Angioimmunoblastic T cell lymphoma (AILD)
F. Angiocentric lymphoma
G. Intestinal T cell lymphoma (enteropathy associated)
H. Adult T cell lymphoma/leukemia (ATL/L)
I. Anaplastic large cell lymphoma (ALCL), CD30+, T and null-celltypes
   1. CD30+ -cell type
   2. T-cell type
   3. Null-cell types
J. Provisional entity: anaplastic large cell lymphoma, Hodgkin’s-like

**Hodgkin's Disease**

I. Lymphocyte predominance
II. Nodular sclerosis
III. Mixed cellularity
IV. Lymphocyte depletion
V. Provisional category: Lymphocyte-rich classic HD
VI. Provisional category: Anaplastic large cell lymphoma, Hodgkin's like

**Unclassifiable**

1. B cell lymphoma, unclassifiable (low grade/high grade)
2. T cell lymphoma, unclassifiable (low grade/high grade)
3. Malignant lymphoma, unclassifiable
Appendix 2 US National Cancer Institute modification of REAL classification system

I  Plasma cell disorders

II  Hodgkin’s disease

III Indolent Lymphoma/leukaemia

A. Follicular centre cell lymphoma, follicular
   1. Grade I follicular small cleaved cell
   2. Grade II follicular mixed
   3. Grade III follicular large cell (some controversy therefore may be aggressive)
B. Diffuse small lymphocytic lymphoma/chronic lymphocytic leukaemia
   Distinguish: Prolymphocytic leukaemia (aggressive)
   Large granular lymphocytic leukaemia
C. Lymphoplasmacytoid/Waldenstrom’s
D. Marginal zone lymphoma
   1. MALT (extranodal)
   2. Monocytoid B-cell lymphoma (nodal)
   3. Splenic lymphoma with villous lymphocytes
E. Hairy cell leukaemia
F. Mycosis fungoides/Sezary syndrome

IV Aggressive lymphoma/leukaemia

A. Diffuse large cell lymphoma includes diffuse mixed cell, diffuse large cell, immunoblastic
B. Burkitt’s lymphoma/diffuse small non-cleaved cell lymphoma
C. Lymphoblastic lymphoma/leukaemia
D. CNS lymphoma
E. Adult T-cell leukaemia/lymphoma
F. Mantle cell lymphoma (controversial therefore may be low grade)
G. Post-transplantation lymphoproliferative disorder
H. AIDS-related lymphoma
I. True histiocytic lymphoma
J. Primary effusion lymphoma
Appendix 3 Search strategies to identify prospective cohort studies on the natural history of NHL

MEDLINE (Ovid) 1997-Aug 2000

01 lymphoma non hodgkin/
02 lymphoma follicular/
03 lymphoma intermediate grade/
04 lymphoma large cell/
05 lymphoma low grade/
06 lymphoma mixed cell/
07 lymphoma small cell/
08 lymphoma b cell/
09 or/1-8
10 prognosis/
11 survival rate/
12 survival analysis/
13 or/10-12
14 9 and 13
Appendix 4 Search strategy to identify effectiveness of any treatments for NHL

This strategy was designed specifically to target published systematic reviews and was based on the ARIF search protocol. The following strategies were executed in the electronic databases.

MEDLINE (Ovid) 1990-Sept 2000

01 Exp lymphoma non hodgkin/dt,th,rt
02 (meta-analysis or review literature).sh.
03 meta-analy$.tw.
04 metaanal$.tw.
05 meta-analysis.pt.
06 (systematic$ adj4 (review$ or overview$)).tw.
07 review,academic.pt.
08 case report.sh.
09 letter.pt.
10 historical article.pt.
11 review of reported cases.pt.
12 review,multicase.pt.
13 review literature.pt.
14 1 or 2 or 3 or 4 or 5 or 6 or 12
15 7 or 8 or 9 or 10 or 11
16 14 not 15
17 1 and 16

Cochrane Library 2000, Issue 4

01 exp lymphoma non hodgkin:ME
02 lymphoma*
03 1 or 2
Appendix 5 Protocol

West Midlands Development and Evaluation Service

Protocol for the review of:


Full title of research question
Rituximab and fludarabine for blood cancers: non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukaemia (CLL).

Clarification of research question and scope
Rituximab and fludarabine are two relatively new agents for the treatment of blood cancers, consequently it is necessary to confirm that the benefits of these new drugs are worth the costs.

Haematological malignancies are a particularly heterogeneous group of cancers. This is particularly true in the case of the NHL for which complex classification systems have been developed. Inevitably some types of blood cancer may be more susceptible to rituximab and fludarabine than others, particularly in the case of the former which targets a particular marker found only on B-lymphocytes.

Therefore the main focus of this report is the effectiveness and cost-effectiveness of rituximab for stage III – IV follicular lymphoma which is chemoresistant or is in its second or subsequent relapse after chemotherapy and fludarabine for B cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen. These are the specific conditions for which the drugs have been licensed.

However we are aware that these drugs are currently being used and investigated in the treatment of other related conditions and earlier in the course of the diseases for which licences have been granted. Therefore we will also provide a formal scoping review to identify research, both complete and ongoing in conditions outside the licensed implications, to indicate where the agents of interest might be applied in the future, and whether there will be rigorous research to support the use in these areas.

Thus the specific objectives of the report will be (in the order in which they will be tackled):

1. To identify trials, published, unpublished and ongoing, examining the use of rituximab and fludarabine in haematological malignancies.

2. To systematically review the evidence of the effectiveness of rituximab for stage III – IV follicular lymphoma that is chemoresistant or is in its second or subsequent relapse after chemotherapy as indicated in the drug licensing information.

3. To systematically review the evidence of the effectiveness of fludarabine for B cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and has not
responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen as indicated in the drug licensing information.

4. To systematically review the evidence on costs and health economic impact of rituximab and fludarabine in B-cell NHL and B-cell CLL as described in (2) and (3).

5. To relate the effects identified in (2) and (3) to costs identified in (4) and therefore to consider the validity of any existing estimates of health economic impact, particularly cost-effectiveness.

Report Methods
General: There will be no language restrictions and all searches will stop on 1st September 2000

(1) Formal scoping search to indicate developments in the use of rituximab and fludarabine i.e. RCTs published and ongoing.

Searches
Studies will be identified using the following:
- Electronic databases: Cochrane Library, Medline, Embase, Science Citation Index, National Research Register
- Internet Search engines
- Drug company submissions invited by the National Institute for Clinical Excellence
- Citation lists
- Conference abstracts

Inclusion Criteria
Intervention: Rituximab and/or fludarabine
Comparator: Any
Population: Any haematological malignancy
Outcomes: Survival, quality of life, adverse events
Design: RCT

Analysis
As the main purpose will be to indicate the current and future availability of high quality research evidence on rituximab and fludarabine outside of the licensing implications, no attempt to summarize the data will be made. The characteristics or planned characteristics of the trials identified will be presented and sub-divided by the intervention and target condition.

(2 + 3) Systematic review of the effectiveness of rituximab for NHL (2) and fludarabine for CLL (3)

Searches
Studies will be identified using the following:
- Electronic databases: Cochrane Library, Medline, Embase, Science Citation Index, National Research Register
- Internet Search engines
- Drug company submissions invited by the National Institute for Clinical Excellence
- Citation lists
• Conference abstracts

Inclusion Criteria

Intervention:
(2) Rituximab at the dose given on product information sheet.
(3) Fludarabine at the dose given on the product information sheet.

Comparator:
Any, including no treatment

Population:
(2) Stage III/IV follicular B-cell NHL which is chemoresistant or is in its second or subsequent relapse after chemotherapy
(3) B cell CLL with sufficient bone marrow reserve that has not responded to or had progressed during or after treatment with at least one standard alkylating agent containing regime.

Outcomes: Survival, quality of life, adverse events. We will explore the value of tumour response to indicate impact on quality of life if no other data are available.

Design: Ideally RCTs. However we anticipate there will be insufficient numbers to adequately answer the question posed. In this event we will extend the included studies to non-randomized CCTs and if these are not available, before-after studies i.e. with no parallel control arm. In this last instance, quality criteria will be introduced as part of the inclusion/exclusion decisions. These will be designed to protect against the possibility of eligible studies presenting the results of patients unrepresentative of the stated target population.

On this basis included before-after studies will:
• Need to indicate that they were conducted prospectively
• Ideally present the results of a consecutive series
• Give clear indications of the patient characteristics particularly with regard to stage of disease and previous treatments
• That losses to follow-up with respect to particular outcomes of interest are <10%
• Size > 10 subjects

Imputing the effectiveness of rituximab / fludarabine on such studies will inevitably require indirect comparison with information about the natural history of patients in the given condition. A systematic search for prospective cohort studies will be conducted for series giving such information; information provided within studies e.g. from a case-control methodology will not be acceptable.

Application of inclusion/exclusion criteria will be undertaken by two reviewers. Decisions will be made independently of the data extraction and prior to the scrutiny of results.

Quality Assessment

This is partly implicit in the inclusion criteria. If RCTs are present details of relative strengths and weaknesses will be assessed in relation to selection, performance, detection and attrition biases. If non-randomized CCTs are identified established checklists e.g. Jadad will be employed.

Data Extraction

This will be carried out by two reviewers independently.
Analysis
This will be qualitative. It will be amplified by meta-analysis if appropriate. No sub-groups have been identified a priori.

(4+5) Systematic review on the cost effectiveness of rituximab for NHL and fludarabine for CLL
Review question is in relation to the applications of rituximab and fludarabine in (2) and (3) above to assess the costs and relate these to the identified effects and effectiveness of the two agents.

Method
Systematic review of cost assessments and economic evaluations.

Search
Information on cost-effectiveness and quality of life will be sought from Medline, HEED, NEED, DARE, Embase, Science Citation and Internet sites of UK health economics units.

Quality Assessment
Quality of any identified evaluations will be undertaken using a specifically designed checklist based on the BMJ guidelines for economic appraisals.

Analysis
As a minimum a cost-consequence analysis will be conducted. Ideally if quality of life data can be identified, a cost-utility analysis will be undertaken giving cost-per-QALY for each intervention. Where cost data are uncertain a sensitivity analysis will be carries out. The perspective for the health economic analysis will be from the NHS view-point. The main focus of the analyses will be on marginal changes.

Handling the company submissions
Industry submissions will be used to identify effectiveness information, cost data and assessments of health economic impact which meet our inclusion criteria. Any information indicated as being confidential will be marked as such in the final report.

Research in progress
None identified at this stage of the project.

Project Management
(a) Timetable
Deadline for submission of protocol to HTA programme – 22nd September 2000
Deadline for submission of progress report to HTA programme – 7th December 2000
Deadline for submission of draft report to HTA programme – 9th January 2001
[Draft report, without peer reviewers comments to be sent to NICE – 21st December 2000]

(b) Competing Interests
Members of the project management group and advisory panel have been asked to declare any interest they may have (A declaration of competing interests form has already been returned.) None were identified in any of the members of the review team.

(c) Project Management Group
This review will be carried out under the guidance of a project management group, which comprises a lead reviewer (CH), a main author (BW), an information scientist (AFS), a health economist (TR) and an assistant reviewer (CD). A further senior reviewer may be added to this team.
Appendix 6 Search strategies to identify studies on effectiveness of rituximab in NHL

MEDLINE (Ovid) 1966-Sept 2000
1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials/
4 random allocation/
5 double blind method/
6 double blind method/
7 single blind method/
8 or/1-7
9 (animal not human).sh.
10 8 not 9
11 clinical trial.pt.
12 exp clinical trials/
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14 placebo/
15 placebos.ti,ab.
16 random$.ti,ab.
17 research design/
18 or/11-18
19 19 not 9
20 20 not 10
21 comparative study/
22 exp evaluation studies/
23 follow up studies/
24 prospective studies/
25 (control$ or prospectiv$ or volunteer$).ti,ab.
26 or/22-26
27 27 not 9
28 27 not (10 or 21)
29 10 or 21 or 29
30 31 rituximab$.mp.
31 mabthera$.mp.
32 idec-c2b8$.ti,ab.
33 rituxan$.mp.
34 or/31-34
35 exp lymphoma non-hodgkin/
36 (non adj hodgkin$ adj lymphoma$).ti,ab.
37 b cell lymphocytic.ti,ab.
38 (follicular adj lymphoma$).ti,ab.
39 or/36-39
40 40 and 35 and 30

EMBASE (Ovid) 1980-Sept 2000
1 exp nonhodgkin lymphoma/
2 non hodgkin$ lymphoma$.ti,ab.
3 b cell lymphocytic.ti,ab.
4 follicular lymphoma$.ti,ab.
5 or/1-4
6 controlled trial/
7 randomized controlled trial/
8 clinical trial/
9 prospective study/
10 double blind procedure/
11 randomization/
12 major clinical study/
13 trial$.ti,ab.
14 or/6-13
15 rituxan$.mp.
16 rituximab$.mp.
17 idec-c2b8$.ti,ab.
18 mabthera$.mp.
19 or/15-18
20 5 and 14 and 19

Science Citation Index (Web of Science) 1981- Oct 2000
01 rituximab*
02 mabthera*
03 rituxan*
04 idec-c2b8*
05 1 or 2 or 3 or 4
06 lymphoma*
07 5 and 6

Cochrane Library 2000 Issue 3
As for search in Appendix 9
Appendix 7 List of experts contacted as part of search

Dr. C. Fegan
Consultant Haematologist
Department of Haematology
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS

Dr. P. Revell
Consultant Haematologist
Department of Haematology
Staffordshire General Hospital
Weston Road
Stafford
Staffordshire
ST16 3SA

Dr. P. Rose
Consultant Haematologist
Department of Haematology
South Warwickshire General Hospital
Lakin Road
Warwick
Warwickshire
CV34 5BW

Dr. A. Jacob
Consultant Haematologist
Department of Haematology
Walsall Manor Hospital
Lakin Road
Warwick
Warwickshire
WS2 9PS

Professor T.A. Lister
Professor in Medical Oncology
Saint Bartholomew’s Hospital
West Smithfield
London
EC1A 7BE

Dr S.A. Johnson
Consultant Haematologist
Taunton and Somerset Hospital
West Smithfield
Taunton
Somerset
TA1 5DA

Professor A. Burnett
Chairman of the Haemato-Oncology Task Force of the British Committee for standards in haematology on behalf of the British Society of Haematology and the University of Wales, Cardiff
Department of Haematology
University of Wales College of Medicine
Heath Park
Cardiff
CF14 4XN

Appendix 8 Search strategy and methods to identify on-going trials of rituximab
Rituximab for NHL

The following were searched to specifically identify on-going, or completed but currently unpublished randomised controlled trials, involving rituximab:

(1) Bibliographic database search – see Appendix 9 for further details (4 citations scanned)
(2) Cochrane Library 2000 Issue 4 – Cochrane Controlled Trials Register (CD-ROM) (3 hits scanned)
(4) British Society for Haematology web-site (http://www.blacksci.co.uk/uk/society/bsh) (no trials listing available)
(5) British National Lymphoma Investigation web-site (http://www.bnli.ucl.ac.uk) (14 listed trials scanned)
(6) European Organisation for Research and Treatment of Cancer web-site (http://www.eortc.be) (26 “immunotherapy” trial protocols scanned)
(7) European Group for Blood and Marrow Transplantation web-site (http://www.ebmt.org) (ongoing studies for each working party scanned)
(8) Leukaemia Research Fund (http://dspace.dial.pipex.com/lrf-//research/director.pdf) (0 hits in research directory)
(9) Medical Research Council & Current Controlled Trials web-site (http://www.controlled-trials.com) (11 hits scanned)
(10) National Institutes of Health/CancerNet site (http://www.cancertrials.nci.nih.gov) (42 hits scanned – includes open and closed studies)
(11) Roche company web-site (http://www.roche.com) (no trials listing available)
(12) General web-search using Google search engine (94 hits scanned)
(13) Roche Industry submission (all reference lists scanned; does not include anything marked “commercial in confidence” unless already identified by one of other elements of search strategy above)

In general, where search terms could be used, the text words “RITUXIMAB”, “RITUXAN”, “IDEC-C2B8” or “MABTHERA” were employed. For the general web search the phrase “(RANDOMISED OR RANDOMIZED) AND “CONTROLLED TRIAL”) was used in addition. Potentially relevant hits were scanned, and a judgement made on whether it was likely that the study was an RCT, and that it was likely that the effectiveness of fludarabine was being tested. Where search terms could not be used, details of all identifiable trial entries were scanned using the same criteria. If an entry appeared to relate to a trial, and information was brief, further details were sought either from the organisation co-ordinating the trial or the lead investigator. Wherever possible full copies of the trial protocols were obtained. All searches were conducted during the period 1/11/2000 to 15/12/2000.
Appendix 9 Details of bibliographic database search employed to identify ongoing trials involving rituximab

**MEDLINE (Ovid) 1966 to August 2000**

1. rituximab.mp.
2. idec-c2b8$.ti,ab.
3. rituxan.mp.
4. mabthera.mp.
5. or/1-4
6. exp hematologic neoplasms/
7. exp leukemia/
8. exp lymphoma/
9. or/6-8
10. 5 and 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized controlled trials/
14. random allocation/
15. double blind method/
16. single blind method/
17. or/11-16
18. animal/ not human/
19. 17 not 18
20. clinical trial.pt.
21. exp clinical trials/
22. (clinical trials$).ti,ab.
23. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
24. placebos/
25. placebo$.ti,ab.
26. random$.ti,ab.
27. research design/
28. or/20-27
29. 28 not 18
30. 29 not 19
31. 19 or 30
32. 10 and 31

**EMBASE (Ovid) 1980 – May 2000**

1. rituximab.mp.
2. mabthera.mp.
3. idec-c2b8$.ti,ab.
4. rituxan.mp.
5. or/1-4
6. or/1-4
7. exp hematologic disease/
8. exp leukemia/
9. exp lymphoma/
10. malignan$.ti,ab.
11. cancer$.ti,ab.
12. leukemia$.ti,ab.
13. lymphoma$.ti,ab.
14. or/7-13
15. controlled trial/
16. randomized controlled trial/
17. clinical trial/
18. controlled study/
19. clinical study/
20. prospective study/
21. double blind procedure/
22. randomization/
23. major clinical study/
24. trial$.ti,ab.
25. study.ti,ab.
26. studies.ti,ab.
27. or/15-26
28. 5 and 14 and 27
29. limit 28 to human

**Science Citation Index (BIDS) 1981-2000**

1. rituximab*
2. Mabthera*
3. (idec-c2b8*)
4. rituxan*
5. (Lymphoma* or malignan* or cancer* or leukaemia* or leukemia*)
6. 1 or 2 or 3 or 4
7. 5 and 6

**Cochrane Library 2000 Issue 3**

1. rituximab*
2. mabthera*
3. (idec-c2b8*)
4. rituxan*
5. 1 or 2 or 3 or 4
Appendix 10 Details of excluded studies and reasons for exclusion

Rituximab: encouraging preliminary results.  
Reason for exclusion; review

Association of serum Rituximab (IDEC-C2B8) concentration and anti-tumor response in the treatment of  
recurrent low-grade or follicular non-Hodgkin's lymphoma.  
Reason for exclusion; suspicion of duplication (McLaughlin 1998 35)

Czuczman MS.  
CHOP plus rituximab chemoimmunotherapy of indolent B-cell lymphoma.  
Reason for exclusion; doesn’t meet inclusion criteria – not rituximab as a single agent

Reason for exclusion; suspicion of duplication (McLaughlin 1998 35)

IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-  
Hodgkin's lymphoma.  
Blood 1997;90:2188-95.  
Reason for exclusion; suspicion of duplication (McLaughlin 1998 35)

Nguyen DT, Amess JA, Doughty H, Hendry L, Diamond LW.  
IDEC-C2B8 anti-CD20 (rituximab) immunotherapy in patients with low-grade non-Hodgkin's lymphoma and  
lymphoproliferative disorders: evaluation of response on 48 patients.  
Reason for exclusion; suspicion of duplication (Foran 2000 32)

Onrust SV, Lamb HM, Barman Balfour JA.  
Rituximab.  
Reason for exclusion; review

Cost-minimization analysis of CHOP, fludarabine andvrituximab for the treatment of relapsed indolent B-cell  
non-Hodgkin's lymphoma in the UK.  
Reason for exclusion; cost-effectiveness only
Appendix 11 Search strategies to identify cost and quality of life studies

- The NHS Economic Evaluation Database was searched using the following terms: Fludara$, rituximab, mabthera, idec-c2b8$, rituxan.

- Internet sites of the following health economics units were also searched: University of York Centre for Health Economics, Health Economics Research Unit, Health Economics Research Group.

The following strategy was executed in MEDLINE

MEDLINE (Ovid) 1966-Sept 2000
01 economics/
02 exp "costs and cost analysis"/
03 cost of illness/
04 exp health care costs/
05 economic value of life/
06 exp economics medical/
07 exp economics hospital/
08 economics pharmaceutical/
09 exp "fees and charges"/
10 (costs or cost or costed or costly or costing).tw.
11 (economics$ or pharmacoeconomic$. or price$. or pricing).tw.
12 or/1-11
13 fludara$.mp.
14 12 and 13
15 rituximab$.mp.
16 mabthera$.mp.
17 idec-c2b8$.ti,ab.
18 rituxan$.mp.
19 or/15-18
20 12 and 19
21 quality of life/
22 life style/
23 health status/
24 health status indicators/
25 treatment outcome/
26 “outcome assessment (health care)”/
27 or/21-26
28 exp lymphoma non-hodgkin/
29 non hodgkin$. lymphoma$.ti,ab.
30 b cell lymphocytic.ti,ab.
31 follicular lymphoma$.ti,ab.
32 or/28-31
33 27 and 32
34 exp leukemia b cell chronic/
35 cll.ti,ab.
36 b-cell.ti,ab.
37 chronic lymphocytic leuk?emia.ti,ab.
38 or/34-37
39 38 and 27

Set 20 is the output of the search on costs
Set 39 is the output of the search on quality of life
9. REFERENCES


Genentech Inc. Rituxan Full Prescribing Information. [Accessed via http://www.gene.com/products/rituxan/insert.html ]


38 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_13558&PASSTHRU=%3aip%3a147%2e188%2e28%2e144%3a%3aprof%3a-ip:147.188.28.144:prof::recno:1:&SFMT=prot_summary/1/0/0 [Accessed 12/12/2000]


40 http://www.bnli.ucl.ac.uk/uma/version1/CLINICIANS/_PROTOCOL%20EORTC.htm [Accessed 29/11/00]


43 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_13205&PASSTHRU=%3aip%3a147%2e188%2e28%2e144%3a%3aprof%3a-ip:147.188.28.144:prof::recno:1:&SFMT=prot_summary/1/0/0 [Accessed 12/12/2000]

73
Rituximab for NHL

44 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_15539&PASSTHRU=%3aip%3a147.188.28.144%3aprof%3a:ip:147.188.28.144:prof::recno:78:&SFMT=prot_summary/1/0/0 [Accessed 1/12/2000]


46 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_13033&PASSTHRU=%3aip%3a147.188.28.144%3aprof%3a:ip:147.188.28.144:prof::recno:22:&SFMT=prot_summary/1/0/0 [Accessed 12/12/2000]


48 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_15538&PASSTHRU=%3aip%3a147.188.28.144%3aprof%3a:ip:147.188.28.144:prof::recno:23:&SFMT=prot_summary/1/0/0 [Accessed 12/12/2000]


50 http://cancernet.nci.nih.gov/cgi-bin/srchcgi.exe?TYPE=search&DBID=allprotocol&ZUI=199_13276&PASSTHRU=%3aip%3a147.188.28.144%3aprof%3a:ip:147.188.28.144:prof::recno:58:&SFMT=prot_summary/1/0/0 [Accessed 1/12/2000]