National Collaborating Centre for Cancer

Addendum to Haematological Cancers:

improving outcomes (update)

Service Guidance Addendum

Methods, evidence and recommendations

November 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

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.

Funding
Funded to produce guidelines for the NHS by NICE

Contents

Foreword **5**

Methodology **6**

1 Epidemiology **17**

2 Diagnosis and evaluation **28**

2.1 The role of integrated diagnostic reporting in the diagnosis of haematological malignancies. 28

3 Organisation of specialist services **44**

3.1 The staffing and facilities (levels of care) needed to treat haematological cancers and support adults and young people who are having intensive, non-transplant chemotherapy. 44

3.2 Multi-disciplinary teams (MDT) 70

Foreword

Haematological malignancies are a diverse group of cancers that affect the blood, bone marrow, and lymphatic systems. Some forms are highly aggressive, and others are so indolent that they are often only discovered by chance. Symptoms may include:

- lumps caused by enlarged lymph nodes, which are characteristic of lymphomas
- bone fractures and kidney disease/failure, which are characteristic of myeloma
- fatigue and vulnerability to infection and bleeding, which can be caused by most types of haematological cancer but are particularly severe in acute leukaemia.

The main categories of haematological cancer are lymphoma, myeloma, leukaemia, myelodysplastic syndromes and myeloproliferative neoplasms. These categories vary in prevalence, incidence and survival rates. In addition, there are subtypes of lymphoma and leukaemia, as well as rarer haematological cancers that have their own categories.

There are also borderline conditions such as aplastic anaemia and other non-malignant bone marrow failure syndromes (which overlap with hypoplastic myelodysplastic syndrome) and lymphocyte and plasma cell proliferations (which overlap with lymphoma and myeloma) that need specialised facilities for diagnosis and treatment.

Different levels of service are needed to manage haematological cancers, depending on the particular cancer in question. Because of the increased complexity of care and changes in the levels of care from those specified in the 2003 NICE cancer service guidance on improving outcomes in haematological cancers, an update was needed.

There has been progressive and variable adoption of specialist integrated haematological malignancy diagnostic services (SIHMDS), aimed at improving diagnostic accuracy and expertise. Integrated diagnostic reports are well established in some centres but not everywhere. In addition, new diagnostic techniques have been developed since 2003. Because of all this, an update to the diagnostic and evaluation sections in the 2003 guidance was also needed.

Update 2016

Fergus Macbeth

Chair, Guideline committee

John Snowden

Clinical lead, Guideline committee

Methodology

What is service guidance?

Service guidance is a series of recommendations for the organisation and delivery of care for individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE service guidance is based on the best available evidence of clinical and cost effectiveness, and is produced to help commissioners, healthcare professionals and patients make informed choices about appropriate healthcare. It should be noted that most of the published research on cancer topics focuses on clinical evaluations of treatment; little direct research has been carried out on the organisation and delivery of services.

This service guidance is intended to guide health organisations (for example, clinical commissioning groups and trusts), and their managers and healthcare professionals, in improving the effectiveness and efficiency of services for people with haematological cancers. The information and recommendations in this update are based on reviews of the best available evidence.

Updating a NICE cancer service guidance

Guidelines developed by NICE are published with the expectation that they will be reviewed and updated as is considered necessary. In September 2014 the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to update the Improving Outcomes in Haematological Cancers, service guidance (NICE, 2003) in accordance with the NICE interim methods guide for developing service guidance (NICE, 2014) and the guideline development process outlined in the 2014 edition of the guidelines manual (NICE 2014).

The original NICE guidance on Improving Outcomes in Haematological Cancers, service guidance (2003) can be found here: Haemato-oncology (CSGHO) | Guidance and guidelines | NICE. Any sections of this guidance that have not been amended or have been deleted have been highlighted. This addendum to that guidance updates and replaces recommendations in Chapters 3, 4 and 5.

Stakeholders are invited to comment on the new and updated recommendations in this guideline. Recommendations are marked **[2003], [2003, amended 2016] [2016]** or **[new 2016]** to indicate the year of the last evidence review:

- **[2016]** indicates that the evidence has been updated and reviewed but no changes to the 2003 recommendation has been made
- **[new 2016]** indicates that the evidence has been reviewed and a new recommendation has been added or updated.

Stakeholders are also invited to comment on recommendations that NICE proposes to delete from the 2003 guideline. These can be found in Appendix H. The NICE cancer service guidance on improving outcomes in haematological cancers (2003) was developed using very different methods to the current NICE guideline development process. The 2003 guidance presented recommendations in a paragraph format. The Guideline Committee highlighted some sections of the original guidance as still relevant to clinical practice, and other sections as out of date. Recommendations that are no longer relevant have been deleted and the reasons for this are given in Appendix H. Recommendations that are still relevant to clinical practice have been transferred as individual recommendations labelled **[2003]**, and the evidence for these has not been reviewed (Appendix H). If the evidence has not been updated and reviewed since 2003 but the wording of the recommendation has been updated to reflect current practice and terminology, these recommendations have been

Update 2016

labelled **[2003, amended 2016]** and the changes explained in Appendix H. This is an exception to NICE's standard guideline development process and has been done so that relevant recommendations in the chapter not being updated could be carried across into the addendum. As we have not updated these recommendations we can only accept comments on these where stakeholders feel that the meaning has changed. In some cases, we have made minor wording changes for clarification, and these changes are highlighted in yellow.

Who is the guideline intended for?

This guidance is relevant to all commissioners and healthcare professionals who are responsible for the planning and delivery of the management of haematological cancers, as well as to the patients themselves and their carers. It is also expected that this guidance 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 haematological cancers IOG (update) 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 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 service guidance update. 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 clinical 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

Update 2016

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 2014). 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 updated guidance
- 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 update
- inform the development of the clinical questions and search strategies.

The scope was subject to a two week stakeholder consultation in accordance with NICE processes. The full scope is shown in Appendix C. 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 haematological cancers IOG (update) GC was recruited in line with the 'NICE guidelines manual' (NICE 2014). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and shortlisted candidates were interviewed 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. Details of the 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 updated guidance. At the start of the 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

Four GC meetings were held between 8-9 July 2015 and 2-3 February 2016. During each GC meeting (all held over 2 days) clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed, including a standing agenda item.

All members of the GC considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations. These recommendations were then discussed and agreed and signed off by the GC as a whole. The GC also assisted the NCC-C team in drafting sections of the guideline.

Patient/Carer Representatives

Individuals with direct experience of haematological cancer 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 clinical questions, helping to

Update 2016

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.

Expert Advisers

During the development of the guideline the GC identified two areas (treatment related toxicity and duration and range of neutropenia) where there was a requirement for expert input. An expert was identified by the NCC-C (Appendix F) and was invited to advise the GC in their consideration of these areas.

Developing clinical evidence-based questions

Background

The remit for this update was very clear about which patient groups were included and which areas of clinical care should be considered. The four clinical questions and search strategy that covered the topics were agreed during scoping. All the evidence used to inform this update is summarised in the accompanying full evidence review 'Haematological cancers: improving outcomes (update) – evidence review', which includes details of all the studies appraised (see Appendix G).

Method

From each of the questions identified in the scope, the GC formulated a clinical question. For the clinical questions, the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study), I – the index test, or sign/symptom (what is being done; for the signs and symptoms questions, a patient presenting with a sign/symptom was considered to be test positive), C – the comparison (other main test options; in this case the reference standard), O – the outcomes (the measures of how effective the tests have been).

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, Cochrane Databases of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), 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.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GC members) prepared a review protocol. This protocol explains 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 the evidence review.

Table 1: Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GC
Rationale	Using the PICO (population, intervention, comparison and outcome) framework for questions about treatment, or other suitable framework for questions about diagnosis or prognosis. Including the study designs selected.
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 method 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 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'). No language restrictions were applied to the search.

- 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 (all databases 1899 onwards)

Subject specific databases used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1937 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- Psychinfo 1806 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. For the purposes of updating this guideline, 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 the evidence review.

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 inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GC (see evidence review, Appendix G). All evidence was considered carefully by the GC for accuracy and completeness.

Update 2016

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 (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. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

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 clinical question
Imprecision	Results are imprecise when studies include relatively few events and when the confidence interval around the effect estimate includes both no effect and appreciable benefit or harm
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

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2014). In general, no formal contact was made with authors.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was provided. The quality of individual diagnostic accuracy studies was assessed using the QUADAS-2 tool (Whiting *et al*., 2011).

Needs Assessment

As part of the guideline development process the NCC-C undertook a needs assessment (see Appendix B). This aims to describe the burden of disease and current service provision for people with haematological cancers in England and Wales, and inform the development of the guideline.

Update 2016

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by Northern & Yorkshire Knowledge and Intelligence Team, Public Health England as part of the guideline development process.

Incorporating health economics evidence

The aim of providing economic input into the development of this updated guidance was to inform the GC of potential economic issues relating to the topics identified within 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. Health economics was considered in the guideline in accordance with the NICE interim methods guide for developing service guidance (NICE 2014) and the guidelines manual (NICE 2014).

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the priority topics for economic analysis were discussed and agreed. The economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2014):

- 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 clinical 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 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 2014).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE 2014). 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).

Update 2016

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 clinical 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.

Update 2016

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 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

Agreeing the recommendations

For each clinical question the GC were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GC were able to derive the recommendations. The link between the evidence and the view of the GC in making each recommendation is made explicitly in the accompanying 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 are 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)
- '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 are documented in the LETR statements that accompany the recommendations.

LETR (Linking evidence to recommendations) statements

As NICE service guidance was previously formatted, there was limited scope for expressing how and why a GC made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' 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
- 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.

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 30 November 2015 and 14 January 2016 in line with NICE methodology (NICE 2014).

Update 2016

The pre-publication process

An embargoed pre-publication version of the guideline was released to registered stakeholders 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 version of the updated guideline is published as an addendum to the IOG. It is available to download free of charge from the NICE website (www.nice.org.uk). NICE also produces three other versions of this updated guideline which are available from the NICE website:

- the Short guideline, which is a shorter version of this guideline, containing all the 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
- An 'Information for the Public (IFP)' factsheet' which summarises the recommendations from the guideline that are most relevant to patients. It is written in everyday language, and is for patients, their family and carers, and the wider public.

Updating the guideline

Literature searches were completed for all of the clinical questions at the end of the guideline development process, allowing any relevant papers published before 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.

Update 2016

Funding

The National Collaborating Centre for Cancer 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.

References

National Institute for Health and Care Excellence (2014) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

1 National Institute for Health and Care Excellence (2014) NICE interim methods guide for
2 developing service guidance. London: National Institute for Health and Clinical Excellence.
3 Available from www.nice.org

4 Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG,
5 Sterne JAC, Bossuyt PMM, Group Q-2 (2011) QUADAS-2: a revised tool for the quality
6 assessment of diagnostic accuracy studies. Annals of Internal Medicine, 155: 529-536.

7

8

1 Epidemiology

Methods

Information in this section is drawn from a number of primary sources and is a summary of a full needs assessment report prepared by the Northern and Yorkshire Knowledge and Intelligence Team, Public Health England (see Appendix B). This summary highlights key aspects of relevant methodologies, further details can be found through the reference section.

Definition of included cases and disease groups

Haematological cancers are a very diverse group of malignancies, and traditional disease classification systems (International Classification of Diseases version 10 ICD-10) do not always provide a good match to clinically relevant disease groups. However, the following ICD-10 codes have been used to categorise haematological cancers when national data on incidence, mortality and survival are presented.

Table 6: ICD10 codes for haematological malignancies

Disease Group	ICD10 code
Acute Lymphoblastic Leukaemia	C91.0
Acute Myeloid Leukaemia	C92.0, C92.4, C92.5, C93,0 C94.0 C94.2
Chronic Lymphoid Leukaemia	C91.1
Chronic Myeloid Leukaemia	C92.1
Hodgkin Lymphoma	C81
Non Hodgkin Lymphoma	C82, C83, C84, C85
Myeloma	C90
Other	C91.2, C91.3 C91.4, C91.5, C91.7, C91.9, C92.2, C92.3, C92.7, C92.9, C93.1, C93.2, C93.7, C93.9,C94.3, C94.4, C94.5, C94.7, C95.0, C95.1, C95.2, C95.7, C95.9, C96.0, C96.1, C96.2, C96.3, C96.7,C96.9

Update 2016

Data sources

New cases of haematological cancers (incidence) in England are registered by the National Cancer Registration Service (NCRS), which is part of Public Health England (PHE).

All deaths in England are certified by a medical professional and then processed by the Office for National Statistics (ONS). The ONS derive a single underlying cause of death – this is what is counted for official statistics.

Age-standardised Rates

To adjust for variation in the age distributions between areas and across time age-standardised rates have been used for measures of incidence and mortality. Rates have been standardised to the European Standard Population (ESP). 1976 ESP weights and ONS mid-year population estimates have been used throughout.

Relative Survival

In a cohort of cancer patients, overall (observed) mortality can be divided into two components: the background mortality, also known as the expected mortality representing

all-cause deaths in the general population, and the excess mortality due to cancer. Background mortality is calculated from life tables for England.

Relative survival reflects the excess mortality among cancer patients, over and above the background mortality in the country or region where they live. It is the ratio of the observed survival rate to the expected survival rate of the general population with a similar age/sex structure to the cancer patients in the study.

The survival analyses undertaken in this report use relative survival estimated using the maximum likelihood method for individual records, developed by Estève *et al* using the *strel2* command in Stata version 13. This method assumes that the hazard is constant within each interval.

Routes to diagnosis

The Routes to Diagnosis study, established by the National Cancer Intelligence Network (NCIN), defines a methodology by which the route the patient follows to the point of diagnosis can be categorised, in order to examine demographic, organisational, service and personal reasons for delayed diagnosis. Administrative Hospital Episode Statistics (HES) data are combined with Cancer Waiting Times (CWT) data, data from the cancer screening programmes and cancer registration data from the National Cancer Data Repository (NCDR). Using these datasets every case of cancer registered in England which was diagnosed in 2006-2013 is categorised into one of eight 'Routes to Diagnosis' listed in the table below.

The methodology is described in detail in the British Journal of Cancer article "Routes to Diagnosis for cancer - Determining the patient journey using multiple routine datasets".

Table 7: Categories of 'route to diagnosis'

Route	Description
Screen Detected	Detected via the breast, cervical or bowel screening
Two Week Wait	Urgent GP referral with a suspicion of cancer
GP Referral	Routine and urgent referrals where the patient was not referred under the TWO week wait referral route
Other outpatient	An elective route starting with an outpatient appointment, either self referral, consultant to consultant, other referral
Inpatient Elective	Where no earlier admission can be found prior to admission from a waiting list booked or planned
Emergency Presentation	An emergency route via A & E, emergency GP referral, emergency transfer, emergency consultant outpatient referral, emergency admission or attendance
Death Certificate Only	No date available from Inpatient or Outpatient HES, CWT, screening and with a death certificate only from diagnosis flagged by the registry in NCDR
Unknown	No data available from Inpatient or Outpatient HES, CWT, screening within set time parameters or unknown referral

Patient experience survey

The Cancer Patient Experience Survey 2014 is the fourth iteration of the survey following its successful implementation in 2010, 2012, and 2013. The survey covers all 153 acute and specialist NHS Trusts in England that provide adult acute cancer services.

The 2014 Cancer Patient Experience Survey covered over 118,000 NHS patients who were seen for treatment in hospital in the period 1st September 2013 and 30th November 2013

Update 2016

and who had a primary diagnosis of cancer. More than 70,000 cancer patients responded to the survey.

National Audit of Cancer Diagnosis in Primary Care

An audit of cancer diagnosis in primary care was undertaken in 2009/10 as part of the National Awareness and Early Diagnosis Initiative (NAEDI) with the intention to better understand and address the reasons for later diagnosis of cancer in England. Information was collected on patient demographics and the nature of the assessment process in primary care, including the time taken from first presentation to referral.

Key points

Population-based national incidence rates for England (as estimated by cancer registrations) rose over the period 2001-2010 for some haematological cancers: Hodgkin lymphoma, non-Hodgkin lymphoma (NHL) and myeloma. There are no haematological cancers for which incidence rates were in decline over that period.

Registration rates for haematological cancers were subject to change as a consequence of improvements in the ascertainment of new cases and developments in diagnosis and classification of disease; therefore not all observed changes may represent true differences in underlying incidence.

Population-based mortality rates fell over the period 2001-2010 for some haematological cancers: acute lymphoblastic leukaemia, chronic myeloid leukaemia, non-Hodgkin lymphoma and myeloma.

Relative survival improved for individuals in specific age groups who were diagnosed between 2000 and 2010 for a number of haematological cancers: acute lymphoblastic leukaemia (0-14 years males and females; 15-64 years males), acute myeloid leukaemia (15-64 years), chronic myeloid leukaemia, non-Hodgkin lymphoma, and myeloma.

For the most commonly encountered forms of leukaemia in older adult life (65+), acute myeloid leukaemia and chronic lymphocytic leukaemia, there was no evidence of significant change in the outcome for patients diagnosed and registered over this time period.

Although the incidence of haematological malignancy does not generally differ by deprivation, significant differences in the outcomes of patients depending on the level of deprivation in the area in which they live have been noted. For the data examined here, there were some differences observed in incidence by deprivation with higher incidence in the most deprived quintile for acute myeloid leukaemia (AML) and Hodgkin lymphoma. Both Hodgkin lymphoma and NHL showed significantly higher mortality rates in the most deprived quintiles compared to the least deprived; and there were significant differences in relative survival by quintile of deprivation for chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML) and Hodgkin lymphoma at five years, and myeloma and NHL at one and five years.

For the majority of haematological malignancies, GP referral was the most common route to diagnosis, with the exception of AML and ALL where emergency presentation was the most common route with over half of all presentations being via this route. CML and myeloma had similar proportions of GP referral and emergency presentations. All haematological malignancies with the exception of Hodgkin lymphoma had a significantly higher proportion of emergency presentation than all malignancies combined (23%). Relative survival was significantly poorer for emergency presentations for the majority of haematological malignancies. The exception to this was ALL where one-year relative survival for emergency

Update 2016

presentations was similar to all other routes. For some acute haematological malignancies emergency presentation may be the most appropriate route to diagnosis.

The majority of patients included in an audit which asked how many times a patients had consulted their GP prior to diagnosis had consulted their GP once or twice (66%), however a third of myeloma patients (33%) had consulted their GP three or more times, and 14% had consulted their GP five or more times. For lymphoma patients 22% of patients had consulted their GP three times or more, and 8% more than five times.

Introduction

Haematological malignancies are diseases originating in the bone marrow, lymph nodes and, less commonly other sites and include leukaemias, lymphomas and myeloma. They are a very diverse group of diseases affecting people across the whole life course, but with their greatest incidence among the elderly. The prognosis and responsiveness to treatment of these conditions also varies very widely.

Haematological malignancies accounted for 8.4% of all malignant disease (excluding non-melanoma skin cancer) diagnosed in England in the years 2001 to 2010iv.

Data quality and availability

Accurate capture of information on haematological malignancies nationally is an ongoing challenge, although data capture has improved over the period reported. Haematological malignancies are extremely diverse, ranging from highly aggressive forms; to some types so indolent that are often only picked up incidentally. Some blood changes which could be classified as chronic leukaemias often produce no symptoms, and incidence of these conditions is therefore dependent on looking at blood samples from these individuals and clinicians' criteria for deciding whether a malignancy exists. Even when it is clear that malignancy exists, identifying the specific type requires sophisticated diagnostic techniques, and the integration of information from clinical and laboratory sources, the results of which are not always available to the registration service leading to some registrations lacking sufficient detailed information to accurately capture the precise diagnosis. This is particularly true of non-Hodgkin lymphoma (NHL), a large and varied group of conditions, which are often considered as a single entity due to coding being of inadequate quality to distinguish individual types of NHL.

Update 2016

Although the National Cancer Registration Service (NCRS) now operates as one national system for England, historically there were eight separate cancer registries, with different practices and levels of ascertainment of haematological malignancies. This led to regional variations in capture of information. Consequently changes in trends in incidence may be due to improved ascertainment in former registries.

As well as the national data, collected by the National Cancer Registration Service (NCRS) within Public Health England, we have also reported on regional data from the Haematological Malignancies Research Network (HMRN), and predictions for the UK based on these data. The HMRN is a collaboration across the former cancer networks of Yorkshire and Humber and Yorkshire Coast, between researchers from the University of York, a clinical network operating across 14 hospitals, and an integrated Haematological Malignancy Diagnostic Service (HMDS) at St James's Hospital in Leeds.

Covering a population of 3.6 million, with a similar socio-demographic profile to the country as a whole, HMRN collects detailed information about all patients diagnosed with a haematological malignancy within the HMRN region. Within HMRN, all haematological malignancy diagnoses, are centrally coded using the latest World Health Organization (WHO) classifications by clinical staff at HMDS's laboratory. Following diagnosis, patients are individually tracked, and full details of all treatments, responses and outcomes are collected to clinical trial standards.

There is a reasonable expectation that due to the incidence of haematological malignancies not being strongly influenced by social position or deprivation that the incidence observed in the HMRN data for the Yorkshire region is likely to be representative of the national picture. In 2013 the NCIN compared national registration data on haematological malignancies with assumptions about England incidence made using the HMRN data. This analysis found that for 2004-10 the two data sources were largely in agreement for acutely presenting conditions such as ALL, with very little notable variation in recording across the country. However, for conditions which require integration of information from clinical and laboratory sources there was variation; both between the two data sources and geographically – suggesting that this variation is due to different case ascertainment and coding procedures in different registries.

Clinical networks within the HMRN area apply standard treatment protocols in the management of haematological malignancies and therefore regional outcomes are also of value in estimating likely survival patterns for England as a whole.

What is covered in this summary and what is not

This summary focuses on presenting English national data on seven main groupings of haematological malignancies, which have been used in previous reports by the National cancer intelligence network (NCIN). These are: Acute lymphocytic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), myeloma, Hodgkin lymphoma and non-Hodgkin lymphoma grouped together. These groupings are felt to be the most accurate with the data currently available from NCRS. Due to the data quality issues outlined above these have been defined using ICD10 codes. Any specific known data quality issues with each condition are discussed in the relevant section.

Many haematological conditions are not included in detail, but remain important in the picture of haematological malignancies as a whole. These particularly include the myeloproliferative disorders, information on which is not currently collected comprehensively by the NCRS. Where possible information the information presented here is supplemented with available regional data from the HMRN.

Update 2016

All haematological malignancies

Incidence

When considered overall, age-standardised rates of incidence for haematological malignancies have risen significantly from 2001-2010 in both men and women (figure 1). Part of this trend is a consequence of improved ascertainment of these cancers particularly from 2008 onwards.

The incidence of all haematological malignancies in males is consistently significantly higher than females over this time period.

Table 8 shows the incidence of haematological malignancy by site for the main ICD10 groupings. Non-Hodgkin lymphoma is the largest disease group in terms of number of new cases, accounting for over 40% of all haematological malignancies in both men and women. Myeloma is the second most commonly registered haematological cancer, accounting for 17% of all new haematological malignancies annually. Acute myeloid leukaemia and chronic lymphocytic leukaemia each account for about 10% of all haematological malignancies in both sexes, with acute lymphocytic leukaemia and chronic myeloid leukaemia together contributing a further 5% of the total.

Figure 1:

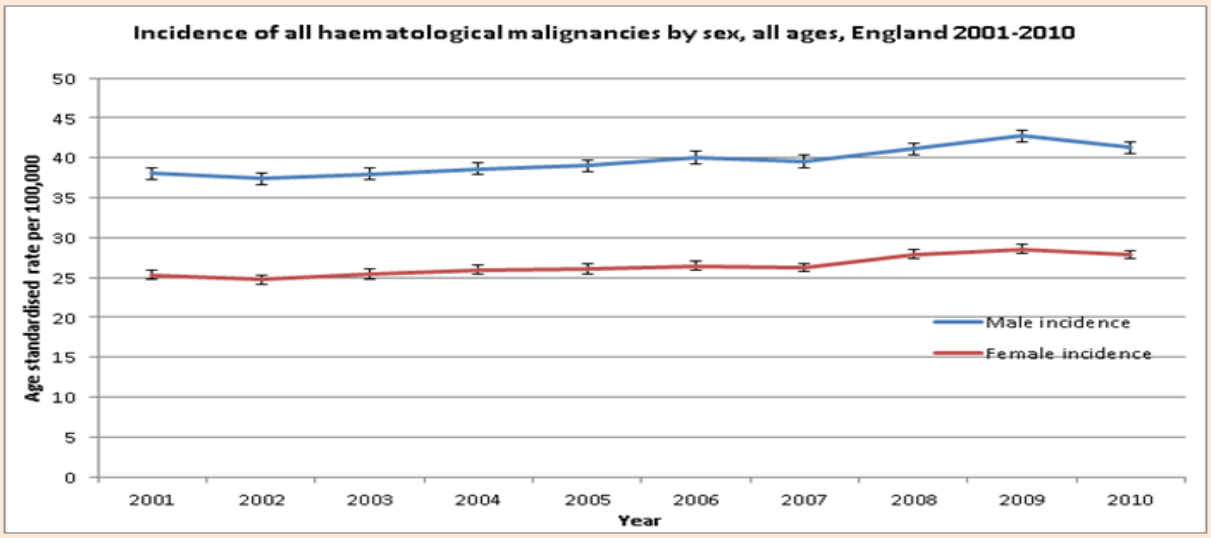


Table 8: Age-standardised incidence rates for haematological malignancies diagnosed in the period 2008-2010 by diagnostic group for males and females

	Males				Females			
Site	Cases	ASR	95% CI		Cases	ASR	95% CI	
All haematological malignancies	12779	41.7	41.3	42.1	10138	28.1	27.7	28.4
Acute lymphoblastic leukaemia	329	1.4	1.3	1.5	250	1.1	1.0	1.2
Acute myeloid leukaemia	1267	4.0	3.9	4.2	1038	2.8	2.7	2.9
Chronic lymphoid leukaemia	1666	5.2	5.0	5.3	1060	2.6	2.5	2.7
Chronic myeloid leukaemia	328	1.1	1.0	1.2	243	0.7	0.7	0.8
Hodgkin lymphoma	860	3.2	3.1	3.3	669	2.4	2.3	2.5
Non-Hodgkin lymphoma	5499	17.9	17.7	18.2	4680	12.9	12.7	13.2
Myeloma	2242	7.0	6.8	7.1	1792	4.5	4.4	4.6
Other	588	1.9	1.8	2.0	407	1.0	1.0	1.1

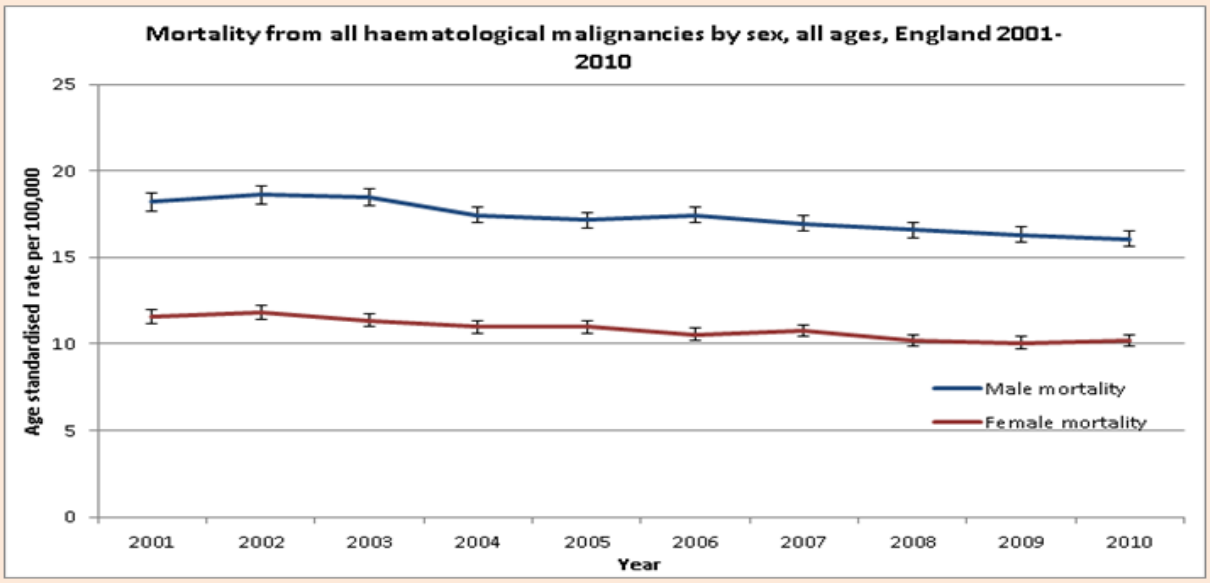
Update 2016

Mortality

Figure 2 shows trends in age-standardised mortality from all haematological malignancies by sex for England between 2001 and 2010. Mortality rates have decreased significantly over this time.

Mortality information is taken from the cause of death recorded on the death certificate for an individual and recorded by ONS. Therefore, accuracy of mortality recording for some of the more complex haematological malignancies must be interpreted with care.

Figure 2:



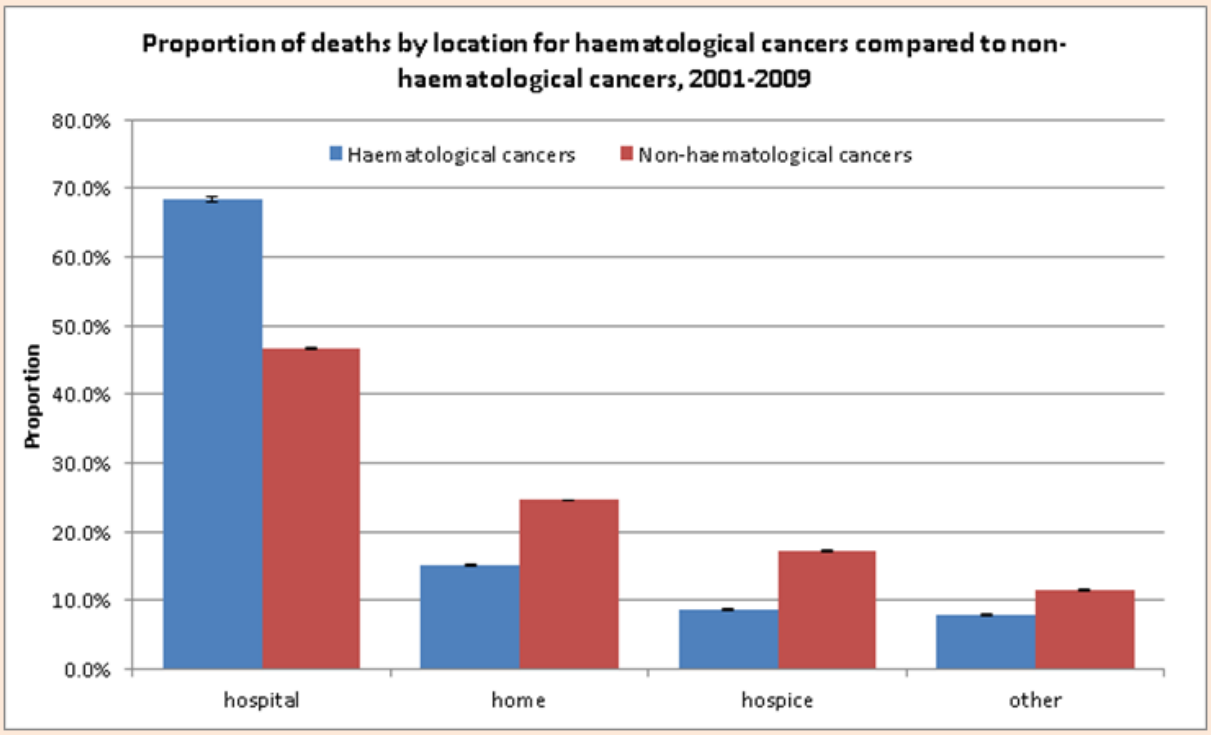
Survival

Place of death

Figure 3 shows the proportion of deaths by location of death for all haematological cancers compared to non-haematological cancers from a report done by NCIN in 2011. It shows that patients with haematological cancers are significantly more likely to die in hospital than patients with other cancers, with fewer than half (46.7%) of patients with other cancers dying in hospital compared to 68.4% of patients with haematological cancers.

Update 2016

Figure 3:



Patient Experience

Results in this section come from the 2014 cancer patient experience survey.

64% of patients diagnosed with a haematological malignancy saw their General Practitioner (GP) no more than twice before being referred to hospital.

75% of patients diagnosed with a haematological malignancy said they had a completely understandable explanation of their test results.

83% of patients said they were told they had a haematological malignancy sensitively.

58% of patients said they completely understood what was wrong with them which is lower than the response from breast cancer where 81% of patients understood what was wrong with them. Haematology scored the lowest of all other cancer sites for this question.

70% of patients said their views were taken into consideration when discussing treatment and 72% said that side effects of the treatment were explained and only 51% said they were told of possible future side effects from the treatment they received.

87% of patients were given a named clinical nurse specialist which is lower when compared to breast, lower gastrointestinal (GI), lung, brain, gynaecological and upper GI cancer patients where between 90% and 93% of patients were given a named clinical nurse specialist.

55% of patients said they were given information on financial help/benefits by staff. This was low for all cancer sites included in the survey.

82% of patients were told they could get free prescriptions.

37% of patients said taking part in research had been discussed with them. This was low for all cancer sites included in the survey.

59% of patients said they were given enough care/help from health or social services.

64% of patients said their general practice did everything to support them.

HMRN incidence data

As previously discussed national NCRS data do not allow a breakdown of all haematological malignancies into separate conditions, and does not include reliable data on conditions including myelodysplastic syndromes. Therefore table 9 shows HMRN regional data on incidence of haematological cancers, including myelodysplasia, and expected UK cases per year, which have been estimated by applying HMRN age and sex specific rates to 2001 UK population census strata.

Table 9: HMRN regional age-standardised rates (ASR) for haematological neoplasms, 2004-13, and expected UK cases per year

	ASR per 100,000			Expected UK cases per yeara
	Total	Male	Female	
All haematological neoplasms	51.2	64.5	41.1	38100
Leukaemias				
Chronic myeloid leukaemia	0.9	1.1	0.7	580
Acute myeloid leukaemia	3.2	4	2.6	2400
Acute promyelocytic leukaemia	0.3	0.3	0.3	170
B-lymphoblastic leukaemia	1	1.1	0.9	550
T-lymphoblastic leukaemia	0.3	0.4	0.2	160
Chronic lymphocytic leukaemia	5.4	7.8	3.5	4100
Hairy cell leukaemia	0.3	0.5	0.1	210
T-cell leukaemias	0.3	0.3	0.3	250
Chronic myelomonocytic leukaemia	0.5	0.8	0.3	440
Non-Hodgkin lymphoma	14.2	16.8	12.1	10280
Marginal zone lymphoma	2.7	3.4	2.1	2050
Follicular lymphoma	2.8	2.7	2.8	1860
Mantle cell lymphoma	0.7	1	0.4	510
Diffuse large B-cell lymphoma	6.8	8	5.8	4990
Burkitt lymphoma	0.4	0.6	0.2	210
T-cell lymphoma	0.9	1.2	0.7	650
Hodgkin lymphoma	2.8	3.3	2.4	1730
Classical Hodgkin lymphoma	2.5	2.8	2.2	1540
Lymphocyte predominant nodular Hodgkin lymphoma	0.3	0.5	0.2	190
Plasma cell neoplasms	5.5	7.4	4	4260
Plasmacytoma	0.3	0.5	0.2	250
Myeloma	5.1	6.9	3.8	4010
Other disorders	16.5	20.5	13.7	12930
Chronic myeloproliferative neoplasms	4.4	4.6	4.3	3320
Myelodysplastic syndromes	2.6	4.1	1.5	2180
Lymphoproliferative disorder NOS	1.4	1.8	1.1	1160
Monoclonal gammopathy of undetermined significance	5.6	6.8	4.7	4290
Primary myelofibrosis	0.4	0.5	0.3	300
Myelodysplastic/Myeloproliferative neoplasms unclassifiable	0.1	0.1	0	50

a Estimated by applying HMRN age and sex specific rates to 2001 UK population census strata

Update 2016

The most common specific types of haematological malignancies are diffuse large B-cell lymphoma (a type of NHL) which accounts for 13.1% of the estimated incidence; monoclonal gammopathy of undetermined significance (MGUS) which accounts for 11.3% and chronic lymphocytic leukaemia and myeloma, which each account for 10.8% and 10.6% respectively. If the non-Hodgkin lymphomas are grouped together, they account for around 27.1% of all haematological malignancies using these data.

These data are not directly comparable to those captured nationally by the NCRS, due to data collection and coding methodological issues discussed earlier. For instance MGUS is not registered as it is an asymptomatic potential precursor to myeloma, which is not easily ascertainable through normal reporting systems.

Table 10 shows five-year relative survival for all individual haematological malignancies derived from the regional HMRN data. It shows that there is significant variation both between types of haematological malignancy and within the different types. Five-year relative survival for all haematological malignancies combined is 68.3%, however this varies from 45.4% for plasma cell neoplasms (including myeloma) to 85.7% for Hodgkin lymphoma. Within types of malignancy there is also significant variation, for instance five-year survival from hairy cell leukaemia is 90.5%, whereas for acute myeloid leukaemia it is 15.2%.

Trends in one- and five-year relative survival for the specific conditions defined in the introduction are discussed in the relevant chapters later on in this report.

Table 10: HMRN regional 5-year relative survival estimates (%)

	5-Year Relative Survival (%)
All haematological neoplasms	68.3
Leukaemia	60.5
Chronic myeloid leukaemia	88.4
Acute myeloid leukaemia	15.2
Acute promyelocytic leukaemia	66.6
B-lymphoblastic leukaemia	64.9
T-lymphoblastic leukaemia	63.7
Chronic lymphocytic leukaemia	83.2
Hairy cell leukaemia	90.5
T-cell leukaemias	75.9
Chronic myelomonocytic leukaemia	18.8
Non-Hodgkin lymphoma	66.9
Marginal zone lymphoma	77.8
Follicular lymphoma	86.9
Mantle cell lymphoma	36.2
Diffuse large B-cell lymphoma	59.6
Burkitt lymphoma	57.1
T-cell lymphoma	48.6
Hodgkin lymphoma	85.7
Classical Hodgkin lymphoma	83.3
Lymphocyte predominant nodular Hodgkin lymphoma	99.7
Plasma cell neoplasms	45.4
Plasmacytoma	61.7
Myeloma	44.1
Other disorders	79.4

Update 2016

	5-Year Relative Survival (%)
Monoclonal B-cell lymphocytosis	96.1
Chronic myeloproliferative neoplasms	92.7
Myelodysplastic syndromes	28.4
Lymphoproliferative disorder NOS	75.3
Monoclonal gammopathy of undetermined significance	88.4
Primary myelofibrosis	40.5

1

2

Update 2016

2 Diagnosis and evaluation

2.1 The role of integrated diagnostic reporting in the diagnosis of haematological malignancies.

Haematological malignancies are a complex set of conditions that range from indolent lymphoid tumours with a relative good prognosis to rapidly growing leukaemias which, untreated, can be rapidly fatal. Making an accurate diagnosis as quickly as possible is key to ensuring that patients get the most appropriate and effective treatment and the best outcomes. Whereas in the past the diagnosis of these conditions relied almost completely on microscopic morphological appearance, the developments in molecular medicine have led to a revolution in diagnostic techniques, many of which are now regarded as essential to the correct categorisation of the condition. These necessary techniques include:

- conventional histopathology and cytopathology
- flow cytometry and immunohistochemistry
- cytogenetics and Fluorescent In Situ Hybridisation (FISH)
- molecular genetics.

The key sources of material are peripheral blood and bone marrow samples (both aspirate and trephine biopsy) and biopsies of lymphoid tissue. Many of the newer techniques require the rapid processing of fresh tissue samples and there may be a problem with the most efficient use of what are often small samples to ensure that all relevant tests are successfully completed without requiring a second invasive procedure. Although there are places in England where the whole spectrum of tests are carried out in a single laboratory, it is currently more usual that samples need to be distributed to different laboratories, each of which issues a separate report. To make a definitive diagnosis all the diagnostic results need to be brought together by a Specialist Integrated Haematological Malignancy Diagnostic Services [SIHMDS]. This can be achieved either by a single laboratory producing the results and generating the report or by a system for integrating the results from the different diagnostic laboratories.

The original NICE guidance on improving outcomes in haematological cancers (NICE, 2003) defined two levels of haemato-pathological service; a local service, which provides initial assessment of specimens and a specialist service to which specimens can be sent for a definitive diagnosis. In current practice patients with acute leukaemia may require urgent treatment before a definitive diagnosis is available from the SIHMDS, but their management will be reviewed when the final integrated report has been produced by the SIHMDS.

A definition for each of the terms used in this section is provided below:

- **Co-located:** service models in which haematological cancer diagnosis is provided in dedicated, purpose-built and localised laboratories.
- **Networked:** service models in which established laboratories work on the same information network, but are geographically separate and not dedicated solely to haematological cancer diagnosis.
- **Integrated report:** A single report summarising all elements of laboratory diagnosis for a specific patient episode i.e. based on available haematological cytology, histopathology, immunophenotyping by flow cytometry, cytogenetics, FISH and molecular genetics and in accordance with the current WHO diagnostic classification.
- **Integration:** The process of producing an integrated report.

The key question is therefore how best to ensure that an integrated diagnostic report that includes all the important results can be delivered reliably and efficiently to ensure timely and appropriate therapeutic decisions.

Update 2016

Clinical Question: Should integrated diagnostic reporting (via Specialist Integrated Haematological Malignancy Diagnostic Services [SIHMDS]) replace local reporting in the diagnosis of haematological malignancies?

What are the effective ways of delivering integrated diagnostic reports (for example, co-located or networked) in the diagnosis of haematological malignancies?

Clinical Evidence

Study Quality

A short checklist of relevant questions was developed to assess the quality of the included studies. These covered areas including patient selection, applicability of the population, relevance of the diagnostic service model, the reference standard, blinding and relevance of the healthcare setting. From this it was judged that the included evidence was of low quality overall because all the studies identified were retrospective case series and none of the included studies directly compared integrated diagnostic services with other forms of diagnostic services.

All studies included relevant populations with either general haematology patients or patients with specific haematology subtypes such as lymphoma patients.

Identified studies broadly compared the rates of discordance in diagnosis of haematological malignancies between the initial diagnosis and the review diagnosis by expert pathologists, sometimes based in a specialist laboratory. But it was unclear in the individual studies whether the expert pathologists were blinded to the initial diagnosis and so there is a high risk of bias from the possible absence of blinding.

The outcomes reported in each of the studies were not specifically those listed in the PICO table, however the outcomes reported (e.g. diagnostic discordance, change in management, survival) were considered to be of some use in informing discussions.

Overall, the quality of the evidence for this topic was considered to be low quality for all outcomes.

Update 2016

Evidence Statements

Low quality evidence from a total of nine retrospective studies of either haematology or lymphoma populations, two of which were UK based (Bowen *et al*, 2014; Chang *et al*, 2014; Herrera *et al*, 2014; LaCasce *et al*, 2005; Lester *et al*, 2003; Proctor *et al*, 2011; Siebert *et al*, 2001, Stevens *et al*, 2012, and van de Schans *et al*, 2013). The discordance rates between initial haematological pathological diagnoses and the expert review ranged from 6%-60%. Revision of one type of lymphoma to another type was the most common source of discordance with discrepancy ranging from 6.5%-23% (Two studies; Bowen *et al* 2014; Chang *et al*, 2014).

Low quality evidence for major discrepancies, leading to a change in treatment or management was recorded in four retrospective studies (Chang *et al*, 2014; Lester *et al*; 2003; Matasar *et al*, 2012 and Stevens *et al*, 2012) with the rates of discordance between the initial diagnosis and review diagnosis ranging from 17.8% to 55%.

Low quality evidence from one retrospective study (Engel-Nitz *et al*, 2014) compared diagnostic outcomes between specialist haematology laboratories and other commercial laboratories. It reported that patients in the specialist laboratory cohort were more likely to undergo more complex diagnostic testing with 26% of patients undergoing molecular diagnostics compared with 9.3% in community-based hospital laboratories. Patients in the

specialist laboratory cohort were 23% more likely to reach a final diagnosis within a 30 day testing period when compared with community based hospital laboratories.

Low quality evidence from one retrospective study compared a national registry of haematological malignancies with a hospital discharge registry to investigate the data quality and the impact of misclassification on survival in haematology patients (Norgaard *et al*, 2005). The overall data completeness was 91.5% [95% CI, 89.6%-93.1%] and the survival of patients registered in the hospital discharge registry was about 20% lower and about 10% lower for patients registered in the national registry when compared with patients registered in both.

Low quality evidence from a single retrospective study evaluating the value of expert pathology review (van de Schans *et al*, 2013) reported no statistically significant difference in 5 year survival between patients with a concordant diagnosis versus a discordant diagnosis (48% [95% CI, 42%-53%] versus 53% [95% CI, 39%-67%]).

Low quality evidence from a retrospective study including 25 cases of Burkitt lymphoma reviewed by 10 pathologists (Rane *et al*, 2014) indicated a low rate of concordance between the pathologists. (κ0.168, SE±0.018). A direct correlation between the level of experience and diagnosis. Expert lymphoma pathologists showed marginally higher concordance rates with general pathologists showing the lowest (κ0.373 versus κ0.138). For consensus diagnosis the level of agreement between pathologists for a revised diagnosis was very high (κ0.835, SE±0.021) and the revision of diagnosis was highest among general pathologists. The concordance between independent diagnosis and consensus diagnosis was low (κ=0.259, SE±0.039; median=0.207; range=0.131-0.667) but increased with increasing experience of being able to diagnose lymphoma.

Low quality evidence from one retrospective study including 25 cases of Burkitt Lymphoma reviewed by 10 pathologists (Rane *et al*, 2014) suggested that expert lymphoma pathologists were significantly more likely to make a correct diagnosis compared with both pathologists with experience (OR=3.14; p=0.012) and general pathologists (OR=5.3; p=0.00032).

In low quality evidence from two retrospective studies (Matasar *et al* 2012 and Strobbe *et al*, 2014) suggested that the rates of discordance between the initial and review diagnoses had dropped between 2001 and 2005, although there was no statistically significant difference. Matasar *et al*, 2012 reported a drop in major revision rates for haematological malignancies from 17.8% to 16.4% (p=0.6) as familiarity with the WHO classification system increased. Strobbe *et al*, 2014 reported a drop in discordance rate of lymphoma diagnoses from 14% to 9% (p=0.06) following the set up of an expert lymphoma review panel.

Low quality evidence from two retrospective studies (Irving *et al*, 2009 and Norbert-Dworzak *et al*, 2008) reported that interlaboratory agreement was high for the use of a standardised protocol for flow cytometry (correlation coefficient ranged from 0.97-0.99 for observed versus expected values).

Low quality evidence from a survey of 10 clinical staff involved in a myeloma program (Gundlapalli *et al*, 2009) reported that clinic staff would be in favour of a single diagnostic report with the ability to view serial changes in key biomarkers and also supported the idea of providing a composite report directly to the patient.

Cost effectiveness evidence

A Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS) has been suggested as an approach to improve diagnosis rates and clinical outcomes over local reporting. Whilst there may be improvements in diagnosis and savings through economies of scale these centres may have significant set up costs.

Update 2016

Economic Evidence Statement

A systematic literature review was performed to assess the current economic literature for this topic. The review identified 99 possibly relevant economic papers relating to the configuration of diagnostic and specialist services for people with haematological cancers. Of these, no papers were deemed relevant for this topic and therefore no papers were included in the review of existing economic evidence.

De Novo Economic Model

The current economic literature did not adequately address the decision problem; therefore a de novo economic evaluation was created to assess cost effectiveness. All analyses were conducted in Microsoft Excel 2007.

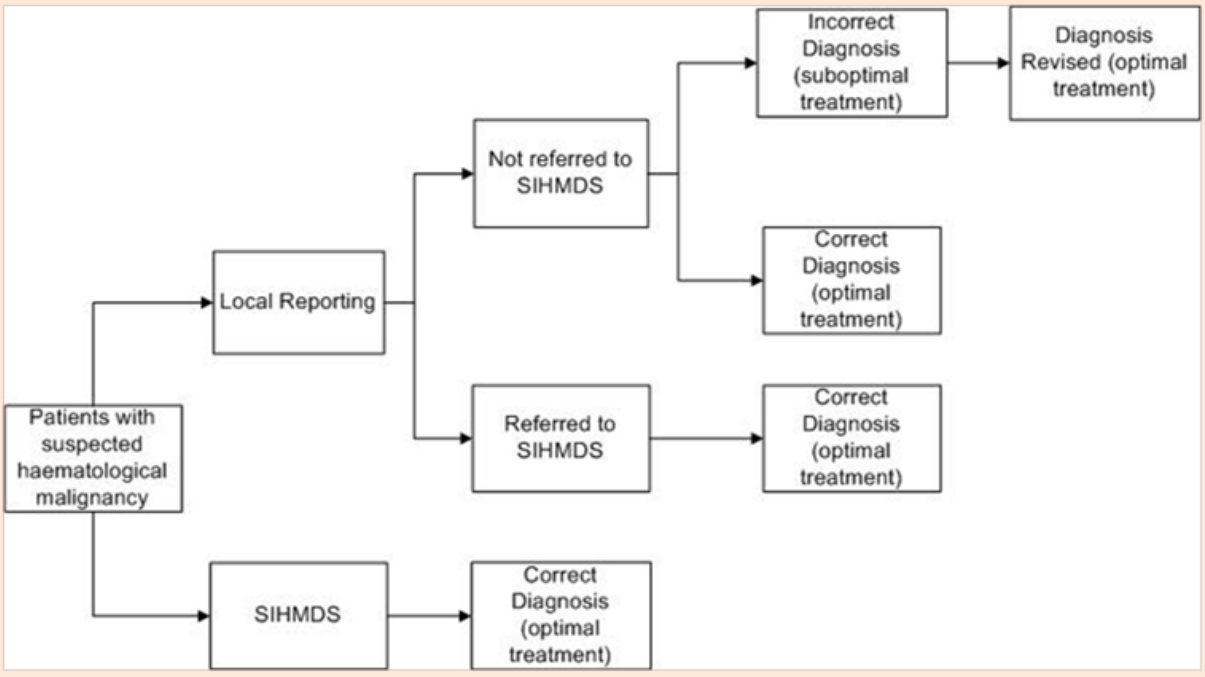
Aims of Analysis

The aim of the economic analysis was to assess the cost effectiveness of both a co-located and networked SIHMDS compared to local reporting from a National Health Service (NHS) and Personal Social Services (PSS) perspective.

Model Structure

The economic model considered three potential ways of configuring diagnostic services for haematological cancers (Figure 4). The base case was assumed to be local reporting with a proportion of samples referred to SIHMDS for review. This was compared to an alternative of sending all samples in people with suspected haematological malignancies immediately for review by SIHMDS. Two configurations of SIHMDS were compared to local reporting- a co-located approach and a networked approach. Detailed definitions of each configuration are presented earlier in this IOG.

Figure 4: Model Structure



In the local reporting arm of the model all samples in people where a haematological malignancy is suspected would have all testing performed locally and synthesised into an integrated report by a local haematologist. A proportion of these tests would be sent on to a SIHMDS after testing for verification of diagnosis. The results of these tests would either be

Update 2016

concordant or discordant with the initial diagnosis made locally. Concordant diagnoses result in the patient's current treatment regimen being maintained. Patients with a discordant diagnosis would have their diagnosis updated resulting in one of three changes to their current treatment regimen-'treatment to no treatment', 'no treatment to treatment' or 'change in oncological treatment'.

In both SIHMDS arms of the model samples are sent off to the SIHMDS for review without any diagnostic workup at a local level. The MDT responsible for the patient's care would then receive an integrated report and treatment would be planned accordingly. The model assumes that diagnoses from the SIHMDS are always correct and optimal treatment would be received.

Prevalence

Prevalence for the base case was taken from one networked SIHMDS, managed from Sheffield serving a population of approximately two million (Dalley et al. 2014) (Table 11).

Table 11: Prevalence of haematological malignancies for base case of economic model

Haematological Malignancy	Prevalence
Acute Lymphoblastic Leukaemia	0.9%
Acute myeloid leukaemia	3.0%
Acute Promyelocytic Leukaemia	0.7%
Aplastic Anaemia	0.5%
Lymphoma - bone marrow	6.7%
Lymphoma - other biopsy	7.6%
Lymphoma - lymph node	14.6%
Chronic Lymphocytic Leukaemia	6.5%
Hairy Cell Leukaemia	0.2%
Waldenstrom/Lymphoplasmacytic Lymphoma	0.2%
Myelodysplastic Syndrome	17.4%
Myeloproliferative Neoplasm: Chronic Myeloid Leukaemia	1.9%
Myeloproliferative Neoplasm: Chronic Myeloid Leukaemia ET	0.9%
Myeloproliferative Neoplasm: Chronic Myelomonocytic Leukaemia	1.2%
Myeloproliferative Neoplasm: Essential Thrombocythemia	9.5%
Myeloproliferative Neoplasm: Graft-Versus-Host Disease	0.2%
Myeloproliferative Neoplasm: Hyper Eosinophilic Syndrome	0.7%
Myeloproliferative Neoplasm: Myelofibrosis	1.4%
Myeloproliferative Neoplasm: Myelofibrosis Essential Thrombocythemia	0.2%
Myeloproliferative Neoplasm: -Unspecified	2.5%
Systemic mastocytosis	0.2%
Myeloproliferative Neoplasm: Polythemia Vera	9.3%
Myeloma	13.7%

Update 2016

Discordance Rate

The discordance rates between local reporting and SIHMDS were estimated in the accompanying clinical evidence review. The base case model used the mean value from the included studies a discordance rate of 16%. As there was no evidence comparing diagnostic accuracy between the different configurations of SIHMDS they were assumed to be identical for both the networked and co-located approaches. This assumption remained for all baseline and sensitivity analyses in the economic analyses.

Change in treatment

The change in treatment as a result of discordant diagnosis was taken from Lester et al (2003) (Table 12). The study only included lymphomas although the clinical evidence review suggested that the vast majority of discordant diagnoses were in these disease areas. Patients with lymphoma were therefore likely to get the majority of the benefit from any improvement in diagnostic accuracy.

Table 12: Change in Treatment in patients who received a discordant diagnosis

Change in Treatment	Proportion
No major change in Treatment	54%
Treatment to No Treatment	20%
No Treatment to Treatment	10%
Change in Oncological Treatment	16%
(Of which) Change Chemotherapy	81%

Proportion of Samples referred from Local Reporting to SIHMDS

No evidence was identified for the proportion of samples that would be forwarded to SIHMDS for expert review from following local reporting. It was however considered by the GC for there to be wide variation across England around the proportion referred on with some centres referring almost all samples onwards with others only referring a much smaller proportion of the more complex diagnoses. Therefore, a range of proportions were investigated along an uninformative range between 0% and 100% of samples referred on to SIHMDS. Threshold analysis was also performed around this parameter to investigate at which values the conclusions of the economic model would change. For the purposes of the base case analysis it was assumed that 70% of samples would be referred for expert review.

Quality of Life

The clinical evidence review identified no evidence around 'quality of life' (QoL) for the three different interventions. It was therefore decided to estimate a range of likely lifetime QALY detriments, in terms of 'quality adjusted life years' (QALYs) associated with discordant diagnosis (Table 13).

Table 13: Estimated Lifetime QALY detriment of a discordant diagnosis

	Estimate Lifetime QALY Detriment
Lower	0
Basecase	0.53
Upper	1.06

The lower end of the range estimated the detriment in QALYs, as a result of an incorrect diagnosis, to be zero. This represented a conservative estimate where misdiagnoses would be identified and appropriate treatment started in a relatively short period of time. Whilst being conservative it also represents the absolute minimum value possible for any treatment for which total QALYS, as a result of treatment, are non negative (i.e. not harmful).

The middle estimate for QALY detriment was taken from the TA243 comparing the addition of rituximab(R) in addition to cyclophosphamide, doxorubicin/adriamycin, vincristine and prednisolone (CHOP) compared to CHOP alone in the treatment of follicular lymphoma. The base case analysis estimated by the TA243 assessment group estimated an incremental QALY of 0.53. Effectiveness data in the model was from RCT evidence with QoL data collected using EQ-5D: NICE's preferred measure of quality of life. An upper QALY detriment was also estimated equal to double the base case estimate.

Update 2016

Costs

Networked SIHMDS

The cost for the networked SIHMDS were taken from the one identified published costing of an English SIHMDS (Dalley et al. 2014). These costs included all costs associated with diagnosis including administrative costs (£23.50 per test) and consultant haematopathologists time (£47.73 and £33.31 for haematology and histopathology laboratory test work respectively). This equated to a cost of £279 per diagnosis.

Co-Located SIHMDS

No published evidence was identified for the costs of a co-located SIHMDS. Costs were therefore calculated from annual accounting data for 2014-2015 from one co-located centre, serving a population of 3.8 million in the Yorkshire area of England. (Haematological Malignancy Diagnostic Service: Leeds, Personal Communication, July 2015) This approach estimated a total cost of the diagnostic portion of the co-located SIHMDS as £675,662 an average cost of £261 per diagnosis, less costly than a networked approach. These estimates however should be interpreted with caution. Both centres are likely to differ in their case mix, the diagnostic pathways and tests used to get to a diagnosis. The cost of samples sent on from local reporting to SIHMDS for review were assumed to cost the same as a sample sent directly to SIHMDS with no local testing.

Local Reporting

Given the large variations in local reporting across England discussed earlier it was difficult to assign a cost to local reporting. In the base case the cost of local reporting was assigned an arbitrary cost of £100. The GC considered this to be a significant underestimate of the true costs of local reporting and would favour local reporting during the economic analysis.

Set Up Costs

Set up costs it were not explicitly considered in the economic analysis.

Cost Discordant Diagnosis

No evidence on the costs of treatment in patients misdiagnosed in haematological malignancies was identified in the economic evidence review. The cost of a discordant diagnosis which resulted in a change from treatment to no treatment was therefore estimated to be £2,981, the cost of one cycle of R-CHOP as estimated in TA243. It was conservatively estimated that there would be no additional cost for changes from ‘no treatment to treatment’ and for changes in treatment.

Discounting

All costs and QALYs were discounted at 3.5% as recommended by the NICE Guidelines Manual 2014. (National Institute for Health and Care Excellence 2014)

Sensitivity analysis

For the base case analyses a range of deterministic and threshold sensitivity analyses were conducted to test the robustness of the results of the economic analysis to different input parameters. PSA was also conducted around the base case to assess the combined parameter uncertainty in the model.

Results

Deterministic Base Case Results

Update 2016

Table 14 show the base case results for the different configurations of diagnostic services for haematological malignancies. In the base case analysis both SIHMDS approaches are dominant (cost saving and health improving) compared to local reporting.

Table 14: Deterministic Base Case Results

	Incremental Cost per diagnosis	Incremental QALY per Diagnosis	ICER
Local Reporting	Reference		
SIHMDS-Network	-£37	0.01129	Dominant
SIHMDS- Co-Located	-£56	0.01129	Dominant

Deterministic and Threshold Sensitivity Analysis

The preferred option remains constant for all possible QALY detriments as a result of a discordant diagnosis with both SIHMDS approaches reaming dominant (Table 15).

Table 15: Impact on the preferred option of varying the lifetime QALY detriment

Lifetime QALY Detriment	0 QALYs		0.53 QALYs		1.06 QALYs	
	Incremental QALY	ICER	Incremental QALY	ICER	Incremental QALY	ICER
Local Reporting	Reference					
SIHMDS-Network	0	Dominant	0.01129	Dominant	0.02257	Dominant
SIHMDS- Co-Located	0	Dominant	0.01129	Dominant	0.02257	Dominant

For all values of laboratory costs for local reporting the ICER for SIHMDS compared to local reporting remains under £20,000 per QALY for both configurations of SIHMDS. Table 16 shows the results of the deterministic sensitivity analysis when zero testing costs are assumed at the local level; an unrealistic assumption but the most favourable possible towards local reporting. Whilst the SIHMDS approach is now estimated to be cost increasing, both ICERs are below the £20,000 per QALY threshold. The incremental costs in this example are identical to the maximum local reporting costs needed for each configuration to be cost saving and health improving. This equates to a maximum difference between the cost of either SIHMDS approach compared to local reporting of £217 per diagnosis for the SIHMDS approach to remain cost saving. For the ICER to remain under £20,000 per QALY the maximum difference would be £442.

Table 16: Sensitivity analysis with local reporting incurs zero cost

	Incremental Cost per diagnosis	Incremental QALY per Diagnosis	ICER
Local Reporting	Reference		
SIHMDS-Network	£63	0.01129	£5,556
SIHMDS- Co-Located	£44	0.01129	£3,931

A similar conclusion is identified with the proportion of samples being referred for review or testing to SIHMDS. Again when a hugely favourable assumption of 0% being referred to SIHMDS from local reporting is assumed the ICERs remain below £20,000 per QALY (Table 17). The Co-Located and Networked configurations become cost saving when the proportions referred to SIHMDS are 50% and 57% respectively.

Table 17: Sensitivity analysis where proportion referred to SIHMDS is equal to zero

	Incremental Cost per diagnosis	Incremental QALY per Diagnosis	ICER

Update 2016

	Incremental Cost per diagnosis	Incremental QALY per Diagnosis	ICER
Local Reporting	Reference		
SIHMDS-Network	£152	0.01129	£13,441
SIHMDS- Co-Located	£133	0.01129	£11,816

When these two favourable assumptions are combined the ICERs for the two configurations of SIHMDS marginally exceed £20,000 per QALY (Table 18).

Table 18: Threshold analysis where local reporting costs and proportion referred to SIHMDS is equal to zero

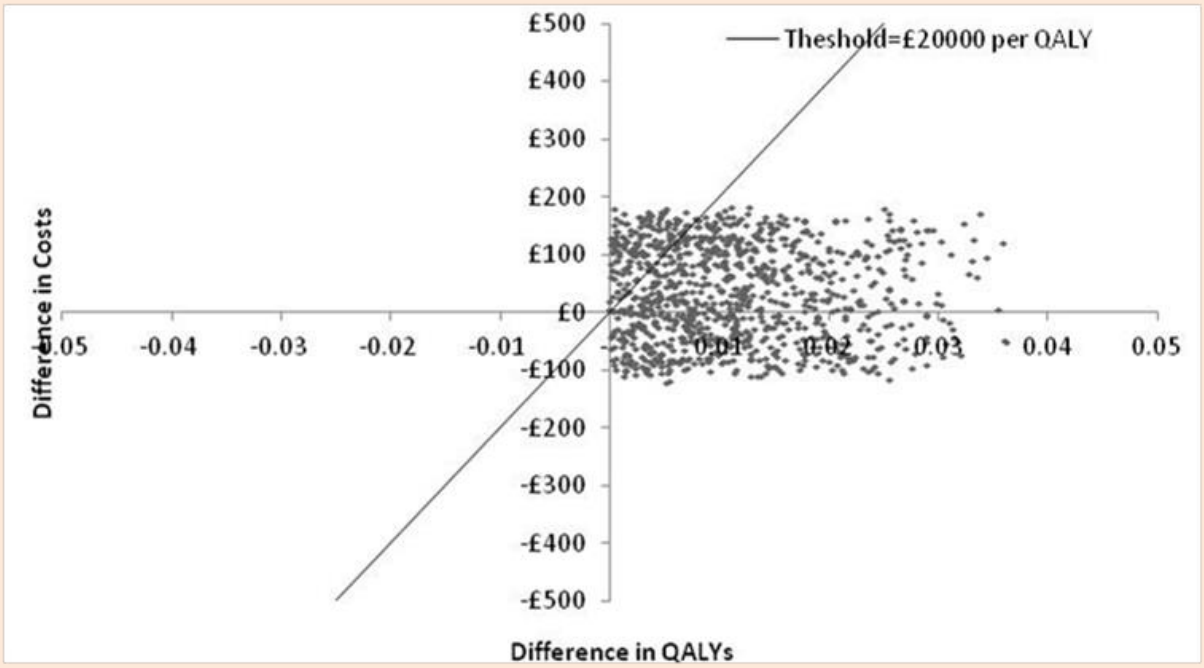
	Incremental Cost per diagnosis	Incremental QALY per Diagnosis	ICER
Local Reporting	Reference		
SIHMDS-Network	£252	0.01129	£22,300
SIHMDS- Co-Located	£233	0.01129	£20,676

Probabilistic Sensitivity Analysis

Figure 5 shows the CEP for a networked SIHMDS approach. The probabilistic result shows that 40.6% of the iterations were cost saving and health improving (in the South East quadrant of the CEP) with 84.6% being below the £20,000 per QALY threshold. Almost identical results are shown for co-located SIHMDS versus local reporting (Figure 6) with 46.5% of iterations being cost saving and health improving and 85.3% being below the £20,000 per QALY threshold.

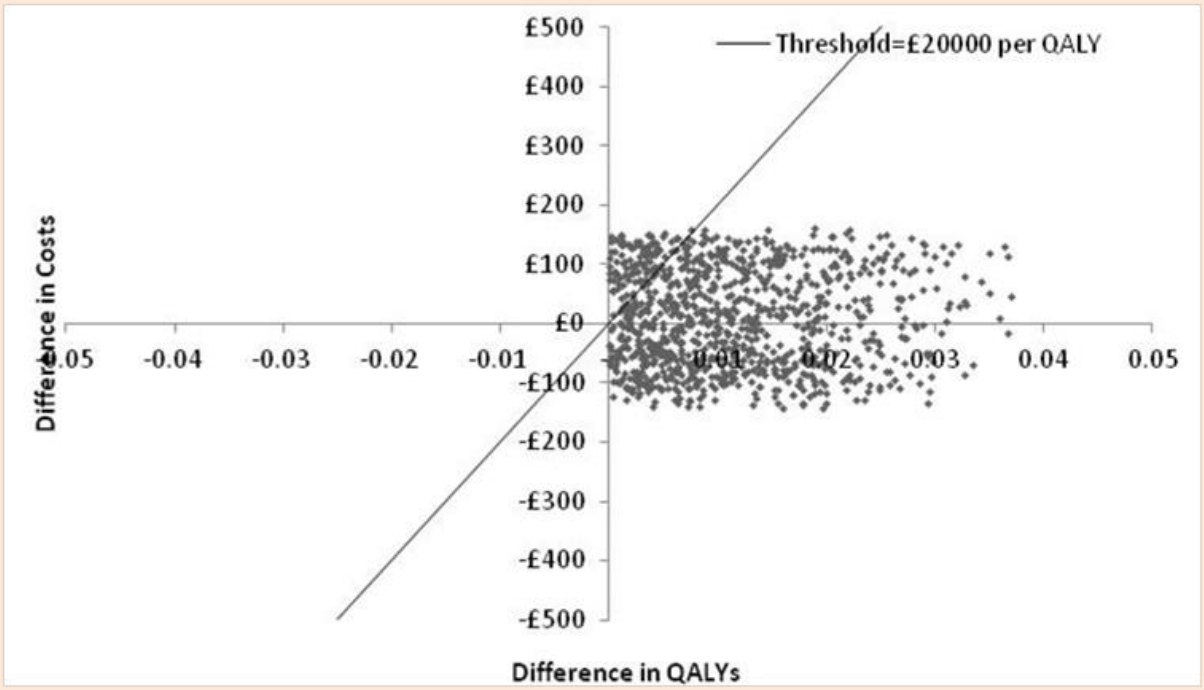
Co-located and networked SIHMDS were not directly compared in this way as the model assumed equal effectiveness for the two interventions throughout all sensitivity analyses. When the costs between the two interventions were compared probabilistically a co-located SIHMDS was cost saving compared to a networked approach in 56% of iterations.

Figure 5: Cost effectiveness plane for Networked SIHMDS versus Local Reporting



Update 2016

Figure 6: Cost effectiveness plane for Co-Located SIHMDS versus Local Reporting



Conclusions

The results of the base case analysis showed that both SIHMDS approaches were preferred over local reporting. This result was robust to sensitivity analysis even under unrealistically favourable assumptions around local reporting. The preferred option remained consistent even under large increases in cost again under otherwise favourable assumptions towards local reporting with the estimated costs of SIHMDS costs needing to increase by over 50% to a difference £442 per diagnosis between local reporting and SIHMDS. This equates to a cost of over £1,000,000 for a centre performing 2500 diagnoses a year, the number of diagnoses estimated for a population of two million (Dalley et al, 2014). The PSA again confirmed the robustness of the results to differing assumptions with over 85 of iterations estimating ICERs below £20,000 per QALY. Even though the results showed a preponderance towards a co-located SIHMDS over a networked configuration it was not possible, given the evidence available, to make any strong conclusions over the preferred configuration of SIHMDS from the results of the economic model.

Update 2016

Recommendations	**The recommendations in this section apply to services for adults (over 24 years), young people (16 to 24 years) and children (under 16 years).** **All specialist integrated haematological malignancy diagnostic services (SIHMDS) should meet the following criteria, which are most likely to be met if the component parts of the service are located at a single site:** • **have clearly defined organisational structures** • **have a formally appointed SIHMDS director who is responsible for the operation of the service, including the design of the diagnostic pathway, resource use and reporting standards** • **have a single quality management system** • **be formally accredited as a SIHMDS by a recognised independent organisation** • **managed by a single trust/organisation**

- **have a business plan in place to coordinate the introduction of new diagnostic and therapeutic technologies**
- **have a central reception point for all specimens**
- **have a full range of protocols covering specimen handling, diagnostic pathways, compilation of integrated reports and relationships with users**
- **ensure that their location, organisation, infrastructure and culture allow effective day to day and ad-hoc communication for rapid resolution of diagnostic uncertainty and accurate diagnosis**
- **have clear and reliable systems for communicating with relevant healthcare professionals outside the service.**
- **have a predefined diagnostic pathway that is followed for each specimen type or clinical problem. The pathway should ensure that:**
  - **the most appropriate diagnostic platforms are selected for a particular clinical situation to avoid unnecessary duplication.**
  - **tests for each specimen are used to provide maximum levels of internal cross-validation, using the current World Health Organization (WHO) principle of multi-parameter disease definitions.**
- **produce integrated reports that include all information needed for initial management, and share these with the multi-disciplinary team.**
- **report diagnoses sub-typed by the current WHO classification**
- **have an IT system that can compile integrated reports and communicate with users. [new 2016]**

The SIHMDS director should be responsible for the overall quality management system, including:

- **laboratory processes and the quality of diagnostic reporting**
- **ongoing assessment of staff competencies**
- **training provision**
- **communication within the SIHMDS and with relevant healthcare professionals**
- **audit and quality assurance**
- **research and development. [new 2016]**

Unless blood film and/or bone marrow aspirate assessment is needed so that urgent treatment can begin, local diagnostic laboratories should send all specimens directly to a SIHMDS without any local diagnostic workup:

- **as soon as a haematological malignancy is suspected**
- **during active investigation of a suspected haematological malignancy.**
- **If patients with an established or previous malignancy have suspected relapse or disease progression. [new 2016]**

SIHMDS should be able to release individual reports before the integrated report is produced, if there is an urgent clinical need. [new 2016]

SIHMDS should be responsible for specimens that are sent to external labs and should integrate the results into the relevant report (unless there are exceptional arrangements in place for clinical trials). [new 2016]

Update 2016

	Disease monitoring **When flow cytometry, molecular diagnostics or cytogenetics are needed for disease monitoring, local diagnostic laboratories should send all relevant specimens directly to a SIHMDS without any local diagnostic workup. [new 2016]**
Relative value placed on the outcomes considered	The guideline committee considered time to diagnosis and diagnostic accuracy to be the most important outcomes for this topic because these are key to improving patient outcomes. These include reducing anxiety by improving the accuracy of diagnosis, ensuring correct treatment and giving patients access to a wider range of treatments through clinical trials. Quality of life, patient satisfaction and staff satisfaction were also listed as outcomes of interest for this topic; however no evidence was identified relating to these outcomes so the GC did not make any recommendations in these areas. Some evidence relating to overall survival was identified and presented to the GC. These data were used to inform the economic model that was developed for the topic but was not considered in isolation as clinical evidence when developing the recommendations.
Quality of the evidence	As the type of evidence identified for this topic did not fit with any of the standard quality checklists, a short checklist of relevant questions was developed to assess the quality of the included studies. Using this it was judged that the included evidence was of low quality overall because all the identified studies were retrospective case series and none of them directly compared integrated diagnostic services with other forms of diagnostic service. All studies included relevant populations - either general haematology patients or specific haematology subtypes. The GC acknowledged that the evidence base was predominantly related to lymphoma patients but felt that recommendations should be made for all haematology patients. There was no evidence to compare co-located and networked haematology diagnostic services. However the GC were aware of the increasing complexity around the diagnosis of haematological malignancies due to the requirement for the number of tests specified by the WHO and felt that this was best addressed within the context of an integrated service. In addition, no evidence was identified which definitively ruled out local or integrated services. One study (Engel-Nitz *et al*, 2014) reported significantly better clinical outcomes for a specialist haematology diagnostic laboratory, but it was unclear from the information reported, whether this study directly compared co-located and networked services. Communication with the author of the study added extra information around the comparisons made in the study and the GC debated whether this warranted a recommendation for a co-located diagnostic service. There was strong consensus amongst the GC that a co-located service was the optimal approach as it allowed more effective processes and procedures to be put in place, better communication between laboratory personnel and better quality control and should therefore be recommended even though there was no strong evidence. The GC agreed that there were a number of barriers to recommending a co-located service and that the priority in any diagnostic service was to be able to produce an integrated report. And although this was likely to be best met through a service with all the component parts located on a single site, this would not be feasible for

Update 2016

	many parts of England and that a networked service would be the most appropriate option. To this end the GC developed a set of consensus based recommendations that outline the key organisational, structural and managerial requirements which should be fulfilled by any diagnostic service, be they co-located or networked. No specific evidence was identified relating to paediatric diagnosis but the GC considered that diagnosis of paediatric patients would not differ from that of adult patients and so the recommendations should cover all age groups. The identified studies broadly compared the rates of discordance in diagnosis of haematological malignancies between initial diagnosis and review diagnosis by expert pathologists, sometimes based in a specialist laboratory. However it was unclear in the individual studies whether the expert pathologists were blinded to the initial diagnosis. There is a high risk of bias based on the potential lack of blinding. One study (Chang *et al*, 2014) recorded much higher discordance rates compared with the other included studies because of the highly selected nature of the population under investigation. Therefore the GC did not consider this to be useful evidence when drafting recommendations.
Trade off between clinical benefits and harms	The GC agreed that the main benefits of a co-located diagnostic service included reduced turn-around times, improved diagnostic accuracy, reduced need for repeat sampling and control costs and such a service would therefore provide a viable and sustainable service and improved patient experience. The main drawbacks of recommending a co-located service were considered to relate to restructuring of the current service, reducing staff satisfaction and recruitment, potential geographical implications for more rural areas, and MDT attendance of haematopathologists. In making a recommendation for a centralised service the GC agreed that the difficulties in service reconfiguration would affect some areas more than others and that improving the service and experience for the patient was a higher priority than the staff experience. It was therefore felt that the benefits of a centralised service outweighed these issues. In recommending that patients with suspected haematological malignancy have all diagnostic specimens sent directly to a specialist integrated haematological malignancy diagnostic service without further workup, the GC considered that this would lead to greater efficiency in sample management and the production of a single report for the clinician/patient, which should lead to a more efficient and accurate diagnoses and more effective treatment for patients. Overall, the GC agreed that the recommendations should lead to shorter times for health care professionals and patients receiving an accurate diagnosis, higher specimen quality and a reduction in the need for repeat sampling. This should in turn lead to more efficient and accurate diagnoses, more effective treatment and less anxiety for patients. A single, integrated diagnostic report for health care professionals was also considered to be a positive aspect of the recommendations made. Balancing these benefits against the potential difficulties around service reconfiguration, staff satisfaction and recruitment, the GC agreed that these recommendations were in the best interests of the service and the patients.
Trade off between net health benefits and resource use	The GC noted that no relevant economic evaluations were identified for this topic. As this topic had the potential for significant impact in terms of resource use and patient quality of life a de novo economic analysis

Update 2016

	was performed. A decision tree model was used to assess the cost effectiveness of local reporting with *some samples* referred on to SIHMDS compared to referring *all samples* of patients with a suspected haematological malignancy to a SIHMDS. Two configurations of SIHMDS were considered, a networked and co-located approach. The economic model predicted the total costs for running a networked and co-located SIHMDS to be £723,192 and £675,662 respectively, assuming a population served of two million. This equated to a cost per diagnosis of £279 and £261 respectively. Given the large variation in practice across England and the lack of evidence the GC were unable to estimate a cost for local reporting although we used threshold analysis to investigate a range of potential costs per diagnosis ranging from £0 to £279 to see how this influenced the conclusions of the economic model. The model assumed equal diagnostic accuracy between networked and co-located SIHMDS given a lack of evidence or GC consensus to differentiate between them. In the base case model both SIHMDS approaches were cost saving and health improving when compared to local reporting, with an incremental QALY of 0.01129 per sample referred and a total cost saving of £37 and £56 per diagnosis for networked and co-located SIHMDS respectively. These cost savings increased to £118 and £137 per sample respectively when the proportion referred on to SIHMDS from local services was increased to 100%. The conclusions of the economic model were robust to changes in parameters with threshold analysis showing that the SIHMDS approach almost always remained the preferred option even under unfavourable assumptions around SIHMDS. The probabilistic sensitivity analysis, varying all parameters in the model, estimated that a co-located SIHMDS would be cost saving in nearly half of iterations and the Incremental Cost Effectiveness Ratio (ICER) under £20,000 in over 85% of iterations when compared to local reporting. Similar results were also identified when comparing networked SIHMDS to local reporting. As the model assumed equal diagnostic accuracy between networked and co-located SIHMDS the model was only able to compare these interventions in terms of total costs with co-located SIHMDS being the preferred option in marginally more iterations. However, given the difference in methodologies, case mixes and population size used to estimate costs for the two SIHMDS approaches and the consequent uncertainty around comparability of the two, the GC were unable to draw strong conclusions, from the model, around which of these two approaches was preferable. Given the lack of identified evidence around economies of scale, optimal population size, patient satisfaction, the need for repeat biopsies and viability of samples sent for reporting the model did not consider these aspects of the topic. The GC agreed strongly though that all of these factors would have strongly weighed in favour of SIHMDS increasing the robustness of the conclusions of the model. Set up and decommissioning costs were not considered by the economic modle although it was considered that these would vary widely across England dependent upon current provision in the region. Threshold sensitivity analysis estimated that a SIHMDS approach would need to cost £442 more per diagnosis compared to local reporting before the ICER was greater than £20,000 per QALY. For a population of two million, estimated to perform just over 5000 diagnoses annually,

Update 2016

	the difference in total cost equates to over £1 million The GC therefore felt that even if the set-up costs of a SIHMDS were significant, given that SIHMDS remained cost effective under both higher costs assumptions and other omissions favourable to local reporting, that there would be a very strong possibility of a SIHMDS approach being cost effective.
Other considerations	None

References

Bowen JM, (2014) *et al*. Lymphoma diagnosis at an academic centre: Rate of revision and impact on patient care. British Journal Haematology 166;2:202-8.

Briggs, Andrew H, et al. (2003) Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. Medical Decision Making 23 (4):341-350.

Burnett AK *et al* (2012) Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia Journal of Clinical Oncology 30, 3924-31

Burnett AK *et al* (2015) A randomized comparison of daunorubicin 90 mg/m2 vs 60 mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood 125;25:3878-85

Chang C. (2014) Hematopathologic discrepancies between referral and review diagnoses: A gap between general pathologists and hematopathologists. Leukaemia and Lymphoma 55(5):1023-30.

Dalley C, et al. (2015) Specialist integrated haematological malignancy diagnostic services: an Activity Based Cost (ABC) analysis of a networked laboratory service model. Journal of clinical pathology 68 (4):292-300.

Engel-Nitz *et al* (2014) Diagnostic testing managed by haematopathology specialty and other laboratories: costs and patient diagnostic outcomes BMC Clinical Pathology 14:17

Fielding AK *et al* (2014) UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 123; 843-50

Gundlapalli *et al* (2009) Composite patient reports: a laboratory informatics perspective and pilot project for personalized medicine and translational research. Summit on Translational Bioinformatics 39-43.

Herrera AF, Herrera AF. (2014) Comparison of referring and final pathology for patients with T-cell lymphoma in the National Comprehensive Cancer Network. Cancer 120; 13:1993-9.

Ireland R. *et al* (2011). Haematological malignancies: the rationale for integrated haematopathology services, key elements of organization and wider contribution to patient care. Histopathology58;1:145-54.

Irving J *et al*. (2009) Establishment and validation of a standard protocol for the detection of minimal residual disease in B lineage childhood acute lymphoblastic leukemia by flow cytometry in a multi-center setting. Haematologica 94;6:870-4.

LaCasce A *et al*. (2005) Potential impact of pathologic review on therapy in non-Hodgkin's lymphoma (NHL): Analysis from the national comprehensive cancer network (NCCN) NHL outcomes project. Blood 106;11:789A.

Update 2016

Lester JF *et al*. (2003) The clinical impact of expert pathological review on lymphoma management: a regional experience. British Journal of Haematology 123(3):463-8.

Matasar *et al* (2012) Expert Second Opinion Pathology Review of Lymphoma in the Era of the World Health Organisation Classification Annals of Oncology 23;159-166

Matthey F *et al* (2009) Facilities for the Treatment of Adults with Haematological Malignancies – 'Levels of Care' BCSH Haemato-Oncology Task Force

National Cancer Action Team (2012) Additional Best Practice Commissioning Guidance For developing Haematology Diagnostic Services Gateway Number: 17241

National Institute for Health and Care Excellence (2014). The Guidelines Manual. London: NICE.

NICE (2003) Improving outcomes in haematological cancers. London: National Institute for Health and Care Excellence

Norbert-Dworzak *et al* (2008) Standardisation of Flow Cytometric Minimal Residual Disease Evaluation in Acute Lymphoblastic Leukaemia: Multicentric Assessment is Feasible Cytometry Part B (Clinical Cytometry) 74B:331-340

Norgaard M. (2005) The data quality of haematological malignancy ICD-10 diagnoses in a population-based hospital discharge registry. European Journal of Cancer Prevention 14;3:201-6.

Proctor IE et al. (2011) Importance of expert central review in the diagnosis of lymphoid malignancies in a regional cancer network. Journal of Clinical Oncology 29;11:1431-5.

Rane SU, *et al*. (2014) Interobserver variation is a significant limitation in the diagnosis of Burkitt lymphoma. Indian journal of medical and paediatric oncology : official journal of Indian Society of Medical & Paediatric Oncology ;35;1:44-53.

Siebert JD, *et al*. (2001) Comparison of lymphoid neoplasm classification - A blinded study between a community and an academic setting. American Journal of Clinical Pathology 115;5:650-5

Sims, J. (1992) Welcan units. Cytopathology 3(4):201-2.

Sive J *et al* (2012a) Outcomes In Older Adults with Acute Lymphoblastic Leukemia (ALL): Results From the International MRC UKALL XII/ECOG2993 Trial. British Journal of Haematology. 157;4:463-71.

Stevens WBC (2012) Centralised multidisciplinary re-evaluation of diagnostic procedures in patients with newly diagnosed Hodgkin lymphoma. Annals of Oncology 23;10:2676-81.

Strobbe L, Strobbe L, van der Schans S. (2014) Evaluation of a panel of expert pathologists: review of the diagnosis and histological classification of Hodgkin and non-Hodgkin lymphomas in a population-based cancer registry. Leukaemia and Lymphoma 55; 5:1018-22.

Van Blerk M, *et al*. (2003) National external quality assessment scheme for lymphocyte immunophenotyping in Belgium. Clinical Chemistry & Laboratory Medicine 41; 3:323-30.

van de Schans SAM, *et al*.(2013) Diagnosing and classifying malignant lymphomas is improved by referring cases to a panel of expert pathologists. Journal of Hematopathology 6; 4:179-85.

Zhang T, *et al* (2007) Inter-laboratory comparison of chronic myeloid leukaemia minimal residual disease monitoring: summary and recommendations. Journal of Molecular Diagnostics 9;4:421-30.

Update 2016

3 Organisation of specialist services

3.1 The staffing and facilities (levels of care) needed to treat haematological cancers and support adults and young people who are having intensive, non-transplant chemotherapy.

Aggressive haematological malignancies, such as acute leukaemia, are potentially curable with intensive chemotherapy. Treatment initially aims to induce complete remission with one or more cycles of 'induction' chemotherapy, which is then followed by 'consolidation' chemotherapy. Relapsed disease is also treated, with the term 're-induction' and 'salvage' chemotherapy used in this setting. The cycles of chemotherapy typically result in a neutrophil count of less than 0.5 $x10^9$/L for one or more weeks. Patients routinely require regular monitoring and supportive care during this period because they are at high risk of potentially life-threatening infections and other complications. Older patients and those with co-morbidities are at a higher risk of complications.

In this guideline the definition of intensive chemotherapy is that which is anticipated to result in severe neutropenia of 0.5 $x10^9$/L or lower for greater than 7 days. The relevant chemotherapy regimens are usually but not exclusively those used for curative treatment of, acute myeloid leukaemia (including acute promyelocytic leukaemia), high-risk myelodysplastic syndrome, acute lymphoblasitc leukaemia, Burkitt lymphoma and lymphoblastic lymphoma. Salvage treatments for Hodgkin and diffuse large cell lymphoma would not usually be included in this definition.

The 2003 Haematological cancers, Improving outcomes guidance (NICE, 2003) referred to the 1995 British Committee for Standard in Haematology (BCSH) standards (these are no longer available) which covered four levels of care including autologous and allogeneic transplantation respectively. With the widespread adoption of the now mandatory FACT JACIE (Foundation for the Accreditation of Cellular Therapy Joint Accreditation Committee) standards for transplantation, the BCSH subsequently redefined their levels of care ranging from 1, 2a, 2b and 3 in 2010. This update redefined level 2b and 3 from the 2010 BCSH guidelines[b] and level 2 from the NICE 2003 improving outcomes guidance using a new definition based on the depth and duration of severe neutropenia (see Table 19).

FACT-JACIE standards define minimum activity for transplant programmes. Although early treatment related mortality from intensive chemotherapy for acute leukaemia is intermediate between autologous and allogeneic bone marrow transplantation, there are no similarly defined standards for this high risk group of patients.

Services administering intensive chemotherapy (levels 2b) require specialist medical and nursing staff and access to other key services, especially intensive care, radiology and laboratory medicine (including transfusion medicine) on both an emergency and elective basis. The patients also need to be cared for in an environment that minimises the risk of infection, although it is unclear what is the most effective way of providing this. There is also increasing delivery of intensive chemotherapy in the ambulatory or outpatient setting in carefully selected patients with appropriate safeguards.

Update 2016

b http://www.bcshguidelines.com/

Clinical Question: How should level of care be defined and categorised for people with haematological cancers who are having intensive (non-transplant) chemotherapy, defined as regimens that are anticipated to result in >7 days of neutropenia of 0.5 x10^9/L or lower, considering:

- **Diagnosis**
- **Comorbidities and frailty**
- **Medicine regimens management of medicine administration and toxicities**

Does the level of care affect patient outcome for people with haematological cancers who are having intensive, non-transplant chemotherapy, considering;

- **Location**
- **Staffing levels**
- **Centre size/specialism**
- **Level of in-patient isolation**
- **Ambulatory care**
- **Prophylactic anti-infective medications**

Clinical Evidence

Levels of Care

A range of different levels of care, corresponding with the variety of diseases treated by haematology services, are used to manage patients with haematological cancers. Patients with acute leukaemia need repeated periods of intensive in-patient treatment lasting between four and seven months (depending on their diagnosis); 85-95% will be re-admitted as emergencies with febrile neutropenia on repeated occasions during this time (Flowers *et al*, 2003). By contrast, patients with conditions at the opposite end of the spectrum of aggressiveness, such as stage A chronic lymphocytic leukaemia, may need little more than annual monitoring.

The level of care required is based primarily on the duration and depth of neutropenia associated with different chemotherapy regimens. Patients being treated with regimens or dose schedules with a risk of brief and / or mild neutropenia can be managed on an outpatient basis. Patients being treated with regimens that usually cause prolonged, severe neutropenia, with a high risk of febrile neutropenia, require additional support and facilities. Whilst some patients requiring these regimens may also be treated in an outpatient setting, pathways need to be put in place to allow rapid access to inpatient care as required.

The British Committee for Standardisation in Haematology (BCSH, 2010) guidelines currently define four levels of care (level 1, 2a, 2b and 3). Level 2b is currently defined as treatment regimens which encompass those that will predictably cause prolonged periods of neutropenia. This would normally be given on an inpatient basis, and which may need to be given at weekends as well as during the week. According to the BCSH guidelines, these regimens are more complex to administer than at the current level 1 or 2a and have a greater likelihood of resulting in medical complications in addition to predictable prolonged neutropenia. Consequently, the resources required to deliver these more complex regimens are greater than those needed for level 1 or 2a regimens. Level 3 care refers to complex regimens such as therapy for acute lymphoblastic lymphoma.

Historically, patients receiving treatment for salvage chemotherapy for Hodgkin lymphoma and diffuse large B cell lymphoma were considered to be at risk of severe neutropenia. As a result these patients were treated according to the BCSH guidelines for level 2b patients. Data for the commonly used salvage regimens for Hodgkin lymphoma and Diffuse large B-cell lymphoma (eg DHAP, ESHAP and GDP with or without Rituximab) however show that these patients have a much lower risk of prolonged, severe neutropenia than previously thought (see table 19). Consequently these patients may not require the same complex level

Update 2016

of care, resource or facilities use as patients requiring induction therapy for conditions such as acute myeloid leukaemia or Burkitt lymphoma.

The Guideline Committee considered both the original levels of care defined in the NICE haematology improving outcomes guidance (NICE, 2003) and the BCSH guidelines (Matthey et al, 2009) in conjunction with published data relating to toxicity of different regimens. Their aim was to redefine level 2b and 3 care from the BCSH guidelines (Matthey et al, 2009) and level 2 care from the NICE haematology improving outcomes guidance (NICE, 2003) using a new definition based solely on the depth and duration of severe neutropenia expected for each regimen and patient group. The levels of care have therefore been redefined as non intensive chemotherapy, intensive chemotherapy and autologous and allogeneic Hematopoietic Stem Cell Transplantation (HSCT) (Table 19).

This guideline is concerned with patients receiving intensive chemotherapy regimens. The definition of intensive chemotherapy is any regimen which is anticipated to result in severe neutropenia of less than 0.5 $x10^9$/L for greater than 7 days, which largely limits the chemotherapy regimens to those used for AML (including acute promyelocytic leukaemia), high-risk MDS, ALL, Burkitt and lymphoblastic lymphomas (Table 19).

The use of other regimens that produce this degree of neutropenia is rare, but exceptional intensive treatment of other haematological malignancies is not excluded from this definition (Table 20).

Table 19: Levels of Care

Non-intensive chemotherapy	All other chemotherapy not included in the definitions below.
Intensive chemotherapy	Anticipated to result in severe neutropenia (0.5x10^9/litre or lower) for 7 or more days. The relevant chemotherapy regimens are usually but not exclusively those used for curative treatment of acute myeloid leukaemia, high-risk myelodysplastic syndrome, acute lymphoblastic leukaemia, Burkitt lymphoma (and other rare aggressive lymphomas treated on Burkitt lymphoma like protocols) and lymphoblastic lymphoma. Salvage treatments for other types of lymphoma would not usually be included in this definition.
Autologous and allogeneic haematopoietic stem cell transplantation (HSCT)	Previously referred to as high-dose therapy in the original 2003 NICE guidance on improving outcomes in haematological cancers. Commissioned centrally through specialised commissioning and a centre should meet FACT-JACIE accreditation standards.

Update 2016

Table 20: Chemotherapy regimens and associated toxicities

Disease	Regimen	Rate of severe neutropenia (<0.5 x 10^9/l)	Days of severe neutropenia (neuts < 1.0 x 10^9/l)	Infection rate / febrile neutropenia	Induction death rate
DLBCL Lymphoma (Crump *et al*, 2014)	R-DHAP / R-ESHAP	70%	2-3 days (with GCSF support) Documented for R-DHAP. R-ESHAP assumed to be similar	20 -23%	<1%
	R-GDP		Not documented but less than R-DHAP	9%	<1%
Burkitt Lymphoma (Mead *et al* 2008)	CODOX-M	97%	25 days	61%	3%
	CODOX-M / IVAC	99%	21-27 days	88%	5%
ALL	UKALL XII induction phase I and II (or similar protocol)	100%	8-17 days (with GCSF support)(Thomas *et al*,Ye SG *et al*)	70% <55yrs (Sive *et al*, 2012a)	4% <55yrs
			12.5-24 days (without GCSF support) (Ye SG *et al*)	81%>55yrs (Sive *et al*, 2012a)	18% >55yrs
	HyperCVAD (Kantarijan HM *et al*)	100%	18 days	63%	6%
AML	Cytarabine based induction (Gardner *et al*)	100%	20-21 days (<0.5 x 10^9/l)	29-35%	
	DA (Burnett *et al* 2015)				
	AML 17	100%	30 days		5%

Study Quality

The evidence for this topic comprises one systematic review and meta-analysis; one randomised trial; one randomised cross-over study; one prospective study; one audit and four retrospective comparative studies.

A number of factors were identified which affected the quality of the evidence including study populations which were not exclusively low risk haematology patients, retrospective, non-randomised methodology, selection bias, small sample sizes and possible recall bias.

Evidence Statements

Isolation Factors

Survival

Very low to moderate quality evidence (GRADE table 1) from one systematic review and meta-analysis which included 40 studies (randomised trials and observational) (Schlesinger *et al*, 2009) showed protective isolation with any combination of methods that included air quality control reduced the risk of death at 30 days (RR=0.6; 95% CI 0.5-0.72; 15 studies, 6280 patients); 100 days (RR=0.79, 95% CI, 0.73-0.87; 24 studies, 6892 patients) and at the longest available follow-up (between 100 days and 3 years) (RR=0.86, 95% CI 0.81-0.91; 13 studies, 6073 patients).

Infection related Mortality, Risk of Infection, Antibiotic use

Very low to moderate quality evidence (GRADE table 1) from one systematic review and meta-analysis which included 40 studies (randomised trials and observational) (Schlesinger *et al*, 2009) showed protective isolation reduced the occurrence of clinically and/or microbiologically documented infections (RR=0.75 (0.68-0.83) per patient; 20 studies, 1904 patients; RR=0.53 (0.45-0.63); per patient day, 14 studies, 66431 patient days).

Very low to moderate quality evidence (GRADE table 1) from one systematic review and meta-analysis which included 40 studies (randomised trials and observational) (Schlesinger *et al*, 2009) showed no significant benefit of protective isolation (all studies used air quality control) was observed in relation to mould infections (RR=0.69, 0.31-1.53; 9 studies, 979 patients) nor was the need for systemic antifungal treatment reduced (RR=1.02, 95% CI 0.88-1.18; 7 studies, 987 patients).

Very low to moderate quality evidence (GRADE table 1) from one systematic review and meta-analysis which included 40 studies (randomised trials and observational) (Schlesinger *et al*, 2009) showed gram positive and gram negative infections were significantly reduced, though barrier isolation was needed to show a reduction in gram negative infections (RR= 0.49 (0.40-0.62) with barrier isolation (12 trials/n=1136) versus RR=0.87 (0.61-1.24) without barrier isolation (4 trials/n=328).

In very low to moderate quality evidence (GRADE table 1) from one systematic review and meta-analysis which included 40 studies (randomised trials and observational) (Schlesinger *et al*, 2009), the need for systemic antibiotics did not differ when assessed on a per patient basis (RR=1.01, 0.94-1.09; 5 studies, 955 patients) but the number of antibiotic days was significantly lower with protective isolation (RR=0.81, 0.78-0.85; 3 studies, 6617 patient days).

Update 2016

Room facilities

Very low quality evidence from one retrospective cohort-control study (GRADE table 1) comparing outcomes before and after ward renovation in 63 patients (Hutter *et al*, 2009) reported that patients treated before renovation (two patients per room, six patients sharing a toilet placed outside the room, washing basin inside the room, shower across the hospital corridor, no ventilation system, air filtration or room pressurisation, no false ceilings) stayed three days longer compared with those treated on the newly renovated ward (two patients per room, separate rest room in each room equipped with toilet, wash basin and shower, no ventilation system, air filtration or room pressurisation, no false ceilings). 39% of pre-renovation patients and 34% of post-renovation patients developed an invasive pulmonary aspergillosis (p=0.79) with the diagnosis usually determined on CT scan.

Ambulatory Care

Survival

Very low quality evidence (GRADE table 2) from one systematic review and meta-analysis (Schlesinger *et al*, 2009), showed febrile patients were discharged for further antibiotic treatment at home if stable. All cause mortality was significantly lower in the outpatient setting (RR=0.72, 95% CI 0.53-0.97) at longest follow-up (median follow-up 12 months; range 1-36).

Unpublished data collected by the Sheffield Ambulatory Care Unit and University College Hospital, London Ambulatory Care Unit reported no deaths in the Ambulatory Care Unit between during the period January 2011-March 2015 (Appendix 1).

Hospital Admissions and length of stay

Very low quality evidence (GRADE table 2) from one UK audit of a hotel based, ambulatory care unit (Sive *et al*, 2012b) showed there were 1443 admissions to the ambulatory care unit (ACU) (9126 patient days) during the study period(688 patients from 18-79 years of age), whose length of stay ranged from 1 to 42 days (median 5). 82% of admissions were in haematology oncology patients with lymphoma being the largest single group of patients by days of use.

Patients receiving less myelosuppressive regimens tended to be discharged home on treatment completion while patients receiving more intensive treatment almost always required readmission to the ward at some point. 813/1443 (56%) patients were discharged directly home; 53/630 (9%) patients admitted to the ward were scheduled in advance.

Very low quality evidence (GRADE table 2) from one UK audit of a hotel based, ambulatory care unit (Sive *et al*, 2012b), 456/576 (79%) of unscheduled ward admissions were within ACU working hours, 66 (11%) were out of hours and 54 (9%) had no time recorded. The most common reason for unscheduled admission included infection or fever, nausea and vomiting and poor oral intake or dehydration.

Very low quality evidence (GRADE table 2) from one retrospective study in which patients who were fit for home care were given a choice between home care and inpatient care (Sopko *et al*, 2012), 17/41 patients required ambulatory management only while 24 patients required re-hospitalisation, primarily due to febrile neutropenia.

In 36 febrile episodes a microbiologically documented infection was the most common cause of fever (61%) with the remaining episodes being of unknown origin.

Patients re-hospitalised were admitted for a mean 10.9 days (6-35 days) versus a mean hospitalisation time of 30 days for inpatients (17-38). Mean duration of hospitalisation for inpatients from the time they became febrile to discharge was 14.3 days (7-22 days).

Update 2016

Very low quality evidence (GRADE table 2) from one retrospective analysis of 30 patients (Bakhshi *et al*, 2009) showed 25/69 consolidation cycles resulted in hospital admission and all were associated with febrile neutropenic episodes or documented infections. Hospital stay was significantly shorter in outpatient cycles compared with inpatient cycles ($p<0.001$) leading to a saving of 269 patient-days for the entire study group.

Unpublished data collected by the Sheffield Ambulatory Care Unit and University College Hospital, London Ambulatory Care Unit was combined to calculate inpatient bed days saved through the use of an ambulatory care program. An average of sixteen inpatient bed days per patient was saved for Acute Myeloid Leukaemia, an average of nine inpatient bed days were saved for Acute Lymphoblastic Leukaemia and sixteen inpatient bed days for Burkitt Lymphoma (Appendix 1)

Infections

Very low quality evidence (GRADE table 2) from one systematic review and meta-analysis (Schlesinger *et al*, 2009) showed febrile patients were discharged for further antibiotic treatment at home if stable and febrile neutropenia or documented infections occurred less often in the outpatient group (RR=0.78, 95% CI 0.7-0.88; 8 studies, 757 patients), rates of bacteraemia were lower in the outpatient group but the difference was not significant (RR=0.68, 95% CI 0.43-1.05; 2 studies. 252 patients).

Very low quality evidence (GRADE table 2) from one retrospective analysis of 30 patients (Bakhshi *et al*, 2009) showed significantly fewer outpatients required second line antibiotics compared with inpatients ($p=0.03$) and mean duration of antibiotic administration was significantly lower in the outpatient group ($p=0.04$).

Transfusions

Very low quality evidence (GRADE table 2) from one retrospective analysis of 30 patients (Bakhshi *et al*, 2009) reported a median of 1 (0-4) unit of packed red blood cells was transfused per consolidation cycle in the outpatient setting and 2 (0-5) in the inpatient setting and a median of 1 (0-13) platelet transfusions were administered at the outpatient clinic and 2 (0-12) in the inpatient setting.

Quality of Life

In very low quality evidence (GRADE table 2) from one randomised cross over trial (Stevens *et al*, 2005) quality of life for 29 paediatric patients treated at home or in hospital (standard care) was assessed. Children were assigned to home or hospital chemotherapy for 6 months (phase 1) and home patients were transferred to hospital administration for phase 2 and vice-versa.

Children in the home group experienced a decrease in factor 1 (sensitivity to restrictions in physical functioning and ability of maintain a normal physical routine) of the Paediatric Oncology Quality of Life Scale (POQOLS) measures when they switched from home based treatment to hospital based treatment with an average change of+ 5.2 (an increase in score indicates a decline in quality of life) while hospital care patients experienced an improvement in quality of life (QoL) when they switched to home based treatment with an average score of -10.5 ($p=0.023$). There was no significant difference ($p=0.60$) in factor 1 values between the two groups at long-term comparison, measured at 6 months after the start of phase 2.

Changes in factor 2 (emotional distress) and factor 3 (reaction to current medical treatment) measures did not differ significantly between the two patient groups. Patients in the home-based group had significantly higher scores for factor 2 (emotional distress) measures, indicating lower quality of life, compared with the hospital treatment group (pair wise comparison at the end of each 6 months phase $p=0.043$).

Update 2016

In very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005) 33 health practitioners (hospital and community based) reported that home-based care appeared to have a positive impact on daily life and psychological well-being of children and families particularly in relation to disruption and psychological stress, reporting a reduction in disruption due to reduced travelling, reduced hospital clinic waiting time and reduced time missed from school and work.

"I think the big advantage is certainly it helps the children and their families to maintain a more normal routine on that day – to be able to avoid having to miss work and school – and have a big disruption and cost added to their day to come all the way down here for treatment that could be provided in a much shorter period and at a time that's more convenient for them."

Health practitioners also reported noting fewer signs of psychological distress in children and parents during the home chemotherapy phase; children appeared happier and more comfortable while parents appeared to have more of a sense of control over the illness and treatment.

"Most kids seem to like it [chemotherapy] at home; they are happier. But I find that with community nursing in general. Some of the kids are so withdrawn when they come into the hospital, and are so different at home. So are the parents. Parents are usually more at ease at home, feel they have more control at home."

The advantages conferred by consistency in personnel and practice were emphasised by hospital based practitioners. Children in the hospital setting were seen by the same practitioner helping parents and children become comfortable and trusting while in the community setting, care providers were less consistent.

"I'm the consistent person that gives the chemotherapy and the children; they adapt to you and the way you do things, and you get to know them. That's consistent, that helps them." [Clinic Nurse]

"Whoever was working that day would go to see the patients. It was mostly the three of us...whoever was working was going. It took longer, but generally not in the first time but within a few times; they would get comfortable with the procedure" [Community Nurse]

Patient Satisfaction

Very low quality evidence (GRADE table 2) from one retrospective study in which 17 patients were treated at home for 46 cycles (Luthi *et al*, 2012), patients reported that they were 'very satisfied' with home care and one case reported being 'satisfied'. None of the patients showed a preference for inpatient care for the next chemotherapy cycles.

38% of patients stated a preference for home care and others had no declared preference. Patient reported benefits of home care included a higher comfort level (100%), freedom and the possibility to organise their own time (94%) and the reassurances and comfort of having a relative present (88%).

78% of patients were not concerned about the absence of a nurse and 87% did not record any anxiety during home care treatment

Very low quality evidence (GRADE table 2) from one retrospective study in which 17 patients were treated at home for 46 cycles (Luthi *et al*, 2012) showed that the main patient reported disadvantages were feelings of dependency on a relative (19%) and or being a burden (6%) however, relatives who returned questionnaires (63%) and all were in favour of home care and 97% were in favour of home care for next treatment.

Update 2016

Primary concerns about home care included the presence of strangers (nurse, physician) at home (16%), request for continuous presence as patients were not allowed to be alone for more than one hour (14%), anxiety and fatigue (14%) and lack of freedom for leisure and holidays (14%).

Burden of Care

Very low quality evidence (GRADE table 2) from one randomised cross over trial (Stevens *et al*, 2005) including 29 paediatric patients treated at home or in hospital (standard care) reported no evidence of an effect of the location of chemotherapy administration was observed on the parental burden of care (assessed using the care giving burden scale).

Impact on Practitioners

In very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005), it was suggested that community health practitioners should have specific education in relation to home care, administration of chemotherapy to children and meeting psychological needs of children with cancer and their families. Four home care nurses took part in a three day educational session on chemotherapy administration and reported that they found the course extremely valuable.

Very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005), health practitioners agreed that the major benefit of hospital treatment was that the resources and treatments were all centralised and orchestrated.

"Their [children and parents] only experience has been with [hospital name] and you whip your child in and they get a little finger poke and then sometimes an hour or two later the results are back and then it's very smooth."

While having home chemotherapy, children had to go to community laboratories to have their blood test done, many technicians lacked paediatric experience and were insensitive to their needs.

"The biggest one [problem] we have run into has been the whole lab issue and the fact that we've discovered that laboratories in the community are not very child friendly [hospital programme director]

There was also an issue with laboratory results not being communicated to the community nurses for subsequent drug prescription and home delivery resulting in increased workload while nurses retrieving results from hospital physicians. It was suggested that there should be one central person to liaise between the hospital and community.

Very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005), showed that some hospital physicians reported feeling less confident about prescribing chemotherapy agents for children due to the inability to assess the child directly and be in charge of the healthcare process in the community. They also reported feeling unclear about issues relating to liability and responsibility.

From very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005), two clinic nurses and three paediatric oncologists reported no change in their workload; five clinic nurses and 1 physician reported an increase due to the higher volume of paperwork and three clinic nurses reported a decrease.

Update 2016

13/14 community health practitioners reported an increase in workload primarily due to increased paperwork and increased time communicating with other health practitioners to expedite the process.

"It has added to my responsibilities, the day before having to give chemo, I am doing a lot of phone calling. Labs, clinic, chemo.. it can be very time consuming and very frustrating but the actual visit time is not the issue." [community nurse]

Community practitioners reported they had increased their repertoire of skills and 'felt good' about helping families which increased their personal satisfaction. It was also reported that partnership between community and hospital was enhanced by effective communication with opportunities to collaborate and share ideas and optimise treatments.

Very low quality evidence (GRADE table 2) from a nested qualitative study (Stevens *et al*, 2004) within a randomised cross over trial (Stevens *et al*, 2005), the home chemotherapy programme was associated with less interaction with children and families which was considered to be both a positive (fewer patients in outpatient clinics, health practitioners less busy, more time for children in attendance) and negative (distressing because they were not sure how the children were coping with treatment) process.

"You look forward to their visits, I do anyways. Because the communication of how they're really doing and how things are going is sort of broken down, there's a gap because you don't see them every two weeks." [hospital clinic nurse]

Responses suggested an increased level of frustration as the home chemotherapy programme was challenging to accommodate in terms of scheduling between health practitioners and families.

"I found that we were juggling a lot. Trying to work around the teenagers schedules because you would end up calling them to say that you were going to come and do the chemo and they would say 'Oh no I'm off to something or other tonight' So I had to go the home early at 7:30 the next morning. So of course we tried to do that but when you have a lot of patients you just cannot do it. We can't always work around their schedule and I think that really needs to be made clear." [community nurse]

Feasibility

Very low quality evidence (GRADE table 2) from one retrospective study in which 17 patients were treated at home for 46 cycles (Luthi *et al*, 2012), reported that home treatment required one physician visit and two nurse visits per day accounting for 621 visits during 46 treatment cycles (207 days of home treatment). 32 additional home visits were required as a result of technical problems with the pump (median, 1 visit per cycle; range 0-4 visits per cycle) and most visits were needed at the start of treatment.

Pump failure due to air bubbles was the main technical problem and was resolved by flushing the tube (n=21 cases).

Partial disconnection at the exit channel occurred in nine cases and needle disconnection from the port of the catheter occurred in two cases.

Two major pump failures were reported resulting in one overnight hospitalisation and a four day hospitalisation.

Advice on restrictions on social contact, pets and food

From one retrospective audit of 336 institutions in 27 countries (Lehrnbecher *et al*, 2012), 107 centres (32%) had written protocols for non-pharmacological anti-infective approaches and n=64 (64%) had a general agreement without a written policy. In 85 centres (25%) practitioners used an individualised approach

A physician was involved in the instruction of parents in 89% (n=299) of centres and a nurse in 71% of centres (n=238).

A handout was provided to parents in 52% (n=174) of centres and was the only information given in 4% (n=14) of cases.

42% of parents received a handout and were additionally provided with verbal information by a nurse or physician.

Restriction scores in Europe were significantly higher than in USA, suggesting greater restrictions; restriction scores did not differ by centre.

In relation to social contact, most centres did not allow children with AML to visit indoor public places, attend daycare, nursery or school while recommendations for patients with ALL varied considerably. Restrictions mostly related to neutropenia (58%) and to chemotherapy regimens and the health of surrounding people was a pre-condition for reduced restrictions in 16% of centres.

In relation to pets, there was wide variation in recommendations for both AML and ALL patients. Restrictions under certain circumstances related to appropriate hand-washing after contact (27%), keeping animals already at home without introducing new pets (25%), restriction of pets in the bedroom or on the bed (22%), ensuring pets were assessed by a veterinary specialist (17%) and restrictions on cleaning of cages/litter trays (16%).

In relation to food, most centres had restrictions on raw meat, raw seafood and unpasteurised milk for both AML and ALL patients. There were wide variations in food restrictions around salad, nuts, takeaway food and unpeeled vegetables. In 68% of cases, restrictions were generally related to neutropenia and specific chemotherapy regimens .If uncooked vegetables or salad were allowed, appropriate cleaning was advised (12%).

In relation to the use of face masks, 9% (n=30) institutions recommended children with ALL wear face masks in public while 34% (n=114) recommended face masks for AML patients. 54% (n=181) never suggest facemasks for children with ALL and 41% (n=138) never suggest facemasks for children with AML.

Update 2016

1 **GRADE Table 1: Isolation compared to No isolation/Placebo for low risk patients**

2

Isolation compared to No isolation/Placebo for low risk patients						
Patient or population: low risk patients Settings: haematological oncology Intervention: Isolation Comparison: No isolation/Placebo						
Outcomes			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	No isolation/Placebo	Isolation				
All cause mortality - Randomised studies Follow-up: 30 days	Study population 385	453	0.66 (0.49-0.87)	838 (9 studies)	moderate[3]	Pooled RR for randomised and observational studies: 0.60 (0.50-0.72)
All cause mortality - Observational studies Follow-up: 30 days	Study population 4423	1019	0.57 (0.45-0.71)	5442 (6 studies)	very low[3,4,5]	
All cause mortality - Randomised studies Follow-up: 100 days1	Study population 461	554	RR 0.78 (0.66 to 0.92)2	1015 (12 studies)	moderate[3]	Pooled RR for randomised and observational studies: RR=0.79 (0.73-0.87)
All cause mortality - Observational studies Follow-up: 100 days1	Study population 4615	1262	RR 0.80 (0.72 to 0.88)	5877 (12 studies)	very low[3,4,5]	
Infection (all) related mortality - Randomised studies Follow-up: 3-36 months	Study population 400	459	RR 0.61 (0.52 to 0.71)[2]	859 (11 studies)	moderate[3]	Pooled RR for randomised and observational studies: RR=0.75 (0.68-0.83)
Infection (all) related mortality- - Observational studies Follow-up: 3-36 months	Study population 471	574	RR 0.92 (0.79 to 1.06)[2]	1045 (9 studies)	very low[3,4,5]	
Infection (gram-positive) – Randomised Studies Follow-up: 3-36 months	Study Population 416	550	RR 0.55 (0.40-0.76)	966 (10 studies)	moderate[3]	Pooled RR for randomised and observational studies:

Infection (gram-positive) – Observational Studies Follow-up: 3-36 months	Study Population 254	261	RR 0.76 (0.62-0.91)	515 (7 studies)	very low3,4,5	RR=0.66 (0.56-0.79)
Infection (gram-negative) – Randomised Studies Follow-up: 3-36 months	Study Population 497	639	RR 0.49 (0.40-0.62)	1136 (12 studies)	moderate[3]	Pooled RR for randomised and observational studies: RR=0.55 (0.46-0.66)
Infection (gram-negative) – Observational Studies Follow-up: 3-36 months	Study Population 254	261	RR 0.70 (0.54-0.91)	515 (7 studies)	very low[3,4,5]	
Infection (mould) related mortality-randomised studies Follow-up: 3-36 months	Study population 174	214	RR 0.84 (0.33 to 0.214)[2]	388 (6 studies)	moderate[3]	Pooled RR for randomised and observational studies: RR=0.69 (0.31-1.53)
Infection (mould) related mortality - observational studies Follow-up: 3-36 months	Study population 267	324	RR 0.42 (0.08 to 2.10)[2]	765 (3 studies)	very low[3,4,]	
Need for antibiotics (all study types) Follow-up: 3-36 months	Study population		RR 1.01 (0.94 to 1.09)[2]	0 (5 studies6)	very low[3,4,]	
Number of antibiotic days Follow-up: 3-36 months	Study population		RR 0.81 (0.75 to 0.85)[2,7]	0 (3 studies6)	very low[3,4,]	
Room Facilities Follow up: 8 years	Study Population 28	35	N/A	63 (1 study)	very low[4, 8]	39% of pre-renovation patients and 34% of post-renovation patients developed an invasive pulmonary aspergillosis (p=0.79) with the diagnosis usually determined on CT scan.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

[1] Follow-up closest to 100 days from each study
[2] RR=Risk Ratio
[3] Patients may not all be low risk patients. The population in the systematic review included patients with solid tumours, haematological malignancies and/or HSCT recipients.
[4] These are not randomised studies
[5] There were more observational studies with a much larger number of patients and the results were similar to those when pooling the results of the randomised studies.
[6] This is a pooled result and may include data from randomised studies and observational studies.
[7] 6617 patient days
[8] Patient population may include patients other than standard risk haematology patients

1
2
3

1 **GRADE Table 2: Ambulatory Care versus inpatient care**

Ambulatory care/Outpatient care compared to Hospital care/Inpatients care for standard risk haematological oncology patients						
Patient or population: Standard risk haematological oncology patients Settings: Haematological oncology Intervention: Ambulatory care/Outpatient care Comparison: Hospital care/Inpatients care						
Outcomes			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Hospital care/Inpatients care	Ambulatory care/Outpatient care				
Mortality (Schlesinger *et al*, 2009) Follow-up: median 12 months	Study population		RR 0.72 (0.53 to 0.97)	705 (7 studies)	very low[1,2,5]	
	319	386				
Febrile neutropenia/documented Infections (Schlesinger *et al*. 2009) Follow-up: median 12 months	Study population		RR 0.78 (0.7 to 0.88)	757 (8 studies)	very low[1,2]	
	N/R	N/R				
Hospital admission and length of stay (Sive *et al*, 2012)	Length of stay ranged from 1-42 days (median 5 days)		N/R	668 (1 study)	very low[1]	
Hospital admission and length of stay (Sopko *et al*, 2012)	24 patients required rehospitalisation and were admitted for a mean 10.9 days (6-35 days)	Mean hospitalisation time was 30 days (17-38) for inpatients	N/R	45 (1 study)	very low[1]	
Hospital admission and length of stay (Bakhshi *et al*, 2009)	N/R	N/R	N/R	30 (1 study)	very low[1]	
	Hospital stay was significantly shorter in outpatients cycles compared with inpatient cycles					

	(p<0.001)					
	82	82				
	Ambulatory care was associated with less red blood cell units (median 2 (0-24) versus median 6 (0-12) and platelet transfusions (median 1 (0-18) versus median 4 (1-5) p<0.001.					
Transfusions (Bakhshi *et al*, 2009)	Study population		N/R	0 (1 study)	very low[1]	
	Median of 1 (0-4) unit of packed red blood cells Median of 1 (0-13) platelet transfusions	Median of 2 (0-5) units of packed red blood cells Median of 2 (0-12) platelet transfusions				
Antibiotic use (Bakhshi *et al*, 2009)	Study population		N/R	0 (1 study)	very low[1]	
	Significantly fewer patients in the outpatient setting required second line antibiotics (p=0.03) and mean duration of antibiotic administration was significantly lower (p=0.04)					
Quality of life and burden of care (Stevens *et al*, 2004)	See evidence statements and evidence tables for detailed results		N/R	0 (1 study)	very low[1]	Paediatric Patients
Patient satisfaction (Luthi *et al*, 2012)	Study population		N/R	0 (1 study)	very low[1]	
	See evidence statements and evidence tables for detailed results					
Impact on practitioners (Stevens *et al*,	See evidence statements		N/R	0	very low[1]	Paediatri

2004)	and evidence tables for detailed results		(1 study)		c Patients
Feasibility (Luthi *et al*, 2012)	Study population See evidence statements and evidence tables for detailed results	N/R	0 (1 study)	very low[1]	
GRADE Working group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: 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 quality: We are very uncertain about the estimate.					
[1] Not randomised [2] All patients were stem cell transplant patients [3] p=0.04 [4] p=0.05 [5] Each of the studies measured and reported the outcome in slightly different ways					

1

Cost effectiveness evidence

A systematic literature review was performed to assess the current economic literature for this topic. The review identified 99 possibly relevant economic papers related to the configuration of diagnostic and specialist services for people with haematological cancers. Of these, no papers were deemed relevant for this topic and therefore no papers were included in the review of existing economic evidence.

Recommendations	**In this guideline ambulatory care is a planned care system in which patients at risk of prolonged neutropenia are based at home or other specified accommodation. There should be specific safeguards to minimise the risk from potentially life-threatening complications of chemotherapy.** **The recommendations in this section apply to young people (16–24 years) and adults (over 24 years) with haematological malignancies who are:** • **receiving intensive (non-transplant) chemotherapy for induction or re-induction of remission, or consolidation, and** • **at risk of more than 7 days of neutropenia of 0.5×10^9/litre or lower (see table 19).** **This includes young people and adults having treatment for:** • **acute myeloid leukaemia (including acute promyelocytic leukaemia)** • **acute lymphoblastic leukaemia/lymphoblastic lymphoma** • **high-risk/hypoplastic myelodysplastic syndrome** • **Burkitt lymphoma** • **bone marrow failure caused by other haematological malignancy, such as plasma cell leukaemia.** **These recommendations do not apply to people with relapsed or refractory lymphoma who are having salvage chemotherapy regimens likely to result in fewer than 7 days of neutropenia of 0.5×10^9/litre or lower.** **For guidance on staffing and facilities for children with cancer see the NICE cancer service guidance on improving outcomes in children and young people with cancer.** ***Centre size*** **Specialist haematology centres should provide intensive (non-transplant) chemotherapy for induction or re-induction of remission to a minimum of 10 patients per year who have new or relapsed haematological malignancies and are at risk of more than 7 days of neutropenia of 0.5×10^9/litre or lower. [new 2016]** **Facilities** ***Isolation facilities*** **Inpatient isolation facilities for patients who have haematological malignancies and are at risk of more than 7 days of neutropenia of 0.5x10^9/litre or lower should consist of a single-occupancy room with its own bathroom. [new 2016]**

Update 2016

Update 2016

Consider installing clean-air systems into isolation facilities for patients who have haematological malignancies and are at risk of more than 7 days of neutropenia of 0.5x10^9/litre or lower. [new 2016]

Other facilities

Ensure that there is provision for direct admission to the ward or unit. [2016]

Ensure that there are specific beds available in a single dedicated ward within the hospital with the capacity to treat the planned volumes of patients. [2016]

Ensure that there is a designated area for out-patient care that reasonably protects the patient from transmission of infectious agents, and provides, as necessary, for patient isolation, long duration intravenous infusions, multiple medications, and/or blood component transfusions. [2016]

Ensure that there are full haematology and blood transfusion laboratories on site. Ensure that there is rapid availability of blood counts and blood products including products such as CMV seronegative and gamma-irradiated blood components. [2016]

Ensure that there are on-site facilities for emergency cross-sectional imaging. [2016]

Ensure that cytotoxic drug reconstitution is centralised or organised at the pharmacy. [2016]

Central venous catheter insertion should be performed by an experienced specialist. [2016]

Ensure that there is on-site access to bronchoscopy, intensive care and support for patients with renal failure. [2016]

Ambulatory care

Consider ambulatory care for patients who have haematological malignancies that are in remission and who are at risk of more than 7 days of neutropenia of 0.5x10^9/litre or lower. [new 2016]

Standard operating procedures for all aspects of an ambulatory care programme should be clearly defined and include the following:

- **local protocols for patient eligibility, selection and consent**
- **procedures for patient monitoring**
- **access to a dedicated 24-hour advice line staffed by specifically trained haematology practitioners**
- **clear pathways for rapid hospital assessment in the event of neutropenic sepsis or other chemotherapy-related complications or toxicities**
- **clear pathways for re-admission to specialist haematology centres**

Update 2016

	• written and oral information for patients and their family members or carers • audit and evaluation of outcomes [new 2016] Take into account the following when assessing patients to see if ambulatory care is suitable: • patient preference • comorbidities • distance and travel times to treatment in case of neutropenic sepsis and other toxicities (see the NICE guideline on neutropenic sepsis) • the patient's or carer's understanding of the safety requirements of ambulatory care and their individual treatment plan • access to and mode of transport • accommodation and communication facilities • carer support [new 2016] *Clinical policies and audit* Specialist haematology centres should ensure that there are written policies for all clinical procedures. [2016] Specialist haematology centres should ensure that there is participation in audit of process and outcome. [2016] *Staffing* Specialist haematology centres should have consultant-level specialist medical staff available 24 hours a day. This level of service demands at least three consultants, all full members of a single haematology multidisciplinary team (MDT) and providing inpatient care at a single site. [2016] Cover in specialist haematology centres should be provided by specialty trainees and specialty doctors who are: • haematologists or oncologists • involved in providing care to the patients being looked after by the centre • familiar with and formally instructed in the unit protocols [2016] There should be enough nurses in specialist haematology centres to provide care for the patients, based on the severity of their clinical status. [2016] Specialist haematology centres for patients with neutropenic sepsis should have the same level of nursing staff as that in a high-dependency unit. [2016] There should be at least 1 trained specialist nurse on the ward in the specialist haematology centre at all times, and they should be able to deal with indwelling venous catheters, recognise early symptoms of infection, and respond to potential crisis situations. [2016]

Update 2016

	Specialist haematology centres should have access to consultant-level microbiological advice at all times. There should be access to specialist laboratory facilities for diagnosing fungal or other opportunistic pathogens. [2016] **Specialist haematology centres should have access to a consultant clinical oncologist for consultation, although radiotherapy facilities do not need to be on site. [2016]** **Specialist haematology centres should have access to on-site advice from a specialist haematology pharmacist. [2016]** **Specialist haematology centres should have dedicated clinical and administrative staff to support patient entry into local and nationally approved clinical trials and other prospective studies. 2016]**
Relative value placed on the outcomes considered	The outcomes of interest for this topic included survival, readmission rates, infection rates, antibiotic/antifungal use, length of stay, treatment delay, patient satisfaction and health related quality of life. The outcomes of most importance relating to the location of chemotherapy delivery included survival outcomes, patient satisfaction and heath related quality of life. Very low quality evidence comparing inpatient and outpatient chemotherapy administration was identified, but was considered to be more appropriate to the ambulatory care intervention, so no specific recommendations on location of chemotherapy delivery were made. The GC considered that although administering chemotherapy in either a community setting or at home might lead to greater patient satisfaction and quality of life; patient safety should not be compromised. For interventions on the level of inpatient isolation and the ability to isolate patients, the most important outcomes were considered to be infection rates, antibiotic/antifungal use and health related quality of life. There was some evidence on the level of isolation but none on the ability to isolate patients. Increased isolation may reduce infection rates in immunocompromised patients but remaining in isolation may have an impact on patient well-being and psychological outcomes and lead to reduction in quality of life. For ambulatory care, survival outcomes, readmission rates, infection rates, antibiotic/antifungal use and patient outcomes (such as satisfaction and quality of life) were the most important outcomes. In order to make a recommendation that patients might be treated in an ambulatory care setting, the GC wanted to be sure that patient safety (particularly infection rates and antibiotic use) would not be compromised compared to being treated as an inpatient, and that patient well-being would not be affected by, for instance, increased anxiety due to being away from the hospital environment. Survival outcomes, readmission rates, infection rates and antibiotic/antifungal use, as well as patient outcomes (such as satisfaction and quality of life) were considered to be the most important outcomes when assessing the evidence about centre size and specialisation. The GC wanted to find out whether patients

Update 2016

	preferred to be treated at larger centres with access to specialist health care professionals rather than at smaller, local centres/hospitals where the patient numbers treated might be fewer and therefore clinical experience might not be as great, and also whether there was a difference in survival outcomes between the two centre types.
Quality of the evidence	No evidence was identified for the location of chemotherapy delivery, the ability to isolate patients or centre size and specialism. Limited evidence was identified about isolation factors and ambulatory care, the quality of which ranged from very low to moderate on GRADE assessment. **Isolation Factors** *Survival* Very low to moderate quality evidence *Infection related Mortality, Risk of Infection, Antibiotic use* Very low to moderate quality evidence *Room Facilities* Very low to moderate quality evidence **Ambulatory Care** *Survival* Very low to moderate quality evidence *Hospital Admissions and length of stay* Very low quality evidence *Infections* Very low quality evidence *Transfusions* Very low quality evidence *Quality of Life* Very low quality evidence *Burden of Care* Very low quality evidence Impact on Practitioners Very low quality evidence. As a result of the poor quality evidence the GC agreed not to make strong recommendations on clean air systems. The evidence on ambulatory care was poor, but there was no evidence that ambulatory care patients have worse outcomes and there is unpublished data and clinical experience to show it is safe and patients preferred it. The GC agreed that this warranted making strong recommendations about the development and provision of an ambulatory care programme because they believed that ensuring patient safety and well being was important in this setting.

Update 2016

	Due to the lack of evidence, the GC used clinical experience to develop recommendations on minimum centre volumes which they agreed appropriately considered the current and widely implemented FACT-JACIE standards.
Trade off between clinical benefits and harms	*Isolation:* The primary benefit of isolating patients is to reduce infection rates and mortality, but some patients experience short and long term psychological effects of being isolated from health professionals and family. The GC felt that the benefit to the patient in terms of a reduced risk of serious infection and death were more important and that the comparatively small risk to the patients' psychological well being should not prevent them making a recommendation on this topic. *Ambulatory Care:* The main benefit of an ambulatory care programme is better patient experience. The clinical consensus of the GC was that treating patients in an ambulatory care setting also reduces infection rates, length of hospital stay and costs. In addition, the GC agreed that not being in hospital may reduce the risk of hospital associated harms such as pressure sores, Venous Thromboembolism (VTE), falls and hospital acquired infections. Potential harms associated with treating patients in an ambulatory care setting away from the ward or hospital were identified including delayed access to specialist care, the risk of patients not recognising symptoms of serious infection, and increased patient anxiety. But the GC felt that in this situation these risks could be balanced against the better patient experience and quality of life provided that appropriate safeguards were in place. Acknowledging this, the GC made recommendations on protocols and other measures to reduce the risk from adverse clinical events such as delay in treatment of neutropenic sepsis. *Centre size:* Although no evidence was identified, the GC agreed that a recommendation on centre size was important as the potential benefits from care in a larger centre include better access to clinical trials, the ability to audit outcomes, increased patient confidence, and better access to resources and expertise including the use of dedicated isolation facilities. One drawback of this recommendation was increased travel times and costs for the patients and their family and carers because there are no local services which they can attend. The recommendation may lead to a need for unit reconfiguration, deskilling of staff at smaller centres and reduced staff satisfaction. The GC used clinical experience in determining a minimum number and based their recommendation for a minimum of 10 patients on the current FACT-JACIE standards. The GC acknowledged that travel distance and cost could adversely affect the patients' satisfaction and quality of life but considered that there were benefits from higher staff expertise, access to clinical trials and informal psychological support from access to patients with similar conditions and specialist nurses. The GC also noted that patients cared for in a larger centre were more likely to be able to access ambulatory care.
Trade off between net	No health economic evidence was identified and no economic model

Update 2016

health benefits and resource use	was developed for this review question. *Centre Size* A larger centre size is likely to lead to economies of scale and consequently a reduced cost per patient. Along with potential improved survival outcomes, reduced early treatment related mortality and better access to isolation facilities and specialist care, this recommendation could possibly be cost saving and health improving *Isolation Facilities* There is likely to be increased resource use through the creation of isolation facilities and through the use of clean air facilities. The majority of these costs are likely to be up front around setting up these facilities although costs would continue through maintenance and replacement of filters. The impact of increased physical limitation and isolation may also increase the use of support services such as psychological support and rehabilitation. The provision of these facilities is likely to lead to a reduction in hospital acquired infections and improved quality of life and reduced costs associated with their aversion. Whilst the GC considered that this recommendation was likely to be cost increasing and mya have some quality of life detriment through physical limitation and isolation, this was justified by the reduction and subsequent improvement in outcomes from avoiding hospital acquired infections. *Ambulatory Care* The recommendation will lead to additional resource use where dedicated residencies or hotels are used as opposed to a patient's usual residence and through implementation of a dedicated 24-hour advice line. There may also be significant upfront costs to build dedicated residences and implement the telephone advice line. However there will be cost savings through the reduction in use of hospital beds and reduction in hospital acquired infections and subsequent treatment costs. The GC considered it highly probably that these cost-savings may outweigh additional costs. With the improved health outcomes by protection against hospital acquired infection and improved patient experience related to partially avoiding the physical limitations and psychological effects of isolation the GC felt there was a strong possibility this recommendation could be both cost saving and health improving.
Other considerations	The GC acknowledge that there may be the potential for inequitable access to ambulatory care programs if patients are non English speakers, have learning difficulties or physical disabilities. The GC therefore included recommendations which aim to outline the importance of assessing patient's needs and developing standard operating procedures which allow those needs to be met to ensure that no patient is disadvantaged.

Update 2016

References

Bakhshi *et al* (2009) Outpatient consolidation chemotherapy in paediatric acute myeloid leukaemia: a retrospective analysis Haematology 14;5:255

Burnett AK *et al* (2012) Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia Journal of Clinical Oncology 30, 3924-31

Burnett AK *et al* (2015) A randomized comparison of daunorubicin 90 mg/m2 vs 60 mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood 125;25:3878-85

Crump M *et al* (2014) Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas: NCIC-CTG LY.12. Journal of Clinical Oncology 32;31:3490-3496

Fielding AK *et al* (2014) UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood 123; 843-50

Flowers CR *et al* (2013) Antimicrobial Prophylaxis and Outpatient Management of Fever and Neutropenia in Adults Treated for Malignancy: American Society of Clinical Oncology Clinical Practice Guideline Journal of Clinical Oncology31; 6:794-810.

Gardner A *et al* (2008) Randomized Comparison of Cooked and Noncooked Diets in Patients Undergoing Remission Induction Therapy for Acute Myeloid Leukemia. Journal of Clinical Oncology 10;26(35):5684-8

Gratwohl A, *et al* (2014). Use of the quality management system "JACIE" and outcome after hematopoietic stem cell transplantation.Haematologica 99:908-15.

Hutter *et al* (2009) Correlation between the incidence of nosocomial aspergillosis and room reconstruction of a haematological ward Journal of Infection Prevention 10;6

Kantarjian HM *et al* (2000)Results of Treatment With Hyper-CVAD, a Dose-Intensive Regimen, in Adult Acute Lymphocytic Leukemia. Journal of Clinical Oncology 18;3:547-61

Lehrnbecher *et al* (2012) Variations in non-pharmacological anti-infective measures in childhood leukaemia – results of an international study Haematologica 97;10

Luthi *et al* (2012) Home Care – a safe and attractive alternative to inpatient administration of intensive chemotherapies Support Care Cancer 20:575-581

Matthey F *et al* (2009) Facilities for the Treatment of Adults with Haematological Malignancies – 'Levels of Care' BCSH Haemato-Oncology Task Force

Mead GM *et al* (2008) A prospective clinicopathologic study of dose-modified CODOX-M/IVAC in patients with sporadic Burkitt lymphoma defined using cytogenetic and immunophenotypic criteria (MRC/NCRI LY10 trial). Blood 112;6 2248-2260

NICE (2003) Improving outcomes in haematological cancers. London: National Institute for Health and Care Excellence

Schlesinger A *et al*. (2009) Infection Control Interventions for Cancer Patients after Chemotherapy: A Systematic Review and Meta-Analysis Lancet Infectious Diseases 9;97-107

Sive J *et al* (2012a) Outcomes In Older Adults with Acute Lymphoblastic Leukemia (ALL): Results From the International MRC UKALL XII/ECOG2993 Trial. British Journal of Haematology. 157;4:463-71.

Sive *et al* (2012b) Hotel based ambulatory care for complex cancer patients: a review of the University College London Hospital experience Leukaemia and Lymphoma 53;12:2397-2404

Update 2016

Sopko *et al* (2012) The feasibility of an early hospital discharge following chemotherapy for the acute myeloid leukaemia Bratisl Lek Listy 113;5

Stevens *et al* (2005) Hospital and home chemotherapy for children with leukaemia: a randomised cross-over study Paediatric Blood and Cancer 47;3:285-92

Stevens *et al* (2004) Home chemotherapy for children with cancer: perspectives from health care professionals Health and Social Care in the Community 12;2:142-149

Thomas X *et al* (2004) Efficacy of granulocyte and granulocyte-macrophage colony-stimulating factors in the induction treatment of adult acute lymphoblastic leukemia: a multicenter randomized study. Hematology Journal. 5;5:384-94.

Ye SG *et al* (2015) Colony-stimulating factors for chemotherapy-related febrile neutropenia are associated with improved prognosis in adult acute lymphoblastic leukemia. Molecular and Clinical Oncology 3;3:730-736.

3.2 Multi-disciplinary teams (MDT)

The following recommendations were published in chapter 4 of the original 2003 Improving outcomes in Haematological cancer guidance. The evidence for these recommendations has not been reviewed as part of this update but have been included in this section as they are still relevant to staffing and facilities (levels of care) for adults and young people with haematological cancer.

Recommendations	
	Clinical services for patients with haematological cancers should be delivered by multi-disciplinary haemato-oncology teams. [2003] **Haemato-oncology MDTs should serve a population of at least 500,000 people. [2003]** **Every patient with any form of haematological cancer (as defined by current World Health Organization [WHO] criteria) should be cared for by a haemato-oncology MDT. [2003, amended 2016]** **All patients should have their care discussed in formal MDT meetings attended by members involved in the diagnosis, treatment, or care of that particular patient, and all the clinicians in the MDT should regularly treat patients with the particular forms of haematological cancer with which that MDT deals. [2003, amended 2016]** **These MDTs should be responsible not only for initial recommendations about what treatment should be offered, but also for delivery of treatment and long-term support for patients. [2003, amended 2016]** **Individual clinicians should be responsible for discussing the MDT's recommendations with their patients, who should have the opportunity to be informed of the outcome of MDT meetings. [2003, amended 2016]** **Clinicians who are not members of the MDTs should refer any patient with suspected or previously diagnosed haematological cancer to an appropriate haemato-oncology MDT. [2003, amended 2016]** **Written referral policies should be disseminated both within hospitals (particularly to departments such as gastroenterology, dermatology, rheumatology and medicine for the elderly) and to primary care teams, to promote prompt and appropriate referral. [2003]** ***Core members*** **Each haemato-oncology MDT should include sufficient core members for the following people to be present in person or remotely (for example via video conferencing) at every meeting:** • **Haemato-oncologists (either haematologists or some**

Update 2016

medical oncologists): at least two who specialise in each tumour type being discussed at that meeting (e.g. leukaemia or lymphoma). At least one from each hospital site contributing to the MDT

- **Haematopathologist: at least one haematopathologist from the SIHMDS should be present; to provide the diagnostic information**
- **Nurses: at least one clinical nurse specialist, also ward sisters from hospitals which provide intensive chemotherapy**
- **Palliative care specialist: at least one palliative care specialist (doctor or nurse) who liaises with specialists from other sites. If, because of staff shortages, a palliative care specialist cannot regularly attend MDT meetings, the MDT should be able to demonstrate that it reviews patients regularly with such a specialist**
- **Support staff: staff to organise team meetings and provide secretarial support. [2003, amended 2016]**

Teams established to manage patients with lymphoma should include the following additional core members, who should be fully and regularly involved in MDT discussions:

- **Clinical oncologist: at least one;**
- **Radiologist: at least one, who liaises with radiologists at other sites. [2003]**

Teams responsible for managing patients with myeloma should include at least one radiologist who liaises with radiologists at other sites and is fully and regularly involved in MDT discussions. Teams which care for patients with myeloma should have rapid access to oncologists for palliative radiotherapy, although it is not necessary for clinical oncologists to regularly attend team meetings. [2003, amended 2016]

Extended MDT members

The MDT should include the following extended team members. They do not have to be present at every MDT meeting;

- **Clinical member of the transplant team to which patients could be referred**
- **Microbiologist (especially for patients with leukaemia)**
- **Pharmacist**
- **Vascular access specialist**
- **Registered dietician**
- **Orthopaedic surgeon (myeloma MDT)**
- **Clinical oncologist (myeloma MDT and leukaemia MDT; provision of cranial radiotherapy for patients with acute lymphoblastic leukaemia (ALL) is an important role for a clinical oncologist) [2003, amended 2016]**

Other specialists

MDTs should have access to the following specialists:

Update 2016

- **Dermatologist**
- **Gastroenterologist**
- **Ear, Nose and Throat (ENT) surgeon**
- **Interventional radiologist**
- **Renal physician. [2003, amended 2016]**

All haemato-oncology MDTs should have access to support staff, including:

- **Allied health professionals including rehabilitation specialists**
- **Liaison psychiatrist and/or clinical psychologist**
- **Social worker**
- **Bereavement counsellor**
- **Support for patients and carers. [2003, amended 2016]**

A clinical nurse specialist should be the initial point of contact for patients who feel they need help in coping with their disease, its treatment or consequences. This nurse should be able to arrange re-admission, clinical review, or meetings between patients and support staff such as those listed above. Networking between nurses with different types of expertise should be encouraged. [2003]

Responsibilities of haemato-oncology MDTs

Haemato-oncology MDTs should meet weekly, during normal working hours. All core members should have a special interest in haematological cancer and attend MDT meetings as part of their regular work. They should attend at least two thirds[c] of meetings. [2003, amended 2016]

At each meeting, the MDT should:

- **ensure that all new diagnoses have had SIHMDS review and integrated reporting**
- **establish, record and review diagnoses for all patients with the forms of cancer that fit the team's definition criteria**
- **assess the extent of each patient's disease and discuss its probable course**
- **work out treatment plans for all new patients and those with newly-diagnosed relapses**
- **review decisions about treatment, particularly those made in the interval between MDT meetings. This review should cover not only the clinical appropriateness of the treatment but also the way patients' views were elicited and incorporated in the decision-making process**
- **discuss the response to treatment, both during therapy and when the course of treatment is complete**
- **think about the appropriateness of radiotherapy in the light of the response to chemotherapy**

Update 2016

c Cancer Quality Improvement Network System (2013) Manual for Cancer Services: Haemato-oncology Cancer Measures – Haemato-oncology MDT Measure 13-2H-104

- **think about the patients' other requirements such as palliative care or referral to other services. MDTs should be able demonstrate effective systems for collaboration with hospital and community palliative care services**
- **discuss discontinuing treatment. Each MDT should develop a specific process for considering discontinuation of treatment when its effectiveness has become so limited that adverse effects might outweigh potential benefits**
- **agree dates for reviewing patients' progress**
- **discuss clinical trials and audit results [2003, amended 2016]**

The MDT should:

- **review all SIHMDS reports of borderline conditions such as aplastic anaemia and other non-malignant bone marrow failure syndromes (which overlap with hypoplastic myelodysplastic syndrome), and lymphocyte and plasma cell proliferation of uncertain significance (which overlap with lymphoma and myeloma)**
- **identify requirements for staff and facilities for any form of treatment it provides**
- **liaise with primary care teams, palliative care teams, services for the elderly and voluntary organisations such as hospices**
- **ensure that adequate information, advice and support is provided for patients and their carers throughout the course of the illness**
- **ensure that GPs are given prompt and full information about the nature of their patients' illness or treatment, any changes in management, and the names of individual MDT members who are primarily responsible for their patients' management**
- **record, in conjunction with the cancer registry, the required minimum dataset for all cases of haematological cancer within its specified catchment area, including those cared for by clinicians who are not haemato-oncology MDT members**
- **identify the training needs of MDT members and make sure these needs are met;**
- **be involved in clinical trials and other research studies**
- **Collaborate in planning, and collecting data for audit. [2003, amended 2016]**

One member of each team, usually the lead clinician, should act as the administrative head of the team, taking overall responsibility for the service it delivers. [2003]

Lead clinicians from all haemato-oncology teams in each MDT should collaborate to develop and document evidence-based clinical and referral policies which should be consistently applied across the MDT as a whole. They should agree process and outcome measures for regular audit. All teams should be involved in audit and clinical trials. [2003, amended 2016]

Update 2016

There should be an operational policy meeting at least once a year at which each MDT discusses its policies and reviews the way it functions. [2003]

Maximising the effectiveness of MDT meetings

Suitable facilities should be provided to support effective and efficient team working. In addition to basic physical facilities such as adequate room and table space, there should be appropriate equipment, for example to allow the group to review pathology slides and imaging results. [2003]

Every MDT meeting should have a designated chairperson. Whilst this may be the lead clinician, teams should consider rotating the role of chairperson between members. Teams should aim for an egalitarian mode of interaction, to facilitate open discussion to which all members feel able to contribute. [2003, amended 2016]

Each MDT should have named support staff who take the roles of team secretary and co-ordinator. Since these roles overlap, one person may be able to cover both functions in smaller teams. If a team decides that a clinical nurse specialist should be responsible for co-ordinating meetings, secretarial and administrative support should be provided for this nurse. [2003, amended 2016]

The team co-ordinator should arrange meetings, inform all those who are expected to attend, and ensure that all information necessary for effective team functioning and clinical decision-making is available at each meeting. This will include a list of patients to be discussed and copies of their case notes, along with diagnostic, staging, and pathology information. [2003]

The secretary should take minutes at all meetings, and record and circulate decisions made by the team within the case notes and both to both MDT members and to those others identified as appropriate for routine circulation by the MDT, such as GPs, who may require this information. Confidentiality dictates that these records go to relevant clinicians only. [2003]

A designated member of the team's support staff, working with the administrative head of the team, should be responsible for communication with primary care, palliative care, and other site specific MDTs. [2003, amended 2016]

Local services

Local services should be developed around MDTs which include at least three haematologists whose sole or main specialist interest is in haemato-oncology. [2003]

Update 2016

	Teams should specify which patients they can treat locally and make specific arrangements for the delivery of clinical services which they do not provide. [2003] **All in-patients undergoing intensive forms of treatment such as complex chemotherapy under the care of this team should be treated either at one hospital, or, where there is a locally agreed case for providing this service at more than one hospital, in hospitals which then each must independently meet the full criteria for the safe delivery of these treatments. [2003]** **Each haemato-oncology MDT which provides intensive chemotherapy should have facilities as specified in recommendations 3.1, and should be able to demonstrate adequate arrangements for 24-hour cover by specialist medical and nursing staff. These arrangements should be sufficiently robust to allow cover for holidays and other absences of team members. [2003, amended 2016]** **All hospitals which give intensive (non-transplant) chemotherapy for induction or re-induction of remission, or consolidation, or which are likely to admit patients undergoing chemotherapy as medical emergencies, should have documented clinical policies, agreed with haematology and oncology staff, which clearly specify arrangements for the care of such patients. [2003, amended 2016]**

Update 2016