The scope has been amended. The role of centralised specialist laboratories offering integrated diagnostic reporting in the diagnosis of Non-Hodgkins lymphoma has been removed from the scope and added as a topic within the update of the Improving Outcomes in Haematological Cancers service guidance, which is now in development. For more information please see http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0747

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

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

1.1 Short title

Non-Hodgkin's lymphoma

2 The remit

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

3 Need for the guideline

3.1 Epidemiology

a) Non-Hodgkin's lymphomas are a diverse group of conditions that are categorised according to the cell type affected (B cell or T cell), as well as the clinical features and rate of progression of the disease. Most people with a diagnosis of non-Hodgkin's lymphoma (approximately 90%) have a B-cell lymphoma. The most common B-cell lymphomas are diffuse large B-cell and follicular lymphoma. Other less common types of B-cell lymphoma include mantle cell lymphoma, MALT lymphoma and Burkitt's lymphoma.

b) According to data published by Cancer Research UK (CRUK), non-Hodgkin's lymphoma accounts for 4% of cancers in men and women in the UK, with 12,180 new cases and 4436 deaths recorded in 2010. The incidence of non-Hodgkin's lymphoma increases with age. It is the fourth most commonly diagnosed cancer in adults aged 25–49 years and the fifth most commonly diagnosed cancer in adults aged 50–74 years. The incidence rises sharply in people over 50 years and more than 70% of all cases of non-Hodgkin's lymphoma are diagnosed in people over 60 years.

c) The age-standardised relative survival rates for non-Hodgkin's lymphoma (all subtypes combined) in England over the period 2005–2009 show that 76% of men are expected to survive for at least 1 year, with 61% surviving 5 years or more. The survival rates for women are slightly higher, with 79% expected to survive for 1 year or more and 66% surviving for at least 5 years.

d) Data from HMRN (Haematological Malignancy Research Network) show that 1-year survival rates are significantly higher for follicular lymphoma (96%) than for diffuse large B-cell lymphoma (65%) and mantle cell lymphoma (71%). Five-year survival rates follow a similar pattern, with rates significantly higher for follicular lymphoma (87%) and significantly lower for mantle cell lymphoma (27%) compared with the other lymphoma subtypes.

e) Relative survival for non-Hodgkin's lymphoma is improving. In men, 1- and 5-year age-standardised relative survival rates (all subtypes combined) in England increased by 26 and 34% respectively between 1971–1975 and 2005–2009. In women, 1- and 5-year age-standardised relative survival rates increased by 27 and 34% during the same time period.

f) Using HMRN data for 2004–2011, it is estimated that 48% of all non-Hodgkin's lymphoma cases diagnosed in the UK are diffuse large B-cell lymphoma. This is an aggressive cancer that needs

immediate treatment. The aim of treatment in most patients is a complete remission and cure.

g) Follicular lymphoma is the second most common type of non-Hodgkin's lymphoma (19%). It frequently demonstrates an indolent behaviour and responds to initial therapy, but has a tendency to relapse after treatment.

h) MALT lymphoma is the third most common type of non-Hodgkin's lymphoma with a median age at presentation of 61 years. The stomach is the most frequently involved organ, and in many cases there is a strong association between gastric MALT lymphoma and chronic *Helicobacter pylori* infection. Other sites that may be involved include the salivary glands, eyes, lung, intestinal tract, skin and thyroid gland. It is generally regarded as an indolent or low-grade lymphoma, but high-grade histological transformation can occur.

i) Mantle cell lymphoma accounts for less than 10% of all non-Hodgkin's lymphoma and is characterised by the chromosomal translocation t(11;14)(q13:32). This results in over-expression of the cell cycle regulator protein cyclin D1. The median age at onset is 60–65 years. Mantle cell lymphoma has an unusual clinical phenotype because it is an aggressive cancer in most patients, but a few patients will be cured with chemo-immunotherapy regimens used for aggressive lymphomas.

3.2 Current practice

a) The non-specific clinical presentation of non-Hodgkin's lymphoma (such as enlarged lymph glands, anaemia or other abnormal blood tests) often results in delays and inconsistencies in diagnosis.

b) Diagnosis of non-Hodgkin's lymphoma is made on tissue biopsy using immunohistochemistry and often flow cytometry and molecular studies. Diagnosis can be complex and the 2008 World

Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues lists over 25 subtypes of B-cell non-Hodgkin's lymphoma alone.

c) Significant improvements in the understanding of the biology of non-Hodgkin’s lymphoma have led to more specific and targeted treatment for the different subtypes.

d) Staging is an integral part of the initial work-up in every patient with non-Hodgkin’s lymphoma, and includes laboratory assessment, different types of imaging (for example, CT scan, MRI and positron emission tomography [PET]), and nuclear medicine techniques.

e) A wide range of treatments are used for managing non-Hodgkin's lymphoma. Management also includes observation for some patients with certain disease subtypes. For those patients who need treatment, there can be several phases: induction therapy, assessment of disease response to treatment, maintenance treatment, treatment at the point of first relapse, consolidation after relapse and palliative treatment.

f) Radiotherapy and immunotherapy have established roles in the treatment of non-Hodgkin's lymphoma.

g) Several novel chemotherapy agents have been licensed for treating non-Hodgkin’s lymphoma in the past 10 years and there is variation in the use of chemotherapy regimens particularly for second and third-line treatment.

h) High-dose chemotherapy with bone marrow transplantation is frequently used for relapsed non-Hodgkin's lymphoma.

4 The guideline

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

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

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

4.1 Population

4.1.1 Groups that will be covered

a) Adults and young people (16 years and older) referred to secondary care with suspected non-Hodgkin's lymphoma.

b) Adults and young people (16 years and older) with newly diagnosed or relapsed non-Hodgkin's lymphoma.

4.1.2 Groups that will not be covered

a) Children and young people under 16 years.

b) Adults and young people (16 years and older) with chronic lymphocytic leukaemia or small lymphocytic lymphoma.

c) Adults and young people (16 years and older) with lymphoblastic lymphoma.

d) Adults and young people (16 years and older) with rare T-cell lymphomas, such as, NK T-cell lymphoma, mycosis fungoides, Sezary syndrome, anaplastic large-cell lymphoma of T/null type ALK-, anaplastic large-cell lymphoma of T/null type, anaplastic large cell lymphoma of T/null type ALK+, enteropathy-type T-cell lymphoma, primary cutaneous CD30-positive T-cell lymphoproliferative disorder, extranodal NK/T-cell lymphoma, nasal type, adult T-cell lymphoma/leukaemia (HTLV-1 positive).

e) Adults and young people (16 years and older) with post-transplant lymphoproliferative disease.

f) Adults and young people (16 years and older) with skin lymphoma.

g) Adults and young people (16 years and older) with central nervous system lymphoma.

4.2 Setting

a) All settings in which NHS care is received.

4.3 Management

4.3.1 Key issues that will be covered

a) The specific information and support needs of people with non-Hodgkin's lymphoma and their carers at the time of diagnosis and treatment planning, as well as during and after treatment.

b) The role of image-guided core biopsy compared with excision biopsy in the diagnosis of non-Hodgkin's lymphoma.

c) The role of centralised specialist laboratories offering integrated diagnostic reporting in the diagnosis of Non-Hodgkins lymphoma has been removed from the scope and added as a topic within the update of the Improving Outcomes in Haematological Cancers service guidance, which is now in development. For more information please see http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0747.

d) The role of genetic and molecular testing in the diagnosis and prognosis of non-Hodgkin's lymphoma (for example, FISH [fluorescence in situ hybridisation] and gene expression profiling).

e) The role of PET-CT in initial staging, evaluating interim response to treatment and post-treatment assessment for people with non-Hodgkin's lymphoma.

f) The frequency and nature of follow-up for people with non-Hodgkin's lymphoma after attaining remission.

g) The most effective first-line treatment for early-stage follicular lymphoma.

h) The role of autologous and allogeneic transplantation in people with follicular lymphoma.

i) The role of immediate compared with deferred chemotherapy (watch and wait) in treating advanced asymptomatic follicular lymphoma.

j) The most effective first-line treatment for people with MALT lymphoma, including the role of antibiotic therapy, radiotherapy and chemo-immunotherapy.

k) The most effective first-line treatment for people with mantle cell lymphoma, including the choice of first-line treatment, the role of consolidation of high-dose therapy with stem cell support and the role of maintenance treatment.

l) The most effective first-line treatment for peripheral T-cell lymphoma.

m) The most effective first-line treatment for Burkitt's lymphoma.

n) The role of consolidation radiotherapy in first-line treatment of diffuse large B-cell lymphoma.

o) The initial treatment of composite/discordant and transformed follicular lymphoma.

p) The most appropriate salvage strategies, including indication for autologous and allogeneic transplantation, for people with diffuse large B-cell lymphoma.

q) Indications and methods for central nervous system prophylaxis for people with diffuse large B-cell lymphoma.

r) The survivorship issues for people treated for non-Hodgkin's lymphoma.

4.3.2 Issues that will not be covered

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

4.4 Main outcomes

a) Overall survival.

b) Progression-free survival.

c) Disease-related morbidity.

d) Disease-related mortality.

e) Treatment-related morbidity and mortality.

f) Diagnostic accuracy.

g) Health-related quality of life.

h) Cost effectiveness.

4.5 Review questions

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

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

- at the point of first diagnosis
- during treatment

- after treatment
- for those considering palliative care? [4.3.1a]

b) Is core biopsy an acceptable alternative to excision biopsy for the accurate diagnosis of non-Hodgkin's lymphoma? [4.3.1b]

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

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

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

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

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

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

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

j) What is the most effective first-line treatment for people with early-stage follicular lymphoma (for example, radiotherapy [at various

dose levels, types of field radiation therapy], chemotherapy, interferon and observation)? [4.3.1g]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.6 Economic aspects

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

4.7 Status

4.7.1 Scope

This is the final scope.

4.7.2 Timing

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

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

5.1.2 NICE guidance to be incorporated

This guideline will incorporate the following NICE guidance:

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

- Rituximab for aggressive non-Hodgkin's lymphoma. NICE technology appraisal guidance 65 (2003).

5.1.3 Other related NICE guidance

- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Coeliac disease. NICE clinical guideline 86 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Erythropoetin (alfa and beta) and darbepoetin for the treatment of cancer-treatment induced anaemia. NICE technology appraisal guidance 142 (2008).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Laparo-endogastric surgery. NICE interventional procedure guidance 25 (2003).
- Haemato-oncology. NICE cancer service guidance (2003).

5.2 Guidance under development

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

- Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. NICE technology appraisal. Publication expected February 2014.
- Bendamustine in combination with rituximab for the first-line treatment of advanced indolent non-Hodgkin's lymphoma. NICE technology appraisal. Publication expected July 2014.

- Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma. NICE technology appraisal. Publication date to be confirmed.
- Suspected cancer: recognition and management of suspected cancer in children, young people and adults (update). NICE clinical guideline. Publication date to be confirmed.

6 Further information

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

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

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