National Institute for Health and Care Excellence

NICE guideline NG52

Non-Hodgkin's lymphoma: diagnosis and management

NICE guideline: methods, evidence and recommendations

Final version, July 2016

Methods, evidence and recommendations

This guideline was developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Final

Commissioned by the National Institute for Health and Care Excellence

Update information

Minor changes since publication

October 2021: We added links to HIV in Europe's HIV indicator conditions and NICE's guideline on HIV testing to section 1.1 on diagnosis. See the surveillance report on HIV indicator conditions for more information.

These changes can be seen in the short version of the guideline at: http://www.nice.org.uk/ng52

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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ISBN: 978-1-4731-1999-4

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Foreword

Non-Hodgkin’s lymphoma is the sixth most common cancer in the UK. There are many different subtypes of the disease, with markedly different clinical courses and requirements for therapy. Diagnosing non-Hodgkin’s lymphoma and the precise subtype is challenging, and optimising the diagnostic process is central to improved management. Significant improvements in our understanding of the biology of non-Hodgkin’s lymphoma have contributed to improved diagnosis and also allowed for more targeted therapies.

The treatment of non-Hodgkin’s lymphoma has been a beacon for the development of specific treatment strategies (now applied to many other forms of cancer), but paradoxically there is a paucity of large randomised clinical trials to define best practice in treating the various subtypes. As a consequence there are considerable differences between centres and countries in the ways in which some subtypes of the disease are diagnosed and managed.

There have been some improvements in outcome for people with non-Hodgkin’s lymphoma in the last decade, but these have been relatively modest and there is still a need for improvement. This is a rapidly developing field, with a number of new therapies proving to be exciting in initial studies. It is too soon, however, to judge their long-term impact, and ongoing assessment of these new agents compared with standard therapy will be needed.

This guideline aims to facilitate standardisation of practice in treating non-Hodgkin’s lymphoma. But because of the rapid development of new therapies as a result of improved understanding of the biology of the disease, continual re-evaluation will be essential.

Professor David Linch
GC Chair

Dr Christopher McNamara
GC Lead Clinician

Methodology

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Who is the guideline intended for?

This guideline covers adults and young people (16 years and older) referred to secondary care with suspected non-Hodgkin's lymphoma or with newly diagnosed or relapsed non-Hodgkin's lymphoma. Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as ‘evidence-based textbooks’ or making recommendations on topics where there is already agreed clinical practice. As a result this guideline does not include recommendations covering every aspect of the diagnosis and management of non Hodgkin’s lymphoma. Instead, the guideline has tried to focus on areas in which providers and commissioners of care or services most need advice, for example (i) areas in which there is unacceptable variation in practice or uncertainty about best practice; (ii) areas of unsafe practice; (iii) uncertainty around the optimal service configuration (iv) where there is a lack of high quality evidence; or (v) where new evidence suggests current practice may not be optimal. More detail on how this was achieved is presented later in the section on ‘Developing clinical evidence based questions’.

This guideline is relevant to all commissioners and healthcare professionals who are responsible for the planning and delivery of the management of people with non Hodgkin’s lymphoma, as well as to the people with non Hodgkin’s lymphoma themselves and their carers and families. It is also expected that the guideline will be of significant value to those involved in clinical governance to help ensure that arrangements are in place to deliver appropriate care.

The remit of the guideline

Involvement of Stakeholders

Key to the development of all NICE guidelines is the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the ‘NICE guidelines manual’ (NICE 2014). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the non Hodgkin’s lymphoma guideline can be found in Appendix F.

The guideline development process – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012, NICE 2014). A team of health professionals, lay representatives and technical experts known as the Guideline Committee (GC) (Appendix F), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- defining the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GC
- developing review questions
- identifying the health economic priorities
- developing the review protocols
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- consultation and validation

The scope

The scope was drafted by the GC Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the review questions and search strategies.

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The suggested key clinical issues for inclusion were discussed and revised before the formal consultation process began. Comprehensive details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a four week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix E. During the consultation period, the scope was posted on the NICE website. Comments were invited from registered stakeholder organisations and NICE staff. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed and signed off by NICE and posted on the NICE website.

The Guideline Committee (GC)

The non Hodgkin's lymphoma GC was recruited in line with the 'NICE guidelines manual' (NICE 2012). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed in person prior to being offered the role. The NCC-C Director, GC Chair and Lead Clinician identified a list of specialties that needed to be represented on the GC. Adverts were sent to all the registered stakeholder organisations including patient organisations/charities (Appendix F). Individual GC members were selected for interview by the NCC-C Director, GC Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GC, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GC members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, research funding (either in the form of programme or project grants or personal research awards), fellowships and support from the healthcare industry. At all subsequent GC meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix F).

Guideline Committee meetings

Fourteen GC meetings were held between 4-5 March 2014 and 4–5 April 2016. During each GC meeting (held over either 1 or 2 days) clinical and health economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed, including a standard agenda item.

The NCC-C project manager divided the GC workload by allocating specific review questions, relevant to their area of clinical practice, to small sub-groups of the GC in order to simplify and speed up the development process. These groups considered the evidence, as appraised by the researcher, and synthesised it into draft recommendations before presenting it to the GC. These recommendations were then discussed and agreed by the GC as a whole. Each review question was led by a GC member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GC subgroups often helped refine the review questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/carer members

Individuals with direct experience of non Hodgkin's lymphoma services gave an important user focus to the GC and the guideline development process. The GC included three patient/carer members. They contributed as full GC members to writing the review questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GC.

Developing clinical evidence-based questions

Background

The scope for this guideline was very clear about which patient groups were included and which areas of clinical care should be considered (see Appendix E – Scope). The 24 review questions and search strategies that covered the guideline topics were agreed during scoping. All the evidence used to inform this guideline is summarised in the accompanying full evidence review 'non Hodgkin's lymphoma: diagnosis and management – evidence review', which includes details of all the studies appraised (see Appendix G).

Method

From each of the key clinical issues identified in the scope, the GC formulated a review question. For intervention questions the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study); I – the intervention(s) (what is being done); C – the comparison (other main treatment or test options); O – the outcomes (the measures of how effective the interventions have been). Diagnostic review questions specified the population, index test, reference standard test and the target condition.Prognostic review questions specified the population, prognostic factors and outcomes.

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: NHS Evidence, NICE, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), TRIP, SIGN, NHS Economic Evaluations Database (NHSEED), Health Economic Evaluations Database (HEED), Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines/guidance (local, national or international) produced by other groups or institutions which were cross checked for relevant evidence.

Developing the review protocol

For each review question, the information specialist and researcher (with input from other technical team and GC members) prepared a review protocol. This protocol explained how the review was to be carried out (Table 1) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in Appendix J.

Table 1: Components of the review protocol

Component	Description
Review question	The review question as agreed by the GC
Rationale	An explanation of why the review question is important. For example, is the topic contentious? Is there variation in practice across the UK?
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. Searches should not necessarily be restricted to RCTs.
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the lead NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GC. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on ‘Incorporating Health Economic Evidence’).

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when necessary. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards
- Web of Science [specifically Science Citation Index Expanded (SCI-Expanded) 1900 onwards and Social Sciences Citation Index (SSCI) 1900 onwards]

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1937 onwards
- PsycINFO 1806 onwards
- Allied and Complementary Medicine (AMED) 1985 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

In accordance with the 'NICE guidelines manual' (NICE 2012) searches were updated and re-run 8 weeks before the guideline was submitted to NICE for stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 1st September 2015 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in Appendix I).

Critical Appraisal and Evidence Grading

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. When papers were obtained, the researcher applied the inclusion and exclusion criteria outlined in the review protocol to select appropriate studies. Each study was then critically appraised using a methodology checklist appropriate for its design (appendices B to I of the 'NICE guidelines manual', NICE 2012): for example the quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting *et al*., 2011).

When high quality published systematic reviews were identified, the inclusion and exclusion criteria and outcomes were carefully checked against the guideline review protocol and any relevant systematic reviews included as evidence. The risk of bias of the evidence base in the systematic review was estimated using the reported study characteristics. Lists of studies in systematic reviews were checked against any other included studies to avoid double counting.

If results from a study were published as more than one paper, the most recent or complete publication was used. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GC (see Appendix G). All evidence was considered carefully by the GC for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using GRADE (NICE 2012; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. A narrative summary of the evidence (evidence statement) was also prepared.

Each outcome was examined for the quality elements defined in Table 2 and subsequently graded using the quality levels listed in Table 3.

Table 2: Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and the review question
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

The reasons for downgrading or upgrading specific outcomes were explained in footnotes and were categorised as due to limitations, inconsistency, indirectness or imprecision.

Limitations in study design or conduct were considered per outcome and included observational study design, inadequate randomisation, inadequate allocation concealment, lack of blinding and loss to follow-up.

Evidence was downgraded for inconsistency if there was unexplained heterogeneity of results (for example some studies showing appreciable benefit and others appreciable harm), after accounting for any subgroups in the review protocol. If meta-analysis was done, a large I-squared value could be used as a criterion for downgrading and was explained in a footnote.

Evidence was downgraded for indirectness when there were important differences between the populations, interventions or outcomes of the included studies and the inclusion criteria of guideline review protocol.

Evidence was downgraded for publication bias only if it was apparent in funnel plots or there was other clear reason to suspect reporting bias. Unpublished evidence was not searched for, however, so it is possible that publication bias was underestimated

Imprecision in the evidence reviews was assessed according to the 95% confidence interval of the effect estimate for each outcome. The effect estimate was judged imprecise when its confidence interval included both no effect and clinically important benefit or harm. The GC typically used the GRADE default minimal important difference (MID): a 25% relative risk reduction or relative risk increase was used, corresponding to clinically important harm and benefit thresholds of 0.75 and 1.25 respectively for the risk ratio. For survival outcomes, however, a smaller relative risk reduction was potentially clinically important in such cases imprecision judgements were explained in footnotes to the GRADE profile.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2012). In general, evidence was based on published data only but for some review questions conference abstracts were included when there was a lack of published data. Study authors were contacted only to resolve any ambiguities, such as unclear presentation of data, or where clarification was needed in order to include or exclude a paper in the evidence review.

For non-interventional questions, for example questions regarding diagnostic test accuracy, prognosis or qualitative evidence, a narrative summary of the quality of the evidence was provided.

Data synthesis

There were no opportunities for new meta-analyses of randomised trials due to the lack of multiple similar trials in the evidence base (although a published meta-analyses of randomised trials was included as evidence). Formal adjusted indirect comparison of a pair of randomised trials was done using the method suggested by Bucher et al (1997).

Meta-analysis of diagnostic data was done using the bivariate model of Reitsma et al (2005) via the R package mada (Doebler, 2015). Any original meta-analysis was accompanied by forest plots or ROC plots of confidence regions for sensitivity and specificity.

Data from observational studies were summarised per outcome in GRADE using the range of reported values. For interventions where the only available data came from non comparative observational studies, single arm data were entered into the GRADE evidence profile although relative effect estimates were not estimable.

When data could not be combined (due to differences in study populations, interventions or outcomes) results were summarised and included in GRADE on an individual study basis.

Incorporating health economics evidence

The aim of providing economic input into the development of the guideline was to inform the GC of potential economic issues relating to the topics identified in the scope. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the review questions had been defined, and with the help of the health economist, the priority review questions for economic analysis were discussed and agreed. These priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2012):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

A review of the economic literature was conducted at scoping. Where published economic evaluation studies were identified that addressed the economic issues for a review question, these are presented alongside the clinical evidence.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies of 'cost of illness' studies are generally excluded from the reviews (NICE 2012).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2012). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GC for a specific topic within the guideline. There are two parts of the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table 4).

Table 4: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table 5).

Table 5: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should

	usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific review question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GC, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GC subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There are several published technology appraisals (TAs) which are relevant to this guideline (see www.nice.org.uk/TA/published). In line with NICE methodology, the recommendations from these TAs have either been cross-referenced (TA 370) or incorporated (TA137 and TA243) (see Developing NICE guidelines: the manual, 2014).

Agreeing the recommendations

For each review question the GC were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. The GC derived their guideline recommendations from this information. The link between the evidence and the view of the GC in making each recommendation was made explicitly in the accompanying linking evidence to recommendations (LETR) statement (see below).

Wording of the recommendations

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations were based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences. This discussion should help the patient reach a fully informed decision. Terms used within this guideline are:

- ‘Offer’ – for the vast majority of patients, an intervention will do more good than harm (based on high quality evidence)

- ‘Do not offer’ – the intervention will not be of benefit for most patients (based on high quality evidence)
- ‘Consider’ – the benefit is less certain, and an intervention will do more good than harm for most patients (based on poor quality evidence or no evidence). The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for an ‘offer’ recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Any exceptions to the above were documented in the LETR that accompany the recommendations.

LETR (Linking evidence to recommendations)

Each recommendation is accompanied by a section describing the decision making process of the GC and how they used the evidence.This is known as the ‘LETR’ and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost effectiveness of an intervention
- the quality of the evidence (see ‘GRADE’)
- the degree of consensus within the GC
- other considerations – for example equalities issues.

Where evidence was weak or lacking the GC agreed the final recommendations through informal consensus.

Research recommendations

If published evidence was weak or lacking and there were no ongoing research studies, the GC considered making recommendations for future research. When deciding research recommendations the GC considered the potiental impact of the research on patient outcome and the feasibility of such research studies. Three research recommendations were agreed by the GC.

Consultation and validation of the guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GC Chair and Lead Clinician. This was then discussed and agreed with the GC and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix F) had one opportunity to comment on the draft guideline which was posted on the NICE website between 29 January 2016 and 11 March 2016 in line with NICE methodology (NICE 2014).

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders who have signed a confidentiality form to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication (NICE 2014).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GC and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk).

NICE also produces three other versions of the non-Hodgkin's lymphoma guideline which are available from the NICE website:

- the Short version, containing all recommendations and the research recommendations.
- NICE pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Information for the Public (IFP)', which summarises the recommendations in the guideline in everyday language for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were repeated for all of the review questions at the end of the guideline development process, allowing any relevant papers published before 1st September 2015 to be considered. Future guideline updates will consider evidence published after this cut-off date.

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

Funding

The National Collaborating Centre for Cancer (NCC-C) was commissioned by NICE to develop this guideline.

Disclaimer

The GC assumes that healthcare professionals will use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

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Research recommendations

- **In people with diffuse large B-cell lymphoma stage II or above, does a baseline FDG-PET-CT scan have any advantages over a baseline CT scan in the correct interpretation of the end-of-treatment FDG-PET-CT scan?**

A number of consensus-based guidelines and a body of clinical opinion advocate baseline FDG-PET-CT imaging as being important for interpreting end-of-treatment response using FDG-PET-CT, although there is little published evidence for this. Baseline FDG-PET-CT is also considered to have an important contribution 'over and above' that of contrast-enhanced diagnostic CT in assigning the International Prognostic Index (IPI), in terms of identifying disease stage and number of extranodal sites involved (influencing the decision to offer central nervous system prophylaxis). A prospective trial is needed to determine whether baseline FDG-PET-CT is needed to interpret end-of-treatment FDG-PET-CT and its role in assigning IPI. People with newly histologically diagnosed diffuse large B-cell lymphoma would have baseline contrast-enhanced CT, baseline FDG-PET-CT and end-of-treatment FDG-PET-CT imaging. Readers would need to be trained in both imaging techniques and be experienced members of lymphoma multidisciplinary teams.

The reference standard would be histological confirmation of any positive or equivocal end of-treatment FDG-PET-CT findings, or follow-up if there is a negative end-of-treatment scan

- **In people with high-grade transformation of follicular lymphoma, which biological and clinical factors predict good outcomes with immunochemotherapy alone.**

Before rituximab, it was accepted that high-grade transformation of follicular lymphoma to diffuse large B-cell lymphoma portended a poor prognosis. Recent data suggests that although transformation remains an important clinical event, outcomes have improved. It is unclear which people are likely to do well with conventional treatment (such as R-CHOP) and which people may benefit from intensive treatment with, for example, high-dose therapy and autologous stem cell transplantation. Many factors are likely to influence outcome, including clinical factors (such as age, stage at transformation and extranodal involvement at transformation), radiological findings (such as early improvement of disease identified using an interim FDG-PET CT scan) and molecular factors (such as certain driver mutations present at transformation, the presence of MYC translocation and response of circulating tumour DNA to treatment). A better understanding of which factors are associated with high-risk or low-risk disease would enable therapy to be tailored to the person's needs, reducing unnecessary toxicity for people at low risk and reserving intensive therapy for people at high risk. Outcomes of interest include progression-free survival and overall survival in subgroups defined by clinical factors, radiological findings and molecular analyses

- **In people presenting with diffuse large B-cell lymphoma and sites of bulky disease, are outcomes improved by radiotherapy to those sites following a full course of chemotherapy?**

The role of radiotherapy to sites of original bulky disease in treating diffuse large B-cell lymphoma is uncertain. Some clinical teams will consider radiotherapy in this setting while others will not because of concerns about morbidity and late effects of treatment. In a recent randomised trial of chemotherapy in people over 60 years old with diffuse large B-cell lymphoma, people having radiotherapy were identified and compared with a cohort having no radiotherapy. Significant improvements in event-free, progression-free and overall survival were seen in the group having radiotherapy. These results have encouraged some teams to reconsider radiotherapy for bulky diffuse large B-cell lymphoma. A definitive randomised trial is needed to address this question. Outcomes of interest include overall survival, disease-

free survival, progression-free survival, treatment-related mortality, treatment-related morbidity, health-related quality of life, patient satisfaction, patient preference and overall response rate (complete or partial remission).

1 Epidemiology

Non-Hodgkin's lymphoma (NHL) is the 6th most common type of cancer in the UK (CRUK, 2012). It is more common in people aged over 65 years (Figure 1) and the increasing age of the population therefore impacts markedly on the total number of patients with NHL. NHL is more frequent in men than in women (Figure 2), and in 2013 the age standardised rate of NHL in England per 100,000 of the population was 27.6 for men and 19.9 for women. This equated to 6,195 newly diagnosed men and 5,218 newly diagnosed women in that year. There has been a moderate increase in the reported age standardised incidence of NHL in England since 2001 but it is not clear whether this is a true increase in the incidence of the disease or is a reflection of improved diagnostic testing. It is noteworthy that the major part of the apparent increase has been in people aged 70 years which may be a result of more rigorous investigation of elderly patients. There has been no reported increase in the incidence of NHL in Wales over the same time-period. There is no evidence from the English data that the incidence of NHL is influenced by socio-economic deprivation.

Figure 1: Incidence of non-Hodgkin lymphoma (ICD-10 code C82-C85), distribution of age at diagnosis, Persons, England 2013.

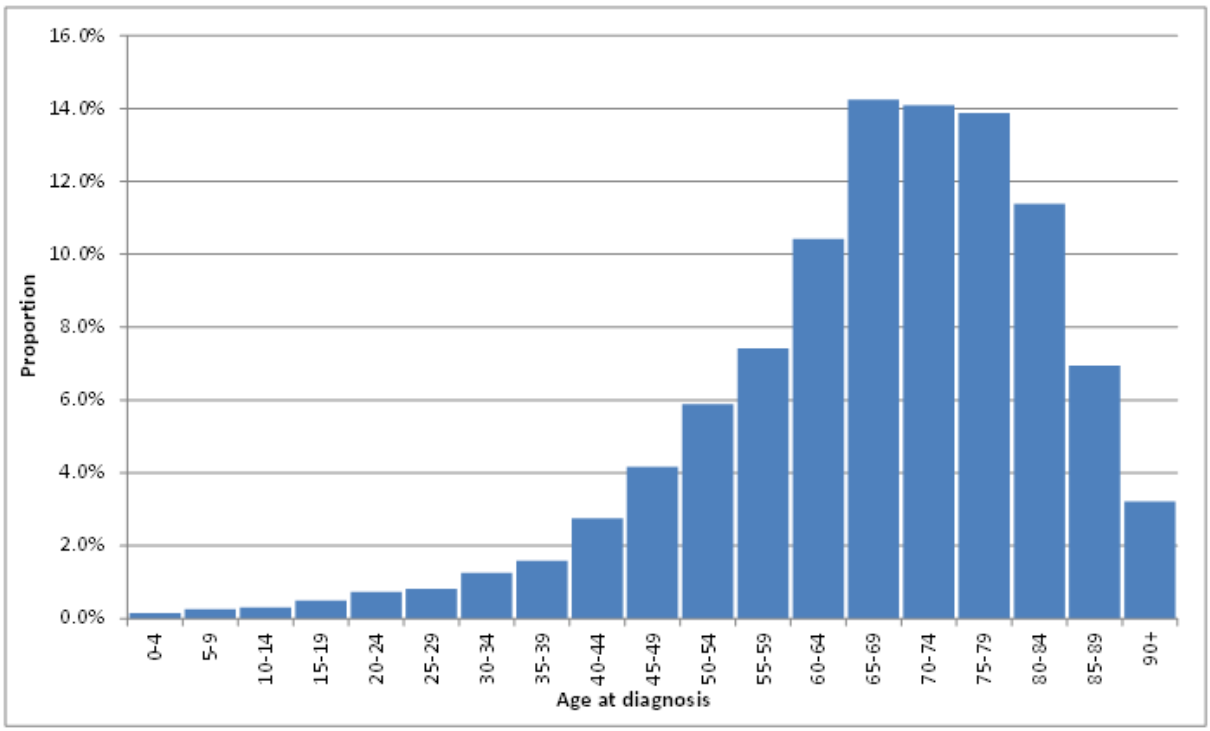
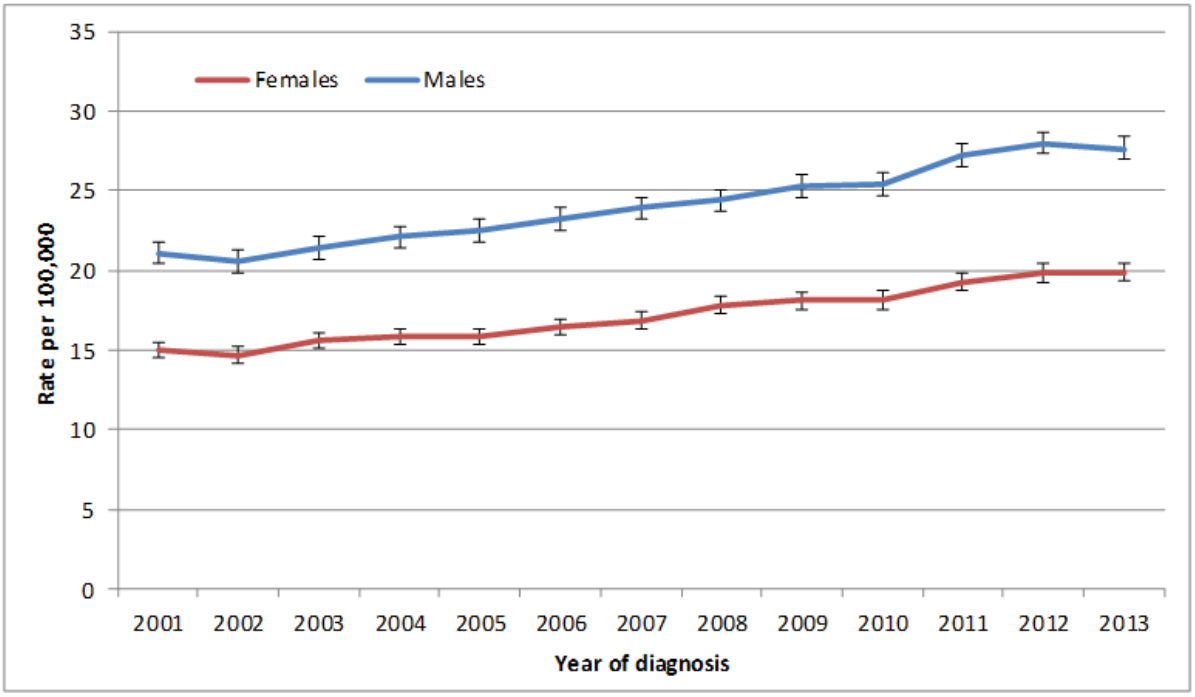


Figure 2: Incidence of non-Hodgkin lymphoma (ICD-10 code C82-C85), age-standardised rate per 100,000 by sex, England 2001-2013.



NHL is a heterogeneous group of malignancies with over 60 subtypes and 9 provisional sub-types. Two of the most common subtypes are follicular lymphoma (F-NHL) and diffuse large B-cell lymphoma (DLBCL) representing the archetypal low grade or histologically indolent lymphoma and the high grade or histologically aggressive lymphomas. The most frequently quoted incidence of the different subtypes is taken from the International Non-Hodgkin's Lymphoma Classification Project (Anon 1997) which was based on cases from selected hospitals who submitted cases to this project (Table 6). The incidence of the most frequent lymphomas has by contrast been determined by the Haematological Malignancies Research Network (HMRN) on a population basis (Table 7). The HMRN includes a population of 3.6 million people from the Yorkshire and Humber regions in which the socio-demographic profile is similar to the country/UK/England as a whole.

Table 6: Proportion of new NHL cases according to the main NHL subtypes

Subtype	Proportion of NHL
Follicular lymphoma (F-NHL)	22.0%
Marginal zone lymphoma (MZL)	9.0%
Mantle cell lymphoma (MCL)	6.0%
Diffuse large B-cell lymphoma (DLBCL)	35.0%*
Burkitt Lymphoma	1.0%
T-cell lymphoma	7.0%
All	

** Includes primary mediastinal B-cell lymphoma and Burkitt-like lymphomas*

Source: Anon (1997)

Table 7: Incidence of NHL in the UK based on extrapolation of the HMRN data

Subtype	Proportion of NHL	Expected cases per year in the UK
Follicular lymphoma (F-NHL)	18.1%	1860
Marginal zone lymphoma (MZL)	19.9%	2050

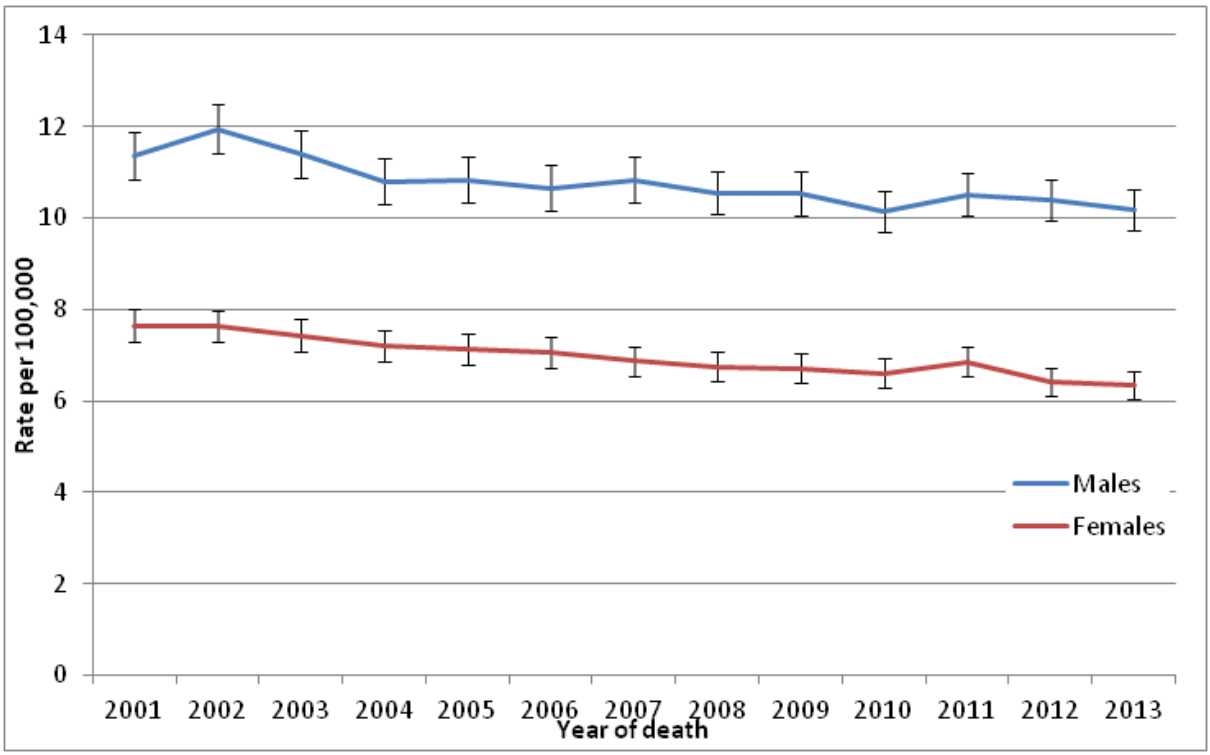
Subtype	Proportion of NHL	Expected cases per year in the UK
Mantle cell lymphoma (MCL)	5.0%	510
Diffuse large B-cell lymphoma (DLBCL)	48.5%	4990
Burkitt Lymphoma	2.0%	210
T-cell lymphoma	6.3%	650
All		10,280

It is noteworthy that DLBCL and MZL are more common than previously estimated and F-NHL represents fewer than 20% of all cases.

The behaviour of the NHL varies widely between different histological types. Low grade lymphomas such as F-NHL, tend to grow relatively slowly and can usually be induced into remission without very intensive therapy. The relapse rate is, however, high and can occur after protracted periods of remission. High grade lymphomas such as DLBCL are typically faster growing and clinically more aggressive. Early deaths are more frequent than in low grade lymphomas but the majority of patients who achieve a complete remission are cured of their disease. In the long term, therefore, the prognosis of high grade lymphoma is better than low grade lymphoma. In addition to the variation in outcome based on histological subtype, there is also a major impact of age with older patients faring considerably worse. This is due to more intrinsically chemotherapy–resistant disease in the elderly, the inexorable decline in the function of many organs with age which can limit the tolerability of many of the drugs used to treat lymphoma, and co-morbidities which are much more frequent in the elderly and may make it impossible to deliver the most effective drug regimens. A number of other prognostic factors have also been indentified such that consideration of global NHL outcome data has very limited relevance to individual patients.

Despite these reservations about global outcome data, this information is of value in the assessment of unmet need and as a crude indicator of therapeutic progress. Overall, the age-standardised mortality rate from NHL per 100,000 of the English population in 2013 was 10.2 for men and 6.3 for women which is approximately 30% of the incidence. There has been some improvement in mortality over the last decade (Figure 3) but the improvement is modest and disappointing as this has been a decade in which a number of therapeutic advances have apparently been made. In England the one and five year relative survival rates (adjusted for expected deaths from other causes) is significantly lower in most socio-economically deprived populations. The 5 year relative survival is 61.3% in the least deprived population quintile and 54.3% in the most deprived quintile. It is also apparent from US sources that outcomes vary according to racial group but there is limited UK data addressing this issue.

Figure 3: Mortality from non-Hodgkin lymphoma (ICD-10 code C82-C85), age-standardised rate per 100,000 by sex, England 2001-2013



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Anon (1997) A clinical evaluation of the International Lymphoma Study Group Classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 89: 3909-3918

CRUK (2012) Non-Hodgkin's Lymphoma Statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma

2 Diagnosis

2.1 Type of biopsy

A surgically excised tissue biopsy is widely accepted as the gold standard for the diagnosis of lymphoma based upon the current international guidelines (Lugano 2014 and ESMO 2015). An excision biopsy of a lymph node (or other tissue) allows assessment of micro-architecture, provides adequate material for immunocytochemistry, flow cytometry if received unfixed, FISH studies and extraction of DNA and RNA for molecular diagnostics. Concordance between the results of these investigations provides a high level of confidence in the diagnosis. Where the disease process is focal an excision biopsy is more likely to be diagnostic by virtue of the volume of tissue obtained and excision biopsies, in addition are typically less prone to processing artefacts which can impair morphological interpretation.

The major disadvantages of an excision biopsy are the need for general anaesthesia and the delays that can result from seeking a surgical opinion. These issues can be addressed by using needle core biopsies, but at the expense of a reduction in the range and quality of investigations that can be performed, unless multiple 10-15 mm cores have been taken when the amount of tissue may be similar to some excision biopsies. However, single thin cores of 5mm or less are common and this severely compromises all of the investigations listed above. Inadequate or too few core biopsies reduces the degree of confidence that can be placed in the diagnosis and judging when a needle core biopsy is adequate to support the immediate treatment of the patient is subjective and can be very difficult. This is compounded by routinely cutting step levels through these blocks, which results in a significant amount of the available tissue being discarded; this is common practice in many pathology departments. These problems frequently result in repeat biopsies being required with further delays to diagnosis and treatment.

An additional factor, in the near future, will be the need for a much higher standard of tissue collection and handling to support the diagnostics required for precision medicine. It is likely that unfixed tissue will be required to support sequencing-based techniques and that conditions under which samples are collected, transported and stored will become much more rigorous than is the case at present.

The critical question to be addressed is the circumstances where the loss of information and diagnostic confidence can be justified by logistical benefits and patient convenience. The main determinants will be the site of disease, urgency of treatment, patient preference and fitness.

Clinical question: Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of suspected non-Hodgkin's lymphoma at first presentation?

2.1.1 Clinical evidence (see section 2.1.1 in Appendix G)

The review identified no evidence that met the inclusion criteria of the review.

2.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider an excision biopsy as the first diagnostic procedure for people with suspected non-Hodgkin's lymphoma at first presentation.** **In people with suspected non-Hodgkin's lymphoma for whom the risk of a surgical procedure outweighs the potential benefits of an excision biopsy, consider a needle core biopsy procedure. Take the maximum number of cores of the largest possible calibre.** **For people with suspected non-Hodgkin's lymphoma in whom a diagnosis is not possible after a needle core biopsy procedure, offer an excision biopsy (if surgically feasible) in preference to a second needle core biopsy procedure.** **Pathology departments should ensure that tissue is conserved when handling needle core biopsies, so that further analysis can be carried out if needed.**
Relative value placed on the outcomes considered	The GC considered accurate classification of non Hodgkin's lymphoma (NHL) to be the most important outcome when drafting the recommendations because treatment is crucially dependent on this.
Quality of the evidence	No published evidence was identified for this topic and so the GC based their recommendations on clinical expertise and experience.
Trade off between clinical benefits and harms	The GC decided that although no evidence was identified it was still important to make recommendations because accurate initial lymphoma diagnosis can reduce treatment delay and avoid incorrect treatment with serious adverse effects for the patient. Following initial lymphoma diagnosis, the patient typically enters the treatment pathway without further verification, unlike many other cancers where diagnosis is confirmed on material obtained during therapeutic surgery. It is therefore imperative that the correct diagnosis is obtained when a patient initially presents with suspected lymphoma. The GC considered that a correct diagnosis is usually easier to achieve when an excision biopsy has been obtained. The committee acknowledge that diagnosis using excision biopsy takes longer than a core biopsy, and that this delay might harm some patients with suspected lymphoma. However, the GC considered that this would apply to a minority of patients with aggressive disease and centres treating lymphomas should be able to ensure that appropriate services are provided in these cases. The GC also noted that repeat non-diagnostic core biopsies can themselves result in diagnostic delay. Other potential harms of excision biopsy include general anaesthesia and surgical complications. The GC agreed that the benefits of an accurate lymphoma diagnosis outweighed the potential harms because it will ensure the patient enters the correct treatment pathway, but the GC balanced the benefits and harms of the recommendations by allowing for factors specific to an individual patient to guide the choice of diagnostic procedure. The GC noted that inadequate sample quality is a frequently occurring problem and presents a major challenge for diagnostic

	pathologists in confidently diagnosing suspected lymphoma. The GC therefore made recommendations that collectively serve to ensure that adequate quality tissue samples are obtained for a confident diagnosis to be made. The GC considered the potential benefit of these recommendations will be that a correct diagnosis will be achieved in the highest possible number of patients with suspected lymphoma.
Trade off between net health benefits and resource use	No economic evidence was identified for this topic and no model was built. The GC estimated that the recommendations will increase the rate of excision biopsy and the associated costs, but this will be balanced by the decrease in cost associated with fewer diagnostic and non-diagnostic core biopsies and by the reduction in downstream costs associated with more accurate diagnoses.
Other considerations	The GC estimated that the change in practice needed to implement the recommendations will be varied: some centres currently carry out this practice, however there will be a significant change in centres where this is not the case. The GC acknowledged that there would be an impact on surgical resources and uptake would be dependent on availability of surgical services.

2.2 Genetic testing

Genetic and molecular testing has provided important insights into lymphoma biology. When applied to many lymphoma subtypes they have also demonstrated that the diagnosis and subclassification of lymphomas is more accurate when compared with traditional diagnostic methods such as standard microscopy and immunohistochemistry. Advances in this field may reduce heterogeneity in patients included in clinical trials, allow for greater confidence in the diagnostic process and improve patient outcomes.

2.2.1 Testing strategies to diagnose B-cell lymphomas

Aggressive B-cell lymphoma can be subdivided into six main categories, as well a number of minor or rare subtypes. For the purposes of this question the six main categories are:

- Burkitt Lymphoma
- Primary Mediastinal B-cell Lymphoma
- DLBCL- GCB type
- DLBCL- ABC type
- DLBCL- Type 3
- DLBCL- *MYC* rearrangement with other translocations (‘Double hit”)

At present only the accurate diagnosis of Burkitt Lymphoma impacts on choice of therapy.

In the case of Burkitt lymphoma the presence of a *MYC*-IGH rearrangement as the sole abnormality identified by FISH in the context of a *BCL2* negative germinal centres phenotype is the defining characteristic. The molecular subtypes of DLBCL are determined by gene expression profiling, which is the gold standard for identifying these subtypes, but is not routine practice.

The main problem is that most lymphoma diagnostic technologies are in a phase of rapid change. Data on these newer technologies is limited. Immunocytochemistry is increasingly

recognised as being a poorly reproducible method unsuited for biomarker analysis. There is a large body of sequencing data (whole exome, targeted re-sequencing) that is highly relevant particularly to the diagnosis of Burkitt Lymphoma and the differentiation of GCB and ABC types of DLBCL and identification several of the genes within each category that are targets for specific therapy. Combinations of expression profiling and targeted sequencing are likely to become the method of choice over the next few years but experience in routine application is limited at the present time.

Clinical question: What is the most effective genomic/phenotypic testing strategy to diagnose the subtypes of aggressive b-cell non-Hodgkin's lymphoma?

2.2.1.1 Clinical evidence (see section 2.2.1 in Appendix G)

Twenty six studies provided information on diagnostic tests. All were retrospective cross sectional studies using retrospectively collected data.

2.2.1.1.1 Diagnostic accuracy of testing strategies for sub-typing aggressive non-Hodgkin's lymphomas (NHL)

Burkitt lymphoma (BL) versus diffuse large B-cell lymphoma (DLBCL)

Four studies (Barrans *et al.*, 2013; Gormley *et al.,* 2005; Soldini *et al.*, 2013 and Iqbal *et al.*, 2015) including 796 patients assessed testing strategies to differentiate between BL and DLBCL. Low quality evidence from one study (Soldini *et al*, 2013) indicated all patients were accurately classified to their original diagnosis when using FISH. Low quality evidence from two studies (Barrans *et al.*, 2013 and Iqbal *et al.*, 2015) indicated that classic diagnostic methods can accurately diagnose BL and DLBCL compared to gene expression profiling at rates of 93.59-95.4%. Finally, one study (Gormley *et al.*, 2005) provided low quality evidence that immunohistochemistry (IHC) can accurately diagnose patients into BL/DLBCL and GC/ABC subtypes compared to morphology at a rate of 85.5%.

Burkitt lymphoma (BL) versus other NHL subtypes

Two studies (Dave *et al.,* 2006 and Hummel *et al.*, 2006) including 291 patients assessed testing strategies to differentiate between BL and other NHL subtypes. Low quality evidence from one study (Dave *et al.*, 2006) indictaed that pathological review provides more diagnostic accuracy (87.3%) compared to classic diagnostic methods (73.2%) when diagnosing Burkitt lymphoma. One study (Hummel *et al.*, 2006) provided low quality evidence that morphology can accurately diagnose patients into BL versus other NHL subtypes at a rate of 83.6%.

Primary mediastinal B-cell lymphoma (PMBL) versus diffuse large B-cell lymphoma (DLBCL)

One study (Votavova *et al*, 2010) including 82 patients assessed the use of histopathological and clinical review compared to gene expression profiling in the diagnosis of PMBL reporting low quality evidence of a diagnostic accuracy rate of 85.4%.

Diffuse large B-cell lymphoma (DLBCL) versus other NHL subtypes

One study reporting low quality evidence (Deffenbacher *et al*, 2010) including 17 patients assessed the use of pathological review compared to gene expression profiling in the diagnosis of HIV DLBCL, with a diagnostic accuracy rate of 64.7%.

2.2.1.1.2 Diagnostic accuracy of testing strategies for sub-typing diffuse large B-cell lymphoma (DLBCL)

Sub-typing diffuse large B-cell lymphoma into germinal centre B-cell (GCB) and activated B-cell (ABC)-like lymphomas

Five studies (Barrans *et al* 2012; Malik *et al*, 2010; Booman *et al*, 2006; Scott *et al*, 2013 and Choi *et al* 2009) including 472 patients provided low quality evidence comparing various immunohistochemistry (IHC) algorithms to gene expression profiling (GEP). The highest rates of diagnostic accuracy (>90%) were reported when using IHC (93.4%; Malik *et al*. 2010), IHC Hans (91.5%; Scott *et al*., 2013), IHC Tally (93.6%; Scott *et al*., 2013) and IHC Choi algorithms (training set: 92.9%, validation set: 93.7%; Choi *et al*., 2009) and the lowest rate of diagnostic accuracy using IHC reported by Booman *et al*. (2006; 70%). Rimsza *et al*. (2009) assessed the use of qNPA at two thresholds (>0.8 and >0.9) compared to GEP reporting low quality accuracy rates of 92.3% (threshold >0.9) and 100% (threshold >0.8). Su *et al*., (2013) assessed the value of a bivariate mixture model reporting the a diagnostic accuracy rate when using a two-species analysis (human and canine) of 89.7% compared to 89.1% when using a human species alone analysis (89.1%). Finally, Williams *et al*. (2010) providing low quality evidence on the use of formalin-fixed paraffin embedded tissue when sub-typing DLBCL, reported a 97.7% accuracy rate compared to the use of fresh frozen tissues, and Mareschal *et al*. (2015) also providing low quality evidence found that GEP using a RT-MLPA assay accurately subtyped patients at a rate of 100% compared to GEP Affymetrix.

Sub-typing diffuse large B-cell lymphoma into Germinal centre B-cell (GCB) and non-GCB-like lymphomas

Four studies (Poulsen *et al*, 2005; Gutierrez-Garcia *et al*, 2011; Haarer *et al*, 2006 and Visco *et al* 2012) including 569 patients provided low quality evidence comparing various immunohistochemistry (IHC) algorithms to gene expression profiling (GEP). The highest rates of diagnostic accuracy (>90%) were reported when using IHC (92.7%; Poulsen *et al*., 2005) and a 3-marker algorithm (92.6%) or 4-marker algorithm (92.8%; Visco *et al*., 2012) and the lowest rate of diagnostic accuracy was reported when using the IHC Choi algorithm (59.1%; Gutierrez-Garcia *et al*., 2011). When assessing studies that had reported using the same IHC algorithms (Hans and Choi) there was wide variation between the reported diagnostic accuracy of these algorithms (59.1% compared to 90% for the Choi algorithm and 65.3% and 87.2%).

2.2.1.1.3 Comparison of testing strategies for the identification of genes in non-Hodgkin's lymphomas.

One study (Chang *et al*, 2010) assessed the use of FISH compared to polymerase chain reaction in the detection of t(14;18) in 227 patients with NHL reporting low quality evidence of a 70.5% accuracy rate. One study (Dunphy *et al*, 2008) assessed the use of FISH compared to PCR in the detection of BCL2 in 22 patients with primary mediastinal B-cell lymphoma reporting low quality evidence of a 95.5% accuracy rate. One study (Lynnhtun *et al*, 2014) assessed the use of FISH compared to immunohistochemistry plus FISH in the detection of *MYC* in 41 patients with high-grade B-cell lymphomas reporting low quality evidence of accuracy rates of 58.5% with a ≥40% IHC-FISH threshold and 87.8% at ≥70% and ≥80% IHC-FISH threshold. One study (Mationg-Kalaw *et al*, 2012) reported the use of pathological review compared to immunohistochemistry plus FISH in the detection of Ki67 in 432 patients with diffuse large B-cell lymphoma reporting low quality evidence of a 38.4% accuracy rate at >70% threshold and a 61.6% accuracy rate at >90% threshold. Finally, one study (Zeppa *et al*, 2012) assessed the use of flow cytometry, immunohistochemistry-FISH and polymerase chain reaction compared to histology and follow-up in the detection of immunoglobulin heavy-chain (IGH) signals in 48 patients with non-Hodgkin's lymphoma, reactive hyperplasia

and small lymphocytic lymphoma/chronic lymphocytic leukemia reporting low quality evidence of accuracy rates of 95.8%, 86.4% and 80% (respectively).

2.2.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider using FISH (fluorescence in situ hybridisation) to identify a *MYC* rearrangement in all people newly presenting with histologically high-grade B-cell lymphoma.** **If a *MYC* rearrangement is found, use FISH to identify the immunoglobulin partner and the presence of *BCL2* and *BCL6* rearrangements.**
Relative value placed on the outcomes considered	Diagnostic accuracy including sensitivity, specificity, positive predictive value and negative predictive value were considered to be the critical outcomes for this topic. The GC considered sensitivity to be important in avoiding incorrect treatment as a result of disease misclassification. Test reproducibility and turnaround time were also important but no evidence was found for these outcomes.
Quality of the evidence	The quality of the evidence was low as assessed using QUADAS2. The reason for this was because the primary focus of the studies was not diagnostic accuracy so the publications lacked information about the index and reference standard tests. Additionally, studies provided limited information on selection of participants/samples and tended to use small sized hospital samples or databases without explanation for inclusion and exclusion of participants resulting in a large amount of uncertainty. Low quality evidence about testing strategies for primary mediastinal B-cell lymphoma came from a single study so the GC decided not to formulate a recommenation for this subgroup. The recommendation to undertake further studies when a *MYC* translocation is identified is based on the experience of the GC, as no evidence was identified that compared the outcomes of patients with *MYC* translocations to those of patients with both *MYC*, *BCL2* and/or *BCL6* translocations.
Trade off between clinical benefits and harms	The GC considered that these recommendations would lead to more accurate diagnosis and as a result, treatment could be more appropriately directed. The recommendations will also facilitate informed decision making with the patient. No harms were indentified. The GC recommended investigating cases of diffuse large B-cell lymphoma for the presence of a *MYC* rearrangement, and where a rearrangement is detected, to undertake further studies to identify rearrangements of *BCL2* and *BCL6*. Distinguishing between cases with *MYC* as a sole abnormality and those with additional abnormalities is important in the differential diagnosis of Burkitt lymphoma and poor prognosis DLBCL. There was evidence that the presence of 2 or 3 of these abnormalities in DLBCL portends an adverse clinical outcome and although other factors (for example

	age) might modify this the GC thought that patients and clinicians would want to know this information. The GC also noted that there is an important clinical issue about misdiagnosis of Burkitt lymphoma as DLBCL and these recommendations will assist with this problem
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The recommended tests are already being used. The GC considered the recommendations would be cost neutral due to a greater number of FISH tests but fewer immunohistochemistry tests.
Other considerations	The GC noted that FISH is currently the only method that can be used on a formalin fixed sample. It is also well documented that looking for evidence of the gene abnormality could be more useful in this context than looking for protein expression because the latter is unreliable. There was a lack of consensus on the methodology of gene expression profiling (GEP); although the various systems worked in research settings they were not yet robust enough to be used in routine practice. Research is moving towards newer practices so efforts are now being made to establish the best GEP platforms.

2.2.2 Stratification of high grade B-cell lymphomas using laboratory techniques

Advanced molecular diagnostics will have a major impact on the diagnosis and stratification of all patients with lymphoma. Although the technologies are the same across lymphoma subtypes the data supporting its routine clinical application is greatest in high grade B-cell lymphomas.

In high grade B-cell lymphoma the application of molecular diagnostics is important in two areas:

- **Identifying very poor prognosis diffuse large B-Cell lymphoma (DLBCL).** DLBCL with an abnormality of the *MYC* gene and one of several additional genetic abnormalities detectable by FISH have a very poor clinical outcome ('double and triple hit lymphomas') and there is no consensus on treatment of these patients. This group is likely to expand when mutations of specific genes are added to the abnormalities detectable by FISH. Again, attempts to replicate this by immunocytochemistry have been reported.
- **Identifying very good prognosis DLBCL.** The International Prognostic Index (IPI) has been used for many years to stratify patients with DLBCL. There is preliminary data that a statistical modification of the IPI (use of continuous variables) combined with gene expression and mutational analysis can identify a set of patients with a very high probability of cure by R-CHOP. This has important implications for trial design, the application of new therapies and patient information.

Clinical question: What is the most effective genomic/phenotypic testing strategy to determine therapeutic stratification and prognostic subtypes of aggressive b-cell non-Hodgkin's lymphoma?

2.2.2.1 Clinical evidence (see section 2.2.2 in Appendix G)

43 studies provided evidence about the prognostic value of molecular diagnostics in people with high grade B-cell lymphoma.

2.2.2.1.1 GCB versus non-GCB: IHC (Hans)

Moderate quality evidence from 22 studies (n=5065 patientes) reported overall survival does not differ between patients with GCB and non-GCB DLBCL subtype, although two additional studies suggest that overall survival may be inferior in patients with non-GCB (Molina, 2012, 2013; Mitrovic , 2013; n = 776; reported HRs ranged from 1.9-2; low quality). Progression-free survival (17 studies; n = 3177; moderate quality) does not differ between patients with GCB and non-GCB DLBCL subtype, although one additional study suggest that progression-free survival may be inferior in patients with non-GCB (Molina, 2012, 2013; n = 640; HR = 1.9; low quality).

2.2.2.1.2 GCB versus non-GCB/ABC: IHC (Choi)

Moderate quality evidence from 12 studies (n=1804 patients) reported overall survival does not differ between patients with GCB and non-GCB DLBCL subtype, although low quality evidence from one additional study suggest that overall survival may be inferior in patients with non-GCB (Perry, 2014 validation set; n = 215; reported HRs ranged from 2.07-2.14).

Moderate quality evidence from 9 studies (n=1396 patients) reported similar progression/event-free survival is either similar between patients with GCB and non-GCB/ABC DLBCL while low to moderate quality evidence from 3 studies (n=592 patients) reported lower progression/event free survival in patients with the non-GCB/ABC DLBCL subtype (HRs ranged from 2-2.27).

2.2.2.1.3 GCB versus non-GCB: IHC (Visco-Young)

Five studies (n=1127 patients) provided low quality evidence that overall survival is either similar between patients with GCB and non-GCB DLBCL (4 studies; n = 652) or inferior in patients with the non-GCB DLBCL subtype (1 study; n = 475; HR = 0.56). Four studies (n=1187 patients) provided low quality evidence that progression-free survival is either similar between patients with GCB and non-GCB DLBCL (3 studies; n = 475) or inferior in patients with the non-GCB DLBCL subtype (1 study; n = 712; HRs ranged from 0.59-0.63).

2.2.2.1.4 GCB versus non-GCB: IHC (other algorithms than Hans, Choi and Visco-Young)

Twelve studies (n=2051 patients) provided low-moderate quality evidence that overall survival does not differ between patients with GCB and non-GCB/ABC DLBCL.

Eight studies (n=1173 patients) provided low to moderate quality evidence that progression-free survival does not differ between patients with GCB and non-GCB/ABC DLBCL.

2.2.2.1.5 GCB versus ABC/non-GCB: GEP with/without IHC

Low to moderate quality evidence from 6 studies (n=1573 patients) reported that overall survival is similar between patients with GCB and non-GCB/ABC DLBCL while five studies (n=1768 patients) provided low to moderate quality evidence that overall survival was inferior in patients with the non-GCB/ABC DLBCL subtype (reported HRs ranged from 0.53-2.1 [these span 0 as different reference groups are used]). There was large patient overlap between these studies. Progression-free survival is either similar between patients with GCB and non-GCB/ABC DLBCL (4 studies; n = 1488; low-moderate quality) or inferior in patients with the ABC DLBCL subtype (4 studies; n = 1577; HRs ranged from 0.63-2.6 [these span 0 as different reference groups are used]; low-moderate quality).

2.2.2.1.6 MYC translocation

Seven studies (n=1821 patients) provided low to moderate quality evidence that overall survival is either similar between patients with and without *MYC* translocation while 4 studies (n=1066) provided low to moderate quality evidence that overall survival was inferior in patients with *MYC* translocation (reported HRs ranged from 1.68-4.87). Progression-free

survival (9 studies; n = 1967; low-moderate quality) does not differ between patients with and without *MYC* translocation (as assessed by FISH), although one additional study found inferior progression-free survival in patients with *MYC* translocation (Kojima, 2013; n = 100; HR = 2.717; unclear quality).

No evidence was found for the following comparisons:

- patients with *MYC* translocation versus patients with a *MYC* translocation AND a *BCL2*/T(14,18)/18q21 translocation (Double hit)
- patients with *MYC* translocation versus patients with a *MYC* translocation AND a *BCL6*/3q27 translocation (Double hit)
- patients with *MYC* translocation versus patients with a *MYC* translocation AND a *BCL2*/T(14,18)/18q21 translocation AND a *BCL6*/3q27 translocation (Triple hit)

2.2.2.1.7 BCL2 translocation

Low to moderate quality evidence from nine studies (n=2139 patients) reported no difference in overall survival and from eight studies (n=1771 patients) reported no difference in progression-free survival between patients with and without *BCL2* translocation (as assessed by FISH), although one additional study may have found inferior overall survival in patients with *BCL2* translocation (Horn, Ziepert, Bart *et al*., 2013; n = 112; unclear quality).

2.2.2.1.8 BCL6 translocation

Low to moderate quality evidence from seven studies (n=1982 patients) showed no difference in overall survival while low to moderate quality evidence from four studies (n=1247 patients) showed no difference in progression-free survival between patients with and without *BCL6* translocation (as assessed by FISH).

2.2.2.1.9 Turnaround time of the test

One study reported that the turnaround time of the GEP testing strategy employed was less than 1 day and repeated testing of up to 40 patients in parallel was possible (Rumimy, 2013; n = 141; unclear quality).

2.2.2.1.10 Health-related quality of life

No studies were identified that reported health-related quality of life.

2.2.2.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Do not use immunohistochemistry to assess the prognostic value associated with cell of origin in people with diffuse large B-cell lymphoma.** **Interpret FISH results (*MYC*, *BCL2* and *BCL6* rearrangements) in the context of other prognostic factors (particularly the person's age and International Prognostic Index [IPI]).** **Explain FISH results and their potential prognostic value to people with B-cell lymphoma.**
Relative value placed on	The GC considered overall survival (OS) to be the critical outcome

the outcomes considered	when drafting the recommendations as OS and progression free survival (PFS) are closely aligned in diffuse large B cell lymphoma (DLBCL) with only a small number of relapsing patients being cured by salvage therapy. Health related quality of life and turnaround time for the test were also important but no comparative evidence was identified for these outcomes.
Quality of the evidence	The quality of the evidence about overall and progression free survival, assessed using the NICE checklist for prognostic studies, varied from low to moderate quality. There was a high degree of overlap in the populations used by the included studies resulting in an over-estimation of population sizes for each comparison. As a result the GC decided to treat the gene expression profiling (GEP) evidence with caution. The GC noted that the evidence suggested the adverse prognostic impact of *MYC* translocations may be modified by age and IPI, and could be difficult to interpret. The GC were aware of studies looking at outcomes of people with double hit lymphomas treated with modern as well as experimental chemotherapy arms which suggested the negative impact of these abnormalities is reduced by patient age, such that younger patients may not experience the same adverse outcomes when these genetic abnormalities are present. Approximately half of the included studies did not control separately for the effect of age on test results, which may have confounded the results.
Trade off between clinical benefits and harms	A strong recommendation was made not to use immunohistochemistry to assess the prognostic value associated with cell of origin in people with DLBCL on the basis of a large body of moderate quality evidence showing overall and progression free survival did not consistently differ between GCB and non-GCB or ABC subtypes identified using immunohistochemistry. The GC concluded that the survival difference seen in GEP-based studies between ABC and GCB groups is not consistently replicated in immunohistochemistry studies. The GC also considered, based on their clinical experience, that immunohistochemical tests are associated with insufficient reliability and reproducibility, which limits its use as a biomarker. The GC were unable to make any recommendations for GEP because although this is a highly effective technique with consistent results across the major studies the technology and analytical methods are rapidly changing at the present time. The GC noted that although the various systems worked in research settings they were not yet robust enough to be used in routine practice. Based on their clinical experience, the GC decided to recommend that results from FISH should be an integral part of patient information and should be interpreted in the context of other prognostic factors specifically age and IPI because the adverse prognostic effect of *MYC* rearrangements is much smaller in younger patients with lower IPI compared to older patients and patients with high IPI. Overall the GC considered the benefits to these recommendations are improved diagnostic accuracy and prognostic stratification, which will, in turn, improve the patient outcomes and experience.

	The GC identified no additional associated harms because the recommendations refer to further analyses conducted on samples already taken from the patient.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The recommendation will increase the number of FISH tests performed. Although this will be counteracted by some reduction in the use of immunocytochemistry there is likely to be a net increase in cost overall. However, the GC thought that this increased cost would be justified by an improvement in diagnostic accuracy and prognostic stratification, which should also lead to improvements in patient outcomes making the recommendations potentially cost effective.
Other considerations	The GC acknowledged these recommendations will require a more systematic approach to the investigation of DLBCL to be implemented in all centres. The extent of change will vary according to current practice.

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3 Staging

3.1 Role of PET-CT in staging

The observation that many lymphomas are fluorodeoxyglucose (FDG)-avid has led to significant interest in the technique of FDG-PET scanning being applied to stage patients with lymphoma. Functional imaging with this technique has the potential to identify disease sites even when there is minimal or no anatomical distortion of tissues. Stage is an important factor in many prognostic indices and may affect treatment decisions, so an accurate assessment of stage is an important aspect of patient care.

3.1.1 Staging using FDG-PET-CT

Pre-treatment staging defines disease extent enabling appropriate therapy. The Ann Arbor staging system was originally developed to define patients who may be candidates for radiation therapy from those who would benefit from systemic treatment. Originally relying on physical examination and bone marrow assessment, the system has evolved over the last 40 years to include anatomical computed tomography (CT), which is currently routinely used for baseline staging in lymphoma. CT relies on lesion size however, and numerous studies demonstrate that metabolic imaging with positron emission tomography (PET-CT) is more accurate than CT for detecting sites of disease involvement in a number of lymphoma histological subtypes. Discordance between PET-CT and CT occurs in a proportion of patients at staging, predominantly in favour of PET-CT (with more lesions being detected); however, in most patients stage is not usually changed and treatment is altered in an even smaller proportion. There is currently no evidence for a change in patient outcome as a result of staging PET-CT data. It should be noted that PET only scanners are no longer manufactured and all radiology departments in the UK now use PET-CT.

Most lymphomas are 18F-Fluorodeoxyglucose (FDG) avid, including high grade aggressive disease such as diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma and aggressive T-cell lymphomas, as well as some low grade lymphomas such as follicular lymphoma (FL). Mantle cell lymphoma (MCL) and mucosal associated lymphoid tissue (MALT) lymphoma demonstrate more variable levels of FDG uptake with false negative PET findings in various anatomical sites (e.g. diffuse gastrointestinal tract infiltration). PET-FDG is not reliable for differentiating FL from high grade lymphoma, because FL also demonstrates high PET FDG activity levels.

Clinical question: What is the staging value of pre-treatment functional imaging with PET-CT compared with other initial assessments for people with different subtypes of non-Hodgkin's lymphoma?

3.1.1.1 Clinical evidence (see section 3.1.1 in Appendix G)

The evidence included 27 cross-sectional studies (21 using retrospectively collected data) of FDG-PET-CT for staging and 16 cohort studies (seven prospective) reporting the use of both pre and post treatment FDG-PET-CT.

3.1.1.1.1 FDG-PET-CT and bone marrow biopsy for the detection of bone marrow involvement (BMI)

Moderate quality evidence from 14 studies including 1737 patients suggests FDG-PET-CT has a sensitivity of 79.5% (95% CI 69.8% to 86.6%) and a specificity of 96% (95%CI 93.1% to 97.7%) for the detection of bone marrow involvement in patients with newly diagnosed DLBCL. If prevalence of BMI is assumed to be 15% then FDG-PET-CT has a positive

predictive value of 80% and a negative predictive value of 96% for bone marrow involvement.

Moderate quality evidence from 12 studies including 1603 patients suggests bone marrow biopsy of the iliac crest has a sensitivity of 55.8% (95%CI 43.2% to 67.7%) and a specificity of 100% for the detection of bone marrow involvement in patients with newly diagnosed DLBCL. If prevalence of BMI is assumed to be 15% then bone marrow biopsy has a positive predictive value of 100% and a negative predictive value of 92% for bone marrow involvement.

3.1.1.1.2 FDG-PET-CT for the detection of lymph node involvement

Three studies including 289 patients (Morimoto *et al* 2008; Pinilla *et al* 2010; Papajik *et al* 2010) provided low quality evidence on the sensitivity and specificity of FDG-PET-CT for the detection of lymph node involvement in NHL. One study (Morimoto *et al*, 2008; n=66), limited to retroperitoneal and pelvic lymph nodes, reported FDG-PET-CT sensitivity ranging from 75% to 100% (PPV 60% to 98%) and specificity from 81% to 92% (NPV 71% to 100%), depending on the location of the lymph node. Pinilla *et al* (2010) and Papajik *et al* (2010) reported FDG-PET-CT diagnostic accuracy for any lymph nodal involvement, sensitivity ranged from 97% to 100% with specificity 94% to 96%.

3.1.1.1.3 FDG-PET-CT for the detection of extranodal organ involvement

Two studies including 223 patients (Papajik *et al* 2011; Pinilla *et al* 2010) provided low quality evidence on the sensitivity and specificity of FDG-PET-CT for the detection of extranodal organ involvement in NHL. The sensitivity ranged from 94% to 96% and specificity from 81% to 92%, but insufficient detail was provided to calculate predictive values.

3.1.1.1.4 FDG-PET-CT and change in stage and treatment

FDG-PET-CT changed the allocated stage of patients with localised follicular lymphoma to stage III/IV in most cases. 5/10 (50%) of patients with stage I-II follicular lymphoma in Le Dortz *et al* (2010) were upstaged to stage III or IV and 15/24 (63%) in Luminari *et al* (2013). Although the impact of this change on treatment was not reported it could have implications for the use of limited-field radiotherapy in this population.

Staging with FDG-PET-CT increased the number of patients with stage IV DLBCL by as much as 25% when compared to staging using bone marrow biopsy (Khan *et al* 2013; Pelosi *et al* 2010) but it was not reported whether treatment was also changed.

Raanani *et al* (2005) reported that compared to CT-scan stage, disease was upstaged by FDG-PET-CT in 31% and down staged in 1% in a cohort of 68 patients with NHL. The suggested treatment strategy (based on CT scan) was changed following FDG-PET-CT in 17/68 patients (25%). Papajik *et al* (2011) reported that treatment strategy (based on CT-scan stage) was changed following FDG-PET-CT in 3/122 patients (2%).

Use of pretreatment FDG-PET-CT to evaluate end of treatment response Sixteen studies observational did baseline FDG-PET-CT as well as interim or end of treatment FDG-PET-CT. Although some used baseline FDG-PET-CT to evaluate the quality of interim treatment response, none reported the use of baseline FDG-PET-CT in evaluating end of treatment response

3.1.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer FDG-PET-CT imaging to confirm staging for people diagnosed with:** • **stage I diffuse large B-cell lymphoma by clinical and CT criteria** • **stage I or localised stage II follicular lymphoma if disease is thought to be encompassable within a radiotherapy field** • **stage I or II Burkitt lymphoma with other low-risk features.** **For people diagnosed with other subtypes or stages of non-Hodgkin's lymphoma not listed in the above recommendation, consider FDG-PET-CT imaging to confirm staging if the results will alter management.**
Relative value placed on the outcomes considered	Treatment change was the outcome of most importance for this topic due to its potential impact on patient outcome. Other important outcomes included diagnostic accuracy, test-related morbidity, health-related quality of life, bone marrow involvement and upstaging/down-staging. No evidence was identified about test related morbidity or health related quality of life.
Quality of the evidence	The quality of evidence was low as assessed using QUADAS-2. The main source of bias was that the reference standards used in the individual studies usually included the index tests. For example focal bone marrow involvement seen on FDG-PET-CT would often be classified as true positive in the absence of other confirmatory tests. The GC decision to recommend the use of FDG-PET-CT to confirm staging in patients with stage I diffuse large B-cell lymphoma by clinical and CT criteria, stage I/II follicular lymphoma or early stage Burkitt lymphoma, was based on the evidence. However due to the low quality of the evidence, the GC were not confident in the evidence suggesting superior sensitivity of FDG-PET-CT and chose not to offer routine staging in all patients in NHL but to consider this where the results would change management.
Trade off between clinical benefits and harms	The GC thought the recommendations would result in fewer patients with false positive results on staging which could lead to unnecessary treatment or further tests. The GC made different recommendations for subtypes and stages of NHL based on their consensus about the impact of FDG-PET-CT staging on the management of patients in these subgroups. The GC thought that while FDG-PET-CT could improve the accuracy of staging in general, it would be particularly useful for staging I/II follicular lymphoma and early stage Burkitt lymphoma due to the impact it would have on therapy. As a result of the recommendations such patients will receive more appropriate treatment (for example localised radiotherapy). The evidence indicated that patients with apparently localised follicular lymphoma were often upstaged to stage III or IV following FDG-PET-CT. There was little published evidence that a baseline FDG-PET-CT contributed to the interpretation of the end of treatment FDG-PET-CT for people with NHL or influences management decisions. For this reason the GC made a research recommendation. The GC also acknowleded the body of clinical opinion and

	international guidelines that baseline FDG-PET-CT has a role for end of treatment FDG-PET-CT response assessment and in dectecting extradnodal sites during staging. The GC therefore made a recommendation to consider FDG-PET-CT to confirm staging if the results would alter managemement. The potential harms considered by the GC were the side-effects of addtional scans, and this was therefore reflected in the recommendation to consider FDG-PET-CT only where it could change the management decision. The GC thought that the ability to make more appropriate management decisions outweighed the harms which would be experienced by a small proportion of patients
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. Overall, the GC estimated that there should be no change in the number of FDG- PET-CT scans performed as the recommendations reinforce clinical practice. In cost-effectiveness terms, the GC thought that the high cost of FDG PET-CT scans (relative to other investigations) was justified by the more appropriate management decisions that could be made based on improved staging accuracy. The GC expected that there would be QALY gains and cost offsets associated with making better management decisions. For example, upstaging a patient to a more intensive treatment following a FDG PET-CT scan should lead to improved clinical outcomes (PFS, OS) and could reduce the number of treatment lines that a patient requires. The GC thought that such QALY gains and cost offsets should be substantial enough to make the use of FDG PET-CT cost-effective in cost per QALY terms.
Other considerations	The GC did not make recommendations on CT as it is a routine and established test used in UK haematology and lymphoma units for staging and for assessment of interim and end of treatment response. The GC noted, however, that the use of FDG-PET-CT in this context is variable across the UK and made the recommendations due to the need for guidance on the use of FDG-PET-CT for staging, interim response assessment and end of treatment response.
Research Recommendation	**In people with diffuse large B-cell lymphoma stage II or above, does a baseline FDG-PET-CT scan have any advantages over a baseline CT scan in the correct interpretation of the end-of-treatment FDG-PET-CT scan?**
Why is this important	A number of consensus-based guidelines and a body of clinical opinion advocate baseline FDG-PET-CT imaging as being important for interpreting end-of-treatment response using FDG-PET-CT, although there is little published evidence for this. Baseline FDG-PET-CT is also considered to have an important contribution 'over and above' that of contrast-enhanced diagnostic CT in assigning the International Prognostic Index (IPI), in terms of identifying disease stage and number of extranodal sites involved (influencing the decision to offer central nervous system prophylaxis). A prospective trial is needed to determine whether baseline FDG-PET-CT is needed to interpret end-of-treatment FDG-PET-CT and its role in assigning IPI. People with newly histologically diagnosed diffuse large B-cell lymphoma would have baseline contrast-enhanced CT, baseline FDG-PET-CT and end-of-treatment FDG-PET-CT imaging. Readers would need to be trained in both imaging techniques and be experienced members

	of lymphoma multidisciplinary teams. The reference standard would be histological confirmation of any positive or equivocal end-of-treatment FDG-PET-CT findings, or follow-up if there is a negative end-of-treatment scan.

3.1.2 Assessing response to treatment using FDG-PET-CT

Only a proportion of patients with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) are cured with a rituximab-CHOP-like regimen. A prolonged progression free survival (PFS) is achieved only in a proportion of treatment resistant or relapsed patients following salvage therapy (high-dose therapy followed by autologous stem cell transplantation). A tool able to reliably predict an unfavourable outcome early in the management of these patients may lead to risk-adapted change in therapy.

Anatomical Computed Tomography (CT) is conventionally used for interim response evaluation, assessing changes in lesion size. Tumour volume reduction may require time, with metabolic changes on Positron Emission Tomography (PET-CT) preceding anatomical volume changes. In DLBCL rapid reduction in FDG (Fluorodeoxyglucose) uptake during chemotherapy with a negative interim PET-CT scan seems to predict a favourable outcome. In the rituximab era, the positive predictive value (the ability of a positive PET scan to predict persistent disease or future relapse) is limited due to false positive uptake.

The current evidence base in this area is largely limited to DLBCL, as there was very limited evidence or current clinical application in other NHL subtypes.

Clinical question: What is the prognostic value of an interim assessment using functional imaging with PET-CT during the treatment of diffuse large B-cell non-Hodgkin's lymphoma?

3.1.2.1 Clinical evidence (see section 3.1.2 in Appendix G)

Moderate quality evidence came from seventeen cohort studies including 2326 patients compared survival outcomes according to FDG-PET-CT scan during RCHOP or RCHOP-like chemotherapy for DLBCL. The interim FDG-PET-CT was typically done following cycle 2 and across studies the mean proportion with a positive interim FDG-PET-CT scan was 35% (range 20% to 60%). Survival outcomes were consistently poorer in those with positive interim FDG-PET-CT. Progression free survival at three years was between 18% and 78% (median 32%) lower in patients with positive interim FDG-PET-CT. Overall survival at three years was between 0% and 48% (median 26%) lower and event free survival between 22% and 59% (median 41%) lower in those with positive interim FDG-PET-CT.

In multivariate analysis (taking other prognostic variables such as IPI and its components and post treatment FDG-PET-CT into account) interim FDG-PET-CT (negative versus positive) was not always an independent prognostic factor for outcome. In four studies reporting multivariate analyses of overall survival in patients with DLBCL (Cox *et al* 2012, Lanic *et al* 2011, Mamot *et al* 2015 and Mylam 2014), interim FDG-PET-CT (negative versus positive) was a significant independent prognostic factor for survival in all studies except for Mamot *et al* (2015).

There was uncertainty about the usefulness of interim FDG-PET-CT as an independent predictor of progression free survival (Cox *et al*, 2012; Lanic *et al*, 2011; Mylam *et al*, 2014, Pregno *et al* 2012) and event free survival (Carr *et al*, 2012; Mamot *et al* 2015 and Gonzalez-Barca *et al* 2013) when other prognostic variables such as interim CT and post-treatment FDG-PET-CT are taken into account.

3.1.2.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Do not routinely offer FDG-PET-CT imaging for interim assessment during treatment for diffuse large B-cell lymphoma.**
Relative value placed on the outcomes considered	The GC considered progression free survival (PFS) and treatment change the critical outcomes in drafting this recommendation.
Quality of the evidence	The quality of the evidence was moderate as assessed using NICE checklists for prognostic studies. This was because some studies had not controlled for the effect of potential confounders when looking at the prognostic utility of interim FDG-PET-CT.
Trade off between clinical benefits and harms	The evidence concerned the prognostic utility of interim FDG-PET-CT rather than its direct impact on patient outcomes. Although the evidence showed that interim FDG-PET-CT results did predict survival, a number of studies showed that the end-of-treatment scan was a better predictor (see following section) and that some patients with positive iterim scans would have negative end-of treatment scans. It was the consensus of the GC that the recommendation would stop inappropriate therapy changes and reduce radiation exposure and discomfort from FDG-PET-CT. No harms associated with the recommendation were identified. The GC thought that patients who would benefit from more intensive treatment would be identified on their post-treatment FDG-PET-CT scan.
Trade off between net health benefits and resource use	No health economic evidence was identified for this topic and no health economic model was built. The GC estimated that, as a result of this recommendation, there should be fewer FDG-PET-CT scans. Fewer patients would require intensification in therapy, because some patients with positive interim FDG-PET-CT scans have negative post-treatment scans.
Other considerations	The GC thought the recommendations would generate a moderate change in practice because although some centres will need to stop interim FDG-PET-CT scanning, most centres have already stopped. The GC acknowledged that interim FDG-PET-CT may be useful in a small number of patients to investigate clinical concerns. For this reason the recommendation was worded in such a way as to allow interim scans such patients.

3.1.3 End-of-treatment assessment using FDG-PET-CT

Achieving complete remission after first-line systemic therapy is important in high-grade non-Hodgkin lymphoma (NHL) patients, as this usually leads to a longer progression-free survival (PFS), whereas incomplete response is usually associated with poorer patient outcomes. Computed Tomography (CT) is usually used for response assessment in patients at treatment completion. However, in the common situation of a mass remaining at the end of

treatment, anatomical CT imaging cannot accurately discriminate residual active lymphoma from either necrosis or fibrosis. Defining the true nature of the residual mass is important, enabling consolidation treatment in patients with remaining active disease, and avoiding unnecessary further therapy or treatment related morbidity in patients in complete remission. The positive predictive value (PPV) of CT (the ability of a positive CT scan to predict persistent disease or future relapse) is low.

In contrast, functional imaging using Positron Emission Tomography (FDG-PET-CT) provides metabolic information and is more accurate than anatomical CT alone in this setting, due to its superiority to CT at distinguishing viable remaining lymphoma from fibrosis in residual mass (es). In general, the negative predictive value (NPV) of PET (the ability of a negative PET scan to exclude persistent disease or future relapse) across studies including high-grade NHL such as diffuse large B-cell NHL is high. The false-negative rate with FDG-PET is mostly related to its inability to detect microscopic disease which results in future relapse. The PPV of FDG-PET-CT in high-grade NHL is lower and more variable, however superior to CT. The lower PPV is due to the non-specific nature of the PET tracer 18F-Fluorodeoxyglucose (FDG), taken up in tissues affected by inflammation, which can occur due to immunochemotherapy.

Clinical question: What is the prognostic value of functional imaging with PET-CT performed after the various types of treatment for non-Hodgkin's lymphoma are completed?

3.1.3.1 Clinical evidence (see section 3.1.3 in Appendix G)

Moderate quality evidence about the post treatment FDG-PET-CT scan results and outcomes came from ten retrospective cohort studies including 915 patients. Five concerned DLBCL (Abo-Sheisha *et al* 2014; Mylam *et al* 2014; Gonzalez-Barca *et al* 2013; Pregno *et al* 2012; Cashen *et al*, 2011) , three follicular lymphoma (Trotman *et al*, 2014; Tychyj-Pinel, 2014; Le Dortz *et al*, 2010) and one each mantle cell (Mato, 2012) and primary mediastinal B-cell lymphoma (Martelli *et al*, 2014).

The usefulness of post treatment FDG-PET-CT as a predictor of outcome was examined in multivariate analyses of survival (Cox et al, 2012; Mylam et al, 2014 and Mato et al 2012), progression free survival (Cox et al, 2012; Mylam et al, 2014, Pregno et al 2012 and Mato et al 2012) and event free survival (Carr et al, 2012 and Gonzalez-Barca et al 2013). In all of the DLBCL studies (Carr et al, 2012; Cox et al, 2012; Gonzalez-Barca et al 2013; Pregno et al 2012 and Mylam et al, 2014) post-treatment FDG-PET-CT was an independent prognostic factor for each outcome survival examined. In Mato et al (2012) post-treatment FDG-PET-CT was an independent prognostic factor for progression-free survival but not for overall survival in patients with Mantle cell lymphoma.

Evidence from two retrospective studies including 167 patients (The PRIMA study [Trotman et al, 2010 and Tychyj-Pinel et al, 2014] and Le Dortz et al, 2010) suggests that FDG-PET-CT post-induction therapy predicts progression free survival and overall survival in patients with follicular lymphoma. Patients with positive FDG-PET-CT (interpreted by local physicians) following induction therapy had progression free survival of 33% at 3.5 years compared with 71% for those with negative FDG-PET-CT (Trotman et al 2010). Overall survival at 3.5 years was 79% versus 97% for patients with positive versus negative post-induction FDG-PET-CT respectively (Trotman et al 2010). Subsequent analysis of the PRIMA FDG-PET-CT data by Tychyj-Pinel et al (2014) suggests that the difference is less clear when FDG-PET-CT scans are reviewed centrally using standardised criteria – 3 year progression free survival was 41% versus 59% for FDG-PET-CT positive and negative patients in this analysis (HR 1.9 [95% C.I. 0.8 to 4.6]).

3.1.3.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer FDG-PET-CT imaging to assess response at completion of planned treatment for people with:** • **diffuse large B-cell lymphoma** • **Burkitt lymphoma.** **For people with other subtypes of non-Hodgkin's lymphoma not listed in the above recommendation, do not routinely offer FDG-PET-CT imaging to assess response at completion of planned treatment unless the results will alter management.** **Consider FDG-PET-CT imaging to assess response to treatment before autologous stem cell transplantation for people with high-grade non-Hodgkin's lymphoma.**
Relative value placed on the outcomes considered	The GC considered progression free survival (PFS) and treatment management change to be the critical outcomes for this topic. Health related quality of life (HRQL) was also considered though no evidence was identified
Quality of the evidence	The quality of the evidence was moderate as assessed using NICE checklists for prognostic studies. This was because some studies had not controlled for the effect of potential confounders when looking at the prognostic utility of end-of-treatment FDG-PET-CT.
Trade off between clinical benefits and harms	The GC considered the benefit of the recommendations to be the accurate identification of patients who may require closer follow-up or more intensive treatment leading to improved survival outcomes. Similarly those not requiring more intensive treatment would avoid the harms of over-treatment. The GC made recommendations according to subtype of NHL based on their consensus about the impact of FDG-PET-CT staging on the management of these patients. Their consensus view was that FDG-PET-CT at the completion of planned treatment would usually inform further treatment decisions for patients with DLBCL or Burkitt lymphoma but was not routinely useful for those with follicular lymphoma, mantle cell lymphoma or MALT lymphoma. The GC noted that residual masses are sometimes observed on completion of treatment CT scans in some patients with DLBCL or Burkitt lymphoma. It is not possible on CT alone to assess whether these masses are inactive treated tissue (fibrotic residua) or whether active lymphoma is still present. The ability of FDG-PET-CT to visualise metabolic activity in patients with active DLBCL or Burkitt lymphoma means it is useful in differentiating fibrotic residua from remaining active disease. It was the GC consensus that offering patients with remaining active disease further radiotherapy or systemic treatment should improve their outcome, whereas those who are FDG-PET-CT negative can be

	spared such potentially toxic treatment. Although evidence suggested that post-induction FDG-PET-CT is predictive of outcome in patients with follicular lymphoma the GC decided to recommend that FDG-PET-CT should not be rountinely offered to this group of patients unless the results will alter management. The GC considered the initial results of the PRIMA study (which this evidence was based on), were biased due to its retrospective nature and the reliance on the local physician's interpretation of the nuclear medicine report. The GC noted there is uncertainty about whether additional treatment should be given according to results of post-induction FDG-PET-CT with ongoing trials in this area. The GC thought that much of this patient group would have bone marrow infiltration by follicular lymphoma (stage IV disease) and questioned the specificity of FDG-PET-CT for the detection of bone marrow disease. Currently standard staging and response assessment in this patient group comprises CT, bone marrow aspirate and trephine biopsy and the GC agreed there was insufficient evidence to suggest that FDG-PET-CT would be of additional benefit to this standard workup. The GC acknowledged that there could be increased radiation exposure for patients. There is also the potential for false positive results which may lead to over-treatment in some patients as well as anxiety. Further diagnostic tests may also be needed to investigate a positive FDG-PET-CT. The GC considered that although there was a risk of over-treatment in patients who have a false positive result, this would affect a minority of patients and this risk was outweighed by the fact that FDG-PET-CT assessment would lead to an overall increase in the number of patients treated appropriately.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The GC considered that, overall there would be an increase in the number of FDG-PET-CT scans as a result of these recommendations. However, while this would increase upfront costs, there are potential cost savings downstream associated with a reduction in over- and under-treatment. Overall it was thought that the recommendations would most likely lead to a net cost increase. However, it was expected that the additional costs would be justified by the effectiveness improvements expected with more appropriate treatment decisions. Thus, the recommendations were considered likely to be cost-effective in cost per QALY terms.
Other considerations	The GC considered the recommendations would lead to a moderate change in practice as current practice is variable so many centres will need to start doing end of treatment FDG-PET-CT scans.

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4 Management

4.1 Follicular lymphoma

Follicular lymphoma is a relatively common lymphoma subtype that typically has a chronic, relapsing and remitting disease course with a long overall survival. Significant heterogeneity in disease behaviour exists, however, and there is risk of transformation to more aggressive disease subtypes. Molecular testing has already added to the understanding of disease behaviour and is highly likely to complement or supplant existing clinical prognostic scoring systems.

4.1.1 First line treatment for early stage

In stage IA follicular lymphoma a large proportion of patients can be cured by local radiotherapy and in some cases after complete excision observation only may be considered.

In stage IIA disease there is considerable controversy as to most appropriate therapy varying from watchful waiting to radiotherapy or immunochemotherapy.

This topic focuses on the most effective first line treatment for stage IIA disease in the PET era. Relatively low dose radiotherapy delivering 24Gy is effective in follicular lymphoma and if the disease is truly localised and encompassed in the radiation field then cure is possible. Acute toxicity is low. There are limited data on long term effects. Most cases will involve irradiation to the neck, axilla or supraclavicular fossa. Localised mediastinal or abdominopelvic presentations of follicular lymphoma are rare and so the more serious long term effects of radiotherapy such as cardiac deaths and second malignancies of the breast and lung are not major concerns.

Clinical question: What is the most effective first-line treatment for people with stage IIA follicular lymphoma?

4.1.1.1 Clinical evidence (see section 4.1.1 in Appendix G)

The evidence included ten studies: two randomised controlled trials, four retrospective cohort studies and four case series.

4.1.1.1.1 Radiotherapy alone

Very low quality evidence of overall survival rates came from three studies (two retrospective case series and one prospective cohort study: MacManus *et al*. 1996; Sack *et al*. 1998; Wilder *et al*. 2001) including 189 patients. These studies reported overall survival rates of 86% (5-8 years), 65% (10 years) and 43% (15 years) in patients with stage I (<50% of total sample size) and II follicular lymphoma. MacManus *et al*. (1996) and Sack *et al*. (1998) also reported relapse free survival rates between 69% and 88.8%. Recurrence rate at 5 years was 31% and at 7 years was 44% (Sack *et al*. 1998) with a 45% freedom from relapse rate at 10 years (MacManus *et al*. 1996). Wilder *et al*. (2001) reported a 15 year progression free survival rate of 26% and a cancer specific survival rate of 54%.

4.1.1.1.2 Radiotherapy versus no radiotherapy

One observational study (Pugh *et al*. 2010) including 2140 patients provided very low quality evidence of an overall survival benefit (higher disease specific survival: Hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.65-0.94 p=0.01; higher overall survival rates: HR 0.78, 95% CI 0.65-0.94 p=0.01) in 505 patients with stage II follicular lymphoma treated with

radiotherapy (external beam radiation therapy) compared to 1,635 patients treated with no radiotherapy (no information provided on type of treatments used in the comparison group).

4.1.1.1.3 Radiotherapy versus radiotherapy and chemotherapy

One observational study (Besa *et al*. 1995) provided very low quality evidence of a survival benefit (higher rate of freedom from relapse, p=0.008 [15 year rate]) in 80 patients with stage I (~30%) and II follicular lymphoma treated with radiotherapy and chemotherapy compared to 45 patients treated with radiotherapy alone. Overall survival (15 years) did not significantly differ according to treatment group (63% in the chemotherapy and radiotherapy group compared to 53% in the radiotherapy group) but no statistical analyses were presented to assess significant differences in relapse rates (0 at 7.5 years in the chemotherapy and radiotherapy group compared to 1 at beyond 15 years in the radiotherapy group) or the incidence of acute leukaemia (5 cases in the chemotherapy and radiotherapy group compared to 6 in the radiotherapy group).

4.1.1.1.4 Radiotherapy and chemotherapy alone

Very low quality evidence came from one non-comparative study (Seymour *et al*. 2003) which reported 10 year overall survival and freedom from treatment failure rates of 87% and 70% in 47 stage II follicular lymphoma patients treated with chemotherapy and involved field radiotherapy.

4.1.1.1.5 Radiotherapy versus rituximab versus radiotherapy and rituximab

One observational study (Mondello *et al*. 2014) provided very low quality evidence of lower relapse rates, higher progression free survival rates and longer time to next treatment in patients with stage I (47%) and II treated with either rituximab (n=38) or rituximab and radiotherapy (n=34) compared to patients treated with radiotherapy alone (n=36). Complete response rates were not significantly different according to the three treatment groups.

4.1.1.1.6 Chemotherapy versus chemotherapy and rituximab

Very low quality evidence came from one randomised controlled trial (RCT: Bachy *et al*. 2013) which compared rituximab plus CHVP to CHVP alone in 39 patients with stage II follicular lymphoma. This trial reported uncertainty about the relative effectiveness of the treatments in terms of event free survival (HR: 0.855 95% CI: 0.330-2.217; where HR < 1 favours chemo+rituximab).

4.1.1.1.7 Chemotherapy versus watch and wait

One randomised controlled trial (RCT: Ardeshna *et al*. 2014) provided low quality evidence of uncertainty about the relative median time to start of new treatment in 19 patients with stage IIA follicular lymphoma treated with rituximab compared to 17 patients with stage IIA follicular lymphoma who were randomised to a watch and wait programme (HR: 0.55 95%CI: 0.18-1.63).

4.1.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer local radiotherapy as first-line treatment to people with localised stage IIA follicular lymphoma.**

	Consider 'watch and wait' (observation without therapy) as first-line treatment for people with stage IIA follicular lymphoma who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable. **Offer the same treatments that might be offered to people with advanced-stage (stages III and IV) symptomatic follicular lymphoma to people with stage IIA follicular lymphoma who are symptomatic and for whom radiotherapy is not suitable.** **Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. [This recommendation is from Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 226).]**
Relative value placed on the outcomes considered	The critical outcomes for this topic were disease specific survival and overall survival. Other important outcomes of interest included progression free survival, treatment related mortality and morbidity, health related quality of life and patient preference, although no evidence was found for treatment related mortality, treatment related morbidity, health related quality of life or patient preference.
Quality of the evidence	The evidence for this topic was assessed using GRADE and ranged from very low to low quality overall. The evidence was downgraded due to imprecision (small sample sizes and low event rates), limited descriptions of methods and indirectness of populations (limited data on stage IIA). The lack of comparative studies for some of the interventions meant that non-comparative studies were also included as evidence. It was not possible to compare outcomes across studies as each study compared different interventions, thus making it difficult to summarise across the evidence base. Although there was an absence of high quality, randomised trial evidence, the GC thought that radiotherapy should be recommended strongly because it has low toxicity, potential curative benefit (indicated by a large SEER dataset showing a 9% improvement in overall survival at ten years with radiotherapy for stage II follicular lymphoma) and further trials are unlikely in this area. Evidence about 'watch and wait' from the randomised trial was of low quality due to imprecision and the GC could not make a strong recommendation about this intervention.
Trade off between clinical benefits and harms	The GC considered that there was a potential for cure with radiotherapy in a minority of patients. Although not reported in the evidence the GC acknowledge the potential harms of radiotherapy including low risk of second malignancies, and location specific toxicity, but they thought that current radiotherapy techniques were likely to help minimise this. The GC made a separate recommendation for patients whose asymptomatic disease could not be treated by a single radiotherapy volume. The GC thought that for asymptomatic disease deferring chemotherapy toxcity by using a 'watch and

	wait' approach was a reasonable option. For those with symptomatic stage IIA disease not suitable for treatment with radiotherapy the GC consensus supported a strong recommendation to offer the same treatment as for advanced stage follicular lymphoma, given that active treatment is required for symptomatic disease. The GC acknowledged that patients treated with watch and wait may experience anxiety; although the evidence about the effectiveness of watch and wait was inconclusive the GC thought that such patients would benefit from delaying or avoiding treatment toxicity.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The recommendations are likely to result in increased resources spent on radiotherapy as it will be used more while watch and wait or immediate chemotherapy will be used less. In terms of costs, radiotherapy is likely to be similar to chemotherapy (possibly slightly cheaper) but more expensive than watch and wait. However, in terms of effectiveness, radiotherapy is appears to be superior with a possibility for cure in a minority of patients. Therefore, even if the use of radiotherapy is more costly, it was thought likely to be cost-effective in cost per QALY terms.
Other considerations	The GC consider recommendations will lead to a change in practice in some centres, who use either watch and wait or standard chemotherapy for people with localised stage IIA follicular lymphoma. The recommendation for rituximab maintenance therapy as an option after first line induction therapy with rituximab in combination with chemotherapy came from NICE technology appraisal guidance 226.

4.1.2 Consolidation therapy in follicular lymphoma

Follicular lymphoma is a comparatively indolent disorder in most patients, and the majority will respond to salvage therapies. Nevertheless, conventional immuno-chemotherapy is not curative and many patients will be considered candidates for some form of transplant procedure at some point in the treatment pathway. Escalation to high dose therapy with autologous stem cell transplantation (ASCT) offers improved progression free survival in selected patients, with a significant fraction achieving longer term disease stability, which has been equated to 'functional' cure. Given the older age of patients with follicular lymphoma (median age of onset 60 years), it has also been argued that cure should not be the therapeutic goal for most patients with the disorder, as control of the disease and maintenance of quality of life may allow patients to live with their disease until other medical issues intervene.

There are, however, groups of patients that can be identified with worse overall prognoses. Such patients are often best identified according to the level and duration of response to prior therapies, and by prognostic indices at relapse or progression. When high dose consolidation and ASCT is contemplated, the question also arises as to whether allogeneic transplantation (alloHSCT) – which is generally held to offer the best chance of overall cure but at the expense of an increased risk of morbidity and mortality – should be considered, or whether this should be reserved for those relapsing after ASCT.

In most patients ASCT or alloHSCT are reserved for second or subsequent response. The published data supporting such strategies come largely from single arm studies and registry data. Comparison between the two modalities is technically difficult as patient groups being offered either modality are generally not well matched for disease characteristics, age or co-morbidities. Current practice therefore varies widely across the UK.

This is one area in which pharmaco-economic analyses may help to define future practice given the often closely balanced clinical issues. Current improvements in pharmacological therapies also complicate the picture. Whilst on the one hand they may offer improved rates of progression free survival, making transplantation strategies less appealing, this will undoubtedly come at considerable financial cost and may just delay transplantation.

Clinical question: Is autologous transplantation, allogeneic transplantation or no transplantation the most effective treatment for people with follicular lymphoma at various time points?

4.1.2.1 Clinical evidence (see section 4.1.2 in Appendix G)

4.1.2.1.1 Transplantation in previously untreated people with follicular lymphoma

Using autologous transplantation with high-dose chemotherapy may significantly improve PFS when compared to allogeneic transplantation but not when overall survival is considered in patients at first line who have responded to chemotherapy. Similarly, auto-transplantation + high dose chemotherapy showed significantly better PFS compared to rituximab + chemotherapy but this did not remain significant when overall survival is compared, in examination of a meta-analysis reported by Schaaf *et al*. (2012).

This meta-analysis of 4 randomised control trials (RCTs) evaluated high dose chemotherapy + autologous transplantation (HDCT +ASCT) compared to chemotherapy or chemo-immunotherapy. This review provided low quality evidence, from 1093/1105 evaluable people, that significantly increased progression-free survival (PFS) was seen after HDCT+ASCT compared to chemotherapy (HR=0.42, 95% CI 0.33-0.54; p=<0.00001) but no significant difference seen in overall survival (OS) (HR=0.97, 95%C) 0.76-1.24, p=0.81). No significant differences were seen in treatment related mortality (TRM), onset of secondary myeloid leukemia/myelodysplasia syndromes or solid cancers. Adverse events were seldom reported and reporting differed between trials which did not allow for meta-analysis. However, they were generally higher in people in the HDCT +ASCT arm. When HSCT +ASCT was compared to rituximab +chemotherapy; PFS remained advantageous in the HDCT +ASCT group (HR= 0.36, p=0.001); with no significant difference in OS (RR=0.88, p=0.75).

4.1.2.1.2 First transplantation after relapse

Autologous transplantation versus chemotherapy.

In their review, Schaaf *et al* (2012) reported on one trial in which 70 relapsed people were treated with HDCT + ASCT versus chemotherapy with no prior rituximab (Schouten *et al*. 2003). Schouten *et al*. (2012) provided low quality evidence of a survival advantage of HDCT +ASCT compared to chemotherapy in terms of progression-free survival (HR=0.3); 95%CI 0.15-0.61, and overall survival HR=0.4 95%CI 0.18-0.89) but no other outcomes were reported.

Autologous transplantation versus Immuno-chemotherapy.

There is limited evidence on long-term QOL outcome with one study providing evidence. That people with FL reported have lower QOL when compared to the general population.

The impact of treatment on QOL outcomes when measured by different instruments (cancer-specific versus general QOL measures) is inconsistent.

Very low quality evidence came from a cross-sectional study (Andresen *et al*. 2012) from Germany which compared the quality of life (QOL) of 124 long-term survivors after HDCT+ASCT compared to R-CHOP using the EORTC QLQ-C30 and EQ-5D. The study reported QOL differences between the two groups (HDCT+ ASCT versus R-CHOP) with significant differences seen in the social functioning scale and pain (p=0.04 and 0.01) and index score of the EQ-5D (p=0.049) in favour of HDCT +ASCT. However, for both groups, QOL scores were lower than the general population with a significant decrease in QoL for the HDCT group in four of five subcategories of the EORTC QLQ-C30 functional state (physical, role, cognitive and social functioning and six of the nine subcategories of the symptomatic state (fatigue, dyspnea, insomnia, constipation, diarrhea and financial difficulties)(p<0.05).

Autologous transplantation following rituximab treatment

One observational study compared rituximab status prior to autologous transplantion in 194 relapsed FL patients (Phipps *et al* 2015). Rituximab status was categorised as rituximab-sensitive (RS) (n= 35), rituximab- refractory (RR) (n=65) and no rituximab (noR) (n=94). This study provided very low quality evidence that 3 year PFS was better for RS patients compared to RR and no R patients (85% vs 35% vs 49%, p=0.004) and OS (97% vs. 63% 73.4%, p=0.03). On multivariate analysis, only RS was associated with improved OS and PS (HR 0.24, p=0.01 and HR 0.35, p=0.006) respectively.

Autologous transplantation versus allogeneic transplantation (mixed conditioning regimens)

The evidence comparing autologous and allogeneic transplantation, from studies where patients received a variety of different conditioning regimens is inconsistent.

Three studies provided very low quality evidence about the use of ASCT versus alloHSCT with mixed conditioning regimens. Evens *et al*. (2013) reported on a review of the National Comprehensive Cancer Network NHL Outcomes database in the USA. No significant difference in 3 year EFS reported in the ASCT group (n=135) vs. alloHSCT (n=49) of 57% vs 52%, p=0.14. Eighty-nine percent of people received prior rituximab-based therapy. However, statistical significant differences were reported in 3 year OS (87%vs 61%, p= <0.0001) and 100 day and 3 year non-relapse mortality (1% vs 6% and 3% vs 24%, p=<0.001) in favour of auto-transplantation In the ASCT group, 69% of deaths were due to progressive disease compared to 38% in the alloHSCT; with deaths due to second malignancy 15% vs 10% respectively.

Grauer *et al* (2009) reviewed 117 people from a single cancer centre in the USA receiving ASCT (n=81) vs alloHSCT (n=36) with rituximab therapy not reported. 5 year OS was reported as 53% vs 49% for those with relapsed or refractory disease; with higher non-relapsed mortality (NRM) in alloHSCT (25% vs 11%) with OS for all people favouring alloHSCT (67% vs 57%). 5 year PFS was higher in alloHSCT (46% vs 38%).

A retrospective cohort study of 35 people at a single USA centre transplant programme assessed outcomes following ASCT or alloHSCT of which 7% and 33% respectively received prior rituximab)(Reddy *et al* 2012). No significant difference as reported in 5 year PFS (73.3% vs 43%) or rate of relapse (26.6% vs 22.5%), but significant differences in 5 year OS (91.7 vs 53.9%, P=0.01) in favour of auto-transplantation. Non-relapse mortality was 42% in the alloHSCT group and 0% in the ASCT group. No adverse events were reported.

BEAM-Conditioning Transplantation

There is limited evidence on the use of the BEAM- conditioning (BiCNU, etoposide, ara-C and melphalan) regimen in auto and allogeneic transplantation.

One study (Noriega *et al* 2014) was graded as very low quality in which a retrospective analysis of outcomes for 171 people (of which 65% received prior rituximab) receiving BEAM-auto hematopoietic stem cell transplantation or BEAM-alemtuzumab allogeneic hematopoietic stem cell transplantation was undertaken in 2 UK centres. The median follow up was 6.5 (0.4 -18.2 years). A separate analysis of 59 and 38 people with non-transformed FL was reported. A 10 year cumulative relapse rate was reported at 61.6% vs. 30.5% in ASCT vs. alloHSCT, p=0.018, with all other reported outcomes including 71 people with transformed FL.

Myeloablative allogeneic transplantation vs. autologous transplantation

There was inconsistent evidence when myeloablative allogeneic transplantation is compared to autologous transplantation.

Two studies provided very low quality evidence about ASCT versus alloHSCT where myeloablative conditioning regimens were used. Deshpande (2004) reported a US-based retrospective analysis of people receiving ASCT (n=186) or alloHSCT (n=18) with a conditioning regimen of cyclosphamide and TBI in 54% and 72% of people respectively with no reporting of rituximab therapy. In a median follow up of 7.8 years (range 1.7-1.92 years); the 5 year EFS was reported as 41% vs. 71%, p=0.034 in favour of myeloablative allo-transplantation; and 5 year OS as 61% vs. 76% p=0.18, again in favour of allo-transplantation

van Besien *et al*. (2003) reported on a retrospective analysis of 904 people registered with the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry, followed up for a median of 36 months for allogeneic transplantation (n=176), 49 months for purged autologous transplantation (n=131) and 41 months for unpurged allogeneic transplantation (n= 597) with no prior rituximab therapy reported. Five year overall survival was 51%, 62% and 55% for purged auto-transplantation, unpurged auto transplantation and allogeneic transplantation respectively. With regard to causes of non-relapse mortality, death was recorded in 50 (28%) , 18 (13.7%) and 45 (7.5%) of people for purged auto-transplantation, unpurged auto transplantation and allogeneic transplantation respectively; with new malignancies reported as cause of death in 5 and 9 people receiving purged and unpurged autologous transplantation and 10 cases attributed to GVHD.

Allogeneic transplantation vs. autologous transplantation (unknown conditioning regimen)

De Fontbrune (2009) reported a retrospective cohort study of 143 people which provided very low quality evidence on outcomes comparing ASCT or alloHSCT. Median follow up was 4.4 years and 4 years respectively in each group. Five year EFS and OS were reported as 46% vs. 58% and 73% vs 58% (ASCT versus alloHSCT); and after propensity score matching; 52.4% vs. 66% and 77% vs. 67% which were not statistically significant.

Klyuchinikov *et al* 2015 reported 5 year outcomes following reduced intensity conditioning allogeneic transplantationor. ASCT, in 518 patients. This study provided very low quality evidence on the probability of NRM, relapse/progression, PFS and OS was 5% vs. 26% (p<0.001); 54% vs.20% (p<0.001), 41% vs.58% (p<0.001) and 74% vs. 66% (P=0.05) in favour of alloHSCT. On multivariate analysis, ASCT was associated with reduced NRM (RR 0.21, p<0.0001) and time varying effects seen in other outcomes.

Non-myeloablative allogeneic transplantation vs. autologous transplantation

There is inconsistent and very low quality evidence about the use of non-myeloablative allo-transplantation on outcomes when compared to auto-transplantation. The role of adding rituximab to conditioning regimens prior to transplantation was assessed in one retrospective observational study from the USA (Khouri *et al* 2005) which compared autologous versus non-myeloablative allogeneic transplantation after high-dose rituximab containing conditioning regimens for chemo sensitive FL. This study included 68 people who were followed up for a median of 34 months. Three year DFS and OS were reported as 84% vs. 85% (auto versus allo) and 84% and 88% (p=0.8); with risk of progression reported as 5% and 3% respectively. In those that had previously failed auto-SCT (n=8), a 4 year DFS of 87% was reported.

A retrospective cohort study of 40 people at a single cancer centre in the USA who underwent BEAM conditioning ASCT (n=20) and alloHSCT with conditioning regimen of cyclophosphamide, fludarabine and TBI provided very low quality evidence on outcomes reported at median time of 34 months follow up (Lunning 2012). No report of prior rituximab use was given. Three year EFS and OS were reported as 60%vs 79% and 62% and 85% (not statistically significant) respectively, In people whose previous remission duration was <12 months (11/20 and 20/20); 3 year EFS was reported as 36% vs. 79%, p= <0.03).

Reduced-intensity Conditioning Allogeneic Transplantation vs. autologous transplantation

A retrospective review of 875 people in the European Bone Marrow Transplant Registry (Robinson *et al* 2013) provided low quality evidence on outcomes of people who underwent ASCT (n=726) versus alloHSCT in order to compare outcomes of reduced intensity alloHSCT with median follow up of 59 months (range 3-108 months). 53% and 61% received prior rituximab in each respective group. The NRM was significantly worse for people undergoing reduced-intensity alloHSCT, with 100 days, 1 year and 5 year NRM reported as 2%vs6%, 3%vs 17% and 5%vs 22%, p<0.001). For PFS, there was a survival benefit at 1 year PFS favouring ASCT (77%v 68%) but in 3 and 5 years this PFS benefit favoured alloHSCT 57% vs. 62% and 48% vs. 57%, all these differences statistically significant. p=<0.001,. Non-significant differences were reported for OS with 1, 3 and 5 year rates reported as 90% vs. 80%, 78% vs68% and 72% vs. 67%, (p=0.84), respectively in favour of ASCT . The number of non-relapse deaths were 37 (5%) in the ASCT group and 32 (21%) in the alloHSCT group.

Further very low quality evidence was provided by an observational study of long-term outcomes of RIC alloHSCT compared to ASCT in Grade I/II patients FL patients (Klyuchnikov *et al*, 2015). The 5 year adjusted probabilities of NRM, relapse/progression, PFS and OS of ASCT vs. alloHSCT groups were 5% vs. 26% (p<0.001); 54% vs. 20% (p<0.0001); 41% vs. 58% (p <0.001) and 74% vs. 66% (p=0.05) respectively. On multivariate analysis, ASCT was associated with reduced NRM (RR=0.21, p<0.0001) and time varying effects were seen on other outcomes.

Autologous transplantation (no comparator)

Very low quality evidence froma single centre, non–comparative study of, Jagadesh *et al*, (2014) reported that in 127 patients in whom 93% had prior exposure to rituximab, 10 year PFS and OS were 33.2% and 52.4% respectively, with age at transplant and number of prior therapies (>3 vs. 1-3) significant prognostic factors in both univariate and multivariate analysis (Higher age HR1.76, 95% CI 1.23-2.52, p=0.002) and >3 prior therapies (HR 2.58,95% CI 1.21-5.12,p=0.006). Oh *et al* 2014 reported outcomes of 180 patients following relapse of chemotherapy. Very low quality evidence from this study indicated that, in univariate analysis, 5 year OS was significantly higher in patients receiving ASCT at 1st/2nd Line compared to no ASCT and ASCT beyond second relapse (92.4% v 66.5% v62.5%,

p=<0.001). Allogeneic transplantation did not affect OS (p=0.62). In a multivariate analysis, ASCT at 1st/2nd relapse was associated with improved OS (HR=4.55, p=0.002) independent of Follicular Lymphoma International Prognostic Index (FLIPI) score 0-2 at diagnosis, no transformation and ever use or rituximab with chemotherapy or as maintenance.

An observational study of 640 patients undergoing HDT/ASCT between 1989-2007from the Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GELTAMO) registry provided very low quality evidence on outcomes with a median follow up of 12.2 years from transplantation (Ubito *et al*, 2014). The median PFS and OS were 9.4and 21.3 years with patients transplanted at first complete response achieving a significantly better PFS (68%) and OS (74%) then those transplanted at 2nd complete response, p=0.005

In another longer term follow up of outcomes with HDCT+ ASCT, Arcani *et al* (2015) report on 117 patients with relapsed/refractory follicular lymphoma. This study provided low quality evidence on the 5 year PFS and OS of patients after a median follow up of 6.7 years, with median time to relapse of 17months in 46 patients who relapsed after treatment. For the 117 patients, 5 year PFS was 54% (95% CI: 45-63%) and 5 years OS was 83% (95% CI: 74-89%). For patients who were in first relapse, the 5 year OS was 85.3% (95%CI: 74.4-91.9%) and 74% (95%CI:54.5-86./1%) for patients who underwent ASCT after 3 or more lines (p=0.05).

Allogeneic transplantation (no comparator)

A US based observational study (Khouri *et al* 2008) of 47 patients who receivedalloHSCT with non-myeloablative conditioning with fludarabine, cyclophosphamide and rituximab provided very low quality evidence on outcomes after a median follow up of 60 months after transplantation. Five year PFS and OS was 85% and 83%. The incidence of grade 2 acute GVHD was 11% and chronic and chronic extensive GVHD was 60% and 36% respectively. Seven patients died (6 due to infection), with no cases due to recurrent lymphoma. Transplantation at second relapse (including relapse following prior autologous transplantation)

Robinson *et al* (2013) provided very low quality evidence of subsequent outcomes for people who relapsed after their ASCT (n=292); with 17 (6%) receiving a second autologous transplantation and 56 (19%) proceeding to an alloHSCT. Only 1 of the 29 patients relapsing in the ASCT received a second transplant (myeloablative alloHSCT). In 56 patients receiving an alloHSCT, the 3 year NRM, disease progression, PFS and OS rates were 30%, 30%, 39% and 50% respectively.

Very low quality evidence came from a retrospective observational study (Okoroji *et al*, 2010) in a single cancer centre in the USA which reported outcomes for 50 people after receiving non-myeloablative allogeneic stem cell transplantation or conventional treatment (single agent rituximab, combination chemo-antibodies or unknown treatment), with reporting that this followed the introduction of rituximab). The median follow up was 49 (range 23-113) months for people receiving alloHSCT and 37 months (range 17-130) months for those not allo-transplanted. Four year actuarial survival was reported as 73% vs. 71%, p=0.9.

Very low quality evidence came from a retrospective analysis of 146 patients in the Germany Registry for Stem Cell Transplantation, Heinzelman *et al* (2015) which reported survival outcomes. This included 90/146 patients who received a prior ASCT (data not reported separately), with a median follow-up of 9.1 years (range 3.6-15.7 years). The estimated 1, 2, 5 and 10 year OS was 67%, 60%, 53% and 48% respectively. The EFS was estimated at 63%, 53%, 47% and 40%. Multivariate analysis suggested treatment-sensitive disease, limited chronic GvHD and TBI-based conditioning in treatment refractory patients as independent prognostic factors for OS (data not reported).

4.1.2.2 Cost-effectiveness evidence (see also Appendix A)

4.1.2.2.1 Background

To date, there is no consensus on the optimal treatment strategies for people with relapsed follicular lymphoma. As summarised in the clinical evidence review, the evidence base is of generally low quality, consisting of mostly observational studies which report contradictory results on the clinical effectiveness of the different strategies at different time points. While there is some prospectively collected (pre-rituximab) evidence to suggest that autologous stem cell transplantation (ASCT) might be superior compared to conventional chemotherapy (Schouten at al. 2003), the only prospective trial comparing allogeneic transplantation (allo-HSCT) to ASCT had to close prematurely due to insufficient patient recruitment. Furthermore, no full economic evaluations have been published that address the question of the optimal treatment strategy for people with relapsed follicular lymphoma. Thus, as well as the uncertainty around clinical effectiveness the cost-effectiveness of these strategies in the UK context is as yet unknown.

4.1.2.2.2 Aim

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

4.1.2.2.3 Existing Economic Evidence

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

4.1.2.2.4 De novo economic model

Since no current economic literature could be found to address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. An individual patient simulation model was developed using Microsoft Excel with coding in Visual Basic for Applications (VBA).

Clinical data used in model

The strongest clinical evidence to inform the economic analysis was provided by Schouten *et al*. (2003), who compared ASCT to chemotherapy after first relapse in a randomised controlled trial. We used observational data reported by Robinson *et al*. (2013) for the direct comparative data of ASCT vs. allo-HSCT. We utilised the best available evidence from the clinical review and additional literature searches to populate parameters not covered by these studies to compare the three treatment options. All data inputs underwent full validation by the GC and uncertainty was considered within the sensitivity analysis. A 20% risk increase per additional treatment line was applied to all clinical inputs where no data specific to treatment line was available.

Relapse rates

Relapse rates were converted into annual probability of relapse and, following GC advice, were staggered to reflect the curative potential of ASCT and allo-HSCT apparent in the cumulative relapse incidence curves which show a decrease in relapse rate after year one and then again after year 3 for ASCT and a marked decrease of relapse rate after year 1 for allo-HSCT (Table 8). Annual probability of relapse for allo-HSCT as a second transplant option could not be staggered as only 3-year CRI was reported. Annual probability of relapse for R-chemotherapy was calculated by applying the hazard ratio of 0.3 reported by Schouten *et al*. (2003) to the values for ASCT used in the model. While this RCT was conducted before the introduction of rituximab and the relapse rate for chemotherapy (CHOP) could be

considered too high when applied for R-CHOP, the GC was of the opinion that it was appropriate for the higher risk population that would be considered for transplantation.

Table 8: Annual probability of relapse after third-line treatment

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

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

Disease-related mortality

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

Non-cancer mortality

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

Treatment- related mortality

The high treatment-related mortality of allo-HSCT and to a lesser extent ASCT was considered a crucial parameter that could influence the potential cost-effectiveness of

transplantation strategies compared to R-chemotherapy to a significant degree. Treatment-related mortality for ASCT and allo-HSCT was extrapolated from 1-year and 3-year non-relapse mortality (NRM) rates reported by Robinson *et al*. (2013), adjusted for the appropriate non-cancer mortality for the cohort (50 years, 55% male) and converted into annual probabilities. Following the NRM curves, probability of treatment-related death was staggered with a higher rate in year 1 and lower rates in years 2 and 3 (Table 9). No treatment-related mortality was assumed beyond year 3 following transplantation.

Table 9: Annual probability of treatment-related death after third-line treatment

Comparator	P(TRD)	Source
R-chemotherapy	0.0040	vanOers *et al*. 20066
Rituximab maintenance	0.0000	vanOers *et al*. 20107
Autologous transplantation (year 1)	0.0274	Robinson *et al*. 20133
Autologous transplantation (years 2/3)	0.0074	Robinson *et al*. 20133
Allogeneic transplantation (year 1)	0.1674	Robinson *et al*. 20133
Allogeneic transplantation (years 2/3)	0.0227	Robinson *et al*. 20133
Allogeneic transplantation as second transplant†	0.1095	Robinson *et al*. 20133
†Allogeneic transplantation rates as a second transplant could not be staggered as only 3-year data was available.		

Adverse events

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

In the allo-HSCT arm, we applied a probability of grade 3/4 acute graft versus host disease (GVHD) of 12.08% based on 18 out of 149 people reported by Robinson *et al*. (2013) to have developed acute GVHD in the year of transplantation only. Additionally, an annual probability of chronic extensive GVHD of 13.69% was applied in years 2 and 3 only based on 38 of 149 affected people over 2 years reported by Robinson *et al*. (2013) and converted to annual probability.

Costs

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

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

Costs of R-chemotherapy and rituximab maintenance

Cost of second and third-line R-chemotherapy was assumed to be the cost of R-CHOP based on the outcome data being mainly reported for this regimen. The drug costs of R-CHOP and rituximab maintenance were estimated using dosages and unit costs from the British National Formulary (BNF) and the Electronic Market Information Tool (eMit). The cost associated with delivering rituximab and chemotherapy was estimated using cost codes for the delivery of chemotherapy (weighted for outpatient and daycase) from NHS reference costs 2013/14. It was assumed that granulocyte-colony stimulating factor (GCSF) would be used in 50% of patients receiving chemotherapy. The unit costs associated with GCSF agents (lenograstim or filgrastim, including biosimilars) were sourced from the BNF as unit costs were not available from eMIT. It was assumed that GCSFs would be administered for seven days based on guidelines for the use of GCSF from St Luke's Cancer Alliance at a cost of £414.10 per patient.

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

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

Costs of transplantation

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

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

The costs associated with delivering chemotherapy were sourced from NHS Reference costs. Based on the advice of the guideline committee, it was further assumed that R-ESHAP or R-DHAP would be delivered in an inpatient setting whereas R-GDP or R-ICE would be delivered in an outpatient setting. The costs associated with delivering outpatient chemotherapy were sourced from NHS Reference costs (using the same proportions as those used in the sections above). Following NHS Reference costs methodology the cost of inpatient chemotherapy was estimated using bed day costs (as there is no specific code for inpatient chemotherapy delivery). Therefore, inpatient chemotherapy costs were estimated using the average cost of an excess bed day in patients with malignant Lymphoma, including Hodgkin's and non-Hodgkin's (£348.88) multiplied by the number of days where chemotherapy is delivered. The unit costs of drugs were sourced from Emit. Where eMIT costs were not available, BNF costs were used.

The total cost for three cycles of R-ESHAP, R-DHAP, R-GDP and R-ICE was estimated to be £11,380.19, £9,161.62, £7,763.82 and £9,338.43, respectively. As above, the cost of GCSF was added to the chemotherapy cost for 50% of the patients resulting in an average cost per patient of £10,032.17 for chemotherapy prior to transplant.

Cost of subsequent lines of chemotherapy

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

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

The total costs for the regimens not already specified above were estimated to be £11,932.05 for six cycles of R-CVP, £14,212.38 for six cycles of R-bendamustine, £8,366.64 for four cycles of R-GEMP, £8,102.06 for four cycles of R-FC, £7,896.05 for three cycles of R-GCVP, £11,383.98 for two cycles of R-Mini-BEAM delivered on an inpatient basis and £8,138.32 for two cycles of R-Mini-BEAM delivered as an outpatient procedure. The overall average cost of the subsequent immunotherapy regimens was estimated to be £9,996. Cost of GCSF was added to the chemotherapy costs as described above resulting in a total average cost of chemotherapy in fourth and fifth line of £10,772.34.

Costs of surveillance/follow-up

It was assumed that, at each follow-up visit, the patient would undergo a physical examination and enquiry about symptoms as well as various tests (£156.41), full blood count (£6.92), full profile- U&E, LFT, Ca (£18.85), serum IgG, IgA, IgM and electropheresis (£27.67). It was also assumed that patients would receive a CT scan if relapse/progression was suspected or to evaluate the response to treatment (e.g. to evaluate the response to rituximab at 12 months).

While there is likely to be some variation in clinical practice, the follow-up frequency reported in the BJH Guidance by McNamara *et al*. 2011 was thought to provide a good estimate of current UK practice and was therefore used as a basis in the economic model. People were assumed to receive a follow-up examination 3-monthly in year 1, 4 to 6-monthly in year 2 and 3 (equating to an average 2.47 follow-up visits per year) and annually thereafter.

Costs of adverse events

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

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

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

Cost of disease-related death

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

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

Cost of non-disease specific death

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

Cost of treatment-related death

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

Cost of palliative care

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

Health-related quality of life

The model estimates effectiveness in terms of quality-adjusted life years (QALYs) so that both the quantity and quality of life are taken into account. QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. For the purposes of this economic evaluation, the QoL data shown in Table 10 below were utilised.

Table 10: Quality of life values applied in the model

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

The model assumes that quality of life is worst in the initial treatment stage and then increases the longer the patient remains progression free. This means that people who have been progression free for more than 3 years are assumed to have a higher QoL (0.88) compared to people whose remission length is still shorter than 3 years (0.8050). Furthermore, quality of life is assumed to be generally lower in fourth and fifth line compared to second and third line. Most QoL data were sourced from an unpublished Oxford Outcomes study (Wild *et al*. 2005) that was utilised in the NICE technology appraisal for rituximab in the first-line treatment of stage III-IV follicular lymphoma. Further details of the study were subsequently published in the accompanying technology assessment report by ScHARR. For QoL beyond fourth line, we followed the approach used by Prica *et al*. 2015 who assumed a deterioration of QoL in subsequent treatment lines and based utility values beyond second line on a cost-effectiveness analysis performed by Fagnoni *et al*. 200916 which was using data from the GOELAMS 072 study.

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

The model applies utility decrements of 0.075 for R-chemotherapy and 0.1 for transplants as well as 0.018 for adverse events, 0.05 for grade 3/4 acute GVHD and 0.1 for chronic extensive GVHD.

Base case results

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

The base case results of the analysis are presented in Tables 11 and 12 below. It can be seen that, in comparison to R-chemotherapy, both autologous and allogeneic transplantation were found to be cost-effective with ICERs of £4,814 and £12,246 per QALY gained, respectively. Using dominance rank to ascertain the optimal strategy overall, it can be seen that autologous transplantation is the most cost-effective strategy. Allogeneic transplantation was found to be slightly less effective with a substantially increased cost which means it is dominated by autologous transplantation as a first transplant option in second and third line.

Table 11: Base case cost-effectiveness results against common baseline (R-chemotherapy)

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

Table 12: Base case cost-effectiveness results using dominance rank

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

Deterministic sensitivity analysis

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This analysis is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the one-way sensitivity analysis are shown in the Table 13 below.

Table 13: One-way sensitivity analysis results

Parameter change	Optimal strategy
Number of R-CHOP cycles = 4	ASCT
Number of R-CHOP cycles = 8	ASCT
R-chemotherapy is R-CVP	ASCT
R-chemotherapy is R-bendamustine	ASCT
Chemotherapy before transplant is R-CHOP	ASCT
NHS reference costs for transplantations	ASCT
No utility increase with increasing remission length	ASCT
No utility decrease with subsequent treatment lines	ASCT
No decrements assumed for treatments	ASCT
Double decrements assumed for treatments	ASCT
No decrements assumed for adverse events	ASCT
Double decrements assumed for adverse events	ASCT
Lower hazard ratio (0.15) for relapse rate of R-chemotherapy (79.5%)	ASCT
Upper hazard ratio (0.61) for relapse rate of R-chemotherapy (19.6%)	ASCT
Relapse rates form Schouten *et al*. 2003 used for chemotherapy (41.7%) and ASCT (21.26% - not staggered) and HR from Robinson *et al*. 2013 (2.3) for allo-HSCT (6.1% - not staggered) relapse rates	Allo-HSCT
No staggering of transplantation relapse rate but use linear rate for ASCT (11.92% pa) and allo-HSCT (4.36% pa)	Allo-HSCT
Staggering of R-chemotherapy relapse rate based on ASCT using HR=0.3 (Schouten *et al*. 2003) at each stage	ASCT
Use relapse rate of second-line treatment throughout model horizon irrespective of subsequent treatments	Allo-HSCT
Assume no risk increase in subsequent treatment lines	ASCT

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

Probabilistic sensitivity analysis (PSA)

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

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using the cost-effectiveness acceptability curve (CEAC) below (Figure 4), which shows the probability of each diagnostic strategy being considered cost-effective at various thresholds on the x axis.

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

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

Summary

The base case results suggest that both ASCT and allo-HSCT are cost-effective compared to R-chemotherapy with ICERs of £4,812 and £12,244, respectively. Allo-HSCT is more expensive and less effective compared to ASCT and is therefore dominated. Sensitivity analyses confirm these results. However, allo-HSCT does emerge as the optimal strategy in scenarios where ASCT relapse rates are increased compared to allo-HSCT. The base case result was also strengthened in the probabilistic sensitivity analysis where ASCT was found to be the optimal strategy in 94.8% of runs with allo-HSCT being the optimal strategy in the remaining 5.2% of runs. It can therefore be concluded that the economic evaluation provides robust evidence that ASCT is the most cost-effective treatment strategy for people with relapsed follicular lymphoma in second and third line. Furthermore, ASCT is the most cost-

effective transplantation strategy at the point of first transplant. However, allo-HSCT can be cost-effective compared to ASCT in cases where ASCT is not expected to be successful.

Recommendations	**Offer consolidation with autologous stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial) who have not already had a transplant and who are fit enough for transplantation.** **Consider consolidation with allogeneic stem cell transplantation for people with follicular lymphoma in second or subsequent remission (complete or partial):** • **who are fit enough for transplantation and** • **for whom a suitable donor can be found and** • **when autologous stem cell transplantation has not resulted in remission or is inappropriate (for example, because stem cell harvesting is not possible).**
Relative value placed on the outcomes considered	The key outcomes for this recommendation were overall survival, progression free survival, treatment related morbidity or mortality and health-related quality of life, although health-related quality of life was not reported in the evidence.
Quality of the evidence	The quality of the evidence ranged from low to very low using GRADE. Quality was downgraded for the following main reasons: non-randomised study design, inclusion of some patients with stage IIIB disease and imprecision. There was a lack of randomised trial evidence comparing allogeneic transplantation with other treatments.
Trade-off between clinical benefits and harms	The evidence indicates that consolidation with allogeneic stem cell transplantation improves progression free and overall survival when compared to conventional chemotherapy, but with increased treatment toxicity. The GC judged that the recommendations could improve both quality of life and survival which would offset any acute and late transplantation related toxicity. The GC noted that autologous or allogeneic transplantation is never appropriate as a first line treatment (i.e. first remission) and this is why their recommendations specify second or subsequent remission. The GC noted that consolidation with autologous transplantation would not be appropriate for some patients – for example when stem cell harvesting was not possible, but these patients might still benefit from allogeneic transplantation.
Trade-off between net health benefits and resource use	No published health economic evidence was found but a de novohealth economic model was developed, which was used to inform the recommendations. The model was used to estimate the cost-effectiveness of autologous transplantation, allogeneic transplantation and R-Chemotherapy in patients with follicular lymphoma. The results of the analysis indicated that both autologous and allogeneic transplantation were cost-effective compared to R-chemotherapy. In the base case, autologous transplantation had an ICER of £4,814 per QALY compared to R-chemotherapy alone, whereas allogeneic transplantation was dominated.

	At a willingness to pay threshold of £20,000 per QALY, probabilistic sensitivity analysis indicated that autologous transplantation had a 95% probability of being cost effective compared with 5% for allogeneic transplantation and 0% for R-chemotherapy alone. The results from this model informed the recommendation to offer autologous transplantation. The recommendation to consider allogeneic transplantation where the use of autologous transplantation is not appropriate or where its use has not resulted in remission was also informed using the results of the economic model. When the use of autologous transplantation was removed from the analysis, allogeneic transplantation was found to be the most cost-effective option with an ICER of £12,246 per QALY compared to R-chemotherapy. It was anticipated that the recommendation may have a substantial resource impact through an increased use of autologous transplantation. However, as stated above, autologous transplantation is expected to be cost-effective and so this is an appropriate use of resources.
Other considerations	The GC considered that the recommendations would lead to increased autologous transplantation and may result in decreased use of allogeneic transplantation, but would eventually result in more uniform practice. The GC considered that patients with pre-existing co-morbidities are unlikely to be candidates for autologous transplantation and that this will disproportionately affect older patients. The GC therefore based their recommendations on patient fitness rather than age.

4.1.3 Treating advanced-stage asymptomatic follicular lymphoma

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

The evidence supporting this approach is based on data from the pre-rituximab era and there have been significant changes in the management of follicular lymphoma since then. In particular: immunochemotherapy achieves a higher number of responses and prolonged relapse free survival compared to chemotherapy alone; more intensive chemotherapy (CHOP) is more effective than previous approaches using oral chlorambucil or CVP; bendamustine has high activity in follicular lymphoma and may now rival CHOP as the chemotherapy agent of choice; maintenance treatment continuing for two years beyond completion of immunochemotherapy further prolongs relapse free survival; a recent large trial of watch and wait compared to immediate immunotherapy with rituximab has found that twice as many patients in the watch and wait group required treatment after three years compared to those who received a short course of rituximab. However it remains the case that 15-20% of patients may never need intervention over a period of 10-15 years for whom early therapy would be unnecessary

Diagnostic procedures have also improved. It is recognised that follicular lymphoma may transform to a more aggressive lymphoma, usually diffuse large B cell lymphoma (DLBCL),

and also that some cases of follicular lymphoma will have coexisting DLBCL. In both of these settings watch and wait would not be considered.

This topic will address the most effective first line strategy in the management of asymptomatic follicular lymphoma.

Clinical question: Is immediate treatment or deferred chemotherapy (watch and wait) the more effective treatment for people with advanced asymptomatic follicular lymphoma?

4.1.3.1 Clinical evidence (see section 4.1.3 in Appendix G)

Three randomised controlled trials and two retrospective cohort studies were included as evidence.

4.1.3.1.1 Chlorambucil versus 'watch and wait'

Very low quality evidence from one randomised trial in 309 patients (Ardeshna *et al* 2003) reported that time to second line chemotherapy (HR = 1.422, 95% CI 1.086-1.861), but not overall survival (HR = 1.026, 95% CI 0.798-1.319) was longer after treatment with chlormabucil compared to 'watch and wait'.

4.1.3.1.2 Rituximab induction versus 'watch and wait'

Very low quality evidence from one randomised trial in 167 patients (Ardeshna *et al* 2014) reported that the need for new treatment (HR = 0.35, 95% CI 0.22-0.56) and progression-free survival (HR = 0.55, 95% CI 0.37-0.83), but not overall survival (HR not reported), time to transformation (HR not reported) and quality of life (HR not reported) were superior after treatment with rituximab induction compared to 'watch and wait'.

4.1.3.1.3 Rituximab imaintenance versus 'watch and wait'

Low quality evidence from one randomised trial in 379 patients (Ardeshna *et al* 2014) reported that the need for new treatment (HR = 0.21, 95% CI 0.14-0.31) and progression-free survival (HR = 0.23, 95% CI 0.16-0.32), but not overall survival (HR = 0.73, 95% CI 0.34-1.54) or time to transformation (HR = 0.62, 95% CI 0.3-1.26) were superior after treatment with rituximab maintenance compared to 'watch and wait'. Quality of life was either superior or similar after treatment with rituximab maintenance compared to 'watch and wait' (HRs not reported).

4.1.3.1.4 Prednimustine versus 'watch and wait'

Very low quality evidence on 'Freedom from treatment'/'freedom from treatment failure' (HR not reported) and overall survival (HR not reported) was reported in one randomised trial with 130 patients (Brice *et al* 1997) with no difference reported after treatment with prednimustine compared to 'watch and wait'.

4.1.3.1.5 Interferon alfa versus 'watch and wait'

Very low quality evidence from one randomised trial with 129 patients (Brice *et al*, 1997) reported that 'freedom from treatment'/'freedom from treatment failure' (HR not reported) and overall survival (HR not reported) did not differ after treatment with interferon alfa compared to 'watch and wait'.

4.1.3.1.6 Chemotherapy ± rituximab (NOS) versus 'watch and wait'

Very low quality evidence from one retrospective cohort study with 79 patients (Pereira *et al* 2014) reported that time to next treatment (HR not reported) and progression-free survival

(HR not reported), but not overall survival (HR not reported) were superior after treatment with chemotherapy ± rituximab (NOS) compared to 'watch and wait'.

4.1.3.1.7 Immunochemotherapy (NOS) versus 'watch and wait'

Very low quality evidence from one retrospective cohort study with 116 patients (Stemmelin *et al*, 2014) reported that overall survival (HR not reported) did not differ after treatment with immunochemotherapy (NOS) compared to 'watch and wait'.

4.1.3.2 Cost-effectiveness evidence (see also Appendix B)

4.1.3.2.1 Background

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

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

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

4.1.3.2.2 Aims

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

- Watchful waiting
- Rituximab induction
- Rituximab induction and maintenance

4.1.3.2.3 Existing Economic Evidence

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

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

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

4.1.3.2.4 De Novo Economic Model

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

Clinical data

Need for new treatment

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

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

For the purposes of the model, these values were converted to annual recurrence rates of 22.8%, 6.7% and 3.9% for the watchful waiting, rituximab induction and rituximab maintenance arms (assuming a constant rate of recurrence over the study period). In the base case, these values were maintained over the time horizon of the model but variations in recurrences after 3 years were extensively explored in sensitivity analysis.

Subsequent relapse/progression rates

Patients may also experience a relapse/progression following subsequent lines of treatment. For simplicity, a constant rate of relapse after subsequent treatments has been assumed in the model. An annual progression rate of 12.8% has been applied based on Van Oers *et al*. 2010.

Disease related and other cause mortality

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

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

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

Costs

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

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

Rituximab induction with and without maintenance

The drug costs of rituximab induction and maintenance were estimated using dosages and unit costs from the British National Formulary (BNF). The cost associated with delivering rituximab was estimated using cost codes associated with the delivery of chemotherapy at first attendance on an outpatient or day case basis (a weighted average of outpatient and day case costs was estimated using the number of procedures in NHS reference costs). The costs of rituximab induction and maintenance were estimated to be £6,388.85 and £9,583.28, respectively.

Watchful waiting and follow-up costs

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

While there is likely to be some variation in clinical practice, the follow-up frequency reported in the BJH Guidance by McNamara *et al*. 2011 was thought to provide a good estimate of current UK practice and was therefore used in the economic model.

It was assumed that, at each follow-up visit, the patient would undergo a physical examination and enquiry about symptoms as well as various tests (£156.41); full blood count (£6.92), full profile- U&E, LFT, Ca (£18.85), serum IgG, lgA, IgM and electropheresis (£27.67) and lactate dehydrogenate (£13.99). It was also assumed that patients would receive a CT scan if relapse/progression was suspected or to evaluate the response to treatment (e.g. to evaluate the response to rituximab at 12 months). The costs of follow-up investigations applied in the model are shown in the table below.

Second and third line treatment

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

Chemotherapy ± rituximab

Most patients experiencing a recurrence are likely to be treated with chemotherapy in combination with rituximab. Based on the advice of the guideline committee, it was assumed that patients would receive R-CHOP, R-Bendamustine or R-CVP. The costs associated with delivering chemotherapy were sourced from NHS Reference costs, with a weighted average of outpatient and daycase delivery costs estimated using the number of procedures in NHS

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

The total cost for six cycles of R-CHOP, R-CVP and R-Bendamustine was estimated to be £12,274.27, £11,932.05 and £14,212.38, respectively.

Autologous transplant

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

The costs associated with delivering chemotherapy were sourced from NHS Reference costs. Based on the advice of the guideline committee, it was assumed that R-ESHAP or R-DHAP would be delivered in an inpatient setting whereas R-GDP or R-ICE would be delivered in an outpatient or day case setting (using the same proportions as those used in the sections above). Following NHS Reference costs methodology the cost of inpatient chemotherapy was estimated using bed day costs (as there is no specific code for inpatient chemotherapy delivery). Therefore, inpatient chemotherapy costs were estimated using the average cost of an excess bed day in patients with malignant lymphoma, including Hodgkin's and non-Hodgkin's subtypes (£348.88) multiplied by the number of days where chemotherapy is delivered. The unit costs of drugs were sourced from Emit. Where eMIT costs were not available, BNF costs were used.

The total cost for three cycles of R-ESHAP, R-DHAP, R-GDP and R-ICE was estimated to be £11,380.19, £9,161.62, £7,763.82 and £9,338.43, respectively.

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

Subsequent immunochemotherapy treatment

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

As above, the costs associated with delivering chemotherapy were sourced from NHS Reference costs, with different costs used depending on whether the regimen is delivered on an outpatient, day case or inpatient basis (using the same methodology as above). The unit costs of drugs were sourced from eMIT or the BNF (where eMIT costs were not available). However, in the case of carmustine, unit costs were not available from eMIT or the BNF. The guideline committee advised that this was due to a recent lack of availability of the drug, which is now only available through specialist importers. A pharmacy colleague of one of the guideline committee members provided the previous price paid for the drug (£358.80 for 100mg), which was utilised in the analysis.

The total costs for the regimens not already specified above were estimated to be £8,366.64 for four cycles of R-GEMP, £8,102.06 for four cycles of R-FC, £7,896.05 for three three cycles of R-GCVP, £11,383.98 for two cycles of R-Mini-BEAM delivered on an inpatient basis and £8,138.32 for two cycles of R-Mini-BEAM delivered as an outpatient. The overall average cost of the subsequent immunotherapy regimens was estimated to be £9,996.

GCSF costs

Based on the advice of the guideline committee, it was assumed that granulocyte-colony stimulating factor (GCSF) would be used in 50% of patients receiving chemotherapy. The unit costs associated with GCSF agents (lenograstim or filgrastim, including biosimilars) were sourced from the BNF as unit costs were not available from eMIT. It was assumed that GCSFs would be administered for seven days based on guidelines for the use of GCSF from St Luke's Cancer Alliance. The average cost for seven days of GCSF was estimated to be £414.10.

Palliative care costs

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

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

Health related quality of life (QoL) values

The model estimates effectiveness in terms of quality adjusted life years (QALYs) so that both the quantity and quality of life are taken into account. QALYs were estimated by combining the life year estimates with utility values (or QoL weights) associated with being in a particular health state. For the purposes of this economic evaluation, the QoL data shown in Table 14 were utilised.

Table 14: Quality of life values applied in the economic model

Health state	Utility score	Source
Asymptomatic follicular lymphoma	0.8800	Unpublished data from Wild *et al*. 2005 for "disease free" patients from ScHARR
Symptomatic follicular lymphoma	0.8050	Unpublished data from Wild *et al*. 2005 for "progression free" patients from ScHARR
Progressive disease	0.7363	Unpublished data from Wild *et al*. 2005 for "disease progression" from ScHARR

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

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

The QoL values associated with symptomatic follicular lymphoma and progressive disease were estimated to be 0.8050 and 0.7363, respectively. This was based upon the Wild *et al*.

2005 QoL study, using the approach adopted in the ScHARR technology assessment report whereby aggregated utility values for a 'progression free' (n=84) and 'disease progression' (n=132) health state were used.

Base case results

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

The base case results of the analysis for are presented in Tables 15 and 16. It can be seen that, in comparison to watchful waiting, both rituximab induction and rituximab maintenance were found to be cost-effective and indeed dominant (i.e. more effective and cost saving). Using dominance rank to ascertain the optimal strategy overall, it can be seen that rituximab induction is the most cost-effective strategy with rituximab maintenance found to be more effective but at a substantially increased cost that means it's not cost-effective with an ICER of £69,406 well above the NICE threshold.

Table 15: Base case cost-effectiveness results against common baseline (watchful waiting)

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

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

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

Deterministic sensitivity analysis

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

Table 17: One-way sensitivity analysis results

Change made	Optimal strategy
Lower hazard ratio (0.14) for starting new treatment after R-maintenance	R-maintenance
Upper hazard ratio (0.31) for starting new treatment after R-maintenance	R-induction
Lower hazard ratio (0.22) for starting new treatment after R-induction	R-induction
Upper hazard ratio (0.56) for starting new treatment after R-induction	R-maintenance
Average age = 50 years old	R-induction

Change made	Optimal strategy
Average age = 70 years old	R-induction
Subsequent relapse rates = 4.8% (rate after R-maintenance in first line)	R-induction
Subsequent relapse rates = 0%	R-induction
Time horizon = 3 years	R-induction
BCNU Carmustine cost = £1,000 per 100mg	R-induction
NHS Reference cost used for autologous transplant	R-induction
Subsequent treatment costs = £0	R-induction
Subsequent treatment costs + 50%	R-induction
Asymptomatic QoL value = progression free QoL value	R-induction
QoL on WW 0.01 higher than QoL with rituximab	R-Induction
QoL on WW 0.05 higher than QoL with rituximab	R-Induction
No differences in QoL values	R-Induction
R-resistance – (relapse rate 50% higher in subsequent lines after R in first line)	R-induction
R-resistance – (relapse rate 100% higher in subsequent lines after R in first line)	R-Induction

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

Threshold analysis

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

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

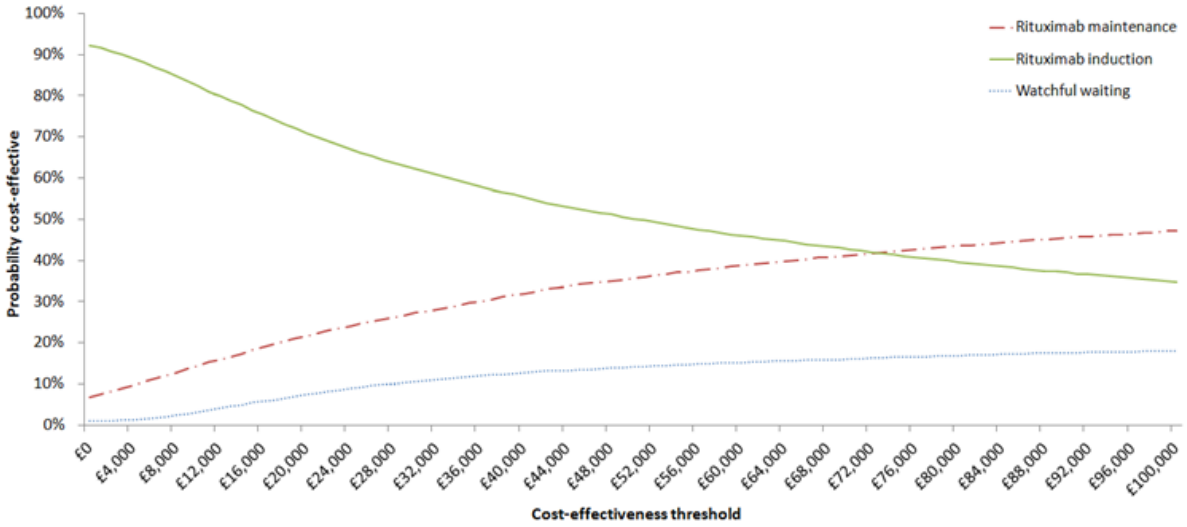
It was found that watchful waiting becomes cost-effective when it was assumed that QoL is 0.105 lower for patients on receiving rituxiumab in comparison to watchful waiting strategies.

Probabilistic sensitivity analysis (PSA)

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

The results of 10,000 runs of the probabilistic sensitivity analysis are shown using the cost-effectiveness acceptability curve (CEAC) below (Figure 5), which shows the probability of each diagnostic strategy being considered cost-effective at various thresholds on the x axis.

Figure 5: Cost-effectiveness acceptability curve (CEAC) for management strategies for asymptomatic follicular lymphoma



It can be seen that, at a willingness to pay threshold of £20,000 per QALY, rituximab induction has a 68% probability of being cost-effective, while rituximab maintenance has a 21% probability of being cost-effective and watchful waiting has 11% probability of being cost-effective.

Conclusion

The results of the base case analysis suggest that rituximab induction alone is the optimal strategy to adopt in patients with asymptomatic follicular lymphoma. This result was shown to be robust in one-way sensitivity analysis, where rituximab induction remained cost-effective in the vast majority of scenarios. The result was further strengthened in probabilistic sensitivity analysis (PSA) where the strategy was found to have a 68% probability of being cost-effective at a threshold of £20,000 per QALY. Furthermore, rituximab maintenance was shown to have the next highest probability of being cost-effective with a 21% probability of being cost-effective at the £20,000 per QALY threshold, suggesting that there is a strong case for active treatment (i.e. 89% probability of active treatment being cost-effective) rather than a watchful waiting approach.

Recommendation	**Offer rituximab induction therapy[a] to people with advanced-stage (stages III and IV) follicular lymphoma who are asymptomatic.**
Relative value placed on the outcomes considered	Overall survival was considered the critical clinical outcome when drafting recommendations.
Quality of the evidence	The quality of the evidence for this topic was moderate to very low as assessed using GRADE. The main issues with the evidence were: imprecision and outcome assessment was not blinded. Although time to next treatment is an unusual primary endpoint due to its subjective component, the results for progression free survival were similar, giving the GC more confidence in the evidence.

a At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports the standard monotherapy dosage of 4 doses of 375 mg/m2 at weekly intervals.

	The rituximab induction treatment arm was stopped early in Ardesha (2014) due to the publication of other rituximab induction and maintenance studies affecting recruitment and resulting in a loss of equipoise. The GC, however, still considered this trial as useful evidence.
Trade off between clinical benefits and harms	The GC considered that the delayed time to next treatment following rituximab induction compared to watchful waiting would result in fewer patients needing further chemotherapy, because their disease would not progress within their lifetime. Rituximab induction treatment would probably result in a reduction in anxiety in those patients receiving active treatment instead of watchful waiting. Although rituximab induction plus maintenance was also effective – it involved significantly more rituximab with associated increased costs and possible increased toxicity compared with induction alone. There are limited, low risk side effects due to induction rituximab which would be an additional harm for some patients whose disease would not have progressed. It is theoretically possible that induction rituximab could reduce the effectiveness of subsequent rituximab. Ardeshna (2014) follow-up has been extended to capture this however these data are not yet available. PRIMA data suggests no impact of prior rituximab maintenance on effectiveness of subsequent rituximab containing therapy. The GC concluded that the risk of harm from rituximab induction was low (and in some cases theoretical) compared with the tangible benefit of reducing the need for further treatment. The evidence suggested that other reported therapies (chlorambucil, prednimustine and interferon alpha) were less effective than rituximab when compared to watch and wait and so the GC did not make recommendations about these treatments.
Trade off between net health benefits and resource use	A cost-utility analysis by Prica *et al*. (2015) was identified. However, the study was only partially applicable to our decision problem as it did not consider the UK health care setting. Therefore this evidence was not used by the GC when agreeing their recommendations. A health economic model was developed for this topic and the results of the analysis were used to inform the recommendations. The base case results showed that rituximab induction was the most cost-effective strategy. In comparison to a watchful waiting strategy, rituximab induction was found to be less expensive and more effective (i.e. dominant). Rituximab induction plus maintenance was found to be marginally more effective than rituximab induction alone but it was not found to be cost-effective (ICER of £52,047 per QALY, well above the NICE threshold of £20,000 per QALY). It should be noted that the superior effectiveness of the rituximab strategies observed in the model were not based on a survival benefit but rather QoL benefits associated with delaying the use of intensive treatments.

	Uncertainty in the clinical evidence as well as the evidence used to inform cost and QoL values was assessed in one-way and probabilistic sensitivity analyses. This result was shown to be robust in one-way sensitivity analysis, where rituximab induction remained cost-effective in the vast majority of modelled scenarios. The result was further strengthened in probabilistic sensitivity analysis (PSA) where the strategy was found to have a 63% probability of being cost-effective at a threshold of £20,000 per QALY. Furthermore, rituximab maintenance was shown to have the next highest probability of being cost-effective (28%), suggesting that there is a strong case for active treatment rather than a watchful waiting approach i.e. 91% probability of active treatment being cost-effective. Thus, despite the clinical data inputs being assessed as low to very low quality, the GC were able to make strong recommendations as the model predicted a high likelihood of rituximab being cost-effective. It should be noted that there may be short term cost increases associated with the increased use of rituximab. However, as shown in the economic model, the use of rituximab is thought to be cost saving in the long term.
Other considerations	This recommendation will result in a major change in practice because rituximab induction is not routinely given in this setting (or licensed for this use). There is likely to be a short term impact on the chemotherapy day care units delivering rituximab induction but in the long term this recommendation should reduce throughput. This is an off license recommendation.

4.1.4 Treating advanced-stage symptomatic follicular lymphoma

NICE has developed a suite of technology appraisal guidance on non-Hodgkin's lymphoma. It has not been possible to develop recommendations on treating advanced stage symptomatic follicular lymphoma in this guideline due to published technology appraisals or those in development.

Recommendations in this guideline will complement the existing technology appraisals.

For more information on the relationship between the technology appraisal and clinical guidelines programmes please see Updating technology appraisals in the context of clinical guidelines.

Recommendations	**Rituximab, in combination with:** • **cyclophosphamide, vincristine and prednisolone (CVP)** • **cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)** • **mitoxantrone, chlorambucil and prednisolone (MCP)** • **cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) or**

	• **chlorambucil** **is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people. [This recommendation is from Rituximab for the first-line treatment of stage III-IV follicular lymphoma (NICE technology appraisal guidance 243).]** **The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with follicular lymphoma, because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first-line treatment of advanced indolent non-Hodgkin's lymphoma' was in development. This technology appraisal is currently suspended.**
	These recommendations are from Rituximab for the first-line treatment of stage III-IV follicular lymphoma (NICE technology appraisal guidance 243). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA243.

4.1.5 Treating advanced-stage relapsed or refractory follicular lymphoma

NICE has developed a suite of technology appraisal guidance on non-Hodgkin's lymphoma. It has not been possible to develop recommendations on treating advanced stage relapsed or refractory follicular lymphoma in this guideline due to published technology appraisals or those in development.

For more information on the relationship between the technology appraisal and clinical guidelines programmes please see Updating technology appraisals in the context of clinical guidelines.

Recommendations	**The recommendations in this section are from Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 137).** **Rituximab, within its marketing authorisation, in combination with chemotherapy, is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma.** **Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab.** **Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).**

	These recommendations are from Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (NICE technology appraisal guidance 137). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA137.

4.1.6 Treating transformed follicular lymphoma

There is an approximately 2% per year risk of a patient with follicular lymphoma transforming to high grade lymphoma. In the pre-rituximab era this event was associated with a poor prognosis, with median survival rates of 7 to 20 months. Many centres therefore adopted high dose therapy with autologous stem cell rescue (ASCT) as standard treatment for transformed lymphoma after response to first-line chemotherapy. Results from observational studies suggest that in the rituximab era, the outcome for transformed follicular lymphoma is more favourable. Other registry studies suggest that ASCT can prolong survival in these patients. Subsequently, practise across the UK is highly variable with some units uniformly consolidating transformation with ASCT, whereas others restrict this to patients who had a high international prognostic index (IPI) score at transformation, or indeed not at all.

The role of allogeneic stem cell transplantation is even less clear. Research suggests that high grade lymphoma arise, not as a sequential step from the low grade lymphoma but rather as a separate lymphoma derived from a common lymphoma progenitor cell. Theoretically, by targeting this cell the graft-versus-lymphoma effect may therefore cure both the high grade and the low grade components, unlike ASCT which is generally held to offer more potential to cure only the high grade component. Some small series report successful allogeneic stem cell transplantation of multiply relapsed high grade lymphoma, and subgroup analyses of those with transformed disease have suggested somewhat superior outcomes compared to those with *de novo* disease, although experience remains limited.

Sometimes patients present with both high and low grade disease at the same time. This can be:

- With both histologies present within the same biopsy (composite lymphoma)
- With high grade disease in the lymph node and low grade lymphoma in the bone marrow (discordant bone marrow involvement)

Traditionally patients with composite lymphoma are usually treated in the same way as other high grade transformation events. However, when the low grade component is in the bone marrow the outcome with immunochemotherapy alone is very encouraging.

Clinical question: What is the effectiveness of first-line consolidation with high-dose therapy with autologous or allogeneic transplantation in people with histological transformation of follicular lymphoma to diffuse large B-cell lymphoma or concurrent presentation with follicular lymphoma & diffuse large B-cell lymphomas, compared with other strategies?

4.1.6.1 Clinical evidence (see section 4.1.4 in Appendix G)

Six retrospective observational studies provided evidence comparing the effectiveness of the two types of transplantation (allogeneic versus autologous), five retrospective observational studies provided evidence comparing the effectiveness of transplantation to other strategies and four single arm retrospective observational studies provided additional evidence of the use of autologous transplantation in patients with transformed lymphoma.

4.1.6.1.1 Autologous versus allogeneic

Overall survival

Five retrospective observational studies (Ban Hoefen *et al*. 2013; Micallef *et al*. 2006; Reddy *et al*. 2012; Villa *et al*. 2013a; Wirk *et al*. 2014) provided very low quality evidence about overall survival rates after autologous versus allogeneic transplantation in 393 patients with histological transformation of indolent lymphoma (76-100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . Reporting overall survival rates (range 2-5 years; follow-up range 0.25 – 7.5 years) of 50-83% in the autologous group compared to 22-68.5% in the allogeneic group. Micallef *et al*. (2006) reported median overall survival time of 3 years in the autologous group compared to 9 months in the allogeneic group. Villa *et al*. (2013a) and Reddy *et al*. (2012) reported no significant difference in overall survival rates in the two groups (Ban Hoefen *et al*. 2013, Micallef *et al*. 2006 and Wirk *et al*. 2014 provided no statistical analysis comparing the two groups).

Progression free survival

Three retrospective observational studies (Reddy *et al*. 2012; Villa *et al*. 2013a; Wirk *et al*. 2014) provided very low quality evidence about 5-year progression free survival rates after autologous versus allogeneic transplantation in 297 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . Reporting 5-year progression-free survival rates (follow-up range 0.25 – 7.5 years) of 35-55% in the autologous group compared to 18-46% in the allogeneic group. Villa *et al*. (2013) and Reddy *et al*. (2012) reported no significant difference in 5-year progression free survival rates in the two groups (Wirk *et al*. 2014 provided no statistical analysis comparing the two groups).

Response rates

Two retrospective observational studies (Reddy *et al*. 2012; Villa *et al*. 2013a) provided very low quality evidence about response rates after autologous versus allogeneic transplantation in 156 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) . The autologous group had complete (56.7%) and partial response rates (23.4%) comparable to those in the allogeneic group (complete: 55.2%, partial: 17.2%).

Adverse events

Five retrospective observational studies (Ban Hoefen *et al*. 2013; Micallef *et al*. 2006; Reddy *et al*. 2012; Villa *et al*. 2013; Wirk *et al*. 2014) provided very low quality evidence about adverse events after the treatment of autologous or allogeneic transplantation in 393 patients with histological transformation of indolent lymphoma (76-100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL) .

Two studies (Ban Hoefen *et al*. 2013; Villa *et al*. 2013a) reported higher rates of death due to treatment related toxicity (follow-up median: 3.4-7.5 years) in the allogeneic group (27.5%) compared to the autologous group (4.1%). Villa *et al*. (2013a) reported that this difference was significant at 1 year post transplantation (p=0.01) and at 4-years post transplantation (p=0.001). Death due to disease progression was comparable between the autologous group (18%) and the allogeneic group (22%) (Ban Hoefen *et al*. 2013). However, non-relapse mortality rates were higher in the allogeneic group (31.4-41%) compared to the autologous group (4.6-8%) (Reddy *et al*. 2012: 0.06; no statistical analysis reported by Wirk *et al*. 2014).

4.1.6.1.2 Autologous versus no transplantation

Overall survival

Two retrospective observational studies (Ban Hoefen *et al*. 2013; Villa *et al*. 2013b) provided very low quality evidence about overall survival rates after autologous versus no transplantation in 250 patients with histological transformation of indolent lymphoma (86-94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL) . Reporting overall survival rates (range 2-3 years; follow-up range 3.3-3.4 years) of 54-83% in the autologous group compared to 7-65% in the no treatment group (Villa *et al*. 2013b reported that patients not treated with autologous transplantation due to progressive disease had an overall survival rate of 7% whilst patients with other reasons [e.g. age ≥65 years; declined the transplant] for not receiving a transplantation had an overall survival rate of 65%). Neither study reported on whether the overall survival rates were significantly different.

Response rates

One retrospective observational study (Villa *et al*. 2013b) provided very low quality evidence about response rates following autologous versus no transplantation in 150 patients with histological transformation of indolent lymphoma (94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL). The autologous group had a better complete (14%) and partial response rate (82%) compared to those in the no treatment group (complete: 6%, partial: 15%, $p<0.001$).

Adverse events

Two retrospective observational studies (Ban Hoefen *et al*. 2013; Villa *et al*. 2013b) provided very low quality evidence about adverse events after the treatment of either autologous or other treatment in 250 patients with histological transformation of indolent lymphoma (76-94% follicular lymphoma) to aggressive B-cell lymphoma (94-100% DLBCL) . The rate of death due to treatment related toxicity (follow-up median: 3.3-3.4 years) was comparable in the two groups (autologous: 3.8% versus no transplantation: 5%). However, Villa *et al*. 2013b reported that there were significantly more late deaths [>100 days] in the autologous group [6%] compared to the no treatment group [0%; $p<0.01$]). Death due to disease progression in the autologous group (8%) was not reported to be significantly different to the rate reported in the no transplantation group (10%, Ban Hoefen *et al*. 2013).

4.1.6.1.3 Allogeneic versus no transplantation

Overall survival

One retrospective observational study (Ban Hoefen *et al*. 2013) provided very low quality evidence about 2-year overall survival ratse after allogeneic versus no transplantation in 68 patients with histological transformation of indolent lymphoma (86% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Reporting a 2-year overall survival rate (follow-up 3.4 years) of 65% (95% confidence interval: 39-83%) in the allogeneic group compared to 53% (95% confidence interval: 39-68%) in the no treatment group. It was not reported if these survival rates were significantly different in the two groups.

Adverse events

One retrospective observational study (Ban Hoefen *et al*. 2013) provided very low quality evidence about adverse events after allogeneic transplantation or other treatment in 68 patients with histological transformation of indolent lymphoma (86% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). The rate of death due to treatment related toxicity (follow-up 3.4 years) was 22% in the allogeneic group compared to 10% in the no transplantation group. Death due to disease progression (follow-up 3.4 years) was 22% in

the allogeneic group compared to 34% in the no transplantation group. It was not reported if these adverse events were significantly different in the two groups.

4.1.6.1.4 Autologous versus chemotherapy plus rituximab

Overall survival

Two retrospective observational studies (Madsen *et al*. 2013; Villa *et al*. 2013a) provided very low quality evidence about5-year overall survival rates after autologous transplantation versus chemotherapy plus rituximab in 245 patients with histological transformation of indolent lymphoma (100% follicular lymphoma in Villa *et al*. 2013a; Madsen *et al*. 2013 did not provide breakdown of indolent lymphomas) to diffuse large B-cell lymphoma (DLBCL; Madsen *et al*. 2013 did not provide detail on transformation diagnosis). Reporting 5-year overall survival rates (follow-up 7.5 years reported by Villa *et al*. 2013a only) of 57-65% in the autologous group compared to 36-61% in the chemotherapy plus rituximab group. Both reported that patients receiving autologous transplantation had a significantly improved overall survival compared with those who received chemotherapy plus rituximab (p=0.09; p<0.001).

One retrospective observational study (Madsen *et al*. 2013) provided very low quality evidence about 5-year overall survival rates after autologous transplantation versus chemotherapy plus rituximab in 95 patients with a primary diagnosis of transformed indolent lymphoma (composite lymphoma). Reporting that the 5-year overall survival rates in the autologous group (80%) did not significantly differ compared to the chemotherapy plus rituximab group (67%).

Progression free survival

Two retrospective observational studies (Madsen *et al*. 2013; Villa *et al*. 2013a) provided very low quality evidence about 5-year progression free survival rates after autologous transplantation versus chemotherapy plus rituximab in 245 patients with histological transformation of indolent lymphoma (100% follicular lymphoma in Villa *et al*. 2013a; Madsen *et al*. 2013 did not provide breakdown of indolent lymphomas) to diffuse large B-cell lymphoma (DLBCL; Madsen *et al*. 2013 did not provide detail on transformation diagnosis). Reporting 5-year progression free survival rates (follow-up 7.5 years reported by Villa *et al*. 2013a only) of 47-55% in the autologous group compared to 6-40% in the chemotherapy plus rituximab group. Madsen *et al*. (2013) reported that patients receiving autologous transplantation had a significantly improved progression free survival compared with those who received chemotherapy plus rituximab (p=0.003).

One retrospective observational study (Madsen *et al*. 2013) provided very low quality evidence about 5-year progression free survival rates after autologous versus allogeneic transplantation in patients with a primary diagnosis of transformed indolent lymphoma (composite lymphoma). Reporting that the 5-year progression free survival rates in the autologous group (75%) did not significantly differ compared to the chemotherapy plus rituximab group (61%).

4.1.6.1.5 Allogeneic versus chemotherapy plus rituximab

Overall survival

One retrospective observational study (Villa *et al*. 2013a) provided very low quality evidence about 5-year overall survival rates after allogeneic transplantation versus chemotherapy plus rituximab in 119 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Villa *et al*. (2013a) reported no significantly difference 5-year overall survival rates (follow-up 7.5 years) in the allogeneic

group (46%: standard error: 11) compared to the chemotherapy plus rituximab group (61%: standard error: 7).

Progression free survival

One retrospective observational study (Villa *et al*. 2013a) provided very low quality evidence about 5-year progression free survival rates after allogeneic transplantation versus chemotherapy plus rituximab in 119 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL). Villa *et al*. (2013a) reported no significantly different 5-year progression free survival rates (follow-up 7.5 years) in the allogeneic group (46%: standard error: 11) compared to the chemotherapy plus rituximab group (40%: standard error: 7).

4.1.6.1.6 Autologous transplantation

Overall survival

Two non comparative retrospective observational studies (Eide *et al*. 2011; Williams *et al*. 2001) provided very low quality evidence about 5-year overall survival rates after autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Reporting 5-year overall survival rates (follow-up 4.92 years, reported in Williams *et al*. 2001 only) of 47-51%.

Progression free survival

Two non comparative retrospective observational studies (Eide *et al*. 2011; Williams *et al*. 2001) provided very low quality evidence about 5-year progression free survival rates after autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Reporting 5-year progression free survival rates (follow-up 4.92 years, reported in Williams *et al*. 2001 only) of 30-32%.

Response rates

Two non comparative retrospective observational studies (Eide *et al*. 2011; Williams *et al*. 2001) provided very low quality evidence about response rates after autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Complete response rates were 76.3% and partial response rates were 31.3%, with Eide *et al*. (2011) reporting a relapse rate of 43.3%.

Adverse events

Two non comparative retrospective observational studies (Eide *et al*. 2011; Williams *et al*. 2001) provided very low quality evidence about adverse events after autologous transplantation in 80 patients with histological transformation of indolent lymphoma (91-100% follicular lymphoma) to any high grade lymphoma (76-100% DLBCL). Death due to disease progression (follow-up 4.92 years, reported in Williams *et al*. 2001 only) was reported in both observational studies at a rate of 21.3% with procedure related death reported in one study (Williams *et al*. 2001) at 18%.

4.1.6.1.7 Exposure to rituximab prior to transplantation

Five retrospective observational studies assessed prior exposure to rituximab and use of transplantation (Ban Hoefen *et al*. 2013; Calvo-Villas *et al*. 2011; Muccilli *et al*. 2009; Villa *et al*. 2013b; Wirk *et al*. 2014).

Overall survival

Two non comparative retrospective observational studies (Calvo-Villas *et al*. 2011; Muccilli *et al*. 2009) provided very low quality evidence about 5-year overall survival rates after autologous transplantation in 125 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL, transformation diagnosis not reported in Muccilli *et al*. 2009). Reporting 5-year overall survival rates (follow-up 61 months, reported in Calvo-Villas *et al*. 2011) of 36-66.4%. These two studies also reported the overall survival rates according to prior exposure to rituximab, finding that overall surival rates in the autologous with no prior exposure group were between 36-48.2% compared to 51-66.4% in the autologous patients who had prior exposure to rituximab. Calvo-Villas *et al*. (2011) reported that there was no significant difference between the two groups, however, Muccilli *et al* (2009) reported a trend for prior exposure to improved overall survival compared to no prior exposure(p=0.11). Wirk *et al*. (2014) reported that 37% of their sample (n=141) had prior exposure to rituximab finding that exposure prior to transplantation had no impact on overall survival rates in the patients receiving autologous or allogeneic transplantations. Ban Hoefen *et al*. (2013) reported that 70% of their sample (n=118) had prior exposure to rituximab finding that there was no survival difference based on rituximab exposure prior to transplantation. Villa *et al*. (2013b) reported that 77% of their sample (n=105) had prior exposure to rituximab finding that there was no survival difference based on rituximab exposure prior to transplantation.

Progression free survival

Two non comparative retrospective observational studies (Calvo-Villas *et al*. 2011; Muccilli *et al*. 2009) provided very low quality evidence about 5-year progression free survival rates after autologous transplantation in 125 patients with histological transformation of indolent lymphoma (100% follicular lymphoma) to diffuse large B-cell lymphoma (DLBCL, transformation diagnosis not reported in Muccilli *et al*. 2009). Reporting 5-year progression free survival rates (follow-up 61 months, reported in Calvo-Villas *et al*. 2011) of 22-67.2%. These two studies also reported the progression free survival rates according to prior exposure to rituximab, finding that the rates in the autologous with no prior exposure group were between 22-48.4% compared to 55-67.2% in the autologous patients who had prior exposure to rituximab. Calvo-Villas *et al*. (2011) reported that there was no significant difference between the two groups, however, Muccilli *et al* (2009) reported a significant difference for prior exposure to improved progression free survival compared to no prior exposure (p=0.04). Wirk *et al*. (2014) reported that 37% of their sample (n=141) had prior exposure to rituximab finding that exposure prior to transplantation had no impact on overall progression free survival rates in the patients receiving autologous or allogeneic transplantations.

4.1.6.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider consolidation with autologous stem cell transplantation for people with transformation of previously diagnosed follicular lymphoma that has responded to treatment and who are fit enough for transplantation.** **Consider consolidation with autologous or allogeneic stem cell transplantation for people with transformation of**

	follicular lymphoma who need more than 1 line of treatment for a response and who are fit enough for transplantation. **Do not offer consolidation with high-dose therapy and autologous or allogeneic stem cell transplantation to people presenting with concurrent diagnoses of follicular lymphoma and diffuse large B-cell lymphoma that have responded to first-line treatment.**
Relative value placed on the outcomes considered	The critical outcomes when drafting the recommendations included overall survival, progression free survival and toxicity (treatment related morbidity). There was no evidence relating to health related quality of life (HRQoL), patient satisfaction or patient preference or diagnosis at relapse.
Quality of the evidence	All the evidence for each outcome was rated very low quality as assessed using GRADE and NICE quantitative checklists. The primary reason for downgrading studies was imprecision due to small sample sizes and low frequency of events. Additionally evidence was downgraded for indirectness due to a mix of populations (five studies used populations of patients with an original diagnosis of any indolent lymphomas not specifically follicular lymphoma; four studies used populations of patients with transformation to any aggressive lymphoma not specifically diffuse large B-cell lymphoma) and there was a lack of clarity regarding whether patients were receiving consolidation therapy receiving first-line therapy or at first response (which might be achieved after multiple lines of therapy). Only one study included patients with a concurrent diagnosis of follicular lymphoma and diffuse large B-cell lymphoma. The definition of transformed lymphoma varied across studies with some studies only including patients for which the transformed diagnosis occurred six months after the initial diagnosis of follicular lymphoma. Because the evidence base concerned different populations of patients who were receiving consolidation therapy after first-line therapy or at first response (which might be achieved after multiple lines of therapy) the GC made separate recommendations according to the following groups: • Patients with transformed follicular lymphoma to diffuse large B-cell lymphoma: ○ Response after first-line immunochemotherapy ○ First response after multiple-lines of immunochemotherapy • Patients with a diagnosis of concurrent follicular lymphoma and diffuse large B-cell lymphoma: ○ First response after immunochemotherapy
Trade-off between clinical benefits and harms	The GC thought that the recommendation to use consolidation therapy would optimise survival rates in patients with transformed follicular lymphoma to diffuse large B-cell lymphoma. The evidence base suggested that such patients with either response after first-line immunochemotherapy or first response after multiple-lines of immunochemotherapy stood to benefit from consolidation therapy.

	The evidence indicated autologous stem cell transplantation was associated with a treatment related mortality of about 3%, due primarily to neutropenic sepsis. Allogeneic stem cell transplantation was associated with considerably higher treatment related mortality. The GC considered that the recommendation to not use consolidation therapy in patients with a diagnosis of concurrent follicular lymphoma and diffuse large B-cell lymphoma would reduce unnecessary treatment related toxicity. For patients with a concurrent diagnosis of follicular lymphoma and diffuse large B-cell lymphoma there was one study, reporting very low quality evidence. The GC expressed their concerns regarding the use of highly toxic consolidation therapies in these patients with no evidence of survival benefit compared to no consolidation therapy and therefore the GC made a 'do not offer' recommendation.
Trade-off between net health benefits and resource use	No relevant health economic evidence was identified and no health economic model was built for this topic The resource impact associated with the majority of these recommendations was thought to be minimal as they are a consolidation of what is widely regarded to be best practice. However, there could be resource implications where best practice is not currently implemented. In particular, it was thought that there may be reduction in the use of autologous stem-cell transplants (and associated costs) for patients with a diagnosis of concurrent follicular lymphoma and diffuse large B-cell lymphoma. The recommendations were also thought likely to be cost-effective as specified below. In comparison to the alternatives, the recommendation to consider consolidation therapy would increase costs but it would also improve survival rates and it was thought that it would be cost-effective in cost per QALY terms. The recommendation to not offer consolidation therapy in patients with a diagnosis of concurrent follicular lymphoma and diffuse large B-cell lymphoma will reduce costs and will also reduce treatment related toxicity (through a reduction in unnecessary treatment). Thus this recommendation would also be highly likely to be cost-effective and in this case even dominant (cost saving and more effective).
Other considerations	The GC noted that the recommendations would lead to a minor change in practice through the reinforcement of current best practice. The GC noted that the recommendations will provide uniformity in practice by reducing uncertainty in which treatment regimen to use in patients with transformed follicular lymphoma. The GC noted that the drafted recommendations are in-line with the EBMT and BSBMT transplantation indication tables. The GC noted there was insufficient evidence about whether biological and clinical factors can be used to identify which patients with high-grade transformation of follicular lymphoma can be treated with immunochemotherapy alone. For this reason they made a research recommendation.

Research recommendation	In people with high-grade transformation of follicular lymphoma, which biological and clinical factors predict good outcomes with immunochemotherapy alone?
Why this is important	Before rituximab, it was accepted that high-grade transformation of follicular lymphoma to diffuse large B-cell lymphoma portended a poor prognosis. Recent data suggests that although transformation remains an important clinical event, outcomes have improved. It is unclear which people are likely to do well with conventional treatment (such as R-CHOP) and which people may benefit from intensive treatment with, for example, high-dose therapy and autologous stem cell transplantation. Many factors are likely to influence outcome, including clinical factors (such as age, stage at transformation and extranodal involvement at transformation), radiological findings (such as early improvement of disease identified using an interim FDG-PET CT scan) and molecular factors (such as certain driver mutations present at transformation, the presence of *MYC* translocation and response of circulating tumour DNA to treatment). A better understanding of which factors are associated with high-risk or low-risk disease would enable therapy to be tailored to the person's needs, reducing unnecessary toxicity for people at low risk and reserving intensive therapy for people at high risk. Outcomes of interest include progression-free survival and overall survival in subgroups defined by clinical factors, radiological findings and molecular analyses.

4.2 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma

4.2.1 First line treatment

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (or MALT lymphoma) is the third most common type of non-Hodgkin's lymphoma in the UK, by annual incidence figures. The stomach is the most commonly involved extra-nodal organ; half of all gastric lymphomas are MALT lymphomas and there is an important association with chronic *Helicobacter pylori* infection in the majority of gastric MALT cases.

Other sites that may be involved by MALT lymphoma include the salivary glands, orbit, lung, intestinal tract, and thyroid gland, breast tissue, the dura, and genitourinary tract. Autoimmune disease has been linked to the development of non-gastric MALT lymphoma.

MALT lymphomas usually demonstrate an indolent clinical behaviour. Very rarely they may demonstrate features of high-grade histology at the time of initial presentation; transformation may occur throughout the disease course.

Diagnosis is based on history, physical examination, radiology, histopathological and immunohistochemical evaluation of the biopsy specimen, and special molecular laboratory techniques.

Treatment is based on the site of disease and severity of symptoms at presentation. Surgery, radiation therapy, immunotherapy and chemotherapy have all been studied. Unlike many other lymphomas, anti-microbial therapy is an important consideration in *H pylori* associated gastric lymphomas- eradication therapy is the mainstay of treatment for localised *H pylori*-positive gastric MALT lymphoma. It remains controversial as to whether other infectious agents may have a pathogenic role in the development of MALT lymphomas at other disease sites.

It may be possible to define a group of patients with disease that is less likely to respond to antibiotic therapy and more likely to require chemo-immunotherapy e.g. *Helicobacter pylori*-negative patients, tumours with a t(11;18)(q21;q21) translocation and those with disease extending through the sub-mucosa.

The effectiveness of endoscopic follow-up of response to treatment has been reported in many clinical trials. Endoscopy also allows for multiple biopsies to be taken and is generally performed every 3-6 months following the end of treatment for up to two years to assess the response to treatment. For patients with disease localised to the stomach, concomitant follow-up with imaging (e.g. with computerised tomography) offers no additional benefit in the majority of cases.

Response rates to antibiotic therapy can be slow. Therefore, escalation to chemotherapy or radiotherapy may not be necessary unless there are specific risks (extensive disease, significant ulceration).

Clinical question: What is the most effective first-line treatment for people with MALT lymphoma?

4.2.1.1 Clinical evidence (see section 4.2.1 in Appendix G)

Three randomised trials and six retrospective cohort studies provided evidence about chemotherapy, surgery or radiotherapy as first line treatment for MALT lymphoma. Evidence about antibiotic therapy in positive gastric MALT lymphoma came from 36 case series (26 prospective) in patients with helicobacter positive disease and 11 case series (4 prospective) in those with helicobacter negative disease. One randomised trial and 29 observational studies (21 prospective) provided evidence about treatment after antibiotic therapy for gastric MALT lymphoma.

4.2.1.1.1 What is the most effective first-line treatment in patients with MALT lymphoma?

Four observational studies (Kalpadakis *et al*., 2009; Oh *et al*., 2010; Papaxoinis *et al*., 2006; Olszewski *et al*., 2014) and one randomised control trial (Zucca *et al*., 2013) assessed the use of chemotherapy, rituximab and radiotherapy as first-line treatment in patients with MALT lymphoma. Overall survival rates ranged from 65-100%.

One observational study (Papaxoinis *et al*., 2006) compared the use of anthracycline chemotherapy (AC, e.g. CHOP, CEOP, CNOP) to non-anthracycline chemotherapy (C) in 97 patients with MALT lymphoma (in more than 12 body sites) provided very low quality evidence. The study reported complete response rate in the AC group of 73% compared to 68% in the C group. The 5-year progression free survival (AC: 37% versus C: 51%) and overall survival rates (AC: 80% versus C: 65%) were not significantly different between the two groups.

The role of adding rituximab to treatment regimens (chlorambucil, CVP, CHOP, other) was assessed in two retrospective observational studies (Kalpadakis *et al*., 2009; Oh *et al*., 2010 [stage IV MALT]) and one randomised control trial (RCT) (Zucca *et al*., 2013). Zucca *et al*. (2013) reported a randomised control trial in which 227 patients with MALT lymphoma previously untreated (apart from prior local therapy) were randomly assigned to either receive chlorambucil plus rituximab (n=116) or chlorambucil alone (n=115). With a median follow-up of 62 months the RCT provided low quality evidence for a higher overall response rate (94% versus 87%), complete response rate (78% versus 65%), 5-year event free survival rate (68% versus 50%), 5-year progression free survival rate (71% versus 62%) and a lower partial response rate (16% versus 22%) in the chlorambucil plus rituximab group compared to the chlorambucil only group. However, only the 5-year event free survival rate was significantly different in the two groups ($p<0.01$).

Kalpadakis *et al*. (2009) compared the use of chlorambucil plus rituximab compared to chlorambucil alone in 44 patients with MALT lymphoma (7 body sites, no gastric MALT). The study reported very low quality evidence of an overall response rate of 95% in the chlorambucil plus rituximab group compared to 79% in the chlorambucil only group. The other observational study (Oh *et al*., 2010) compared the use of chemotherapy plus rituximab to chemotherapy alone in 62 patients with MALT lymphoma. Both observational studies reported very low quality evidence of a higher complete response rates and partial response rates in the chlorambucil plus rituximab group (complete response: 61.3-90%; partial response: 22.6%) versus the chlorambucil only group (complete response: 35.5-75%; partial response: 19.4%) with Oh *et al*. (2010) reporting that the complete response rates were significantly different ($p<0.05$). The 5-year event-free survival rates were higher in the chlorambucil only group (68%) compared to the chlorambucil plus rituximab group (52%) but this group had lower 10-year progression free survival rates (74% versus 94%) and 5-year overall survival rates (90% versus 100%).

The use of radiotherapy compared to other treatments (predominately surgery) was reported in two observational studies (Olszewski *et al*., 2014 and Wohrer *et al*, 2014). Olszewski *et al*. (2014) reported on over 7000 patients with MALT lymphoma (>10 body sites) using the SEER database. The study reported very low quality evidence of an overall lymphoma related death rate ranging from 0-9.3% in the radiotherapy group compared to 4-12.8% in the other treatments group. Olszewski *et al*. (2014) reported no significant differences in the treatment groups and an overall relative survival rate at 10 years of 85.7%. Wohrer *et al*, (2014) reported a retrospective comparison of outcomes according to treatment in a series of 185 patients with extra-gastric MALT. Treatment response ranged from 100% with surgery to 33% with antibiotics, this was very low quality evidence because treatment choice was related to disease stage and site leading to baseline differences in patient characteristics. Five year progression free survival ranged from 68% with surgery to less than 40% with antibiotics.

4.2.1.1.2 Regardless of helicobacter infection, what is the most effective first-line treatment in patients with Gastric MALT lymphoma?

Four studies reported data on the use systemic treatment as first-line treatment in patients with gastric MALT lymphoma. Avilés *et al*. (2005) reported a randomised control trial in which 241 patients with stage I or IIE (according to the Lugano Conference criteria, 1994) low grade Gastric MALT previously untreated were randomly assigned to either receive radiotherapy (n=78), chemotherapy (n=83) or surgery (n=80). With a median follow-up of 7.5 years (range 4.8-11.6 years) the RCT provided high quality evidence for complete response rates of 100% in each treatment arm. The 10-year event-free survival rate was significantly higher in the chemotherapy arm (87%) compared to the radiotherapy (n=52%) and the surgery (n=52%) arms ($p=0.01$). In addition, 10-year overall survival was highest in the chemotherapy arm (87%) compared to the radiotherapy (75%) and the surgery (80%) arms ($p=0.04$). There were no treatment related deaths and late toxicity was reported to be mild in all arms.

One observational study (Amiot *et al*. 2014) compared the use of alkylating agents to rituximab and chemotherapy plus rituximab in 107 patients with gastric MALT lymphoma. The study reported very low quality evidence of significantly higher overall response rates in the chemotherapy plus rituximab group (100%) compared to the rituximab alone group (73%, $p<0.01$)) and the alkylating agents group (68%, $p<0.05$). The chemotherapy plus rituximab group had higher complete response (92%) compared to the rituximab only group (64%, $p<0.05$) and the alkylating agents group (66%, $p<0.05$). In multivariate analysis the 5-year progression free survival rates were higher in the chemotherapy plus rituximab group (89%) compared to the rituximab group (70%) and the alkylating agents group (68%, $p<0.04$). However, overall survival rates did not differ between the three groups (chemotherapy plus rituximab: 96% versus rituximab: 95% versus alkylating agents: 91%). Toxic events were significantly more frequent in the two groups treated with alkylating agents ($p=0.04$ for the

comparison of alkylating agents versus rituximab and p<0.001 for the comparison of combination therapy versus rituximab).

One observational study (Olszewski *et al*., 2013) compared the use of radiotherapy and chemotherapy in 347 patients with MALT lymphoma and the use of chemotherapy plus rituximab versus chemotherapy in 102 patients with MALT lymphoma. The study reported very low quality evidence of no difference in lymphoma related death rates between the rituximab (17.7%) and the chemotherapy plus rituximab groups (22.4%) but a significantly lower rate of lymphoma related deaths when comparing radiotherapy (5.3%) to chemotherapy (19.1%, P<0.001). Increased rate of neutropenic infection was reported in the chemotherapy plus rituximab group compared to the rituximab alone group (p<0.01)

One randomised control trial reported the use of systemic treatment as first-line treatment in patients with high grade MALT lymphoma. Aviles *et al*. (2006) reported a randomised control trial in which 108 patients with stage I or IIE (according to the Lugano Conference criteria, 1994) B-cell CD10+ high grade primary gastric lymphoma (diagnosis according to the criteria of Isaacson, 1994) previously untreated were randomly assigned to either receive combined therapy of surgery and chemotherapy (n=52) or chemotherapy alone (n=50). With a mean follow-up of 88.6 months (range: 61-132 months) the RCT provided high quality evidence for complete response rates in the combined therapy group (94%, 95% CI: 88-99%) that were no different to those in the chemotherapy alone group (96%, 95% CI: 89-100%) (p=0.5). In addition, there were no differences in the 5-year event free survival (combined therapy: 70% versus chemotherapy alone: 67%, p=0.5) and 5-year overall survival rates (combined therapy: 78% versus chemotherapy alone: 76%, p=0.8). There were no treatment related deaths and late toxicity related to surgery was reported to be mild.

4.2.1.1.3 What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, positive for helicobacter infection?

One systematic review (Zullo *et al*., 2009) and two observational studies provided evidence from 36 observational studies reporting very low quality evidence for the use of eradication therapy for *helicobacter pylori* in patients with low graded gastric MALT (and DLBCL-MALT [n=56; 4.7%]) lymphoma positive for the *helicobacter pylori* infection. The 36 studies (26 prospective and 10 retrospective) provided data from 1495 participants (median sample size = 30, range: 4-189) treated most frequently with a standard triple therapy with a proton pump inhibitor plus two antibiotics twice daily (a combination of two of the following: amoxicillin, clarithromycin, metronidazole/tinidazole), administered for 7-28 days. The pooled overall lymphoma regression rate for the 34 observational studies included in the Zullo *et al*. (2009) systematic review was 77.8% and in the Zucca *et al*. (2000) observational study it was 70%. Zucca *et al*. (2000) and Vrieling *et al*. (2008) reported complete remission rates of 66.1% and partial remission rates of 13.4%, with Zucca *et al*. (2000) reporting lymphoma relapse in 7% of their sample (follow-up median: 26 months). Finally, Vrieling *et al*. (2008) reported a 5-year overall survival rate of 89% in their sample.

4.2.1.1.4 What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, negative for helicobacter infection?

Eleven observational studies (data extracted from one systematic review: Zullo *et al*., 2013) reported very low quality evidence for the use of eradication therapy for *helicobacter pylori* in patients with early stage low grade (I, II) gastric MALT lymphoma negative for the *helicobacter pylori* infection. The 11 studies (4 prospective multicentre studies, 6 retrospective single-centre studies, 1 case report) provided data from 110 participants, treated with predominately standard triple therapy (10/11 studies), administered for 7-28 days. The majority of studies reported were from Asia (n=8; 72.7%), with the remaining from Europe (n=2; 18.2%) and the United States (n=1; 9.1%). Complete remission rate was 15.5% (17/110). Zullo *et al*. (2013) extracted data on lymphoma relapse at long-term follow-up in 3 studies (5.5%) with lymphoma relapse reported in 1 patient at 14 months, with the remaining 7 patients still in remission at 25-48 months follow-up.

4.2.1.1.5 What is the effectiveness of antibiotic therapy in patients with Gastric MALT lymphoma, regardless of helicobacter infection status?

Five observational studies reported very low quality evidence for the use of eradication therapy for *helicobacter pylori* in patients with early stage low grade gastric MALT lymphoma (staging systems reported: Blackledge modified Lugano; Ann Arbor). The 5 studies provided data from 455 participants, treated with predominately standard triple therapy (3/5 studies). The majority of patients were positive for the *helicobacter pylori* infection (n=279, 79%; H. pylori status was not reported in two studies). Complete remission rates ranging from 64-90% were reported in 4 observational studies (Choi *et al*., 2013; Park *et al*., 2010; Stathis *et al*., 2009; Ueda *et al*., 2013) and an overall lymphoma regression rate of 73% (Stathis *et al*., 2009; Yepes *et al*., 2012) with partial remission rates of 14.2% (Choi *et al*., 2013; Stathis *et al*. 2009). Lymphoma relapse was reported in 17% of two samples (Choi *et al*., 2013; Stathis *et al*., 2009) with a 10-year overall survival (follow-up median 6.3 years) of 83% (Stathis *et al*., 2009).

4.2.1.1.6 What is the most effective management strategy for patients with Gastric MALT lymphoma after treatment for helicobacter pylori infection eradication?

No response to antibiotic therapy

One systematic review (Zullo *et al*., 2010) provided evidence from 29 studies of low quality evidence assessing treatment of low-grade Gastric MALT lymphoma (stage IE1-IE2 or IIE1 according to Ann Arbor classification as modified by Musshof) unresponsive to *helicobacter pylori* eradication therapy. The 29 studies (21 prospective, 8 retrospective) provided evaluable data from 329 participants, of which 315 underwent oncologic therapy due to lymphoma persistence (successful eradicated patients n=233; infection persistence despite one or more antibiotic therapy n=45; lymphoma relapse at follow-up n=37). A total of 68 (21.6%) received chemotherapy, 112 (35.6%) received radiotherapy; 27 received rituximab (11.6%) and 80 underwent surgery (25.4%). Radiotherapy achieved a significantly higher remission rate (97.3%) compared to chemotherapy (85.3%, p=0.007). Remission rates for surgery (92.5%) were comparable to radiotherapy (p=0.2) and chemotherapy (p=0.2). Following monotherapy, lymphoma remission rate (59.3%) was significantly lower as compared with radiotherapy (p<0.001), surgery (p=0.004) and chemotherapy (p=0.006). When comparing the lymphoma remission rates achieved by a single therapy (overall considered: 287 patients) with that of combined treatments no statistically significant differences emerged (89.6% versus 96.4%, p=0.6). Zullo *et al*. (2010) report that radiotherapy alone was both the most frequently chosen therapy and the most effective in patients with low grade gastric MALT lymphoma unresponsive to anti-*helicobacter* therapy. However, Zullo *et al*. (2010) also reported that of the 329 evaluable patients 14 (4.2%) had a reported remission at follow-up without any further therapy following H. pylori eradiation.

Remission after antibiotic therapy

Hancock *et al*. (2008) reported a randomised control trial in which 110 stage I patients (Blackledge modified Lugano staging system) successfully treated for H. pylori infection were randomised to receive either chlorambucil (n=56, given for a median of 29 weeks [3-39 weeks]) or to be observed (n=54). The trial was stopped early due to slow recruitment (power calculations required a total of 173 patients). With a median follow-up of 58 months (4-115 months) the RCT reported moderate quality evidence for 5-year recurrence rates of 21% in the observation arm and 11% in the chlorambucil arm (95% CI: 9-29%; p=0.15). In total 22 patients (11 in each) had disease recurrence/progression or died with no difference between the two arms (Hazard Ratio [HR] =0.96, 95% CI: 0.41-2.2; p=0.91). The overall 5-year recurrence/progression free rate for all randomised patients was 79%. There was no overall survival difference between the two arms (HR=1.93, 95% CI: 0.39-9.58; p=0.42) with a 5-year overall survival rate for all randomised patients of 93%. As treatment was accepted as

standard treatment in most European countries at the time of the study, toxicity data were not collected in detail without any cases of severe treatment-related toxicity were reported.

One observational study (Kondo *et al*., 2012) reported the follow-up of 61 patients who had responded to *helicobacter pylori* eradication therapy. All patients were underwent a watch and wait strategy involving upper gastrointestinal endoscopy, biopsy and abdominal CT every three months in the first year, every 4 months in the second year and at intervals of 6 months in the third year and beyond. With a median follow-up of 78.4 months the study reported very low quality evidence for 5-year overall survival rates of 100% and a lymphoma relapse rate of 14.8%.

4.2.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Gastric MALT lymphoma: localised disease** **Offer 1 or more lines of *Helicobacter pylori* eradication therapy, without any concurrent therapy, to people with *H. pylori*-positive gastric MALT lymphoma. (see the NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults).** **Consider *H. pylori* eradication therapy for people with *H. pylori*-negative gastric MALT lymphoma. (see the NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults).** **Consider 'watch and wait' (observation without therapy) for people with gastric MALT lymphoma that responds clinically and endoscopically to *H. pylori* eradication therapy but who have residual disease shown by surveillance biopsies of the stomach, unless high-risk features are present.** **For people with residual MALT lymphoma after *H. pylori* eradication therapy who are at high risk of progression [*H. pylori*-negative at initial presentation or t(11:18) translocation], consider a choice of the following, in discussion with the person:** • **chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[b] or** • **gastric radiotherapy.** **For people with progressive gastric MALT lymphoma, offer a choice of:** • **chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[c] or**

[b] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[cc] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed

	• **gastric radiotherapy.** **<u>Gastric MALT lymphoma: disseminated disease</u>** **Offer *H. pylori* eradication therapy to people with disseminated H. pylori-positive gastric MALT lymphoma (see the NICE guideline on gastro-oesophageal reflux disease and dyspepsia in adults).** **Offer chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[d] to people with disseminated gastric MALT lymphoma who need treatment; for example, people who are symptomatic or with threatened vital organ function.** **Consider 'watch and wait' (observation without therapy) for people with disseminated gastric MALT lymphoma who are asymptomatic and do not have threatened vital organ function.** ***Non-gastric MALT lymphoma*** **For people with non-gastric MALT lymphoma, take into account the following before recommending any treatment:** **site of involvement and potential for organ dysfunction** • **whether it is localised or disseminated** • **the morbidity associated with any treatment proposed** • **the person's overall fitness.** **Offer chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[e] to people with non-gastric MALT lymphoma for whom radiotherapy is not suitable or who have disseminated disease and need treatment.** **Consider radiotherapy for people with localised disease sites of non-gastric MALT lymphoma, irrespective of stage.** **Consider 'watch and wait' (observation without therapy) for people with clinically non-progressive localised non-gastric MALT lymphoma that is unlikely to result in vital organ dysfunction, who are asymptomatic and for whom radiotherapy is not suitable.**
Relative value placed on the outcomes considered	The GC considered progression free survival, toxicity (treatment related morbidity), response to first line *helicobacter pylori* eradication therapy, and overall survival to be the critical outcomes for this topic. Survival rates and level of toxicity associated with systemic therapies are of particular importance to people with MALT

consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[d] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[e] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	lymphoma. Response to first-line *helicobacter pylori* eradication therapy was used by the GC to assess the need for systemic therapies in patients with gastric MALT lymphoma. Health related quality of life (HRQoL) was considered an important outcome though no evidence was identified.
Quality of the evidence	The quality of the evidence ranged from very low to high quality for individual outcomes as assessed using GRADE. Evidence was downgraded for imprecision, indirectness and for study limitations. Specific issues with the evidence included: • Underpowered randomised control trials • Non-randomised comparative studies; • Non-comparative study designs • Variation in measurement of outcomes (e.g. lymphoma regression, complete response) • Variation in the diagnostic tests for *helicobacter pylori* detection • Limited available data concerning non-gastric MALT
Trade off between clinical benefits and harms	*Patients with non-gastric MALT lymphoma* Due to lack of high quality evidence (small sample sizes) for antibiotic therapy for treatment of non-gastric MALT the GC were unable to make a recommendation. There was a lack of high quality evidence relating to patients with asymptomatic, non-progressive, localised disease that is unlikely to produce vital organ dysfunction and patients with localised symptomatic disease sites of non-gastric MALT irrespective of stage which meant the GC could not make strong recommendations. Despite this lack of evidence, the GC considered it important to make recommendations for this patient group around observation and treatment of this patient group. Despite a lack of available high quality evidence to recommend chemotherapy for patients for whom radiotherapy is unsuitable or patients with disseminated non-gastric MALT who require treatment, the GC made a strong recommendation for the use of chemotherapy. This was because there was no other treatment available so it was important that a recommendation on the use of chemotherapy was included for this patient group. Chlorambucil and CVP were given as examples of chemotherapy based on the evidence of their effectiveness. The evidence also indicated that the combination of chemotherapy with rituximab was more effective than chemotherapy alone. *Patients with Gastric MALT lymphoma* The GC made a strong recommendation for *helicobacter pylori* antibiotic eradication therapy in all patients with gastric MALT lymphoma because they thought it was important to reduce the use of toxic systemic therapies in some of these patients. There was evidence for the use *helicobacter* eradication therapy in patients with gastric MALT lymphoma positive for *helicobacter pylori*. However, the evidence base for the use of *helicobacter* eradication therapy in patients with gastric MALT lymphoma negative for *helicobacter pylori* was limited but suggested that in these patients around 15% will not require further treatment with

	systemic therapies. In addition, the GC considered that the detection of *helicobacter pylori* can vary depending on the diagnostic test used therefore, the GC used their clinical judgement to make a recommendation to use *helicobacter* eradication therapy in patients with gastric MALT lymphoma negative for *helicobacter* eradication therapy (in case this indicates a false negative). In patients with gastric MALT lymphoma who received antibiotic therapy, the GC considered that the recommendation for these patients needed to include assessment of response to antibiotic therapy in order to inform further treatment in these patients. However as the question had not investigated which assessment strategy (e.g., endoscopy, and imaging) was the most effective, the GC recommended endoscopy on the basis that the majority of the included evidence appraised used endoscopy to assess response to antibiotic therapy, and in their clinical opinion endoscopy is the gold standard for assessing response in these patients. The use of toxic systemic therapies is associated with treatment related morbidity and toxic side effects, and while the GC acknowledged that for some patients this is unavoidable due to the requirement for toxic systemic therapies, they considered that the recommendations for patients with gastric MALT lymphoma will reduce the number of patients needing to receive toxic systemic treatment overall. Specifically, the GC thought that the recommendation to use *helicobacter* antibiotic eradication therapy in all patients with gastric MALT would result in a reduction in the need for upfront toxic systemic therapies in some of these patients due to the high lymphoma regression rates after the eradication therapy. The GC acknowledged that in patients with gastric MALT lymphoma who have received *helicobacter* eradication therapy but no systemic therapy, there might be an increase in psychological distress associated with expectant management of the lymphoma. The GC suggested that a better defined treatment pathway for all patients with MALT lymphoma may help to negate any negative psychological impact of expectant management. The GC considered that in patients with gastric MALT lymphoma who receive *helicobacter* eradication therapy but do not respond or have progression in their lymphoma resulting in a need for systemic therapies, there was no evidence to suggest that the delay in starting intensive systemic therapies as a result of undergoing *helicobacter* eradication therapy first, is unlikely to impact on overall survival rates.
Trade off between net health benefits and resource use	No relevant health economic evidence was identified and no health economic model was built for this topic The resource impact associated with the majority of these recommendations was thought to be minimal as they are a consolidation of current practice. However, the recommendations to use antibiotic therapy differ from some current clinical recommendations and so there could be resource implications. However, it was thought that the use of

	antibiotic therapies would most likely be cost-effective because of its relatively low upfront cost as well as the resulting reduction in the the use of systemic therapies that would be expected.
Other considerations	The GC thought that the recommendations would eliminate variation in practice by providing a better defined treatment pathway for patients with all types of MALT lymphoma. The GC thought that the recommendations would consolidate current practice, providing clarity on the treatment pathway in the patient populations. The GC noted that there will need to be a re-organisation of practice for the treatment of patients with gastric MALT lymphoma and there will be a minor change in practice through the reinforcement of current best practice for the treatment of patients with non-gastric MALT lymphoma. The GC noted that the recommendations about the use of antibiotic therapy in patients with gastric MALT lymphoma negative for *helicobacter pylori* infection differ from current clinical recommendations (e.g. American Society for Haematology). However, the GC considered that the recommendations are justified considering the current evidence base, clinical opinion, and the low cost of antibiotic therapy.

4.3 Mantle cell lymphoma

Mantle cell lymphoma (MCL) accounts for 5-10% of NHL diagnoses, occurring predominantly in people over the age of 50 years. Historically MCL has been considered to combine adverse features of both low grade and high grade NHL in that cure is elusive despite attainment of apparent complete clinical responses following immunochemotherapy, but clinical progression is often relatively aggressive. Most patients present with advanced disease (stage IV), and bone marrow involvement is common. Median overall survival with immunochemotherapy is between 3 and 4 years. MCL is a distinct type of B-cell lymphoma genetically characterised by the t(11;14) translocation and cyclin D1 over-expression in the majority of cases. Although the median overall survival of patients has improved MCL is still has one of the poorest outcomes among the B-cell lymphomas

4.3.1 First line treatment

There is no accepted standard of care for patients with mantle cell lymphoma (MCL). The paucity of randomised control data, the relative infrequency of this lymphoma subtype, historical problems in identifying this entity correctly and finding trials with only MCL patients included have all contributed to this.

The majority of patients have advanced stage disease and require systemic treatment. The regimens that have been studied are mostly similar to those used in other B-cell lymphomas-chemotherapy with or without rituximab. In everyday practice the choice of therapy often depends on whether the patient is fit and considered for intensification with high-dose chemotherapy and autologous stem cell transplantation (ASCT). Several groups have demonstrated excellent activity of cytarabine (cytosine arabinoside)-based combinations, admittedly with greater toxicity than other chemotherapy options.

A small number of patients present with limited stage disease and are frequently considered for radiotherapy. There is also an ‘indolent’ form of MCL which may be indentified clinically.

It may be that newer agents will have a profound impact on the first-line treatment of MCL, on the basis of results of phase 1 studies reported in relapsed MCL patients. As mentioned,

recommendations at this point in time are likely to be dependent on factors such as patient fitness, the MCL prognostic index and the intention of therapy.

Clinical question: What is the most effective first-line treatment for people with mantle-cell lymphoma?

4.3.1.1 Clinical evidence (see section 4.3.1 in Appendix G)

Evidence came from seven randomised controlled trials, 12 cohort studies (one prospective) and one retrospective case series.

4.3.1.1.1 Chemotherapy regimens

CHOP

One randomised control trial (RCT; evidence appraised at two time points: Lenz *et al*. 2005 and Hoster *et al*. 2008) comparing the use of CHOP+rituximab (RCHOP) to the use of CHOP alone in 123 patients with stage III/IV mantle cell lymphoma provided low quality evidence of higher response rates in the patients treated with RCHOP (complete: 33%, complete plus partial: 92%) compared to the patients treated with CHOP alone (complete: 8%, complete plus partial: 75%, $p<0.05$). The patients treated with RCHOP had a longer median time to treatment failure (28 months) and response duration (29 months) compared to the patients treated with CHOP alone (14 months, $p<0.001$; 29 months, $p<0.01$). However, there was no statistically significant difference in the 5 year overall survival rates (RCHOP: 59%, median not reached; CHOP: 46%, 59 months). Patients treated with RCHOP had higher rates of grade 3 and 4 granulocytopenia (63% versus 53%, $p<0.01$) and grade 1 and 2 allergic reactions (6% versus 0%, $p<0.0001$) compared to the patients treated with CHOP alone.

One observational comparative study (Bernard *et al*. 2001) compared the use of CHOP to C-VAD, CVP and Chlorambucil in 33 patients with blastic mantle cell lymphoma (85% stage IV, median age: 62, range: 29-80), reporting very low quality evidence of complete response rates of 57.9% in the CHOP group compared to 14.3% in the C-VAD group and 0% in the CVP and Chlorambucil groups. Treatment failure rates were 21.1% in the CHOP group, 71.4% in the C-VAD group, 75% in the CVP group and 100% in the Chlorambucil group. The patients in the CHOP group had a 90.9% rate of relapse after complete response. No statistical analyses were presented to compare the response rates in these patients.

One observational comparative study (Ying *et al*. 2012) compared the use of rituximab+CHOP (RCHOP) to conventional chemotherapy regimens in 30 patients with stage I-IV mantle cell lymphoma reporting very low quality evidence of uncertainty concerning any survival benefit of the addition of rituximab to CHOP (2 year progression free survival: 53%; 2 year overall survival: 59%) compared to those patients treated with conventional chemotherapy regimens not containing rituximab (PFS: 25%, $p=0.083$; OS: 72%, $p=0.807$). Response rates for the two groups did not differ significantly.

DHAP

Very low quality evidence from one phase II trial (Le Gouil *et al*. 2010) indicated an overall response rate of 92% and a complete response rate of 51% in 63 patients with mantle cell lymphoma (median age: 57 years, range: 30-65; 77% stage IV). One RCT (Hermine *et al*. 2012; 2013) comparing the use of CHOP+DHAP+rituximab+ARA-C versus the use of CHOP+rituximab in 455 patients with stage III-IV mantle cell lymphoma (median age 55 years, whole sample ≤65 years old) provided moderate quality evidence of significantly higher complete response rates of 36% in the CHOP+DHAP+rituximab+ARA-C compared to 25% in the CHOP+rituximab arm ($p=0.012$) but no difference in overall response rates (95% versus 90%), nor relapse rates after response (40% versus 81%). The patients treated with

CHOP+DHAP+rituximab+ARA-C had significantly longer time to treatment failure rates (88 months versus 46 months: p=0.038) and better overall survival rates (median not reached versus 88 months; p=0.045) compared to patients treated with CHOP+rituximab (median follow-up of 51 months). Adverse events were comparable in the two groups with the exception of grade 3/4 haematological toxicity, which were higher in the CHOP+DHAP+rituximab+ARA-C compared to the CHOP+rituximab group (hemoglobin; white blood count; platelets: 30%; 75%; 74% versus 9%; 50%; 10%, no p values presented to assess significance).

FC

One RCT (Rule *et al*. 2011) comparing the use of FC+rituximab (FCR: Fludarabine, Cyclophosphamide) versus the use of FC alone in 370 patients with mantle cell lymphoma (median age: 66 years, range: 36-88) reported moderate quality evidence for better complete and overall response rates in patients treated with the addition of rituximab (complete: 64.7% versus 46.9%, p<0.01; overall: 90.6% versus 79.8%, p<0.01). There was no difference in progressive disease rates between the two groups (FCR: 5.8% versus FC: 11.9%). The patients treated with the addition of rituximab had significantly longer progression free (30.6 months versus 16.1 months: hazard ratio [HR]: 0.56, 95% confidence interval [CI] 0.43-0.73, p<0.001) and overall survival (45.7 months versus 37 months: HR: 0.72, CI: 0.54-0.97, p<0.05) rates (median follow-up 38.8 months) compared to those patients treated with FC alone.

One RCT (Kluin-Nelemans *et al*. 2012) comparing the use of FCR to CHOP+rituximab (RCHOP) in 485 patients with stage II-IV mantle cell lymphoma (median age: 66 years, range: 60-87) provided moderate quality evidence for higher overall response rates in the patients treated with RCHOP (86.2%) compared to the patients treated with FCR (78%) and lower rates of progressive disease (5% versus 14%) but higher complete response rates in the FCR group (39.8%) compared to the RCHOP group (33.9%). However, none of these comparisons were significantly different. Patients treated with RCHOP did have significantly higher overall survival rates (62%) compared to the patients treated with FCR (47%; HR: 1.50, CI: 1.13-1.99, p=0.005) (median follow-up 37 months). Rates of grade 1 and 2 anemia, leukocytopenia, constipation and neuropathy were higher in the RCHOP group (68%; 29%; 28%; 36%) compared to the FCR group (59%; 18%; 15%; 7%: p<0.05). Rates of grade 1 and 2 elevated bilirubin and nausea were higher in the FCR group (15%; 36%) compared to the RCHOP group (8%; 26%, p<0.05). Rates of grade 3 and 4 anaemia and leukocytopenia were higher in the FCR group (20%; 73%) compared to the RCHOP group (12%; 59%, p<0.05)

MCP

One RCT (Nickenig *et al*. 2006) comparing the use of MCP (Mitoxantrone, Chlorambucil and prednisolone) versus CHOP in 86 patients with stage III/IV mantle cell lymphoma (median age: 61, range: 35-79) provided low quality evidence of no difference between response rates (complete: 20% versus 15.2%; overall: 72.5% versus 87%) and treatment failures (90% versus 80.4%) in the patients treated with MCP versus those treated with CHOP. There was no significant difference in the 5-year time to treatment failure (MCP: 9% [CI: 0-19] versus CHOP: 20% [8-32], p=0.08) nor the overall survival rates (MCP: 48 months, 31% [CI: 15-47] versus CHOP: 61 months, 57% [43-72], p=0.058).

One RCT (Herold *et al*. 2007) comparing the use of MCP+rituximab (RMCP) versus MCP alone in 90 patients with mantle cell lymphoma (median age not reported) provided very low quality evidence of no difference between the two groups with regards to complete (RMCP: 31.8% versus MCP: 15.2%, p=0.082) and overall (RMCP: 70.5% versus MCP: 63%, p=0.51) response rates and progression free survival (RMCP: 20.5 months, 31% versus MCP: 19 months 14%, p=0.25), event free survival (RMCP: 19 months, 27% versus MCP: 14 months 11.5%, p=0.14) and overall survival rates at 42 months (RMCP: 56 months, 60% versus MCP: 50 months 61%, p=0.49) (median follow-up: 43 months).

FLU

One RCT (Zinzani *et al*. 2000) comparing the use of FLU-ID (Fludarabin and Idarubicin) to FLU alone in 29 patients with stage II-IV mantle cell lymphoma (median age not reported) provided low quality evidence of uncertainty in the value of adding Idarubicin to the regimen, with no difference in response rates (complete: FLU-ID: 33.3% versus FLU: 27.3%; FLU-ID: 27.8% versus FLU: 45.5%) or relapse rates after complete response (FLU-ID: 16.7% versus FLU: 33.3%) (median follow-up: 19 months). There were no fatalities resulting from drug-toxic effects.

R-HyperCVAD

Three observational comparative studies (LaCasce *et al*. 2012; Udvardy *et al*. 2012; Miura *et al*. 2011) compared the use of R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, high dose methotrexate and cytarabine) to R-CHOP in 197 patients with stage I-IV mantle cell lymphoma (age range: 28 to >60). Two studies (Udvardy *et al*. 2012; Miura *et al*. 2011) provided very low quality evidence of higher complete response rates in the patients receiving R-HyperCVAD (80%) compared to the patients receiving RCHOP (42.3-49%, p<0.05 in the Miura *et al*. 2011 study). One study (LaCasce *et al*. 2012) provided very low quality evidence of lower progressive disease in the patients receiving R-HyperCVAD (37%) compared to the patients receiving RCHOP (72% relative risk: 0.52, CI: 0.36-0.74). Progression free survival was reported to be not significantly different in the Miura *et al*. (2011) study but significantly higher in the R-HyperCVAD group (58% [CI: 44-69]) compared to the RCHOP group (18% [CI: 6-36]) in the LaCasce *et al*. (2012) study (p<0.01). Overall survival rates between the two groups did not differ significantly in both the Miura *et al*. (2011, HR: 0.81, CI: 0.23-2.24) and the LaCasce *et al*. (2012, p=0.07) studies. Udvardy *et al*. (2012) reported that adverse events were significantly higher in R-HyperCVAD group (91.6%) compared to the RCHOP group (55.5%, p<0.05). However, LaCasce *et al*. (2012) reported no significant difference between the two groups concerning rates of febrile neutropenia or the rates of complications requiring hospital admission.

Nordic MCL2

One observational comparative study (Abrahamsson *et al*. 2014) compared seven chemotherapy regimens (CHOP, CHOP/cytarabine, FC, Chlorambucil, cytarabine, CVP, other) to the Nordic MCL2 regimen in 1015 patients with stage I-IV mantle cell lymphoma (median age: 70, range: 28-95) reporting low quality evidence of a poorer survival rate for the patients treated with CVP compared to patients treated with the Nordic MCL2 regimen (p<0.001).

Addition of rituximab to chemotherapy regimens

Three observational comparative studies (Leux *et al*. 2014, Kang *et al*. 2014, Griffiths *et al*. 2011) assessed the addition of rituximab to chemotherapy regimens in 897 patients with stage I-IV mantle cell lymphoma (age range: 26-78). Two studies reported an overall survival benefit from the addition of rituximab. Griffiths *et al*. (2011) provided low quality evidence that the addition of rituximab was associated with significantly lower cancer mortality rates at 2 years (HR for cancer mortality: 0.39, 95% CI: 0.23-0.67, p<0.001) but not non-cancer mortality rates (p=0.77). Patients treated with the addition of rituximab were more likely to be alive two years after beginning their first-line therapy (63%) compared to patients treated with chemotherapy alone (52%, p<0.001). Leux *et al*. (2014) provided very low quality evidence that patients treated with chemotherapy + rituximab had higher median overall survival rates (42 months) compared to those treated with chemotherapy alone (24 months, HR: 0.5, 95% CI: 0.1-0.7). However, Kang *et al*. (2014) provided very low quality evidence of uncertainty in the survival benefit for patients treated with rituximab regimens compared to those treated

with non-rituximab containing regimens (Event free survival HR: 1.60, 95% CI: 0.93-2.75; Overall survival HR: 0.89, 95% CI: 0.51-1.54).

One observational comparative study (Abrahamsson *et al*. 2014) compared the addition of rituximab to eight chemotherapy regimens (Nordic MCL2, CHOP, CHOP/cytarabine, FC, Chlorambucil, cytarabine, CVP, other) to the Nordic MCL2 regimen in 1015 patients with stage I-IV mantle cell lymphoma (median age: 70, range: 28-95) reporting low quality evidence of a higher survival rate for the patients treated with regimens that included rituximab compared to patients treated with chemotherapy alone (p<0.001).

4.3.1.1.2 Radiotherapy

One observational comparative study (Leitch *et al*. 2003) compared the use of radiotherapy to no radiotherapy in 26 patients with stage I-II mantle cell lymphoma (median age not reported, <60:7; ≥60: 19) reporting very low quality evidence of a 5-year progression free survival benefit in patients receiving radiation therapy (73%) compared to those patients who received no radiation therapy (13%, p<0.05). Overall survival and response rates were not significantly different between the two groups (median follow-up time: 59 months, range: 5-85).

One observational comparative study (Dabaja *et al*. 2014) compared the use of radiotherapy and chemotherapy to either treatment alone in 160 patients with stage I-II mantle cell lymphoma (median age not reported ≤60: 70. >60: 90) reporting very low quality evidence of no survival benefit when combining the two treatments (10 year disease free survival rate: 44%; 10 year overall survival rate: 61%) compared to chemotherapy alone (DFS: 40%; OS: 70%) and radiotherapy alone (DFS: 54%, p=0.44; OS: 56%, p=0.68) (median follow-up time: 60 months, range: 4-245).

One observational study (Abrahamsson *et al*. 2014) provided low quality evidence of a 3 year overall survival rate of 93% in 43 patients with stage I-II mantle cell lymphoma receiving radiotherapy.

4.3.1.1.3 Watch and wait

One observational comparative study (Martin *et al*. 2009) compared 97 patients with stage I-IV mantle cell lymphoma receiving early treatment to those undergoing watch and wait (median age not reported, range: 40-89). With a median follow-up time of 42.5 months in the early treatment group and 55 months in the watch and wait group, the study provided very low quality evidence of a median overall survival rate of 64 months (CI: 45-85) in the early treatment group with the median overall survival rate not yet reached the watch and wait (p=0.004).

One observational study (Abrahamsson *et al*. 2014) provided low quality evidence of a 3 year overall survival rate of 79% in 29 patients with stage IV mantle cell lymphoma undergoing watch and wait.

4.3.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer chemotherapy in combination with rituximab[f] as first-line treatment for people with advanced-stage mantle cell lymphoma who are symptomatic. Take the person's fitness into account when deciding on the intensity of chemotherapy.** **Consider cytarabine[g]-containing immunochemotherapy for people with advanced-stage mantle cell lymphoma who are fit enough to tolerate an intensive approach.** **Consider radiotherapy for people with localised stage I or II mantle cell lymphoma.** **Consider 'watch and wait' (observation without therapy) until disease progression for people with clinically non-progressive mantle cell lymphoma who are asymptomatic and for whom radiotherapy is not suitable.** **The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with mantle cell lymphoma, because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first-line treatment of mantle cell lymphoma' was is development. This technology appraisal is currently suspended.**
Relative value placed on the outcomes considered	The critical outcomes for this topic included overall survival and treatment toxicity. Treatment toxicity was considered critical as it may impact on subsequent treatments. Although not listed in the review protocol, evidence was included for response rate. The GC considered this evidence useful as it is likely to be associated with better patient outcomes.
Quality of the evidence	The quality of the evidence for this topic ranged from very low to moderate for all outcomes as assessed using GRADE. Evidence was downgraded for indirectness, limitations in study design and imprecision. Specific issues with the evidence included: • Lack of comparisons between some of the interventions (each study [especially the RCTs] compared different interventions making it difficult to pool and summarise across the evidence base) • Inclusion criteria (e.g. age) varied across trials and observational studies • A number of studies included had low sample sizes • Inclusion of conference abstracts with limited information concerning patient characteristics and study design impacted on

[f] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[g] At the time of publication (July 2016) cytarabine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	the appraisal of these studies. Evidence from such studies was downgraded for limitations in study design. • Limited very low-low quality evidence for outcomes concerning stage I-II mantle cell lymphoma • Limited low-very low quality evidence for outcomes concerning watch and wait • Only one study focused on patients with Blastoid variant MCL reporting very low quality evidence for the outcomes Non-comparative studies such as MCL-2 and other single arm phase 2 trials were excluded due to review protocol criteria. The GC considered that although a recommendation on radiotherapy was necessary and supported by the evidence; the lack of high quality evidence from randomised trials precluded the inclusion of a strong recommendation.
Trade off between clinical benefits and harms	The GC considered the radiotherapy recommendation would spare patients toxicity of chemotherapy while offering a similar or, in some cases, better progression free survival. The GC considered this recommendation for watch and wait would delay the need for chemotherapy in this group of patients without compromising their outcomes. The GC acknowledged that some patients may experience more anxiety with watch and wait programs. When discussing the recommendation for rituximab in combination with chemotherapy the GC acknowledged that the evidence showed that treatment response, progression free survival and overall survival were improved by clinically significant amounts in patients treated with rituximab in combination with chemotherapy when compared to chemotherapy alone. The GC considered the potential harm of rituximab is that it is additionally immunosuppressive, although the published evidence suggested adding rituximab would increase the rate grade 3-4 infections or allergic reactions by around 1%. Based on the evidence the GC considered the primary benefit of cytarabine regimens is the better response rates (with approximately 10% more responders) although they did acknowledge that cytarabine has higher treatment related toxicity (particularly grade 3/4 haematological toxicity) than other appraised regimens. Overall the GC thought that the benefits associated with each of the individual treatment recommendations offset the potential harms, which the GC considered manageable. The guideline committee did not assess evidence or develop recommendations on bendamustine for treating people with mantle cell lymphoma, because a NICE technology appraisal on 'the clinical and cost effectiveness of bendamustine in combination with rituximab within its licensed indication for the first-line treatment of mantle cell lymphoma' was is development. This technology appraisal is currently suspended.
Trade off between net health	No relevant health economic evidence was identified and no

benefits and resource use	health economic model was built for this topic, The GC thought that the recommendations reflected current practice and so no resource impact was expected. In addition, the recommendations were all thought likely to be cost-effectiive for the reasons specified below: The recommendation to offer rituximab in combination with chemotherapy is thought to be cost-effective. In comparison to chemotherapy alone, it will be more costly because of the addition of the rituximab which is estimated to cost £1,222.41 per dose. However the evidence showed that the addition of rituximab improves treatment response, progression free survival and overall survival by clinically significant amounts. These improvements would be expected to translate into greater effectiveness in QALY terms. The GC thought that it was highly likely that the strategy would be cost-effective in cost per QALY terms. This view is supported by cost-effectiveness analyses undertaken as part of NICE technology appraisals on the addition of rituximab to chemotherapy regimens in other NHL subtypes (such as TA243 on the use of rituximab for the first-line treatment of stage III-IV follicular lymphoma). The recommendation to consider cytarabine regimens is thought likely to be cost-effective because of the better effectiveness associated with these regimens at a comparable cost to the alternative chemotherapy regimens. The recommendation to consider radiotherapy in localised stage I or II mantle cell lymphoma is expected to be cost-effective. This is because radiotherapy should be less costly than chemotherapy (the alternative) while being at least equivalent and possibly superior in effectiveness terms (as it has a similar or, in some cases, superior PFS without the toxicitiy of chemotherapy). The recommendation to consider watch and wait is expected to be cost-effective as the need for costly chemotherapy should be delayed without compromising effectiveness.
Other considerations	A number of ongoing NICE technology appraisals (Lymphoma (mantle cell, relapsed, refractory) - lenalidomide [ID739] and Lymphoma (mantle cell, relapsed, refractory) - ibrutinib [ID753]) meant that the GC did not make a strong recommendation for cytarabine and they did not recommend specific, named regimens.

Recommendation	**Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable. [This recommendation is from Bortezomib for previously untreated mantle cell lymphoma (NICE technology appraisal guidance 370).]**
	These recommendations are from Bortezomib for previously untreated mantle cell lymphoma (NICE technology appraisal guidance 370). They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at

www.nice.org.uk/TA370.

4.3.2 Consolidation therapy in mantle cell lymphoma

Since more intensive induction regimens are associated with higher overall response rates, strategies involving consolidation of first response with high-dose therapy followed by autologous transplantation (ASCT) have been investigated. This improves median overall survival >10 years. This approach has therefore become accepted standard of care for those deemed eligible for ASCT. Nevertheless, late relapses beyond 5 years do occur, with no clear plateau on survival curves suggestive of definitive cure. Furthermore, patient groups with worse prognoses can be identified, for example, those with high MIPI-B (mantle cell lymphoma international prognostic index-biological) scores have 10-year overall survival rates of <25%.

Treatment of mantle cell lymphoma with allogeneic stem cell transplantation (alloHCT) has been reported since the late 1990s, mostly in small series, in an attempt to define whether a graft-versus-lymphoma effect is present and can translate into the potential for cure. The introduction of reduced intensity conditioning strategies broadened availability to the generally older patient population with mantle cell lymphoma. More recent studies do suggest the possibility of cure in a portion of patients, but experience remains limited, and toxicities are not insignificant. AlloHCT have frequently been employed later in the disease process, for example following failure of ASCT, with more limited data in first-line usage. Given the higher procedural mortality associated with alloHCT, and the improved overall survival seen following the introduction of ASCT as a consolidation for first-line responses, significant controversy exists over any role in first line treatment strategies. Whilst an argument can be made for a role in patients with high MIPI/MIPI-B scores, or those with less than a complete response to induction, the ability of alloHCT to overcome these adverse prognostic features remains uncertain

Clinical question: What is the effectiveness of first-line consolidation of high-dose therapy with autologous or allogeneic transplantation in people with mantle-cell lymphoma?

4.3.2.1 Clinical evidence (see section 4.3.2 in Appendix G)

Evidence came from one randomised controlled trial and eleven retrospective cohort studies.

4.3.2.1.1 Progression free survival

Upfront consolidation with autologous stem-cell transplantation (ASCT) compared to no consolidation or maintenance therapy significantly improved progression free survival rates in patients with mantle cell lymphoma

One RCT (Dreyling *et al*. 2005) reported moderate quality evidence of a longer median progression free survival in 62 patients with mantle cell lymphoma receiving myeloablative radio-chemotherapy (12Gy) and ASCT (39 months, 54%) compared to 60 patients receiving interferon-α maintenance therapy (17 months, 25%) (p=0.01). Assessing sub-group analyses by induction therapies the author notes that the difference in progression free survival no longer remained significant when only assessing patients treated with R-CHOP as their induction therapy (p=0.73). Lenz *et al*. (2005) reported very low quality evidence of a significant progression free survival benefit of any consolidation therapy (ASCT or interferon-α) in 85 patients with mantle cell lymphoma compared to no post remission treatment in 8 patients with mantle cell lymphoma (p=0.0002).

Five retrospective comparative reviews provided very low quality evidence of a progression free survival benefit in 168 patients with mantle cell lymphoma receiving induction therapy

and ASCT compared to 129 patients receiving induction therapy alone (Nastoupil *et al*. 2015; Frosch *et al*. 2015; Ahmadi *et al*. 2012; Schaffel *et al*. 2009; Hicks *et al*., 2006).

4.3.2.1.2 Overall survival

The value of consolidation with ASCT on overall survival rates in patients with mantle cell lymphoma varied between studies.

Dreyling *et al*. 2005 reported moderate quality evidence of no difference in the 3-year estimated overall survival rates in 122 patients with stage II-IV mantle cell lymphoma randomised to receive ASCT or interferon-α (p=0.18). When comparing consolidation to no further therapy two retrospective comparative studies provided very low quality evidence of no overall survival benefit of ASCT (Nastoupil *et al*., 2015; Schaffel *et al*., 2009) whereas four retrospective comparative studies provided very low quality evidence of an overall survival benefit of ASCT (Abrahamsson *et al*., 2014; Vose *et al*., 2012; Fieldman *et al*., 2010; Hicks *et al*., 2006). However, Fieldman *et al*. (2010) reported that ASCT provided an overall survival benefit only when comparing to patients treated with chemotherapy and rituximab and not when compared to patients treated with R-HyperCVAD. Finally, Cortelazzo *et al*. (2007) reported an increased overall survival rate in patients treated with doxorubicin or cisplatin, rituximab and ASCT compared to patients treated with Anthracycline or fludarabine alone but they did not report significance levels for these comparisons (conference abstract).

4.3.2.1.3 Adverse events

The majority of studies did not report any information concerning adverse events following ASCT. Dreyling *et al*. (2005) reported moderate quality evidence of a higher incidence of grade III and IV adverse events (e.g. Mucositis, anaemia, leukocytopenia, granulocytopenia, thrombocytopenia) in 60 patients treated with interferon-α compared to 62 patients treated with ASCT. However, patients treated with ASCT had a higher rate of infection related mortality (5%) compared to the patients treated with interferon-α (0%) (P value not reported). Nastoupil *et al*. (2015) and Mangel *et al*. (2004) provided very low quality evidence of no treatment related deaths in patients in their studies and Cortelazzo *et al*. (2007) reported 1.3% in their patients treated with ASCT compared to 0.8% in the patients receiving anthracycline or cyclophosphamide-fludarabine alone. Mangel *et al*. (2004) provided very low quality evidence of high rates of neutropenia (90%) and mucositis (60%) and moderate rates of pneumonititis (30% after ASCT) in patients treated with ASCT and rituximab maintenance but provided no comparison to the case controls who received induction therapy only. Finally, Frosch *et al*. (2015) provided very low quality evidence of significantly higher adverse events in patients treated with both R-HyperCVAD induction and ASCT (median 4) compared to R-CHOP and ASCT (median: 2, p=0.007), R-HyperCVAD alone (median: 1, p=0.008) and R-CHOP alone (median: 1.5, p=0.016)

There was no evidence to assess the effectiveness of upfront consolidation with allogeneic transplantation in patients with mantle cell lymphoma.

4.3.2.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider consolidation with autologous stem cell transplantation for people with chemosensitive mantle cell lymphoma (that is, there has been at least a partial response to induction chemotherapy) who are fit enough for**

	transplantation.
Relative value placed on the outcomes considered	Progression free survival was the critical outcome when drafting the recommendation. Other important outcomes for this topic included overall survival, disease free survival, progression free survival, treatment related mortality, treatment related morbidity and health related quality of life. No evidence for health related quality of life was identified.
Quality of the evidence	The quality of the evidence was very low to moderate as assessed using GRADE methodology. Evidence was downgraded for imprecision, study design limitations and indirectness. Apart from one randomised trial comparing autologous transplantation with interferon- α, the evidence came from non-randomised, comparative studies. For this reason the guideline committee were not able to make a strong recommendation.
Trade off between clinical benefits and harms	The GC thought the recommendation to consider autologous transplantation would prolong progression free survival; the evidence suggested a median progression free survival improvement of almost 2 years with autologous transplantation. The use of high dose therapy with autologous transplantation however was associated with toxicity including late effects and in some cases treatment related mortality. The GC considered that the increased progression free survival outweighed the harms due to late effects which can be managed and to some extent mitigated by surveillance.
Trade off between net health benefits and resource use	No economic evidence was identified and no economic model was built. The resource implications associated with the recommendation were thought to be negligible because the use of autologous transplantation as consolidation of induction chemotherapy is the current standard of care for people with chemosensitive mantle cell lymphoma. In comparison to the alternative courses of action, autologous transplantation was thought likely to be cost-effective. There would be increased costs associated with transplantation (in comparison to chemotherapy alone) with an autologous transplantation estimated to cost £34,000. However, the evidence suggested that progression free survival should be greatly improved with an autologous transplantation. These improvements would be expected to translate into superior effectiveness in QALY terms. The GC thought that it was likely that the strategy would be cost-effective in cost per QALY terms. This view is partially supported by extrapolating from the economic analysis conducted for this guideline in another NHL subtype. In patients with follicular lymphoma, it was found that autologous transplantation was cost-effective in comparison to chemotherapy with an ICER of £4,812 per QALY. Thus, it was demonstrated that autologous transplantation was cost-effective despite the high costs of initial therapy because of the substantial gains in effectiveness.
Other considerations	The GC considered that patients with pre-existing co-morbidities are unlikely to be candidates for autologous transplantation and that this will disproportionately affect older patients. The GC

	therefore based their recommendations on patient fitness rather than age. The GC chose not to make a research recommendation about upfront consolidation with allogeneic transplantation because a comparative study would not be feasibile.

4.3.3 Maintenance strategies in mantle cell lymphoma

Choice of initial therapy for MCL is complex due to the lack of available randomised trials. The role of maintenance therapy remains unclear. Interferon alpha has been studied by various groups but the overall effect on MCL outcomes coupled with the side effect profile has meant that this treatment has not been widely adopted.

Maintenance therapy is topical in MCL for several reasons. Progression free survival is significantly prolonged by the use of maintenance with rituximab, with acceptable toxicity, in other lymphoma subtypes. A recent study in MCL demonstrated that maintenance rituximab almost doubled the duration of remission in older patients responding to RCHOP, compared with maintenance interferon-α, although this study administered rituximab maintenance until patients progressed (or withdrew due to toxicity or patient preference). In addition, overall survival was also significantly improved among patients who responded to R-CHOP chemotherapy, though this benefit could not be demonstrated in patients receiving nucleoside analogue therapy. A positive effect has also been demonstrated in younger patients following stem cell transplant.

Clinical question: What is the effectiveness of first-line maintenance strategies compared with observation for people with mantle-cell lymphoma?

4.3.3.1 Clinical evidence (see section 4.3.3 in Appendix G)

Evidence came from two randomised controlled trials and four retrospective cohort studies.

4.3.3.1.1 Efficacy of maintenance therapy post-induction

Three studies reported the effectiveness of rituximab maintenance after first-line induction therapies in 349 patients with mantle-cell lymphoma, suggesting that the use of rituximab maintenance significantly increases duration of remission (Kluin-Nelemans *et al*., 2012) and progression free survival (Ahmadi *et al*., 2012; Vokurka *et al*., 2014) compared to other types of maintenance therapy (interferon-α) or no maintenance therapy at all ($p<0.05$).

One randomised control trial (RCT; Kluin-Nelemans *et al*., 2012) comparing the use of rituximab maintenance therapy to the use of Interferon-α maintenance therapy in 316 patients with stage II-IV mantle cell lymphoma provided low quality evidence of longer durations of remission in the patients receiving rituximab compared to those receiving interferon-α ($P<0.01$). Overall survival rates did not differ significantly between the rituximab and interferon-α groups (79% versus 67%, respectively), however, the author reports that type of induction therapy influenced the survival benefit of rituximab maintenance. In the 111 patients treated with the induction regimen R-FC there was no difference in the rates of remission nor the overall 4-year survival rate in patients treated with rituximab maintenance compared to those treated with interferon-α. Patients (N=163) treated with the induction regimen R-CHOP did show survival benefits from the use of rituximab maintenance, with such patients having longer duration of remission (not yet reached versus 36 months, $p<0.01$) and better 4-year overall survival rates (not yet reached versus 64 months, $p<0.01$) compared to patients treated with interferon-α . Patients tolerated rituximab maintenance better than interferon-α, with a third of patients in the rituximab maintenance group stopping therapy at 4 years (28%) compared to nearly 50% of patients in the interferon-α group at 1 year. In addition, patients receiving interferon-α experienced significantly higher rates of grade 3 and 4 leukocytopenia (33% versus 19%), thrombocytopenia (15% versus 6%),

fatigue (5% versus 1%) and Infection (11% versus 9%) (p<0.05) compared to patients receiving rituximab maintenance.

Two retrospective comparative studies compared rituximab maintenance therapy to no additional therapy (Ahmadi *et al*., 2012; Vokurka *et al*., 2014) and to autologous stem cell transplantation (ASCT) (Ahmadi *et al*., 2012) in 101 patients with mantle cell lymphoma reporting very low quality evidence of longer progression free survival in those receiving maintenance compared to no further therapy (P<0.05). Overall survival was not reported by either study with Vokurka *et al*. (2014) noting that the follow up was not yet long enough to assess overall survival. Ahmadi *et al*. (2012) reported no statistically significant difference between maintenance and consolidation therapy (3.9 years versus 4.5 years).

4.3.3.1.2 Efficacy of maintenance therapy post-consolidation

Three studies compared the effectiveness of rituximab maintenance after first-line consolidation therapy with autologous stem-cell transplantation, reporting a significant benefit, with patients receiving the additional maintenance therapy having an increased event free (Le Gouill *et al*., 2014) and progression free survival rate (Vokurka *et al*., 2014; Mangel *et al*., 2004 [update data from: Hicks *et al*, 2006]) compared to those who did not. There was variation in the overall survival benefit of rituximab maintenance in these studies.

One randomised control trial (RCT; Le Gouill *et al*., 2014; conference abstract) comparing the use of rituximab maintenance therapy to watch and wait in 238 patients with mantle cell lymphoma all treated with ASCT provided low quality evidence of significantly longer event free and progression free survival (p<0.05) in the patients receiving the maintenance therapy. There was however, no significant difference in the 2-year overall survival rates between the patients receiving maintenance (93.4%) compared to those patients undergoing watch and wait (93.9%).

One retrospective cohort study (Vokurka *et al*., 2014) provided very low quality evidence of a significant progression free survival benefit in 14 patients receiving rituximab maintenance (median not yet reached) compared to 12 patients receiving no maintenance therapy (46 months, p<0.05).

One retrospective cohort study (Mangel *et al*., 2004, updated data in conference abstract by Hicks *et al*., 2006) provided very low quality evidence of a significant progression free and overall survival benefit in 20 patients with mantle cell lymphoma receiving consolidation (ASCT) plus rituximab maintenance (5 year: 72%, 80%) compared to 40 patients with mantle cell lymphoma receiving conventional induction chemotherapy alone (19% P<0.001; 38%, P<0.01).

4.3.3.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Consider maintenance rituximab[h], every 2 months until disease progression, for people with newly diagnosed mantle cell lymphoma who are not fit enough for high-dose**

h At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports a dosage of 375mg/m^2 every 2 months until disease progression.

	chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy. **Consider maintenance rituximab[i], every 2 months for 3 years, for people with newly diagnosed mantle cell lymphoma who are in remission after cytarabine-based induction and high-dose chemotherapy.**
Relative value placed on the outcomes considered	Progression free survival and overall survival were considered the critical outcomes when drafting recommendations. Other important outcomes included disease free survival, treatment related mortality, treatment related morbidity and health related quality of life. Health related quality of life and treatment related mortality were not reported in the evidence.
Quality of the evidence	The quality of the evidence ranged from very low to low as assessed using GRADE. Evidence quality was downgraded for study design limitations, indirectness and imprecision. For some of the comparisons there were no randomised trials available so the evidence was drawn from non-randomised comparative studies. The GC recommended that rituximab maintenance be considered rather than offered, reflecting the low quality of the evidence.
Trade off between clinical benefits and harms	The GC considered the recommendations could result in improved progression free survival and overall survival for patients with mantle cell lymphoma The evidence indicated clinically significant improvements in overall survival and progression free survival with rituximab maintenance after first-line induction therapies, when compared to other maintenance therapy or no maintenance. Clinically signficiant improvements in progression free survival were also seen with rituximab maintenance after consoldation with autologous stem cell transplantation. The GC acknowledged that the potential harms of the recommendations were an increased number of hospital visits and a small increased risk of infection due to the immunosuppressive nature of rituximab. Evidence from one randomised trial indicated a grade 3 to 4 infection rate of around 9% with rituximab maintenance versus 11% with interferon-**α** maintenance, following first line induction. The GC noted that this patient group were already frequently visiting hospital at 3 to 6 monthly intervals and any extra visits would be outweighed by improved progression free survival. The recommended durations of rituximab maintenance therapy were drawn from the randomised trials.
Trade off between net health benefits and resource use	No relevant health economic evidence was identified and no economic model was built for this topic, It was thought that the recommendations would increase the number of patients receiving rituximab maintenance (and

i At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. The evidence reviewed for the guideline supports a dosage of 375mg/m^2 every 2 months for 3 years.

	therefore increase the associated costs). Continuing rituximab maintenance until disease progression would mean around 2 years of treatment in the average patient. However, the overall resource impact was thought to be minimal because the absolute number of patients is small due to the rarity of the condition. Due to better progression free survival, cost savings could be made from the increased time to next treatment and avoiding the costs of second and third line therapies. These cost savings coupled with the QALY benefits that would be expected from the superior progression free survival mean that rituximab maintenance is likely to be cost-effective at at threshold of £20,000 per QALY.
Other considerations	The GC acknowledged that use of rituximab maintenance following autologous stem cell transplantation would lead to a significant change in practice. Stopping rituximab maintenance at disease progression (or at 3 years post-ASCT) would also be a change in practice for many centres. The GC acknowledged that while rituximab is not currently licensed for this indication, the evidence supports its use in this context. The GC considered that the recommendations should reduce variation in practice and promote consistency of care for patients with this rare condition.

4.4 Diffuse large B-cell lymphoma (DLBCL)

4.4.1 Radiotherapy in first line treatment

In early stage diffuse large B-cell lymphoma (DLBCL) short course immunochemotherapy followed by radiotherapy is a standard treatment. In advanced stage DLBCL the role of radiotherapy after full course immunochemotherapy remains uncertain. The initial treatment of advanced stage DLBCL is immunochemotherapy and response rates to this are high. Radiotherapy is an effective treatment against DLBCL but limited by the distribution of disease which it can effectively cover. Advanced stage disease will by definition be multifocal and often bulky so that it could not feasibly be covered with conventional radiotherapy fields at presentation. Bulk is variably defined and is usually >7.5cm or 10cm. Furthermore there are concerns derived from data emerging from the treatment of Hodgkin's lymphoma related to the late effects of radiotherapy. In particular there is a risk of second cancers and after mediastinal irradiation cardiac deaths. This may be ameliorated by new techniques which use smaller volumes and lower doses.

Radiotherapy has been used in the past after primary chemotherapy for advanced DLBCL in cases where there is limited residual disease and to sites of bulk at presentation. These are most likely to be the focus for relapse in the future. In general a reduction in local relapse has been shown from this approach but no consistent effect upon survival is seen. The majority of published studies in this setting will reflect both the pre-rituximab era and the pre-positron emission tomography (PET) era. Computed tomography (CT) has conventionally been used for response assessment at treatment completion, however this anatomical technique cannot accurately discriminate remaining active lymphoma (residual disease) from post treatment necrosis or fibrosis. In contrast post-therapy metabolic imaging, e.g. PET-CT, has a high negative predictive value (the ability of a negative PET scan to exclude persistent disease or future relapse). The small false negative rate with PET is mostly related to its inability to detect microscopic disease which results in future relapse. Current practice following immunochemotherapy is for patients with residual disease to be considered for salvage intensive chemotherapy using an autograft or allograft. However there remains a subgroup of older patients or those with significant co-morbidity who will not be able to proceed with salvage chemotherapy to whom radiotherapy will be offered.

There are therefore two potential scenarios where radiotherapy may have a role after full course immunochemotherapy for advanced DLBCL. The first is when given as planned combined modality treatment to sites of original bulky disease for patients in complete remission and the second when given to patients with residual disease which can be encompassed within a radiation field. A recent prospective study has demonstrated a substantial benefit in elderly patients receiving radiotherapy to sites of original bulky disease with a hazard ratio of 4.3 for overall survival, although an important limitation of this study is that PET was not used for post immunochemotherapy response evaluation.

Clinical question: The role of consolidation radiotherapy in first-line treatment of diffuse large B-cell lymphoma.

4.4.1.1 Clinical evidence (see section 4.4.1 in Appendix G)

Evidence came from four cohort studies (one prospective).

Compared to immunochemotherapy alone, immunochemotherapy + consolidation radiotherapy is associated with similar or longer overall survival (4 observational studies [Dorth *et al*., 2012; Held *et al*., 2014; Marcheselli *et al*., 2011; Phan *et al*., 2010]; total N = 1200; very low quality evidence), longer event-free survival (3 observational studies [Dorth *et al*., 2012; Held *et al*., 2014; Marcheselli *et al*., 2011]; total N = 731; very low quality evidence), similar or longer progression-free survival (2 observational studies [Held *et al*., 2014; Phan *et al*., 2010]; total N = 939; very low quality evidence), similar or higher rates of complete response (1 observational study [Held *et al*., 2014]; total N = 470; very low quality evidence), similar or higher rates of treatment-related mortality (1 observational study [Held *et al*., 2014]; total N = 470; very low quality evidence), and similar or higher rates of treatment-related morbidity (1 observational study [Held *et al*., 2014]; total N = 470; very low quality evidence).

4.4.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider consolidation radiotherapy delivering 30 Gy to sites involved with bulk disease at diagnosis for people with advanced-stage diffuse large B-cell lymphoma that has responded to first-line immunochemotherapy. For each person, balance the possible late effects of radiotherapy with the possible increased need for salvage therapy if it is omitted, and discuss the options with them.**
Relative value placed on the outcomes considered	Progression free survival and treatment related morbidity and mortality were considered to be critical outcomes when agreeing the recommendations. These outcomes are crucial when considering the balance for each individual of the possible late effects of radiotherapy with the possible increased need for salvage therapy if radiotherapy is omitted. Overall survival was also considered an important outcome. No evidence was identified relating to health related quality of life, patient satisfaction or patient preference
Quality of the evidence	The evidence for each outcome was rated very low quality as

	assessed using GRADE and NICE checklists for quantitative studies. Evidence was downgraded for baseline differences between the comparison groups, indirect patient populations, and imprecision. For this reason, the GC did not make strong recommendations for the use of radiotherapy in patients who had responded to first-line immuno-chemotherapy. The GC noted that there was a lack of evidence as to whether any groups of patients with extranodal disease may benefit from radiotherapy after chemotherapy. The GC expressed concern that the current evidence base did not reflect contemporary practice due to the length of time for recruitment (>20 years) and the lack of consistency in the use of PET-CT to assess response to first-line therapy. The GC considered that the inconsistency in the low-quality evidence base and in the use of PET-CT to assess response to first-line therapy impacted on their ability to make a strong recommendation.
Trade-off between clinical benefits and harms	The GC thought that the recommendation may reduce the chance of relapse (and thus the need for intensive chemotherapy salvage therapy) and improve overall survival. The evidence indicated a clinically important improvement in overall survival and progression free survival with radiotherapy. The GC acknowledged the possible treatment related adverse events at the treatment site. There is a risk of both short term effects (e.g. transient skin, mucosal and gastrointestinal reactions) and potential late effects of radiotherapy (e.g. skin pigmentation, dry mouth, functional gastrointestinal disturbance). Evidence about treatment related toxcity was limited to a single study which suggested little effect on treatment toxicity when radiotherapy is added to treatment. The GC considered that the benefits of increased overall survival and potential reduction in the need for intensive chemotherapy salvage therapy for patients, outweighed the risks associated with radiotherapy, particularly as the short term morbidity would only occur during active treatment. The focus of the evidence review was not the optimal dose of radiotherapy, however the GC thought that it was important to state dose level in the recommendation in order to confirm best practice. Therefore, they used clinical consensus, experience and evidence from a trial comparing radiotherapy doses to recommend a radiotherapy dose of 30Gy (best practice based on a randomised controlled trial [Aviles et al, 2005] comparing varying dose levels of radiotherapy in the target population included in the PICO reporting no additional local control or survival benefit of doses above 30Gy). The GC considered that the recommendations would consolidate current practice, providing clarity on the treatment pathway in the patient populations and lead to reduced variation in practice.
Trade-off between net health benefits and resource use	No economic evidence was identified and no economic model was built for this topic. The recommendation was largely thought to be a consolidation of

	current practice although there may be increased costs associated with radiotherapy in places not currently providing this level of care. The use of radiotherapy is likely to be cost-effective as the upfront cost (which itself is relatively low in comparison to other treatment areas) would be expected to be justified by the improvements in longer progression free survival. The improved progression free survival would lead to QALY gains and would also offset the upfront cost (at least partially). Thus, the use of radiotherapy is likely to be cost-effective in cost per QALY terms.
Other considerations	The GC made a research recommendation for a trial in patients who had responded (PET-CT negative) to first-line immuno-chemotherapy. This was because there was an inconsistent and low-quality evidence base for this question and the GC noted that an RCT could be achieved in this area and warranted further investigation. In addition, the GC suggested that the outcome of the research recommendation may produce the required evidence to standardise clinical practice in this area. In relation to patients with extranodal disease the GC considered that the lack of patient numbers presenting would prevent success with a randomised trial and suggested that population based data may be the only way to assess use of radiotherapy in this patient population.

Research recommendation	**In people presenting with diffuse large B-cell lymphoma and sites of bulky disease, are outcomes improved by radiotherapy to those sites following a full course of chemotherapy?**
Why this is important	The role of radiotherapy to sites of original bulky disease in treating diffuse large B-cell lymphoma is uncertain. Some clinical teams will consider radiotherapy in this setting while others will not because of concerns about morbidity and late effects of treatment. In a recent randomised trial of chemotherapy in people over 60 years old with diffuse large B-cell lymphoma, people having radiotherapy were identified and compared with a cohort having no radiotherapy. Significant improvements in event-free, progression-free and overall survival were seen in the group having radiotherapy. These results have encouraged some teams to reconsider radiotherapy for bulky diffuse large B-cell lymphoma. A definitive randomised trial is needed to address this question. Outcomes of interest include overall survival, disease-free survival, progression-free survival, treatment-related mortality, treatment-related morbidity, health-related quality of life, patient satisfaction, patient preference and overall response rate (complete or partial remission).

4.4.2 Central nervous system prophylaxis

Central Nervous System (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) occurs infrequently (approximately 5%), but is almost always fatal.

There is significant controversy regarding which factors most reliably identify patients at high risk of this complication. Clarification is also needed regarding the value of the various prophylaxis strategies when contemporary rituximab-containing chemotherapy regimens are

used. Traditionally, involvement of > 1 extranodal site and an elevated lactate dehydrogenase level identifies individuals at highest risk (i.e. > 20% risk of the event). In addition, certain solitary extra-nodal sites (e.g. testis, kidney and breast) have been regarded as being higher risk. Due to the current lack of consensus, a wide variation of practise occurs across the UK with some centres only giving CNS directed prophylaxis to those with the highest risk (such as testicular involvement). Other centres would include patients with epidural disease, paranasal sinus involvement, bone marrow involvement and involvement of kidney or breast.

A high proportion of patients considered to be at high risk of CNS disease may already have occult or sub-clinical disease at the time of primary diagnosis. If these patients could be reliably identified one could separate patients into two risk groups- those with subclinical disease who require a CNS eradication strategy and those high risk patients without disease who may benefit from a prophylactic strategy.

Immunophenotyping by flow cytometry is a promising approach. Widespread use of this technique may redefine what risk and prophylaxis really mean. Intra-thecal and parenterally administered prophylaxis imparts small but definite risks to the patient. In addition, the administration of such prophylaxis is resource intensive. Intrathecal drug delivery requires an elaborate governance structure to avoid the wrong drug being administered, and intravenous administration requires an in-patient stay.

Although subgroups of patients with diffuse large B-cell lymphoma (DLBCL) with a relatively high risk of Central Nervous System (CNS) recurrence (i.e. ≥ 20%) can be identified, the current evidence base supporting the use of prophylactic strategies in patients receiving modern chemo-immunotherapy is limited.

There are also concerns over the efficacy of intra-thecal drugs in that they penetrate the brain substance very poorly and yet up to 40% of CNS lymphoma relapses occur in this way. The use of systemic (intravenous) prophylaxis in various forms is also limited and often confused by heterogeneity of entry criteria and the method of prophylaxis. Theoretically, intravenous prophylaxis would penetrate the brain substance more effectively as implied by results from patients with primary central nervous system lymphoma. Data of superiority in the prophylaxis setting however, are lacking.

The controversy surrounding CNS prophylaxis is unlikely to be answered in the form of a randomised clinical trial due to the rarity of CNS events in the DLBCL population. There are, however, a number of observational studies that may assist in the selection of both patients and strategies to be used to abrogate the risk of CNS disease in this patient group in the modern era.

Clinical question: What are the risk factors associated with central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma?

4.4.2.1 Clinical evidence (see section 4.4.2 in Appendix G)

Evidence came from one randomised controlled trial and seven retrospective case series.

The main challenges to the validity of the evidence as a whole concerned (1) variation in how the outcome (CNS relapse) was measured with two studies using clinical and neurological symptoms alone compared to radiographic and cerebrospinal fluid assessment as standard in the remaining studies; (2) a lack of information from conference abstracts about the prognostic factors included and statistical analyses, and (3) the included samples of participants representing a ‘reduced risk’ population, with those at highest risk of CNS relapse being treated up-front with prophylaxis under individual hospital protocols. Whilst, only a hypothesis, this could explain the lack of consistency in the results of relevant prognostic factors (because allocation to prophylaxis varied across hospital institutions) and

the lack of evidence supporting known CNS relapse risk factors (e.g. involvement of the testis).

Six studies reported the prognostic value of clinical characteristics (age; performance status; lactate dehydrogenase; international prognostic index; involvement of extranodal sites/specific organ sties, *MYC*+BCL2+ and white blood cell count) on the development of secondary central nervous system relapse, in patients with diffuse large B-cell lymphoma. However, only two factors (involvement of the breasts, elevated LDH) were shown to be significantly independent in four of the studies (involvement of the breasts: Tomita *et al*. 2012, Deng *et al*. 2013; elevated LDH: Feugier *et al*. 2004, Morabito *et al*. 2005) with Yamamoto *et al* (2010) reporting no independent prognostic indicator in 375 patients with DLBCL and Tomita *et al* (2012) reporting that four out of seven factors assessed were independently associated with CNS relapse (age, involvement of the breasts, bone or adrenal glands) in 1221 patients with DLBCL.

Two studies (Schmitz *et al*. 2013; Savage *et al*. 2014a) reported the prognostic value of models (containing 5 or 6 factors), which group patients by the number of risk factors (low: 0-1 factors, moderate: 2-3 factors, higher: 4-5(6) factors) with a corresponding percent risk for developing a secondary CNS relapse within two years of diagnosis. Schmitz *et al*. (2013) reported a five factor model including age (>60 years), lactate dehydrogenase (>normal), stage (III or IV), Eastern Cooperative Oncology Group score (>1) and involvement of the kidneys. Savage *et al*. (2014a) reported the same five factor model included in the Schmitz *et al*. (2013) article (with the same cut-off points) but also included the factor extranodal sites (>1) and the involvement of kidneys or the adrenal glands. Both studies reported that an increase in the number of risk factors was associated with an increase risk of CNS relapse within two years of diagnosis with those reporting 0-1 factors having between a 0.6% (95% CI: 0.2-1.0%) and 0.8% (95% CI: 0.0-1.6%) risk for developing a CNS relapse within two-years, those with 2-3 risk factors having between a 3.9% (95% CI: 2.3-5.5%) and 4.1% (95% CI: 2.7-5.5%) risk for developing a CNS relapse within two-years and those with ≥4 factors having between 12% (4-6 risk factors; 95% confidence interval: 7.9-16.1%) and 17% (4-5 risk factors; 95% CI: 9.4-24.6%) risk for developing a CNS relapse within two-years. It is worthy to note that Savage *et al*. (2014a) reported that kidney/adrenal involvement was highly associated with CNS relapse (2 year CNS risk 33%), but no information of individual risk for CNS relapse for the other risk factors included in their factor model was provided because the article was a conference abstract. This could suggest that the risk factors included in the model do not carry equal weighting for CNS relapse risk and this may be problematic when considering a risk factor model that sums the risk factors because a patient with only kidney/adrenal gland involvement may have a higher risk for CNS relapse compared to a patient with 4 or more of the other risk factors.

4.4.2.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Explain to people with diffuse large B-cell lymphoma that they have an increased risk of central nervous system lymphoma if the testis, breast, adrenal gland or kidney is affected.** **Explain to people with diffuse large B-cell lymphoma that they may have an increased risk of central nervous system lymphoma if they have 2 or more of the following factors:**

	• **elevated lactate dehydrogenase (LDH)** • **age over 60 years** • **poor performance status (ECOG score of 2 or more)** • **more than one extranodal site involved** • **stage III or IV disease.** **Explain that the level of risk increases with the number of factors involved.**
Relative value placed on the outcomes considered	CNS disease rate was the critical outcome when agreeing the recommendation because CNS disease is associated with poor survival. CNS disease rate enabled the GC to assess which factors were associated with increased rates of CNS disease
Quality of the evidence	The evidence for this topic ranged from very low to low quality as assessed by the NICE checklist for prognostic studies. The issues with the evidence were: variation in how the outcome (CNS disease) was measured with two studies using clinical and neurological symptoms alone compared to radiographic and cerebrospinal fluid assessment as standard in the remaining studies; and a lack of information from conference abstracts about the prognostic factors included and statistically analysed. The GC considered that the included samples of participants may represent a 'reduced risk' population, with those at highest risk of CNS relapse being treated up-front with prophylaxis under individual hospital protocols. Whilst, only a hypothesis, this may explain the lack of consistency in the results of relevant prognostic factors (because allocation to prophylaxis varied across hospital institutions), and the lack of evidence supporting known CNS relapse risk factors (e.g., involvement of the testis). The GC accepted the possibility that these studies underestimated the baseline risk of CNS relapse, and the prognostic value of risk factors. The GC noted that the evidence base was potentially confounded by exclusion of high risk patients when assessing prognostic factors associated with CNS relapse (due to need to treat high risk patients), and the inclusion of low risk patients (unlikely to ever receive CNS prophylaxis) as the comparator in studies assessing the value of CNS prophylaxis.
Trade-off between clinical benefits and harms	The recommendations would help inform decisions about the need for CNS prophylaxis. The GC did not consider that there would be any harms from the recommendations made. A specific recommendation was made for patients with disease involvement of testis, breast, adrenal gland or kidney because the evidence suggested the risk of CNS replase was higher in such patients. The list of other risk factors is drawn from the evidenc,e which indicatesdpatients with 2 or more of these factors had around 4% risk of CNS relapse within 2 years.
Trade-off between net health benefits and resource use	No economic evidence was identified and no economic model was builtt for this topic. The GC considered that improved risk prediction for a CNS relapse may result in an increase in the number of patients receiving CNS prophylaxis.

	The GC noted that there are resource implications for the use of intrathecal CNS prophylaxis (costly drugs, special expertise and possible transfer to another hospital). However, the targeted use of CNS prophylaxis using the risk prediction criteria set out in the recommendations was thought likely to cost-effective. The increasd cost of CNS prophylaxis would be balanced agains a reduction in CNS relapse. CNS relapse is most often fatal and the costs of the intensive therapy (in a minority of CNS relapse patients who can tolerate the therapy) and/or palliative care costs (for the majority of CNS relapse patients) would be reduced if CNS relapse rates are lower after CNS prophylaxis. Therefore, despite a potential net increase in costs, it was thought that the strategy would be cost-effective in cost per QALY terms because of improvements in effectiveness (through a reduction in CNS relapse rates).

Clinical question: What is the efficacy of central nervous system prophylaxis for people with diffuse large B-cell lymphoma?

4.4.2.3 Clinical evidence (see section 4.4.3 in Appendix G)

Evidence came from two randomised trials and 18 retrospective cohort studies.

4.4.2.3.1 Methotrexate

Intrathecal methotrexate versus no CNS prophylaxis

Eleven studies provided evidence concerning the use of intrathecal methotrexate (ITMTX) for central nervous system (CNS) prophylaxis (n=1084) compared to no CNS prophylaxis (n=4851) in patients with diffuse large B-cell lymphoma (6/11 studies samples were 100% DLBCL). The evidence base was inconsistent with six comparative observational studies reporting very low quality evidence of higher CNS relapse rates and relapse free survival rates in patients receiving ITMTX and four comparative observational studies reporting very low quality evidence of lower CNS relapse rates in these patients compared to patients receiving no CNS prophylactic therapy, but, none of these comparisons were significantly different (4/10 studies did not report significance values for CNS relapse rates). Only one randomized control trial reported the difference between the two groups to be statistically significant, with Tilly *et al*. (2003, 78.9% DLBCL) reporting very low quality evidence of a higher CNS relapse rate in 312 patients receiving no prophylaxis compared to 323 patients receiving ITMTX prophylaxis (8.3% versus 2.8%, p=0.002). However, patients receiving ITMTX had higher rates of treatment related adverse events (leucopenia, thrombocytopenia, infection and Mucositis, p<0.01) and a higher number of treatment related deaths (43%) compared to the patients receiving CHOP alone (23%, p=0.014).

Intravenous methotrexate (+/- intrathecal cytarabine) versus inadequate prophylaxis (IT chemotherapy only) or no CNS prophylaxis

One retrospective cohort study (Ferreri *et al*. 2015) provided very low quality evidence of significantly lower CNS relapse rates in 33 patients with high-risk DLBCL receiving IV MTX (0%) compared to 74 patients with high-risk DLBCL receiving either inadequate prophylaxis (IT chemotherapy only, n=7) or no prophylaxis at all (n=67) (12%; p=0.03). In addition, patients receiving IV MTX had significantly higher 5-year overall survival rates (87±6%) compared to the patients receiving inadequate or no prophylaxis (54±6%, p=0.001).

Intrathecal or intravenous methotrexate versus no CNS prophylaxis

Two cohort studies (Guirguis *et al*. 2012; Kumar *et al*., 2012) provided very low quality evidence of no significant reduction in CNS relapse rates or increased overall survival in 144 patients with diffuse large B-cell lymphoma receiving methotrexate either via intravenous or intrathecal prophylaxis compared to 1059 patients with DLBCL treated with no CNS prophylactic therapy.

Intrathecal methotrexate versus intravenous methotrexate versus HyperCVAD/CODOXM-IVAC

One comparative observational study (Cheah *et al*. 2014) provided very low quality evidence of lower CNS relapse rates in 43 patients receiving HyperCVAD or CODOXM-IVAC therapies (2.3%, 0.3-15.4%) compared to 125 patients receiving IV methotrexate (6.9%, 3.5-13.4%) and 49 patients receiving IT methotrexate (18.4%, 9.5-33.1%) (p=0.009). There was no reported significant difference in the 3-year relapse free survival rates between the three groups (p=0.051: IT: 65.5% [49.8-77.3%]; IV: 82.9% [74.7-88.6%]; HyperCVAD/CODOXM-IVAC: 70.6% [53.9-82.2%]), but the patients receiving HyperCVAD or CODOXM-IVAC had the highest rates of 3-year overall survival (89.2%) compared to the IT (68%) and IV (85.9%) methotrexate groups (p=0.029). The authors noted that in the patients receiving IV methotrexate there were high rates of renal impairment, occurring in 70% of cycles overall, although all patients recovered without the need for haemodialysis. No information regarding adverse events were reported for the other two treatment groups.

Consolidation with intrathecal methotrexate versus no CNS prophylactic consolidation

One randomised controlled trial (Récher *et al*. 2011) comparing the value of consolidative ITMTX in patients with aggressive B-cell lymphoma (97.5% DLBCL) who had been treated with ITMTX during their induction therapy (R-CHOP) provided very low quality evidence of no statistically significant difference in CNS relapse rates in the 196 patients treated with consolidative ITMTX (0%) compared to the 183 patients who received no ITMTX consolidation (1.09%). However, patients who received consolidation ITMTX had a significantly higher 3-year overall survival rate (92%) compared to those who received no consolidation therapy (84%, p=0.0071). Higher rates of adverse events were reported in the ITMTX consolidation group compared to the group not receiving ITMTX consolidation therapy, but significance values were not provided for these comparisons.

4.4.2.3.2 Any CNS prophylaxis

Five comparative observational studies (Aviles *et al*. 2013; Bernstein *et al*. 2009; Wilson *et al*. 2014; Ventre *et al*. 2013) compared the use of any CNS prophylaxis therapy in 1249 patients with DLBCL compared to 2552 patients with DLBCL receiving no CNS prophylaxis therapy. Aviles *et al*. (2013) and Bernstein *et al*. (2009) provided very low quality evidence of no significant benefit of CNS prophylaxis therapy on the CNS relapse rates in their patients. Aviles *et al*. (2013) further reported no relapse free or overall survival benefit from CNS prophylaxis. However, both Ventre *et al*. (2013) and Wilson *et al*. (2014) reported survival benefits in patients receiving CNS prophylaxis with Ventre *et al*. (2013) reporting very low quality evidence of an increased overall survival rate in 40 patients with DLBCL treated with CNS prophylaxis (94±7%) compared to 64 patients with DLBCL who received no CNS prophylaxis (46±6%, p=0.001) and Wilson *et al*. (2014) reporting very low quality evidence of a relapse free survival benefit in 132 patients with DLBCL who received more than 2 doses of intrathecal methotrexate, cytarabine or triple prophylactic therapy compared to 69 patients who received none, or less than 2 doses, of prophylactic therapy (p=0.025).

4.4.2.3.3 Allocation of patients to prophylaxis

Unfortunately allocation to CNS prophylaxis in the majority of the studies was based on level of risk (which varied across studies) or physician discretion (which varied within studies), which may bring into question the value of the comparison of at risk (for CNS relapse) patients treated with prophylaxis to low risk patients not treated with prophylaxis. A non-significant difference when comparing high risk to low risk patients could lend support for the hypothesis that CNS prophylaxis is providing a benefit because the CNS relapse rates after prophylaxis become comparable to those CNS relapse rates in low risk patients where prophylaxis would rarely be considered. Only one study (Tilly *et al*. 2003) reported the value of prophylaxis in a randomised controlled trial, reporting a benefit of prophylaxis. However, these patients did not receive rituximab and whilst the aim of the present study was not to address the use of rituximab in relation to CNS relapse rates, there were no RCTs and only one of the observational studies post rituximab reported a benefit for the addition of prophylaxis when compared to no prophylaxis in patients who were matched on their risk for CNS relapse.

4.4.2.4 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Offer central nervous system-directed prophylactic therapy to people with diffuse large B-cell lymphoma:** • **that involves the testis, breast, adrenal gland or kidney or** • **who have 4 or 5 of the factors associated with increased risk of central nervous system relapse listed in the recommendation on pages 122–123.** **Consider central nervous system-directed prophylactic therapy for people with diffuse large B-cell lymphoma who have 2 or 3 of the factors that are associated with increased risk of central nervous system relapse (listed in the recommendation on pages 122–123.**
Relative value placed on the outcomes considered	The critical outcome for this topic was CNS relapse, specifically: time to relapse, sites of relapse, isolated to CNS compared to systemic relapse, general relapse, parenchymal relapse and meningeal relapse. Additional important outcomes included, overall survival, treatment related mortality, treatment related morbidity and health related quality of life CNS relapse rate was considered critical when agreeing the recommendation because patients who have a CNS relapse have extremely poor survival rates, and therefore this outcome enabled the GC to assess the efficacy of CNS prophylaxis. There was no evidence for health related quality of life in patients undergoing CNS prophylaxis. The evidence relating to adverse events extracted from the evidence review was not considered useful in the assessment of the efficacy of CNS prophylaxis. This was because the GC noted that many of these events were a consequence of induction

	therapies, and were unlikely to be associated with the CNS prophylactic treatments.
Quality of the evidence	The quality of the evidence was very low quality for the outcome CNS relapse rate as assessed using GRADE. Two studies comparing induction regimens (not CNS prophylaxis) were downgraded due to indirectness (inclusion of patients with other types of NHL). Additionally it was unclear how CNS relapse was detected and no information was provided on allocation and detection biases. The remaining studies were downgraded for serious indirectness (sample included patients with other types of NHL; sample included patients with primary CNS DLBCL); serious limitations (unclear decision making for who received prophylactic treatment; allocation to prophylaxis based on risk level so comparison of groups at baseline differed; unclear rationale for detection of CNS relapse) and serious imprecision (due to low sample size and number of events). Allocation to CNS prophylaxis in the majority of the studies was based on level of risk (which varied across studies) or physician discretion (which also varied within studies). This may bring into question the value of the comparison of at risk (for CNS relapse) patients treated with prophylaxis to low risk patients not treated with prophylaxis. The GC acknowledged that such comparisons could underestimate the benefit of prophylaxis. In this situation, no apparent difference between high risk to low risk patients could lend support for the hypothesis that CNS prophylaxis is providing a benefit, because the CNS relapse rates after prophylaxis become comparable to those CNS relapse rates in low risk patients where prophylaxis would rarely be considered. There were no RCT's and only one observational study post rituximab that reported a benefit for the addition of prophylaxis when compared to no prophylaxis in patients who were matched on their risk for CNS relapse. The evidence base for the efficacy of CNS prophylaxis was consistent in terms of CNS relapse rates which the GC thought could reflect a value for the use of CNS prophylaxis (bringing the CNS relapse rate in high risk patients to similar to low risk patients). One study that did isolate comparisons to high risk versus high risk with prophylactic therapy, did report a clinically relevant benefit of prophyalxis. The GC noted that given the need to treat high risk patients with prophylaxis (to reduce the CNS relapse rate), it would be unlikely that evidence would ever be available to directly compare high risk to low risk.There is also little consensus across countries as to the best treatment pathway in these patients, so the evidence found in the review donefor this guideline, is the best available evidence.
Trade-off between clinical benefits and harms	The GC considered that the recommendation will result in a reduction in the CNS relapse rates (an often fatal manifestation of the lymphoma) in patients with DLBCL. The recommendation will provide uniformity of practice. The one randomised trial included reported a reduction of CNS relapse from 8.3% to 2.8% with CNS prophylaxis (although these patients did not receive rituximab).

	The GC acknowledged that patients will be exposed to an increase in toxicity, resulting in an increase rate of morbidity. The GC thought that the benefits of a reduction in a potential fatal relapse was offset by the manageable harms of increased toxicity from the recommended therapy. Separate recommendations were made for patients at high and moderate risk of CNS relapse. These risk groups were based on the evidence identified in the previous section (see section 4.4.3.2). The GC made an “offer” recommendation for the high risk group, despite the low evidence quality, because they judged there was a clear benefit with CNS prophylaxsis in the trade-off between benefits and harms for these patients. In addition, CNS relapse would almost always be fatal and this is the only treatment that can be given. For patients with a moderately raised risk of CNS relapse, the GC considered that on balance the benefits still outweighed the harms. However, given the lower baseline risk a greater number of patients would have to be treated to prevent each case of CNS relapse. Balancing the increased risk of CNS disease in older patients with the toxicity involved in repeat lumbar punctures meant that the GC thought that patients should be involved in these difficult decisions.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no health economic model was developed for this topic. The GC considered that the recommendation may result in increased costs through an increase in the number of patients receiving CNS prophylaxis. The GC noted that there are resource implications for the use of intrathecal CNS prophylaxis (costly drugs, special expertise and possible transfer to another hospital). However, the use of CNS prophylaxis was thought likely to be cost-effective because the increased cost of CNS prophylaxis would be balanced against a reduction in CNS relapse. CNS relapse is most often fatal and the costs of the intensive therapy (in a minority of CNS relapse patients who can tolerate the therapy) and/or palliative care costs, (for the majority of CNS relapse patients), would be reduced if CNS relapse rates are lower after CNS prophylaxis. Therefore, despite a potential net increase in costs, it was thought that the strategy would be cost-effective in cost per QALY terms because of improvements in effectiveness (through a reduction in CNS relapse rates).
Other considerations	The GC considered that the recommendations may result in a minor change in practice and result in a small overall increase in the use of CNS prophylaxis by providing a more uniformed approach to treating patients presenting with DLBCL. The GC could not make a specific recommendation regarding the type of CNS prophylaxis to use (intrathecal versus intravenous methotrexate) due to a lack of evidence comparing the routes of administration. In addition, the GC noted that a research recommendation comparing the routes of administration of the

	therapy would be difficult to implement due to the predicted size of the sample required to power a study and the need for international collaboration, with little international consensus of treatment regimens and CNS prophylaxis eligibility criteria for categorising patients into high and low risk groups.

4.4.3 Salvage therapy

Patients with diffuse large B cell lymphoma (DLBCL) who fail first-line therapy may be categorised into three distinct groups: (1) those relapsing after complete remission, (2) partial responders with persistent disease, and (3) refractory patients.

The survival outcomes are significantly different in each subgroup, becoming progressively worse from relapsed to refractory patients. For patients who are deemed candidates for high dose therapy, the standard strategy is salvage immunochemotherapy followed by autologous stem cell transplantation (ASCT). This approach is most effective in those with chemo-sensitive disease and is associated with prolonged survival in approximately 40% of relapsed patients who achieve at least a partial response to salvage as determined by conventional Computed Tomography (CT)-based criteria.

The main goal of salvage therapy is to minimise the disease burden and demonstrate continued chemo-sensitivity. Complete remission is not required, but demonstration of response is the most predictive factor of outcome after ASCT, and the best outcomes are reported in patients who achieve metabolic complete response before ASCT. The majority of favoured first-line salvage regimens include either one or both of a platinum compound or ifosfamide, and there is no clearly superior regimen. For patients who do not respond to first-line salvage, outcomes are extremely poor with 1-3 year survival rates of <10%. Although many clinicians attempt a second-line salvage regimen in this setting, the ultimate curability of these patients is quite limited.

Support for the role of ASCT in consolidation following salvage is based on one randomised study, and multiple single institution and registry studies confirming similar outcomes following ASCT. The landmark PARMA trial included only patients with relapsed DLBCL; all patients had attained a complete radiological (CT) response to initial induction therapy and were ≤ 60 years of age; patients with bone marrow or central nervous system involvement at relapse were excluded and patients had not received rituximab during induction or salvage. Both overall (OS) and event-free survival (EFS) were superior in the transplant group. Subsequent analyses have confirmed that IPI score at relapse and time to relapse are important prognostic variables. The approach to those excluded from this study (e.g. those with <complete response, those over 60 years, those with bone marrow or CNS involvement) remains more contentious.

Groups of patients with worse overall prognoses can be identified, for example ‘double hit’ lymphomas, those with primary resistant disease, or those failing to achieve a complete response to salvage. The role of allogeneic transplantation (alloHSCT) in these patients remains incompletely defined. The graft-versus-lymphoma effect is less well demonstrated in DLBCL than in other lymphomas. Furthermore, the non-relapse-related procedural mortality associated with such transplants is relatively high in patients with DLBCL (>20% in most series). Nevertheless, a number of published series indicate plateaus in the survival curves for patients undergoing alloHSCT, and it continues to be considered a clinical option in such cases. Some reserve alloHSCT for patients who have failed a prior ASCT or stem cell mobilisation enabling ASCT, recognising that only a minority will be salvaged to a position in which they can undergo such a procedure.

Clinical question: What is the most appropriate salvage strategy for people with relapsed/refractory diffuse large B-cell lymphoma?

4.4.3.1 Clinical evidence (see section 4.4.4 in Appendix G)

Evidence came from three randomised controlled trials, three retrospective cohort studies and four retrospective case series.

4.4.3.1.1 R-BEAM followed by ASCT versus B-BEAM followed by ASCT

Low quality evidence from one study of 224 patients reported that overall rate of grade 3-5 non-haematologic toxicities and grade 3-5 mucositis, but not other individual grade 3-5 non-haematologic toxicities, overall survival, progression-free survival, and treatment-related mortality were significantly lower in R-BEAM than B-BEAM (HRs not reported [BMT CTN 0401]).

4.4.3.1.2 R-ICE followed by ASCT versus R-DHAP followed by ASCT

One study (CORAL) with 477 patients provided moderate quality evidence that overall survival, progression-free survival, and event-free survival did not differ significantly between R-ICE and R-DHAP (HRs not reported).

4.4.3.1.3 (R-)GDP followed by ASCT versus (R-)DHAP followed by ASCT

One study with 619 patients (NCIC-CTG LY.12) provided low quality evidence that quality of life was significantly better or similar in (R-)GDP compared to (R-)DHAP and grade 3-4 nausea, febrile neutropenia and overall occurred significantly less in (R-)GDP than in (R-)DHAP, but the treatment groups did not differ in other individual grade 3-4 adverse events, overall survival, overall survival after transplantation, event-free survival, event-free survival after transplantation, overall response rate and rate of ASCT transplantation (HRs not reported).

4.4.3.1.4 R-ICE versus R-GDP as salvage chemotherapy

Low quality evidence from an indirect comparison of two randomised trials (CORAL and NCIC-CTG LY.12) suggested uncertainty about whether outcomes are better with R-GDP than with RICE.

4.4.3.1.5 R(if CD+)-ICE followed by ASCT (if < 66 years and response) versus R(if CD+)-DHAP followed by ASCT (if < 66 years and response) versus R(if CD+)-GDP followed by ASCT (if < 66 years and response)

Very low quality evidence from one study with 113 patients (Kusano *et al*, 2014) reported median second progression-free survival was longer in (R-)ICE than in two other two treatment groups combined and in (R-)ICE compared to (R-)DHAP alone, but not to (R-)GDP alone. There was significantly more grade 3-4 renal dysfunction with (R-)DHAP than in other two treatment groups, but the three treatment groups did not differ in overall or complete response, overall survival ((R-)ICE versus the other two treatment groups combined), median time from first progression to second progression or last follow up, and grade 3-4 haematological side effects (HRs not reported).

4.4.3.1.6 R-MICE versus R-DICEP

Oh *et al* (2015) provided very low quality evidence that median time to progression was significantly longer in R-MICE than R-DICEP (HR not reported; n=38).

4.4.3.1.7 R-GemOx versus RICE

Very low quality evidence from one study with 65 patients (Zhang *et al*, 2011) suggest that neutrocytopenia and gastrointestinal tract reactions occurred significantly more in RICE than R-GemOx (HR not reported).

4.4.3.1.8 Allogeneic transplantation

Very low quality evidence about outcomes following allogeneic transplantation came from 4 retrospective case series (Avivi *et al*, 2014; Rigacci *et al*, 2012; Sirvent *et al*, 2010 and van Kampen *et al* 2011) including 807 patients. Overall survival at five years after allogeneic stem cell transplant (allo-SCT) ranged from 34% to 43% and five year progression free survival ranged from 30% to 37%. The rates of non-relapse mortality ranged from 28% to 38%, rates of acute graft-versus-host disease ranged from 32% to 51% and rates of chronic graft-versus-host disease ranged from 35% to 42%.

4.4.3.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer salvage therapy with multi-agent immunochemotherapy to people with relapsed or refractory diffuse large B-cell lymphoma who are fit enough to tolerate intensive therapy:** • **explain that this is primarily to obtain sufficient response to allow consolidation with autologous or allogeneic stem cell transplantation, but is also beneficial even if not followed by transplantation** • **consider R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimes and less toxic.** **Offer consolidation with autologous stem cell transplantation to people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy) who are fit enough for transplantation.** **Consider consolidation with allogeneic stem cell transplantation for people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy):** • **that relapses after autologous stem cell transplantation or** • **in whom stem cell harvesting is not possible.**
Relative value placed on the outcomes considered	The critical outcomes were treatment toxicity and overall survival. Important outcomes were health realted quality of life, progression free survival and response to chemotherapy Health related quality of life was not reported in the evidence.
Quality of the evidence	The quality of the evidence was moderate to very low using GRADE. Evidence comparing transplantation to non-transplantation strategies was lacking.The randomised trials involving autologous transplantation compared different salvage chemotherapy regimens Only non comparative studies were available for allogeneic transplantation. This limited the strength of the recommendation that the GC were able to make about allogeneic transplantation.
Trade-off between clinical benefits and harms	The GC considered that the recommendation to offer salvage therapy and consolidation with autologous transplantation would prolong overall survival. Evidence from trials comparing different

	salvage chemotherapies followed by autologous stem cell transplant indicated overall survival of around 40% and event free survival around 30%. The use of high dose therapy with autologous transplantation however is associated with toxicity including late effects and in some cases treatment related mortality. The GC considered that the increased overall survival outweighed the harms due to acute and late effects. The recommendation to consider salvage therapy R-GDP instead of R-DHAP, has the potential to reduce treatment related toxicity without adversely affecting overall survival. This recommendation was informed by a randomised trial which indicated R-GDP was as effective as R-DHAP with similar overall and event free survival, but with fewer serious adverse events (47% versus 60%). Evidence about allogeneic stem cell transplant indicated overall survival of around 40% at five years with similar rates of acute and chronic graft versus host disease.
Trade-off between net health benefits and resource use	No health economic evidence was identified for this topic and no health economic model was developed. The recommendation to offer high dose therapy with autologous transplantation is already the current standard of care for this patient group. Therefore there are unlikely to be significant changes in practice as a result of these recommendations and so the resource impact should be minimal. For places not currently providing this care, there could be resource implications. However, despite its high cost, the use of high dose therapy with autologous transplantation was thought likely to be cost-effective because it substantially prolongs overall survival. Thus, it is likely to be cost-effective in cost per QALY terms. The recommendation to use R-GDP instead of R-DHAP as salvage therapy may be a departure from current practice in some places. However, this recommendation was thought to be cost-effective and indeed cost saving. In QALY terms, R-GDP should be at least as effective as R-DHAP (and possibly more so given the potential to reduce treatment related toxicity). R-GDP is also less costly than R-DHAP with marginally cheaper drug costs and substantially cheaper delivery costs as R-GDP is delivered on a day case basis while R-DHAP is delivered on an inpatient basis. Costs for these regimens were estimated as part of the economic modelling execrcises conducted for the guideline. Three cycles of R-GDP were estimated to cost £8,437 while three cycles of R-DHAP were estimated to cost £9,783. The recommendation to consider allogeneic transplantation where autologous transplantation is not possible or where it has failed, is also likely to be cost-effective because it substantially improves survival in comparison to chemotherapy alone. Therefore, it is likely to be cost-effectiven in cost per QALY terms.

Other considerations	The GC noted that consolidation with autologous transplantation would not be appropriate for some patients – for example when stem cell harvesting was not possible, but these patients might still benefit from allogeneic transplantation.

4.5 Burkitt lymphoma

4.5.1 First line treatment

Burkitt lymphoma (BL) is a rare and highly aggressive subtype of B-cell non-Hodgkin's lymphoma (NHL). Cure rates with intensive first line treatment are high in younger patients, and those with low risk disease (Castillo *et al*, Cancer 2013), although the outlook is generally very poor for patients who relapse as few patients respond to salvage therapy. Risk in Burkitt lymphoma is variably defined and in adults normal LDH, tumour size <10cm, limited stage, one or no extral nodal sites, no CNS or bone marrow disease, and good performance score are often considered features of low risk disease.

The Magrath regimen (Magrath *et al*, JCO, 1996; Mead *et al*, Ann Oncol, 2002; Wang *et al*, Cancer, 2003) - CODOX-M/IVAC - is widely used in the UK and like other intensive first-line approaches such as hyper-CVAD (Thomas *et al*, Cancer 2006; Cortes *et al*, Cancer 2002) and CALGB 9251 (Rizzieri *et al*, Cancer 2004), is highly effective but toxic, especially in older patients. The development of effective and less toxic therapy for BL is desirable. DA-EPOCH-R is emerging as a low intensity regimen which has demonstrated both efficacy and good tolerability in a non-randomised study including sporadic and HIV-associated subtypes of BL (Dunleavy *et al*, NEJM, 2013). Rituximab is frequently added to first-line regimens, such as CODOX-M/IVAC, but the survival benefit of doing so has not been evaluated in randomised trials (Barnes *et al*, Ann Oncol, 2011).

This topic will address the most effective initial therapy for BL.

Clinical question: What is the most effective first-line treatment for people with Burkitt lymphoma?

4.5.1.1 Clinical evidence (see section 4.5.1 in Appendix G)

Evidence came from one randomised controlled trial and seven cohort studies (one prospective).

4.5.1.1.1 Comparison of interventions

Five retrospective cohort observational studies including 650 patients reported comparisons of treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB9251, BFM and CHOP/CHOEP/MEVA/other). Overall survival rates were highest in the patient groups receiving HyperCVAD (82.8%), BFM (77.8-81.7%) and CODOX-M/IVAC (68.6-74.5%) and lowest in the patient groups receiving CHOP/CHOEP/mmCHOP/MEVA/Other regimens (35.5-38.8%). From the two observational studies reporting adverse events, the CHOP-like regimens reported lower rates of adverse events (treatment related mortality, neutropenia, nadir fever) but higher rates of CNS progression compared to the other treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB9251, BFM).

Overall survival

Three observational studies (Wästerlid *et al*., 2013; Walewski *et al*., 2001; Wang *et al*., 2000) including 376 patients provided very low quality evidence of overall survival rates on the effectiveness of CODOX-M/IVAC compared to CHOP/CHOEP/MEVA/other. Reporting

overall survival (range 1-2 years; follow-up median 37.5 months) rates of 68.6-79% in the CODOX-M/IVAC group compared to 30-42% in the CHOP/CHOEP/MEVA/other group. Walewski *et al*. (2001) reported that difference in overall survival was significant in their population (p=0.0003).

Two observational studies (Wästerlid *et al*., 2013; Smeland *et al*. 2004) including 200 patients provided very low quality evidence of overall survival rates on the effectiveness of BFM compared to CHOP/CHOEP/mmCHOP. Overall survival (range 2-5 years, follow-up 13-247 months) rates ranged from 65-81.7% in the BFM group and from 23-38.8% in the CHOP/CHOEP/mmCHOP group. Wästerlid *et al*. (2013) reported that the difference between BFM and CHOP/CHEOP was significant at the univariate level (p<0.001) but did not remain significant at the multivariate analyses (p=0.1).

The Wästerlid *et al*. (2013) study also provided very low quality evidence of overall survival rates when comparing BFM to HyperCVAD and CODOX-M/IVAC, reporting that patients receiving BFM had a two year survival rate of 81.7% compared to 82.8% of patients receiving HyperCVAD and 68.6% of patients receiving CODOX-M/IVAC. The authors reported that these differences were not significantly different.

Complete remission and adverse events

One observational study (Smeland *et al*., 2004) including 49 patients comparing BFM to mmCHOP provided very low quality evidence of higher complete remission rates (73.7% versus 53.8%), higher rates of event free survival (73.7% versus 30.8%) and no events of central nervous system progression (0% versus 30.8%) in the BFM group. However, the BFM group reported more treatment related mortality (10.5% versus 0%) and higher rates of febrile neutropenia (52.6% versus 0%) compared to the mmCHOP group.

One observational study (Wang *et al*., 2000) including 38 patients comparing CODOX-M/IVAC to other treatment regimens (>60% CHOP) provided very low quality evidence of higher complete remission rates (8% versus 41.2%). The patients receiving CODOX-M/IVAC reported higher rates of neutropenia (95.2% versus 64.7%) and Nadir fever (90.5% versus 58.8%) compared to the patients receiving other treatment regimens (>60% CHOP). The author did not report significance level of these differences.

4.5.1.1.2 Role of rituximab

The role of adding rituximab to treatment regimens (HyperCVAD, CODOX-M/IVAC, CALGB 9251, BFM, CHOP/CHOEP, B-NHL86, LMBA) was assessed in four retrospective cohort observational studies (Wildes *et al*., 2014; Wästerlid *et al*., 2013; Dujmovic *et al*., 2012; Barnes *et al*., 2011) inclusing 393 patients and one randomised control trial (Ribrag *et al*. 2012) including 257 patients.

Overall survival

The four observational studies provided very low quality evidence of an overall survival (range 2-5 years; follow-up mean 29.4 months) range of 70.2-83% in the chemotherapy plus rituximab group versus 29.4-66% in the chemotherapy alone. The RCT assessed the addition of rituximab to LMBA reporting very low quality evidence of 3-year overall survival (follow-up median 38 months) of 82% compared to 71.33% in the group treated with LMBA only. Three of the four observational studies and the RCT reported a significant benefit of the addition of rituximab to chemotherapy in overall survival (in all studies p<0.05). The fourth observational study reported a trend in favour of the addition of rituximab. However, the addition of rituximab to chemotherapy failed to remain significant in three observational studies that reported multivariate analyses (Wildes *et al*., 2014; Wästerlid *et al*., 2013; Barnes *et al*., 2011). Age, performance ≥2 and central nervous system involvement were all factors that remained significant at the multivariate level.

Event free survival

Three of the four observational studies (Wildes *et al*., 2014; Dujmovic *et al*., 2012; Barnes *et al*., 2011) and the RCT provided very low quality evidence of higher event free survival (range 3-5 years) in the patients receiving chemotherapy plus rituximab (60.6-83% [observational studies]; 75.8% [RCT]) compared to the patients receiving chemotherapy alone (29.4-61% [observational], 64.3% [RCT]). One of the three observational studies and the RCT reported that the difference in event free survival was significant ($p<0.05$). However, neither of these papers reported multivariate statistical analyses.

Complete remission

Three of the four observational studies (Wildes *et al*., 2014; Dujmovic *et al*., 2012; Barnes *et al*., 2011) provided very low quality evidence of higher rates of complete remission (follow-up mean 29.7 months) in the chemotherapy plus rituximab group (83.3-94.4%) compared to the chemotherapy alone group (37.5-85%). Only one of these studies reported that this difference was significant ($p=0.035$: Dujmovic *et al*., 2012). This study did not report multivariate statistical analyses.

Adverse events

The addition of rituximab to the regimens was associated with very low quality evidence of lower incidence of tumour lysis syndrome reported in two of the observational studies (5.8% versus 14.6%: Dujmovic *et al*., 2012; Barnes *et al*., 2011) but a higher incidence of sepsis (12.5% versus 7.5%) reported in one observational study (Barnes *et al*., 2011). Very low quality evidence of higher rates of treatment related mortality in the chemotherapy plus rituximab group were reported in one observational study (10% versus 5%; Barnes *et al*., 2011) and the RCT (7% versus 5.4%). No statistical information was provided by the studies regarding these reported differences.

4.5.1.1.3 Da-Epoch-R

No comparative evidence was found for the use of Da-epoch-R. One prospective non-comparative study including 30 patients using the WHO 2008 modern diagnostic criteria (Dunleavy *et al*. 2013) provided very low quality evidence for the rate of freedom from progression of disease at medium follow up of 95% (confidence interval [CI]: 75-99%) in the Da-epoch-r group and 100% (CI: 72-100%) in the Sc-epoch-rr group and overall survival rates of 100% (CI: 82-100%) and 90% (CI: 60-98%), respectively. No treatment related deaths were reported but in 19% of the treatment cycles there was fever and neutropenia resulting in hospital admission. In addition, 17% of the patients experienced a neurological sensory impairment after treatment and 7% experienced a neurological motor impairment.

4.5.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Offer intensive immunochemotherapy to people with Burkitt lymphoma who are fit enough to tolerate it. Consider using one of the following:** • **R-BFM**

	• **R-CODOX-M/R-IVAC** • **R-HyperCVAD (HDMTX)** • **R-LMB.** **For people with low-risk Burkitt lymphoma, consider using the less intensive DA-EPOCH-R regimen, supplemented with intravenous and/or intrathecal methotrexate.** **Offer less intensive immunochemotherapy to people with Burkitt lymphoma who are not fit enough to tolerate intensive chemotherapy. Consider using one of the following, alone or supplemented with intravenous and/or intrathecal methotrexate:** • **R-CHOP** • **R-CHEOP** • **DA-EPOCH-R.**
Relative value placed on the outcomes considered	The GC considered overall survival to be the critical outcome when drafting recommendations. The GC also considered the balance between achieving a higher overall survival at an increased risk of treatment related morbidity. There was no evidence available for health related quality of life (HRQoL).
Quality of the evidence	The quality of the evidence was very low, as assessed GRADE. Specific issues with the evidence included: • Imprecision • Retrospective observational studies; • Diagnostic uncertainty with only three studies using the current classification system for Burkitt lymphoma (WHO, 2008) The review found no comparative evidence for two out the eight interventions included in the PICO (SFOP, DA-EPOCH-R). The GC decided to review non-comparative studies for SFOP and DA-EPOCH-R in samples of patients who met the current diagnostic criteria (World Health Organisation [WHO], 2008) published after 2006. No non-comparative evidence for SFOP was found. These issues limited the recommendations that the GC was able to make and instead of recommending a specific treatment regimen, the GC made a strong recommendation to use one of a range of more intensive therapies. Although the GC considered there was insufficient evidence to select a single intensive regimen above the others they thought that a strong recommendation for intensive therapy in general was appropriate. This was because there was very low quality but consistent evidence of higher overall survival rates with intensive therapy when compared with less intensive therapies. The uncertainty in the evidence was largely due to small patient numbers (due to the rarity of the disease) and the inability to implement a comparative trial due to country variation in treatment regimens. Patients receiving treatments such as rituximab based chemotherapy have good overall survival rates so implementing comparison arms in trials by withholding such treatment would not be considered advisable. For these reasons the GC made no research recommendation for this topic.

	None of the recommendations were based solely upon clinical experience. No research recommendation was made for this topic.
Trade-off between clinical benefits and harms	The GC considered that the potential benefits of the recommendations would be an increased overall survival rate. For patients able to tolerate intensive therapy the GC recommended a list of immunochemotherapy regimens based on the evidence which indicated that the addition of rituximab improved overall survival by more than 10% at 3 years with less than 2% increase in treatment related mortality. For those unable to tolerate intensive therapy the GC considered that less intensive immunochemotherapy regimens were more appropriate given this group would be less able to tolerate treatment toxicty. The GC noted that while the evidence indicated that some patients' disease will respond to these less intensive regimens, they are less effective than intensive regimens. The GC made the recommendation to consider DA-EPOCH-R for those with low risk Burkitt lymphoma on the basis of low quality evidence suggesting it is highly effective. In this study selected patients also received intrathecal methotrexate. For this reason the recommendation includes possible supplementation with methotrexate. The recommendations made may potentially lead to an increase in treatment morbidity. However, the benefit of increased overall survival compared to lower treatment related morbidity as a result of using less intensive chemotherapy regimens, was considered the most important outcome to patients with Burkitt lymphoma.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no economic model was developed for this topic. The GC considered that there may be potential costs from these recommendations in terms of increased hospital admissions due to the use of more intensive chemotherapy regimens (and an increased rate of treatment morbidity). However, the increased overall survival from the use of intensive chemotherapy regimens would make this strategy more effective than alternatives and it was thought likely to be cost-effective in cost per QALY terms.
Other considerations	The GC noted that the recommendations would provide reinforcement for current best practice and ensure consistency in care for patients with Burkitt lymphoma.

4.6 Peripheral T-cell lymphoma

Peripheral T-cell lymphoma (PTCL) is a cancer of mature T cells and accounts for roughly 10% of all non-Hodgkin's Lymphomas (NHL). There are a number of subtypes although the most common are peripheral T-cell lymphoma Not Otherwise Specified (PTCL-NOS) and Angioimmunoblastic T-cell Lymphoma (AITL). The other subtypes are much less common and are therefore not included in this analysis.

The cure rate, and survival rates for PTCL are worse than for the more common high grade B-cell NHL with data from the International Peripheral T-cell Lymphoma project showing that at 5 years after diagnosis, only 30-40% of patients are still alive and only 20-30% of patients

have not relapsed. First line treatment for these patients consists of combination chemotherapy. The most frequently used regimen is CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) which although reasonably well tolerated is associated with infections, nerve damage and (more rarely) cardiac damage. The reason for this regimen being standard of care is historical. Before the routine use of immunohistochemistry in diagnostics, T-cell and B-cell high grade lymphomas were treated together. Randomised clinical trials confirmed that CHOP was superior to a number of other, more intensive, combination chemotherapy regimens. With improvement in diagnostics, T-cell lymphomas could be reliably identified as a subset. Until rituximab was available for routine use as part of therapy for B-cell lymphomas, some trials included high grade T-cell and B-cell lymphomas together although interpreting the results for T-cell lymphomas is difficult due to their relatively small number.

The German High Grade Study Group published an influential report which retrospectively looked at T-cell lymphoma patients entered into a number of different prospective randomised high grade lymphoma trials. They performed subgroup analysis which suggested that patients had improved survival rates if they received the drug etoposide as part of their front line treatment regimen. This has led some groups to use etoposide (usually in the form of CHOEP) for first line treatment although it is associated with additional toxicity. Retrospective data has suggested that the use of an anthracycline (e.g. doxorubicin) adds no survival benefit, so other groups have abandoned CHOP as first line treatment altogether. Gemcitabine is an attractive drug to use in combination for PTCL, because it is not affected by proteins which pump chemotherapy drugs out of cells (the so-called P-glycoprotein) which are present in a number of T-cell lymphoma subtypes. Single centre series suggest gemcitabine containing chemotherapy regimens are effective (such as GEM-P) but other results (for example using the PEGS regimen) are disappointing. In the UK, the use of CHOP, CHOEP and gemcitabine-containing regimens is highly variable.

The main question to ask, then, is should CHOP remain the standard of care, or is there sufficient evidence to support the addition of etoposide, or the use of a different chemotherapy backbone altogether?

4.6.1 First line treatment

The recommendation from this section should be read in conjunction with the recommendations in section 4.6.2.

Clinical question: What is the most effective first-line treatment for people with peripheral T-cell lymphoma?

4.6.1.1 Clinical evidence (see section 4.6.1 in Appendix G)

Twenty three studies (two randomised control trials; two retrospective cohort studies, two phase II trials and 17 non-comparative studies [1 systematic review of 16 non-comparative studies]) reported evidence of the effectiveness of six chemotherapy regimens in 2,080 patients with peripheral T-cell lymphoma (PTCL). Of the comparative studies the five chemotherapy regimens were all compared to CHOP/CHOP like regimens.

4.6.1.1.1 Intensive chemotherapy versus CHOP/CHOP like

One retrospective cohort study (Xie *et al*. 2013) provided very low quality evidence of overall survival rates in 276 patients with peripheral T-cell lymphoma (56% PTCL-Not Otherwise Specified [PTCL-NOS] or Angioimmunioblastic T-cell lymphoma [AITL]). Overall survival was 38.9% in patients receiving intensive chemotherapy (ECHOP, Ara-C, Mesna, MINE, ESHAP, GDP, DHAP or Hyper-CVAD) compared to 16.7% in patients receiving CHOP/CHOP like chemotherapy ($p<0.001$).

4.6.1.1.2 CHOEP versus CHOP

One retrospective cohort study of patients ≤60 years of age with either PTCL-U or AITL treated on protocols of the German High-Grade Non-Hodgkin Lymphoma Study Group between 1993 and 2007 provided low quality evidence of 3 year event free survival rates of 60.7% in patients receiving CHOEP compared to 48.3% in patients receiving CHOP (p=0.057) (Schmitz *et al*. 2010). The 3-year overall and event free survival rates for the PTCL-U patients (n=70) were 53.9% (95% confidence interval [CI]: 41.7-66.1) and 41.1% (CI: 29.5-52.7), respectively. The 3-year overall and event free survival rates for the AITL patients (n=28) were 67.5% (CI: 50.1-84.9) and 50.0% (CI: 31.6-68.4), respectively.

4.6.1.1.3 VIP-rABVD versus CHOP

One randomised control trial (Simon *et al*. 2010) compared the effectiveness of VIP-rABVD to CHOP in patients with peripheral T-cell lymphoma (PTCL-NOS n: 58; AITL n: 15) provided moderate quality evidence of no overall survival benefit in patients in the VIP-rABVD arm compared to the patients in the CHOP arm (both 43 months survival rate) nor in the 2-year event free survival rate (45 ±8 versus 41 ±7: p=0.70). Complete response rates in the VIP-rABVD and the CHOP arms (44% versus 33%) and number of deaths during follow-up (n=27 versus 25) did not significantly differ, however, haematological toxicities were significantly higher in the VIP-rABVD arm with 23% versus 8% suffering grade 3-4 neutropenia (p<0.001) and 20% versus 2% had grade 3-4 thrombocytopenia (p<0.001). In addition, red blood cell and platelet transfusions were more frequent in the VIP-rABVD arm (p<0.001). Finally, the overall proportion of cycles resulting in hospitalisation for toxicity were significantly higher in the VIP-rABVD arm compared to the CHOP arm (15% versus 8%, p=0.04).

4.6.1.1.4 CyclOBEAP versus CHOP

One retrospective cohort study (Niitsu *et al*. 2008) provided very low quality evidence of 5-year overall survival in 101 patients with peripheral T-cell lymphoma (PTCL-U n=59; AITL n=42) of 61.7% in patients receiving CyclOBEAP compared to 25.7% in patients receiving CHOP. The 5-year progression free survival rate for the patients receiving CyclOBEAP was 59% compared to 22% in the CHOP group. The authors did not report whether the reported survival rates were significantly different. Niitsu *et al*. (2011) conducted a prospective non-comparative study of the effectiveness of CyclOBEAP in 84 patients with peripheral T-cell lymphoma. In the whole sample the 5 year overall and event free survival rates were 72% (CI: 66-79) and 61% (CI: 56-68), respectively, with a complete response rate of 92%. The 5-year overall survival rate for the PTCL-NOS sample (n=43) was 63% and for the AITL sample (n=27) 74%. The rates of grade 3-4 neutropenia, anaemia, grade 3-4 thrombocytopenia and non-haematological adverse events in the whole sample (n=84) were 95%, 71%, 29% and 38%. There were no treatment related deaths (follow-up median: 82 months).

4.6.1.1.5 CMED versus CHOP

One randomised controlled trial (Avilés *et al*. 2008) compared the effectiveness of CMED to CHOP in 217 patients with peripheral T-cell lymphoma unspecified (PTCL-U) reporting moderate quality evidence of an increased overall survival benefit in patients in the CMED arm compared to the patients in the CHOP arm (64% [CI: 68-79] versus 34% [CI: 31-46]; p<0.01) and increased progression free survival (70% [CI: 58-70] versus 43% [CI: 21-32]; p<0.01). The CMED arm had higher complete response rates compared to the CHOP arm (76% [CI: 77-94] versus 57% [CI: 57-69]; p<0.05). There were no treatment related deaths. Grade 1 thrombocytopenia rates in the CMED arm were 16% compared to 12% in the CHOP arm. The rates of hospitalisation due to toxicity were similar in both arms (CMED: 9% versus CHOP: 10%). 4% of patients in the CMED group reported anaemia compared to none in the CHOP group. Finally, more patients in the CHOP group (23%) suffered from granulocytopenia compared to the CMED group (13%). The authors do not report if the numbers of adverse events differed significantly between the two arms.

4.6.1.1.6 Anthracycline-based chemotherapy

One systematic review (AbouYabis *et al*. 2011) reported 16 studies assessing the use of anthracycline-based chemotherapies in PTCL-NOS (n=432), AITL (n=169) and non-ALCL PTCL (n=417) patients. Pooled statistics for the AITL patients provided very low quality evidence of a 5-year overall survival rate of 32.1% (CI: 27.2-37.5%) and a complete response rate of 42.1% (CI: 33.9-50.9%). Due to heterogeneity the studies with PTCL-NOS or non-ALCL PTCL patients were not pooled. The range of 5 year overall survival rates in the PTCL-NOS sample were 32-45% for 3 retrospective non-comparative studies and for the non-ALCL PTCL sample were 26 (one retrospective study)-35% (one prospective study). Complete response rates in patients with PTCL-NOS ranged from 17.1-57.1% in three prospective studies and 47-69.6% in six retrospective studies. Complete response rates in patients with non-ALCL PTCL ranged from 41-49% in two prospective studies and 58-59% in two retrospective studies.

4.6.1.1.7 CHOP + Avastin

One prospective non-comparative study (Advani *et al*. 2012) provided very low quality evidence for cardiac related adverse events in 44 patients treated with CHOP + Avastin. On average 20% of patients reported cardiac events (CI: 9.1-35.7) with 17% stopping the trial early due to congestive heart failure (CI: 5.6-34.7).

4.6.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider CHOP chemotherapy as first-line treatment for people with peripheral T-cell lymphoma.**
Relative value placed on the outcomes considered	Overall survival and treatment toxicity (treatment related mortality and morbidity) were considered the critical outcomes when drafting the recommendation. No evidence was identified for the outcome health related quality of life (HRQoL).
Quality of the evidence	The quality of evidence for the topic ranged from low to moderate as assessed using GRADE and NICE checklists for quantitative studies. Reasons for downgrading the quality included: • studies not providing a breakdown for each included subtype of peripheral T-cell lymphoma • studies including patients with subtypes of peripheral T-cell lymphoma that were not relevant to the review question • one study reported use of adjuvant therapy but only for patients with bulky disease at diagnosis • some were non-comparative. As a result of the lack of high quality evidence, the GC did not make a strong recommendation about the use of CHOP. The GC noted that CMED is not currently used to treat patients with PTCL-NOS and AITL in the UK. In addition, the GC raised a number of issues concerning the RCT that compared CMED to CHOP: • Population applicability (the GC noted that the median age was younger in the RCT compared to patients with peripheral T-cell

	lymphoma treated in the UK) • Lack of follow-up using CMED to assess any longer-term benefits/harms • Single-centre study • No autograft as part of first line treatment
Trade off between clinical benefits and harms	The GC considered that the recommendation would discourage the use of more intensive/toxic induction therapies (e.g. CMED) when there is currently a lack of evidence to recommend they are better. Although evidence from one RCT showed a survival benefit in patients receiving CMED compared to patients receiving CHOP, with similar short term adverse event rates, the GC did not recommend CMED due to the issues with the trial listed above. The GC concluded the available evidence did not support a change in current practice and that the CHOP treatment regimen should continue to be used to treat patients with peripheral T-cell lymphoma, NOS, and angioimmunoblastic T-cell lymphoma. The GC noted that the recommendation to consider the use of CHOP is recognised within the clinical field as a treatment with limited success but that the current evidence base does not provide a suitable alternative.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The GC noted that the recommendation reflects current clinical practice and will not result in any additional costs, savings or change in practice. It was also thought that, in comparison to the alternatives, CHOP would be cost-effective. The cost of CHOP is similar to many of the alternative regimens and in terms of effectiveness, CHOP is thought to be the best option currently available (although, as mentioned above, it is recognised that CHOP is a treatment with limited success).
Other considerations	The GC noted that the recommendation is in line with the British Committee for Standards in Haematology. As the GC noted that there are current research activities in the target population (two ongoing trials, one currently recruiting within the UK) they agreed that a research recommendation for this topic was not necessary.

4.6.2 Consolidation therapy in peripheral T-cell lymphoma

In an effort to improve the cure rate, high dose therapy with autologous stem cell transplantation (ASCT) in first remission has been employed for those who have responded to first-line chemotherapy. No randomised trials have been performed to investigate the role of either ASCT or allogeneic transplantation (alloHSCT) in PTCL. The best evidence comes from prospective, single arm studies, or from analyses of Registry data. Both have significant potential weaknesses, making definitive conclusions impossible and current practice contentious.

As with other lymphomas it is also possible to identify groups of patients with worse prognostic features. The possible role of alloHSCT has therefore been explored as consolidation either in those with higher risk features, or in younger patients in whom the toxicities and non-relapse-related procedural mortality are likely to be lower. The introduction

of less toxic 'reduced intensity' alloHSCT regimens has more recently allowed evaluation of its role in older patients up to the age of 65 years.

The main alternative management strategy to transplantation is expectant observation following induction chemotherapy. Whilst this may appear economically favourable, it is important to acknowledge the subsequent costs of increasingly expensive salvage regimens in those destined to relapse, in many cases given with the intent to consolidate second remission by either ASCT or alloHSCT.

Clinical question: What is the effectiveness of high-dose consolidation of first-line therapy with autologous or allogeneic transplantation in people with peripheral T-cell lymphoma?

4.6.2.1 Clinical evidence (see section 4.6.2 in Appendix G)

Twenty studies (thirteen observational comparative studies [1 systematic review of 8 studies] and 7 non-comparative studies [1 systematic review of 5 non-comparative studies]) reported evidence of the effectiveness of consolidation therapy using stem-cell transplantation in 1,480 patients with peripheral T-cell lymphoma (PTCL).

4.6.2.1.1 Autologous transplantation versus chemotherapy alone

One systematic review (Yin *et al*. 2013) provided very low quality evidence of 3-year overall survival rates from two studies (PTCL-NOS and AITL, n=93) comparing patients who received either an autologous transplantation or chemotherapy alone after first line therapy finding no statistically significant difference between the two groups (Hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.05-6.94). Six non-comparative studies of patients receiving consolidation therapy in first response (Mounier *et al*. 2004; 5 reported in Yin *et al*. 2013) provided very low quality evidence of 5-year overall survival rates between 52-62%. Finally Mounier *et al*. (2004) reported a 5 year disease free survival rate of 44% in patients receiving autologous transplantation.

One retrospective comparative observational study (Mehta *et al*. 2013) provided very low quality evidence of overall survival rates in 53 patients with peripheral T-cell lymphoma receiving consolidation therapy after first line therapy. In 32 patients with PTCL-Not Otherwise Specified (PTCL-NOS) the 4 year overall survival and progression free survival rates were 75% and 64.3% in the autologous group compared to 12.5% and 6.3% in the patients who received only chemotherapy. In 21 patients with angioimmunioblastic T-cell lymphoma [AITL] the 4 year overall survival and progression free survival rates were 62.8% and 48.2% in the autologous group compared to 66.7% and 33.3% in the patients who received only chemotherapy.

4.6.2.1.2 Complete response versus non-complete response

Very low quality evidence came from one systematic review (Yin *et al*. 2013) included three studies (n=149) comparing complete first response to non-complete first response prior to autologous transplantation. There was uncertainty about the difference in the overall survival of the two groups (HR: 3.17; 95% CI: 0.92-5.42). Three other studies (number of patients not provided by authors) compared complete response to partial response prior to autologous transplantation finding no statistically significant difference between the two groups (HR: 0.73; 95% CI: 0.36-1.48).

4.6.2.1.3 Allogeneic transplantation versus chemotherapy alone

Very low quality evidence about overall survival came from one retrospective cohort study (Mehta *et al*. 2013) in five patients with peripheral T-cell lymphoma receiving allogeneic consolidation therapy after first line therapy. In 4 patients with PTCL-NOS the 4 year overall survival and progression free survival rates were 100% and 50% in the allogeneic group

compared to 12.5% and 6.3% in the patients who received only chemotherapy (n=26). One patient with AITL received an allogeneic transplantation but did not survive.

One non-comparative study (Le Gouill *et al*. 2008) provided very low quality evidence about complete response rates in PTCL-NOS (n=27) and AITL (n=11) patients receiving allogeneic transplantation of 22% and 9%, respectively and 5-year overall survival rates of 63% and 80%. The Le Gouill *et al*. (2008) study contained patients receiving consolidation therapy after more than one line of therapy although the exact numbers were not reported.

4.6.2.1.4 Allogeneic or autologous transplantation versus chemotherapy alone

One retrospective comparative study (Broussais-Guillaumot *et al*. 2013) compared peripheral T-cell lymphoma patients (PTCL-U n=81; AITL n=52; 19.7% complete first response) who had received either an autologous or allogeneic transplantation (n=75) to patients who received chemotherapy alone (n=133). rVery low quality evidence from this study indicated median overall survival of 51 months in the transplantation group compared to 15 months in the chemotherapy alone group.

4.6.2.1.5 Allogeneic versus autologous transplantation

One prospective comparative observational study (Corradini *et al*. 2014) of 61 patients with peripheral T-cell lymphoma (n=33 PTCL-NOS and n=14 AILT), of which 23 received an allogeneic stem cell transplant and 14 received an autologous stem cell transplant provided very low quality evidence about four-year overall and progression free survival rates of 92% and 70% in the autologous group versus 69% and 69% in the allogeneic group. The authors reported that there were no significant differences between transplant types.

One retrospective comparative observational study (Mehta *et al*. 2013) provided very low quality evidence about overall survival rates in five patients with peripheral T-cell lymphoma receiving allogeneic consolidation therapy after first line therapy compared to 34 patients receiving autologous consolidation therapy. In 32 patients with PTCL-Not Otherwise Specified (PTCL-NOS) the 4 year overall survival and progression free survival rates were 75% and 64.3% in the autologous group compared to 12.5% and 6.3% in the patients who received only chemotherapy. In 17 patients with AITL the 4 year overall survival and progression free survival rates were 62.8% and 48.2% in the autologous group (n=16) compared to 0% in the one patient who received allogeneic transplantation.

Very low quality evidence came from one retrospective comparative observational study (Smith *et al*. 2013) including 241 patients with peripheral T-cell lymphoma (PTCL-U n=102, AITL n=27), of which 24% were receiving transplantation in their first complete response. In 102 PTCL-U patients the one and three year progression free survival rates for the autologous transplantation group (n=39) were 60% (CI: 43-74%) and 29% (CI: 14-47) compared to the allogeneic group (n=63) 40% (CI: 28-52) and 33% (CI: 22-45). The one and three year overall survival rates for the autologous transplantation group (n=39) were 64% (CI: 46-77%) and 45% (CI: 27-62) compared to the allogeneic group (n=63) 52% (CI: 38-64) and 42% (CI: 30-55). The non-relapse mortality rates at one and three years in the autologous group were 3% (CI: 0-12) and 3% (CI: 0-12) compared to 16% (CI: 8-26) and 28% (CI: 17-39) in the allogeneic group. The three year chronic GVHD rate was 43% in the allogeneic group.

In 27 AITL patients the one and three year progression free survival rates for the autologous transplantation group (n=15) were 53% (CI: 26-74%) and 47% (CI: 21-69) compared to the allogeneic group (n=12) 67% (CI: 34-86) and 67% (CI: 34-86). The one and three year overall survival rates for the autologous transplantation group (n=15) were 60% (CI: 35-82%) and 51% (CI: 26-76) compared to the allogeneic group (n=12) 92% (CI: 70-100) and 83% (CI: 56-98).

The 3 year progression free survival rate for patients in their first complete response (n=40 was 58% with a one and three year overall survival rate of 80% and 70%, respectively.

4.6.2.1.6 Allogeneic transplantation versus high dose methotrexate

One retrospective comparative observational study (Iriyama *et al*. 2013) provided very low quality evidence about 3 and 5 year relapse rates in 28 patients with peripheral T-cell lymphoma (PTCL-NOS n=13, AITL n=11) receiving autologous transplantation (n=18) or high dose Methotrexate (n=10) consolidation therapy after first line therapy. The 3 and 5 year relapse rates were 68% and 53% versus 58% and 40%.

4.6.2.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**Consider consolidation with autologous stem cell transplantation for people with chemosensitive peripheral T-cell lymphoma (that is, there has been at least a partial response to first-line chemotherapy) who are fit enough for transplantation.**
Relative value placed on the outcomes considered	Overall survival and toxicity (treatment related mortality and morbidity) were considered to be the critical outcomes when wording the recommendation. No evidence was identified relating to health related quality of life (HRQoL) A number of the included articles presented outcomes (e.g. survival rates) by response rate to first line therapy and therefore the GC could establish the value of transplantation according to response to first line therapies.
Quality of the evidence	All the evidence for each outcome was rated as very low quality as assessed using GRADE and NICE checklists for quantitative studies. The primary reason for downgrading the quality of evidence was imprecision with wide confidence intervals as a resuit of small sample size or low event rate.. A number of studies were downgraded due to serious indirectness as a result of not providing a breakdown for each included subtype of peripheral T-cell lymphoma included in the PICO. Some studies also included a minority of patients with subtypes of peripheral T-cell lymphoma not included in the PICO. Other studies included populations of patients who had received more than one line of systemic therapy or included children (<16 years of age). These studies were included due to a lack of higher quality direct evidence, given the relative rarity of peripheral T-cell lymphoma. Due to the low quality of the evidence the GC could not make strong recommendations for the use of autologous transplantation. The GC did not make a recommendation concerning the use of allogeneic transplantation for patients with peripheral T-cell lymphoma as part of first-line therapy, since allogeneic transplantation has mainly been reserved for patients beyond first-line therapy. The only prospective study directly addressing this issue was relatively small and used a donor/no donor strategy to allocate transplant modality (Corradini *et al*, 2014).
Trade off between clinical	The evidence indicated better survival in patients receiving

benefits and harms	consolidation with autologous transplantation. As a result the main benefit associated with the recommendation is likely to be increased overall survival and progression free survival. The GC noted that they have recommended the use of a toxic treatment which may result in an increase in treatment related morbidity. The GC considered that the survival outcomes for patients with PTCL-NOS or AITL are poor with chemotherapy alone and therefore concluded that the potential for increased survival benefits in these patients using consolidation therapy is important and on balance outweighed the possible harms.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built. The recommendation reflects current practice, so the GC did not expect an increase in costs overall. Despite the higher upfront costs and potential adverse events associated with autologous transplantation, its use was considered likely to be cost-effective because of improvements in progression free survival and overall survival. These survival improvements should make the strategy more effective in QALY terms and should also produce downstream cost savings through a reduction in the need for further therapies (for example salvage therapy). Therefore, the GC thought the recommendation is likely to be cost-effective in cost per QALY terms.
Other considerations	The recommendation reflects current practice so the GC agreed there should be no change in practice. The GC noted that there is a need for research in the patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) and Angioimmunioblastic lymphoma (AITL) undergoing first line therapy, but considered that it would not be possible to address issues relating to transplant modality in a randomised fashion due to small patient populations. Although cohort studies are feasible, the GC noted that such studies have already been carried out and did not provide convincing evidence about transplant modality. The GC noted that the recommendation is in line with the British Committee for Standards in Haematology for the treatment of patients with peripheral T-cell lymphoma.

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5 Patient information needs

5.1 Information and support

People living with non-Hodgkin's lymphoma (NHL) or supporting someone who has NHL must have access to the right information at the right time. Including information about the diagnostic tests, disease itself, treatment options, complications associated with NHL, available clinical trials and practical issues. They must cope with the stresses created by a potentially physically demanding illness and health impairment. These effects may be magnified if the right information and support is not available.

In 2004, the National Audit Office found that nearly 40% of cancer patients did not receive information they required. National approaches by leading cancer charities and the National Cancer Action Team (NCAT) have aimed to improve this. There is no standard agreement or approach how best to provide the full array of information needed at various times during and after the cancer treatment. However, it is documented that information should be tailored to the individual needs. It is evident that satisfaction improves and anxiety decreases when information is provided at the right time.

There are many approaches to informing cancer patients about their diagnosis, disease and treatment. The key is to ensure that the right information is in a format accessible to the patient (e.g. paper materials, electronic materials, visual and audio materials). This is of particular relevance for patients with NHL due to the fact there are a number of differing types of NHL, there is the possibility of transformation to a different type of NHL and treatment may be influenced by co-morbidities. Information related to the practical issues is generic and this must not be overlooked as evidence indicates that issues such as finance and work concerns are as important as the disease and treatment itself to patients and carers. A system of providing such information that is up to date, accurate, and reliable and in a language that carers and patients can read and understand needs to be agreed and monitored.

Clinical question: What are the information and support needs of patients with a diagnosis of non-Hodgkin's lymphoma and their carers?

5.1.1 Clinical evidence (see section 5.1 in Appendix G)

Evidence came from 27 cross-sectional studies, four prospective cohort studies and one retrospective case series. Two studies were qualitative in design the remainder were quantitative survey studys of patients with NHL. The overall quality of the evidence was moderate.

Analysis of the subgroup of 2530 patients with non-Hodgkin's lymphoma included in the 2014 Cancer Patient Experience Survey suggested the following (see Appendix H):

- Whilst similar to all cancer patient reports from the survey, there are potential areas where patient needs may warrant further attention around diagnosis , particularly to ensure patients fully understand their test results, have their diagnosis explained fully and are given the opportunity/choice to have a friend/relative present.
- Approximately 70% of patients with NHL reported that their views were taken account and were involved in decisions regarding their treatment and care; similar to all cancer patients. However, the findings suggest an unmet need around information given on longer-term side effects for patients with NHL.
- Ensuring easy access to a CNS for all patients is warranted given the high endorsement that CNS's listened to, and provided understandable answers to their patient's questions all or most of the time.

- There may be unmet needs in informing patients of and allowing access to participation in clinical trials.
- Patients should be assessed on their individual needs to receive information/advice on work/education and choice given to participate in support groups.
- Attention to ensuring easy to understand written information both before and after procedures is relevant and important area to address.
- Approximately 80% of patients expressed satisfaction with their hospital doctors; an unmet need for patients with NHL may be ensuring their carer/relative/friend has sufficient opportunity to ask questions.
- Over 75% of patients with NHL stated positively on the way they were treated by doctors and nurses. Ensuring patients are given opportunity to discuss worries and fear when wanted by the individual patient warrants further consideration.
- Whilst the majority of patients with NHL were given information on what to do and whom to contact, a potential unmet need is the information provided to relatives/friend on how to care for him/her at home.
- The majority of patients with NHL reported positive endorsement of their care given to control side-effects but further attention may be needed to ensure patients have access and opportunity to receive emotional support.
- There are no obvious differences between sub-types, length of treatment, treatment pathway (e.g. in active treatment or follow up).

5.1.1.1 What do patients with non-Hodgkin's lymphoma need during diagnosis and treatment?

Participants reported moderate levels of satisfaction (~60%) with the information they were given during their treatment (Husson *et al*. 2013, Netherlands; Oerlemans *et al*., 2012, Netherlands), with the majority of participants (71%) reporting that their physician always spent enough time during their visits and appointments (Arora *et al*. 2013, USA).

5.1.1.1.1 Feeling involved

Participant's information needs were individualistic. Whilst, the majority of participants (59%) reported that they considered their treatment decision making to be collaborative (whereby the doctor and they shared responsibility for any decisions; Poe *et al*., 2012) and felt that they were at the heart of the communication process and information exchanges made (Wall *et al*., 2011, UK) there were some participants (13%) who preferred for their doctor to make all their treatment decisions (Poe *et al*., 2012, USA), actively avoided seeking out information for fear of further upset to themselves or their family (Wall *et al*. 2011, UK).

Informed decision making

Feeling informed and possessing adequate knowledge about investigations and treatments being undertaken was vital to coping with the process.

Participants reported using previous practical knowledge to make sense of what was happening, probably due to their experience undergoing similar investigations (e.g. ultrasounds, blood tests) or from other people's accounts of such investigations (Wall *et al*. 2011, UK).

Patients undergoing protective isolation as a consequence of receiving high-dose chemotherapy, who felt well-informed for the need for the protective environment, appeared to cope better with the experience, with knowledge having an mediating effect on the experience which was viewed as 'something that I have to do if I want to get well' (Campbell *et al*. 1999, USA). Knowledge of the remission length and levels of treatment toxicity were important attributes considered by patients with follicular lymphoma when deciding whether

or not to go for transplantation, with participants requiring 0.6 years absolute increase in progression-free survival or a 6% absolute increase in 5-year progression-free survival in order to accept the toxicity of autologous stem cell transplantation (relative to chemotherapy) but 3.9 years increase in progression-free survival or a 39% increase in 5-year progression-free survival in order to accept the toxicity of allogeneic stem cell transplantation (relative to chemotherapy) (Shafey *et al*. 2011, Canada).

Knowing who they can discuss issues with

Whilst the majority of participants were willing to discuss any physical functioning issues (93.9%), daily functioning issues (81.6%) and emotional functioning issues (75.5) they may have or had with their doctor, less than half of participants were willing to discuss social (42.8%) or sexual (48.9%) functioning issues with their doctor with the majority of the remaining participants stating that they would prefer not to discuss these issues with their doctor. Participants believed that it was not their doctor's job to discuss these issues (47% social functioning issues, 30% sexual functioning issues) with almost 30% stating that they would not feel comfortable discussing these issues with their doctor. However, less than 20% of participants reported that they felt nothing could be done to help with social (11%) or sexual (16%) functioning issues, suggesting that they may like to access help with these issues but are either unsure whether their doctor is the correct person to discuss these issues with (Arora *et al*., 2013, USA).

5.1.1.1.2 Information needs

Around 30% of patients and survivors would have wanted more information provision during treatment (Husson *et al*. 2013; Oerlemans *et al*., 2012; Jonker-Pool *et al*., 2004, Netherlands), with 22% still reporting an unmet information need one year after the completion of their initial survey (Jonker-Pool *et al*., 2004, Netherlands).

Patients currently receiving treatment wanted more information concerning financial issues and emotional health compared to patients not actively in treatment and those experiencing a recurrence reported significantly higher unmet needs regarding financial concern, access and continuity of care and emotional health compared to participants without recurrence (or unsure if they have a recurrence, $p<0.05$: Hall *et al*. 2014, Australia).

28.8% of survivors of adolescent and young adult NHL reported a need for additional information on how to talk about cancer with their family and friends and half wanting additional information on ways to help them meet other adolescents or young adult cancer patients/survivors (Kent *et al*. 2013).

28% of adult survivors of aggressive NHL wanted more information about factors associated with sexual functioning after a cancer diagnosis and 13% wanted more information about fertility issues, with the greatest reported need for more fertility-related information from younger participants (23-40 years old, $p<0.01$), non-white-race participants ($p<0.01$) and participants that perceived their quality of care received as less-than excellent ($p<0.05$; Hammond *et al*. 2008, USA). Male participants ($p<0.05$) and participants who had received a bone marrow/stem-cell transplantation ($p<0.05$) reported a greater need for more sexual function-related information.

Just over half of participants would have liked to have received exercise counseling and would have felt able to participate in tailored exercise programme. With 80% expressing interest in exercise programmes designed specifically for NHL patients. However, the majority (56.3%) would have preferred to start an exercise programme after treatment was complete (Vallance *et al*. 2005a, Canada).

30% of participants reported that they had not been offered an appointment to attend a fertility clinic during their cancer treatment with only 8% of those offered reporting that they

attended a fertility clinic at some point during or after their treatment (Greaves *et al*., 2013, UK).

5.1.1.2 Strategies to cope with treatment

Patients undergoing protective isolation as a consequence of receiving high-dose chemotherapy appreciated having a natural view (which made them feel less shut out from the outside world), being involved in a nurse-led routine (providing an incentive to do things such as get up for bed-making) and felt that having a clock in the room was useful, enabling them to plan their day ahead. The geographical location of the bedrooms was significant to the patients not feeling alone ("I can't see them [nurses and doctors] from here and I can't hear them, and at times it feels as if it's the Marie Celeste [laughing]…nothing happens"). Whilst visitors were instrumental in providing support, many discouraged family and particularly friends from visiting so as to protect themselves from infection. Whilst face-to face contact was discouraged telephone and media were important ways that the patients could maintain contact with the outside world (Campbell *et al*. 1999). Finally, those who had previously received treatment on the ward where they were in isolation valued the familiarity that they felt towards the nurses, who were commonly portrayed as friends, serving to ameliorate the anxiety associated with the isolation experience (Campbell *et al*. 1999, UK).

5.1.1.2.1 Supportive needs

Support from others: Almost half of male NHL participants surveyed reported that they had received insufficient support (48%) during their treatment, although when measured again one year later after treatment, participants no longer reported any unmet additional support (Jonker-Pool *et al*., 2004, Netherlands). Participants reported that the major emotional support provided to them during decision making came from their family (83.2%; Glover *et al*., 2011, USA). Informational and instrumental support needs mainly came from nurses (79%) with only 12.6% of participants reporting that this support came from the physician (Glover *et al*., 2011, USA). Over 90% of participants reported receiving no formal peer or group support during treatment decision making, and whilst it was not reported whether participants wanted to receive support from these avenues, access to a formal peer support group significantly reduced the time between treatment decisions in patients with relapsed Follicular lymphoma considering undergoing stem cell transplantation ($p=0.045$; Glover *et al*., 2011, USA).

Psychological impact of treatment decision making: Whilst participants did not report significant conflict or regret surrounding their last treatment decision, they did report that treatment decision making was associated with psychological distress (mild: 57% sample, moderate: 33% sample), anxiety (57% sample) and severe levels of cancer specific distress (37% of the sample scored above average for: avoidance subscale and 27% of the sample scored above average: intrusive subscale, Poe *et al*., 2012, USA).

Psychological impact of treatment: Undergoing treatment for non-Hodgkin's lymphoma was associated with poorer overall health related quality of life compared to age-matched norms ($p<0.01$), with patients reporting higher levels of fatigue, dyspnea, sleeping problems, appetite loss and financial problems compared to age-matched norms ($p<0.05$; Oerlemans *et al*. 2014, Netherlands). Certain treatments were associated with poorer physical health and mental well-being, with participants treated with R-CHOP14 reporting significantly more often tingling in hands and feet ($p<0.05$), lower global health status/quality of life ($p<0.05$), higher levels of fatigue ($p<0.01$) and a feeling of being slowed down ($p<0.05$) compared to patients treatment with R-CHOP21 (Oerlemans *et al*. 2014, Netherlands). Levels of psychological distress (fatigue and depression) increased and health related quality of life decreased (measured over 56 weeks, Jerkeman *et al*. 2001, Norway) during chemotherapy, with patients receiving CHOP reporting significantly higher levels of fatigue on day 10 compared to day 21 of the treatment cycle and baseline levels ($p<0.01$; Menshadi *et al*., 2013, Israel) and patients receiving any chemotherapy reporting significantly higher levels of fatigue and

depression on day 7 of the treatment cycle compared to baseline (p<0.05, El-Banna *et al*., 2004, USA). However, increased levels of fatigue and depression returned to baseline levels two weeks post chemotherapy treatment (Menshadi *et al*., 2013, Israel [only fatigue measured] El-Banna *et al*., 2004, USA [fatigue and depression]) and varied during treatment depending on individual coping strategies, with patients who had high levels of learned resourcefulness (use of problem-solving strategies, ability to delay gratification and general belief in one's own ability to regulate internal events) reporting significantly lower levels of treatment-related fatigue (no p-values reported, Menshadi *et al*., 2013). Health related quality of life scores (except role function) measured at the 56th week of the treatment cycle in the majority of patients returned to baseline levels, comparable to an age-matched population (Jerkeman *et al*. 2001, Norway).

Vallance *et al*. (2005b, Canada) reported on patients' levels of exercise engagement during treatment, finding that quality of life and well-being did not differ depending on level of engagement when considering demographic and clinical characteristics.

5.1.1.3 What do patients with non-Hodgkin's lymphoma need after treatment?

The majority (>60%) of participants reported that their follow-up care they had received to date was excellent (Forsythe *et al*. 2014; Arora *et al*. 2013, USA).

5.1.1.3.1 Information needs

Most survivors reported moderate to low levels of need for additional health information (Forsythe *et al*., 2014, USA) about cancer treatment information provision, financial concerns, access and continuity of care, relationships and emotional health (measured levels of unmet needs in the past month; Hall *et al*., 2014, Australia). However, younger participants (<60 years old) reported significantly higher unmet needs (p<0.001: Hall *et al*., 2014, Australia).

When considering what they would want for their longer-term follow-up care/survivorship care, participants reported that continued screening for a possible return of cancer was their most important factor, with monitoring overall health, nutrition and exercise support, insurance and adequate money to afford such monitoring also important (compared to physicians needs) (Friedman *et al*. (2010, USA). Participants rated psychosocial issues as less important compared to medical issues, with male survivors rating sexuality and fertility health issues as more important than women (p=0.004) and younger patients at diagnosis (<60 years old at time of diagnosis) rated having their overall health monitored and have care that took into account sexually and fertility, mental health services and financial issues as more important compared to patients who were over 60 years old at diagnosis (all p<0.05). The majority of participants (63%) would want an oncologist and a primary care physician to co-manage their survivorship/longer-term follow-up care.

5.1.1.3.2 Support needs

The majority of participants reported that they were not as interested in sex and that their sex life was less satisfying now compared to prior to their cancer diagnosis, with 30% reporting that they attributed these low satisfaction rates due to their cancer diagnosis (Greaves *et al*., 2013, UK). Beckjord *et al*. (2011, USA) reported that survivors with a lower than average health status were less satisfied with their sex life compared to participants reporting an above average health status.

Psychological support: Health related quality of life varied across studies with some reporting that the majority of survivors reported medium/high levels of quality of life (Glaser *et al*., 2014, UK; Smith *et al*., 2013, USA; Vissers *et al*., 2013, Netherlands, Tchen *et al*., 2002, France) and others reporting lower levels of quality of life, general health perceptions and high levels of psychological distress compared to age-matched normative samples (Van der poel *et al*., 2014; Oerlemans *et al*., 2014, Netherlands; Smith *et al*., 2009, USA; Mols *et al*.,

2007, Netherlands; Tchen *et al*., 2002, France). One study reported that survivor's reported mental health status was comparable to population norms but their physical function was lower (Jensen *et al*., 2014, USA). Two follow-up studies reported that 25.5% of survivors report a worsening of health related quality of life (measured at least 7 years post diagnosis) and between 20-33% of survivors report persistent symptoms and worries concerning their health and quality of life (measured at least 1 year after diagnosis, mean: 2.6 years) (Oerlemans *et al*., 2014, Netherlands; Smith *et al*., 2013, USA).

5.1.1.3.3 Health related quality of life varied in survivors according to the following factors

Coping strategies

Jensen *et al*. (2014, USA) reported that health related quality of life varied according to participants cognitive health appraisal competencies (Perceived Health Competence Scale and Perceived Personal Control) with participants reporting low levels of health competencies reporting lower levels of physical and mental component summary scores and higher levels of anxiety, depression and fatigue compared to participants who reported high levels of health appraisal competency ($p<0.001$). Meaningful differences were also identified between survivors with low and medium levels of health competency across all health related quality of life outcomes except mental component summary scores. With the exception of physical component summary scores, greater perceptions of personal control was associated with significantly better quality of life outcomes ($p<0.01$).

Age

Older participants scored significantly lower on the physical functioning items compared to younger participants ($p<0.05$ Mols *et al*., 2007, Netherlands) and reported reduced perceptions of cancer having positively impacted on one's life (Smith *et al*., 2013, USA). Younger survivors (18-59 years old) reported higher physical functioning scores ($p<0.01$), higher global health status scores $p<0.05$), higher levels of financial problems ($p<0.01$), lower levels of appetite loss ($p<0.01$) and lower levels of constipation ($p<0.05$) compared to older survivors (76-85 years old) with survivors aged between 60-75 years reporting higher global health status scores ($p<0.05$) and low levels of appetite loss ($p<0.01$) compared to survivors aged between 76-85 years old (Van der Poel *et al*., 2014, Netherlands). Finally, Kourkoukis *et al*. (2004, Canada) reported that older survivors (>65 years) reported more concern about how they consider their appearance to others ($p<0.05$), more impact of general toxicity ($p<0.01$) and the importance of their faith ($p<0.01$) compared to younger patients (≤65 years). Younger patients reported more concern about sex/intimacy issues compared to older patients ($p<0.01$). However, the authors doubted the differences reflected true differences in quality of life due to multiple comparisons increasing the likelihood of finding spurious differences.

Comorbidity

Greater number of comorbidities was a significant predictors of lower physical component scores measured at follow-up ($p<0.01$) (Smith *et al*., 2013, USA). In addition, compared to participants with no additional long-term conditions, the presence of one or two or more long-term conditions was significantly associated with lower quality of life scores, poorer outcomes on the social difficulties inventory (SD) and the functional assessment of cancer therapy (lymphoma items: $p<0.001$: Glaser *et al*., 2013, UK), poorer physical functioning ($p<0.05$) and more pain ($p<0.01$: Mols *et al*., 2007, Netherlands).

Type of treatment

Survivors who reported a greater negative impact on their life at follow-up were more likely to have undergone a transplant (Smith *et al*., 2013, USA), whereas survivors who had received

chemotherapy were more likely to report lower scores on psychological well-being, social well-being and total quality of life (p<0.01; Mols *et al*., 2007, Netherlands).

Current employment

Participants who were employed reported being more vital and had better mental well-being scores compared to participants not working (p<0.01: Mols *et al*., 2007, Netherlands).

Time since diagnosis

Longer time since diagnosis was positively associated with social (p<0.01) and psychological well-being (p<0.05: Mols *et al*., 2007, Netherlands).

Social support

Survivors who report good levels of social support were more likely to report greater perceptions of cancer having positively impacted on one's life at follow-up (Smith *et al*., 2013, USA).

Recurrence/active disease

Compared to participants in remission, participants currently in active treatment, experiencing a recurrence or who were not sure about their disease status had increased odds of reporting lower quality of life and poorer outcomes on the social difficulties inventory (SD) and the functional assessment of cancer therapy (lymphoma items) (p<0.001: Glaser *et al*., 2013, UK).

Physical activity

Higher levels of reported physical activity were associated with increased quality of life in survivors, with each additional day of physical activity reducing the odds of lower quality of life score by 9% (Glaser *et al*., 2013, UK). However, Vallance *et al*. (2005b, Canada) reported that survivors post treatment exercise levels were not associated with health related quality of life when considering demographic and clinical factors.

5.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**To help people with non-Hodgkin's lymphoma (and their family members or carers as appropriate) to make decisions about care, follow the recommendations in the NICE guidelines on patient experience in adult NHS services, improving outcomes in haematological cancers – the manual (patient-centred care), improving supportive and palliative care for adults with cancer and care of dying adults in the last days of life. Pay particular attention to the following areas:** • **establishing the best way of communicating with the person** • **timing and format of information** • **information about treatment, including benefits, short-term**

	risks and late effects • **financial support and benefit advice** • **fertility issues** • **sexual function** • **support groups** • **access to wellbeing services and psychological support.** **Give people with non-Hodgkin's lymphoma (and their family members or carers as appropriate) detailed information about the nature and purpose of diagnostic and staging tests, including:** • **bone marrow biopsies** • **central line insertion** • **core and excision biopsies** • **CT and PET-CT scans** • **lumbar punctures.** **If 'watch and wait' (observation without therapy) is suggested for a person with non-Hodgkin's lymphoma:** • **explain to them (and their family members or carers as appropriate) about what this involves and why it is being advised** • **address any increased anxiety that results from this approach**. **Explain to people with low-grade non-Hodgkin's lymphoma about the possibility of transformation to high-grade lymphoma, taking into account the person's needs and preferences. Involve family members or carers as appropriate.** **Ensure that people with non-Hodgkin's lymphoma have:** • **a named key worker at diagnosis and during treatment and** • **contact details for the specialist team after treatment.** **Discuss exercise and lifestyle with people with non-Hodgkin's lymphoma from diagnosis onwards.**
Relative value placed on the outcomes considered	The GC considered the information and support needs reported by patients and their carers, patient experience and treatment decision making to be the critical measures of information and support needs of patients with a diagnosis of non-Hodgkin's lymphoma and their carers.
Quality of the evidence	The overall quality of the evidence was assessed as moderate using the NICE qualitative study and cohort study checklists. The included qualitative studies generally used appropriate methods and analysis and provided rich data, however recall bias was a potential issue. Some of the cross sectional survey studies had potential for recall bias, some had low response rates and some used non-validated measures. These survey studies were included because they provided information about the scale and relative importance of information and support needs.
Trade off between clinical benefits and harms	There was a lack of evidence about information and support needs during palliative care for people with NHL. However the GC

noted that recommendations on information and support needs during end of life care were adequately covered by other published NICE guidance (CSG4: Improving supportive and palliative care for adults with cancer) and decided not to make further recommendations in this area

Based upon the evidence review, the results of the 2014 National Cancer Patient Experience Survey and their own experience, the GC identified a number of key issues of particular unmet needs for people with NHL which warranted recommendations. These included:

- information on financial issues and emotional health during treatment
- information on relationships and emotional health with younger participants (under 60 years of age)
- access to support groups in order to meet other patients with NHL
- exercise counselling and the opportunity to participate in tailored exercise programmes. Just over half of the participants in 2014 National Cancer Patient Experience Survey would have liked to have received these interventions
- more information about fertility issues, with the greatest reported need in patients aged 23-40.

The GC discussed the specific needs of patients that were on 'watch and wait', although no evidence had been found for this intervention. Because of their experience of the high levels of anxiety during the beginning of the 'watch and wait' process (which reduces over time) the GC agreed to make a recommendation for patients at the beginning of this process.

Uncertainty around rates of transformation was highlighted in the evidence as a particularly important issue to people with low grade NHL, and the GC agreed based on their consensus and experience, that a recommendation should be added to explain this likelihood to patients.

Several issues were identified from the 2014 National Cancer Patient Experience Survey for people diagnosed with NHL. These included:

- improved information was needed to help people better understand diagnosis, including more detailed information on the nature of the test
- easier access to a named key worker/CNS (more information on the role of the key worker can be found at Cancer Quality Improvement Network System (2013) Manual for Cancer Services: Haemato-oncology Cancer Measures – Haemato-oncology MDT Measure 13-2H-113)
- easier to understand information
- a need for improved access to wellbeing services and psychological support

However the survey did not report results according to disease stage, and although the survey presented data for follicular lymphoma, DCBLC and 'other', the GC were therefore unable to make separate recommendations for specific NHL sub types and stage.

	The GC considered the benefits of the recommendations would include better informed patients, with an increased likelihood of better quality of life, less anxiety and potential for earlier identification of recurrence. Although discussions about transformation and late-effects could increase anxiety for some patients, the GC consensus was that the recommendations for better informed patients and carers would improve their experience and the benefits outweighed the relatively small risks that had been identified.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was developed for this topic. The GC noted that it is difficult to know whether the recommendations would require an increased resource use, as it depends upon the time currently spent discussing the highlighted issues with patients. However, it is a possibility that the provision of additional information and discussion could lead to an increase in consultation time. However, the cost associated with spending this additional time was thought to be justified by the benefits of giving patients better knowledge about exercise, lifestyle, late effects and a named key worker. These improvements in patient experience would be expected to translate into QALY gains. In addition, it was thought that they could even lead to cost savings in some instances. For example, if providing more information leads to the earlier detection of recurrence then there could be cost savings associated with this. Therefore, even if the provision of more information is more costly, the GC thought it is likely to be cost-effective in cost per QALY terms.
Other considerations	The GC thought that there would only be a modest change in practice as most MDTs are providing the majority of these information and support services already. No equalities issues were identified.

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6 Follow-up of DLBCL

6.1 Follow up of DLBCL

In patients in remission after treatment with curative intent for non-Hodgkin's lymphoma (NHL), the purpose of follow-up during the first 2-3 years is early detection of relapse for timely re-treatment to improve survival prospects. Follow-up visits usually include a review of symptoms, physical examination, full blood count and biochemical profile including serum LDH. Surveillance scans are performed routinely in some centres, in others this is done only as clinically directed (i.e. if relapse is suspected). With longer follow-up, the risk of relapse diminishes and the focus shifts to monitoring for late effects of treatment, and educating patients about individualised risks and, where appropriate, risk reduction strategies; some centres monitor late effects themselves, others discharge patients back to their general practitioners for follow-up.

The variation in follow-up practice in the UK reflects controversial views on the role and optimal frequency and duration of follow-up including the value of follow-up investigations per se, and the role of the specialised centre.

People with DLBCL in complete metabolic remission after treatment have an excellent prognosis with a low relapse rate and a 5-year overall survival rate of approximately 80%. Follow-up is routinely offered to this patient group. The optimal follow-up strategy has not been well defined. However, since most relapses occur in the first 2 years after treatment, most people are seen frequently during this period, typically 2-3 monthly, followed by 6-12 monthly visits for up to 5 years. Centres with an interest in late effects of treatment may offer longer follow-up. The nature of follow-up is variable and may include a history, physical examination, blood tests and routine surveillance scanning in the form of CT or PET-CT.

This topic addresses DLBCL as it is the most common subtype of curable high grade non-Hodgkin lymphoma.

Clinical question: In patients in remission after treatment with curative intent for non-Hodgkin's lymphoma, what are the optimal method(s), frequency and duration of follow-up?

6.1.1 Clinical evidence (see section 6.1 in Appendix G)

Evidence came from a retrospective case series and a retrospective cohort study.

6.1.1.1 Routine versus patient-initiated follow up for disease relapse

Very low quality evidence from one study with 106 patients (Hong *et al*, 2014) suggests that more relapses were detected during unplanned patient-initiated visits (11/33 visits) than during routine visits (4/823 visits) and the 3-year event-free and overall survival were 86.4% and 93.6%, respectively.

6.1.1.2 Clinic-based follow up for disease relapse

Very low quality evidence from one study of 162 patients (Hiniker *et al*, 2015) reported 5-year freedom from progression and overall survival rates = 80.8% and 81.2%, respectively. 18 patients ultimately experienced relapse. No relapses were detected by surveillance LDH. Similar time from treatment initiation to relapse for patients with relapses suspected by imaging and clinically. Similar survival from the date of relapse or of initial therapy between patients whose relapse was suspected by imaging or clinically.

6.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendation	**For people in complete remission after first-line treatment with curative intent for diffuse large B-cell lymphoma:** • **offer regular clinical assessment** • **consider stopping regular clinical assessment aimed at detecting relapse 3 years after completing treatment for people in ongoing complete remission** • **offer urgent appointments to people who experience a recurrence of lymphoma symptoms or new symptoms that suggest disease relapse** • **do not offer LDH surveillance for detecting relapse** • **do not offer routine surveillance imaging (including chest X-ray, CT and PET-CT) for detecting relapse in people who are asymptomatic.**
Relative value placed on the outcomes considered	The GC considered detection of recurrence to be the critical outcome when drafting the recommendations because early detection is likely to be associated with a better outcome as a result of the treatment options available for fitter patients. Other important outcomes included overall survival, disease progression, disease-specific survival, test related complications, health-related quality of life, patient experience, patient preference, number of scans. Disease-specific survival, test related complications, health-related quality of life, patient experience and patient preference were not reported in the evidence.
Quality of the evidence	The quality of the evidence, assessed using GRADE methodology was very low for all reported outcomes. This was because of the observational, non-comparative design of the studies and imprecision. This meant that the GC treated the evidence with caution and used their clinical expertise alongside the evidence to make the recommendations.
Trade off between clinical benefits and harms	The GC noted that most relapses of diffuse large B-cell lymphoma (DLBCL) will occur within the first 2-3 years following the end of first-line treatment and so recommended routine follow up during this time. The GC recognised that patients may experience symptoms suspicious of recurrence between routine appointments. The evidence indicated that over 70% of relapses were detected during unplanned (patient intiated) visits rather than routine appointments. In addition, not all relapses will occur during the first 2-3 years and patients may experience a recurrence of lymphoma symptoms or new symptoms suspicious for disease relapse outside of this time period. For this reason the GC recommended urgent appointments for people who experience a recurrence of lymphoma symptoms or new symptoms suspicious for disease relapse. The GC recommended that LDH surveillance for disease relapse

	should not be undertaken because the evidence suggests low sensitivity and specificity and is unreliable when performed in isolation (no relapses were detected by surveillance LDH in the one study that examined it). The GC recommended that routine surveillance imaging in asymptomatic patients for disease relapse should not be undertaken because chest X-ray, CT and PET-CT detect very few relapses in asymptomatic patients and carry a risk of false positive results leading to unnecessary investigations. In the single relevant study PET-CT and CT identified asymptomatic relapse in 1% and 0.5% of follow-up imaging tests respectively. False positives occurred at a rate of 14% and 2% respectively in follow-up PET-CT and CT tests. It was GC consensus, in the absence of evidence, that chest X-ray, CT and PET-CT pose additional risks including radiation exposure and increased patient anxiety The GC noted that a potential harm of the recommendations is that asymptomatic patients whose relapse would be detected by routine imaging will experience a delay in the detection of their relapse and initiation of therapy, although this will not affect prognosis for the vast majority of patients. The GC also noted that by the time a relapse can be reliably detected in asymptomatic patients, it will only be a matter of a few weeks before the relapse will be detected clinically, and this short delay is unlikely to have an impact on treatment options and efficacy. The GC also considered that this delay, which would only affect a low number of patients, is far outweighed by the benefits of not being exposed to radiation by routine imaging in a much larger number of patients.
Trade off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The GC estimated that the recommendations will result in a decrease in costs due to removing LDH testing, fewer routine scans being performed and fewer follow up appointments being undertaken. These reductions in the intensity of follow-up were not anticipated to have any negatve consequences on effectiveness. As stated above, any delay in detection is likely to be short and would be unlikely to have any impact on treatment options or efficacy. Therefore, the recommendations are likely to reduce costs without changing effectiveness and are therefore likely to be cost-effective.
Other considerations	In some centres that routinely do surveillance scanning and LDH testing, there will be a cost saving change in practice.

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7 Survivorship

7.1 Survivorship

The number of people achieving long term disease free survival from Non-Hodgkin's Lymphoma (NHL) has increased since the early 1970s. Cancer Research UK 2014 show that while more people are being diagnosed with NHL, especially in older age groups, the 5 year survival rates have now increased to about 60%. The success in treating NHL is bringing about new concerns as more patients achieving long term disease free survival increases the risks of developing delayed or late physical/psychological side effects of treatment.

Chemotherapy and radiotherapy can cause physical problems long after the treatment has ended. Heart damage, peripheral neuropathy, cognitive disorders, second cancers, infertility, chronic tiredness and inability to do day to day tasks are some of the late side effects that can happen after lymphoma treatment. People can also have long term psychological and emotional late effects following NHL treatment, such as depression, anxiety and even post-traumatic stress disorder, affecting families and carers too. The quality of life of long term NHL survivors at 10 years after treatment indicates that up to a quarter of patients surveyed have poor or worsening physical and mental health. This suggests that late effects can continue for many years.

More older people are now diagnosed, treated and achieve long term disease free survival from NHL. This has implications as older people often have other health problems, such as heart disease and diabetes. The 2013 national cancer survey, including lymphoma patients, suggested that cancer treatment makes other health problems worse and reduces quality of life.

There are standard methods of surveillance for late effects and there is also a move away from hospital based follow up. Patients may be discharged earlier but offered an open lymphoma follow up appointment if concerns arise. However, there is concern that the late adverse effects of treatment for NHL could go unrecognised by patients and General Practitioners (GPs), who can be unaware of the increased risks linked to treatment and its effect on mental health.

While late effects monitoring for survivors of paediatric and young adult cancers is better established, it is speculated that late effects surveillance in the United Kingdom for NHL patients is limited and practice varied. As the number of NHL survivors grows, there is scope for nurse led services to support both patients and GPs in the monitoring of late effects and rapid referral to medical teams. There is also scope to link cancer registry data with other national databases to capture specific late effects, such as second cancers or cardiac disease.

Clinical question: What is the effectiveness of surveillance protocols for late adverse effects of treatment in people with non-Hodgkin's lymphoma?

7.1.1 Clinical evidence (see section 7.1 in Appendix G)

Evidence came from a prospective case series and retrospective cohort study.

7.1.1.1 Nurse-led versus medic-led survivorship care

Very low quality evidence from one study suggested that waiting times (n=120) were reduced from 65 min (medic-led) to 10 min (nurse-led) and patients satisfaction (n=50) was either higher or similar for nurse-led compared to medic-led survivorship care).

7.1.1.2 Phone/in person-based follow up for cardiovascular disease

Very low quality evidence from one study with 957 patients reported 75/957 patients had new diagnosis of cardiovascular disease (validated in 57/71 patients: 18 heart failures, 9 myocardial infarctions, 21 arrhythmia, 2 pericarditis, and 10 valvular heart disease. Cumulative incidence of cardiovascular disease at 1, 3, 5, and 7 years was 1.3%, 3.7%, 5.2%, and 7.4%, respectively. Older age was associated with increased risk of overall cardiovascular disease. Gender, radiation therapy, and anthracycline treatment were not associated with the incidence of overall cardiovascular disease. Anthracycline use was associated with development of heart failure and arrhythmia. Radiation was associated with development of arrhythmia. Older age was associated with development of heart failure and arrhythmia.

7.1.2 Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers for this topic. Whilst there were potential cost implications of making recommendations in this area, other questions in the guideline were agreed as higher priorities for economic evaluation. Consequently no further economic modelling was undertaken for this question.

Recommendations	**Provide end-of-treatment summaries for people with non-Hodgkin's lymphoma (and their GPs). Discuss these with the person, highlighting personal and general risk factors, including late effects related to their lymphoma subtype and/or its treatment.** **Provide information to people with non-Hodgkin's lymphoma when they complete treatment about how to recognise possible relapse and late effects of treatment.** **At 3 years after a person with non-Hodgkin's lymphoma completes a course of treatment, consider switching surveillance of late effects of treatment to nurse-led or GP-led services.**
Relative value placed on the outcomes considered	The GC considered detection of treatment-related morbidity (late effects) to be the critical outcome when drafting the recommendations because early detection improves the chance of successfully treating late effects. Other importantant outcomes, overall-survival, cause-specific survival, health-related quality of life, patient preference and psychological well-being, were not reported in the evidence.
Quality of the evidence	The quality of the evidence was very low for all reported outcomes as assessed using GRADE. The primary reason for the very low quality of the evidence because of study design (observational, non-comparative) and imprecision. These issues meant that the GC treated the evidence with caution and used their clinical expertise alongside the evidence when making the recommendations.
Trade-off between clinical benefits and harms	The GC noted that a significant proportion of patients with NHL will experience treatment-related morbidity and that this can have severe health consequences. The evidence indicated that certain patient and treatment factors were associated with late cardiovascular disease.The GC recognised that in general, management of treatment-related morbidity is a non-specialist issue that can be undertaken by general practitioners, but that

prompt treatment of any adverse effects crucially depends on patients acting on any new signs and symptoms that may be related to either treatment or NHL.

The GC noted that late effects of treatment typically do not occur in the first 2-3 years after the completion of treatment for NHL. The evidence indicated that cardiovascular effects, can occur sooner (with a cumulative incidence of 3.7% at 3 years) however the GC considered that patients who experience early cardiovascular effects will still be followed up in hospital so this is not likely to present a problem for general practitioners.

To highlight to patients and their general practitioners, possible late effects and the importance of acting on them, the GC decided to recommend that end of treatment summaries and late effects risk summaries are offered to patients and their GPs, highlighting personal and general risk factors arising. The GC also recommended based on their experience and evidence about treatment related adverse effects elsewhere in the guideline that self-management education on health and well-being, and possible late effects is offered to all patients on completion of NHL treatment.

As the late effects of treatment typically do not occur in the first 2-3 years after the completion of treatment for NHL, the GC decided to recommend nurse-led or GP-led long term surveillance of late effects starting 2-3 years post completion of lymphoma therapy, as the evidence indicated patients were satisfied with nurse-led survivorship care.

The GC thought that the benefits of the recommendation to offer training to patients to help them recognise possible relapse and late effects will be that more patients who experience treatment-related morbidity will recognise and act on them at an earlier stage and that this will translate into longer overall survival and better quality of life, although there was no published evidence about this outcome.

The GC acknowledged some patients and clinicians may feel that putting the balance of responsibility of long term surveillance on to patients or nurses may not be effective because patients and nurses may not be perceived as having the required level of in-depth information.

Although it was not reported in the evidence, the GC thought that some patients may suffer increased anxiety as a result of the responsibility being placed on them and the need to process and understand all the additional information required. The GC thought that discussion of end-of-treatment summaries with patients would help to mitigate anxiety.

The GC acknowledged that hospital-based medical surveillance of late effects will become increasingly hard to maintain, as the numbers of people living with long term disease control increase. The GC therefore made recommendations they consider will support patients to self-manage their long term health after NHL, while allowing access back to specialist care via nurses or GPs. The GC considered that the benefits to this approach outweigh the harms by providing capacity to effectively manage more

	patients and give a better patient experience.
Trade-off between net health benefits and resource use	No health economic evidence was identified and no health economic model was built for this topic. The GC estimated that the recommendations may involve a change in practice for some centres. Thus, there may be an increase in costs through increased nurse or GP led surveillance, the provision of end of treatment summaries and the time spent educating patients when they complete treatment. However, through increasing awareness and surveillance, the recommendations should lead to the earlier detection of treatment related morbidity. Thus, it is anticipated that the increased costs associated with the recommendations will be offset by a decrease in costs and QALY improvements due to identifying, and therefore acting upon, treatment-related morbidity earlier. Thus the recommendations were considered likely to be cost-effecitve in cost per QALY terms.
Other considerations	The GC considered that the recommendations will involve a moderate change in practice. In regions where the recommendations are not current practice, services will need to be developed for: • Use of end of treatment summaries • Promotion of self-management • GP- or nurse-led surveillance of treatment related morbidity.

References

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