Haematological cancers: improving outcomes (update)

Appendix G: Evidence review

Developed for NICE by the National Collaborating Centre for Cancer

Contents

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

Review 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?

Background

The main driver for this recommendation in the improving outcomes guidance and subsequent 2012 revision (agreed by the National Cancer Action Team and the RCPath) was evidence of a significant misdiagnosis rate for haematological malignancies (5-15%) sometimes with major clinical consequences (Clarke et al., 2004; LaCasce et al., 2008; Lester et al., 2003; Proctor et al., 2011). This type of error can be difficult to detect after a patient has been treated and therefore a premium must be placed on being able to demonstrate that a diagnosis is correct and supported by strong evidence across several independent investigative modalities. This approach is intrinsic to the way that disease entities are defined in the World Health Organisation (WHO) classification and is common to all haematological malignancies.

The availability of the necessary investigations varies across the country. To be effective this multi-modality approach to diagnostic quality assurance requires a systematic approach to the investigation of specimens and a clear process to interpret and integrate the results obtained (via integrated diagnostic reporting), most crucially to identify inconsistencies between the results obtained by different investigative techniques. This is most effectively delivered within an integrated diagnostic service able to provide the full range of diagnostic techniques required and to provide a report to the end users that integrates these results into a single diagnostic assessment; this was the rationale behind the current guidance (Ireland et al, 2011). A very important subsidiary consideration is that diagnostic techniques are rapidly evolving and these developing techniques need to be reflected in laboratory organization. The efficient delivery of evolving modern diagnostic approaches, such as molecular genetics and flow cytometry, potentially across a range of specialities with the required quality and economy of scale needs to be balanced against the requirements of specialised integrated reporting, which, on a practical level, are easiest to achieve within a fully integrated laboratory or other closely located laboratory configuration. This is because the diagnosis, classification and prognostic assessment of these conditions requires integration of multiple diagnostic techniques and high levels of ascertainment and data quality can only realistically be achieved in an infrastructure which facilitates routine, direct interaction between component laboratory professionals.

High quality data on diagnosis, treatment and outcome data on cancer patients is a key objective of the NHS. Data quality in haematology has long been a major problem with widely differing levels of ascertainment between regions and the ability to report data in only the broadest categories of limited clinical utility. A greater implementation and standardisation of SIHMDS reporting should improve the quality of data in haemato-oncology and contribute to NHS goals. In addition, the integrated delivery of modern diagnostics in haemato-oncology is a highly active area of research and development that the NHS is uniquely placed to make an internationally competitive contribution.

However, there are a number of other important considerations for example, the availability of suitably trained staff (pathologists, clinical and biomedical scientists) is limited and constrains the

number of centres able to offer this service. To ensure rapid diagnosis and to conserve diagnostic material (which in the case of needle core biopsies, may be sparse) it is important that specimens from patients suspected of having a haematological malignancy are referred directly to the specialist laboratory. This raises two problems, which have proved a significant obstacle to implementing this guidance. It is not always possible to identify specimens that require referral from the patient's clinical features alone and triage by local pathologist and haematologists is important. Concern is also expressed frequently that this means that local pathology staff will become deskilled and more broadly that referral of specialist work of this type undermines the viability and job satisfaction of local hospital laboratories. Although previous consensus recommendations have been made for minimum catchment populations for the delivery of SIHMDS (NCAT 2012), there is no evidence to support such thresholds. Delivery of SIHMDS may be influenced by regional configurations of clinical haematology and oncology services, including MDTs and academic networks, along with broader geographical considerations such as regional infrastructure and transport flows. Although Cancer Networks are no longer in operation, their effect may persist in NHS cancer services in regional working relationships and service delivery.

In recent multicentre UK studies, early mortality following AML induction chemotherapy has been reported as up to 6% and 9% at 30 days and 10% and 15% at 60 days in younger and older patients respectively (Burnett et al, 2015; Burnett et al, 2012).

Reported induction mortality is also substantial in ALL; 4% in patients <55 and 18% in patients over 55 years (Sive et al, 2012). Early mortality in ALL is not improved with the introduction of modern drugs, such as tyrosine kinase inhibitors in Philadelphia positive disease (Fielding AK et al, 2014). Recent data confirm a 2.2% induction death rate in 16-25 year olds treated on paediatric protocols. In 25 – 60 year olds treated on the current NCRI UKALL 14 type schedule, the induction death rate in UKALL 14 currently is 8.5% (personal communication, Dr Clare Rowntree).

Question in PICO format

PICO Table 1			
Population	**Intervention**	**Comparator**	**Outcomes**
Adults and young people (16 years and older) and children presenting with suspected haematological malignancies	Integrated diagnostic reporting via the specialist integrated haematological malignancy diagnostic services	Any other reporting	1. Time to diagnosis 2. Diagnostic accuracy 3. Staff satisfaction (e.g. De-skilling of pathologists)/ hematopathologists 4. Health related quality of life 5. Patient satisfaction
PICO Table 2			
Population	**Intervention**	**Comparator**	**Outcomes**
Adults and young people (16 years and older) and children presenting with suspected haematological	Co-located integrated diagnostic reporting Networked integrated diagnostic reporting	Each Other	1. Time to diagnosis 2. Diagnostic accuracy 3. Staff satisfaction (e.g. De-skilling of pathologists)/ hematopathologists

malignancies			4. Health related quality of life Patient satisfaction

1

2 ## Searching and Screening

Searches:	
Can we apply date limits to the search	2000 Rationale: IOG guideline (2003) supporting evidence of integrated services published since 2000
Are there any study design filters to be used (RCT, systematic review, diagnostic test).	RCT's not likely to be available Case series with one intervention or case reports will not be included due to no comparison to the reference standard/ other interventions.
List useful search terms.	None identified

3 ## Search Results

Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**
Medline	1996-Apr 2015	1591	74	14/042015
Premedline	Apr 10 2015	133	4	13/04/2015
Embase	1996-Apr 2015	3932	113	15/04/2015
Cochrane Library	Issue 4, Apr 2015	505	0	20/04/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1900-2015	3452	62	22/04/2015
HMIC	All	4	1	2004/2015
PscyInfo	1806-Apr 2015	22	1	20/04/2015
CINAHL		1118	13	28/04/2015
Joanna Briggs Institute EBP database	Current to Apr 22 2015	2	0	22/04/2015
OpenGrey		355	1	22/04/2015
HMRN (Haematological Malignancy Research		49	2	28/04/2015

Network)				
British Committee for Standards in Haematology		43	11	29/04/2015

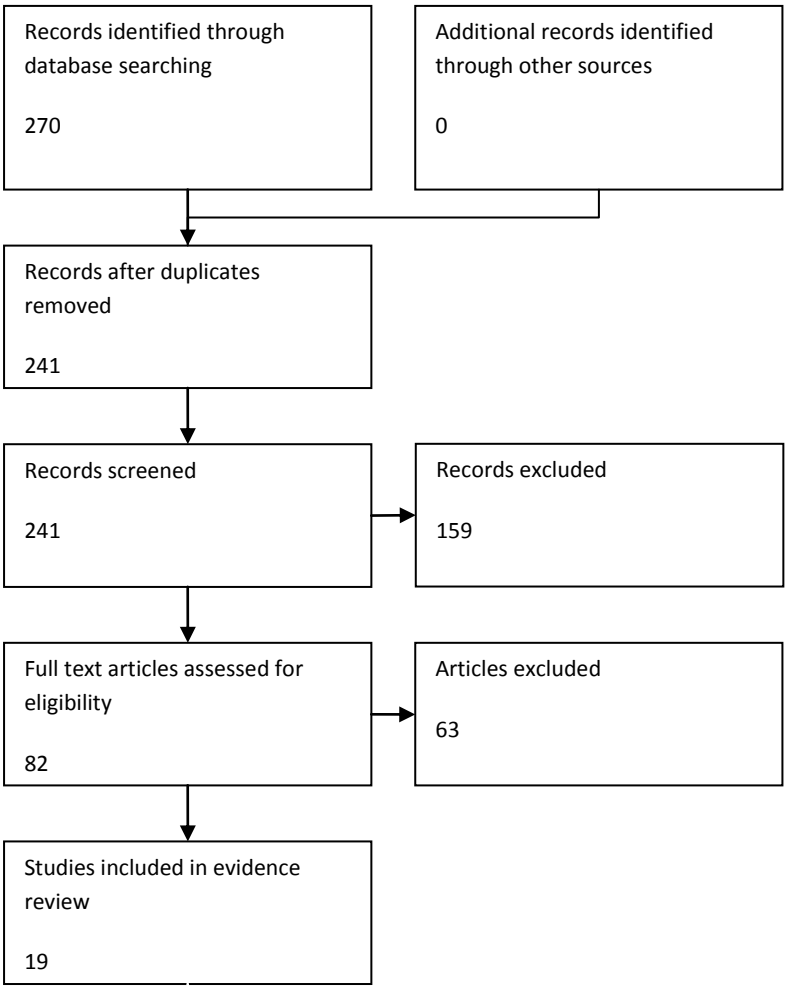
Total References retrieved (after initial sift and de-duplication): 270

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Hematologic Neoplasms/
2. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj1 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma*)).tw.
3. exp Lymphoma/
4. lymphoma*.tw.
5. (lymph* adj1 (cancer* or neopla* or oncolog* or malignan* or tumo?r*)).tw.
6. hodgkin*.tw.
7. lymphogranulomato*.tw.
8. exp Lymphoma, Non-Hodgkin/
9. (nonhodgkin* or non-hodgkin*).tw.
10. lymphosarcom*.tw.
11. reticulosarcom*.tw.
12. Burkitt Lymphoma/
13. (burkitt* adj (lymphom* or tumo?r* or cancer* or neoplas* or malign*)).tw.
14. brill-symmer*.tw.
15. Sezary Syndrome/
16. sezary.tw.
17. exp Leukemia/
18. (leuk?em* or AML or CLL or CML).tw.
19. exp Neoplasms, Plasma Cell/
20. myelom*.tw.
21. (myelo* adj (cancer* or neopla* or oncolog* or malignan* or tumo?r*)).tw.
22. kahler*.tw.
23. Plasmacytoma/
24. (plasm?cytom* or plasm?zytom*).tw.
25. (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
26. Waldenstrom Macroglobulinemia/
27. waldenstrom.tw.
28. exp Bone Marrow Diseases/
29. exp Anemia, Aplastic/
30. (aplast* adj an?em*).tw.
31. exp Myelodysplastic-Myeloproliferative Diseases/
32. exp Myeloproliferative Disorders/
33. exp Myelodysplastic Syndromes/

34. exp Thrombocytopenia/
35. (thrombocytop?eni* or thrombocyth?emi* or poly-cyth?emi* or polycyth?emi* or myelofibros or myelodysplas* or myeloproliferat* or dysmyelopoietic or haematopoetic or hematopoetic).tw.
36. exp Anemia, Refractory/
37. (refractory adj an?em*).tw.
38. (refractory adj cytop?en*).tw.
39. Monoclonal Gammopathy of Undetermined Significance/
40. (monoclonal adj gammopath*).tw.
41. (monoclonal adj immunoglobulin?emia).tw.
42. MGUS.tw.
43. ((oncohaematolog* or oncohematolog*) adj2 (disorder* or disease* or syndrome*)).tw.
44. or/1-42
45. limit 44 to yr="2000 - 2015"
46. Clinical Laboratory Services/
47. Clinical Laboratory Information Systems/
48. Diagnostic Services/
49. (laborator* adj2 (service* or report*)).tw.
50. (laborator* adj1 (integrat* or central* or co-locat* or local* or region* or district* or communit* or hospital* or network* or specialis*)).tw.
51. (diagnos* adj2 (service* or report*)).tw.
52. (diagnos* adj1 (integrat* or central* or local* or region* or district* or communit* or hospital* or network*)).tw.
53. Pathology Department, Hospital/
54. Laboratories, Hospital/
55. Diagnostic Errors/
56. (diagnos* adj discrepanc*).tw.
57. (expert review* or expert patholog* review*).tw.
58. second review.tw.
59. central* review.tw.
60. ((haematopatholog* or hematopatholog* haematolog* or hematolog* or patholog* or histopatholog* or cytopatholog*) adj2 (service* or report*)).tw.
61. ((haematopatholog* or hematopatholog* haematolog* or hematolog*or patholog* or histopatholog* or cytopatholog*) adj1 (integrat* or central* or co-locat* or local* or region* or communit* or hospital* or network* or specialis*)).tw.
62. inter-laborator*.tw.
63. SIHMDS.tw.
64. exp laboratories/
65. Hospital Information Systems/
66. or/46-65
67. 45 and 66

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=0)
Randomized controlled trial (n=0)
Prospective cross sectional study (n=0)
Case Series Studies (n=19)
Qualitative Study (n=0)

Study Quality

A short checklist of relevant questions was developed to assess the quality of the included studies and from this it was judged that the included evidence was of low quality overall as all identified studies were retrospective case series studies 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 specific haematology subtypes such as lymphoma patients included in the individual studies.

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, though it was unclear in the individual studies whether the expert pathologists were blinded to the initial diagnosis therefore there is a high risk of bias based on the potential lack 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.

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
1	**Bowen et al (2014)**	Retrospective Study	To determine the rate of revised diagnosis and subsequent impact on therapy following a second review	N=1010	Second Review Diagnosis	Primary referral diagnosis	• Diagnostic Discrepancies
2	**Chang et al (2014)**	Retrospective Study	To review the final diagnoses made by general pathologists and analyse the discrepancies between referral and review diagnosis	N=395	Expert Review	Initial Diagnosis	• Diagnostic Discrepancies
3	**Engel Nitz et al (2014)**	Retrospective Study Laboratory	To compare diagnostic changes, patterns of additional testing, treatment decisions and health care costs for patients with suspected haematological malignancies/conditions whose diagnostic tests were managed by specialty haematology laboratories and other commercial laboratories.	N=24,664 patients Genoptix N=1,387 Large Labs N=4,162 Other Controls (community hospital labs) N=19,115	Initial interim diagnosis	Final Diagnosis	• Diagnostic Uncertainty • Stability of Diagnosis
4	**Gundlapalli et al (2009)**	Survey	To address the hypotheses that clinical providers perceive composite laboratory reports to be important for the care of complex patients and that such reports can be generated using	N=10 clinical staff	Survery and interview	None	• End user survey opinions

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
			laboratory informatics methods				
5	**Herrera et al (2014)**	Retrospective Study	To evaluate the rate of diagnostic concordance between referring centre diagnoses and expert haematology review for 4 subtypes of T-cell lymphoma	N=89	Review of primary diagnosis at an NCCN centrte	Primary diagnosis at a referring centre	• Concordance
6	**Irving et al (2009)**	Report	To show that the standardised protocol has high sensitivity and technical applicability, has good concordance with the gold standard molecular based analysis and is highly reproducible between laboratories across different instrument platforms.	No details	Standardised protocol for flow cytometry	Gold standard molecular technique	• Internal and external quality assurance testing of flow minimal residue disease • Sensitivity and varibility of the standardised method • Applicability of the standardised method in prospective samples • Comparison of minimal residual disease as measured by PCR and by flow cytometry
7	**LaCasce et al (2005)**	Retrospective Study	To determine the rate of discordance for 5 common B-cell NHL diagnoses in five tertiary centres participating in a large national lymphoma database The determine whether additional information was obtained at the National Comprehensive Cancer Network (NCCN) centre To estimate the likely impact of a change in	N=928	Pathologic diagnosis from the referral centre was compared with the final WHO diagnosis at the NCCN centres Etiology of the discordance was investigated along with the potential impact	No Details	• Pathologic Discordance

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
			diagnosis on treatment		on treatment. A random sample of concordant cases (10%) were also reviewed		
8	**Lester et al (2003)**	Retospective Study	To establish the impact of the All Wales Lymphoma Panel review on clinical management decisions	N=99	Cases submitted for central review	Actual management plan received by the patient	• Change in management
9	**Matasar et al (2012)**	Retrospective Study Laboratory Setting	To test the hypothesis that increased familiarity with the WHO classification of haematological malignancies is associated with a change in frequency of major diagnostic revision at pathology review.	N=719	Diagnosis and review in 2001 using the WHO classification of haematological malignancies	Diagnosis and review in 2006 using the WHO classification of haematological malignancies	• Agreement between the submitted and review diagnosis (most recent diagnosis was considered the submitted diagnosis) • Factors associated with the rate of major diagnostic revisions
10	**Norbert-Dworzak et al (2008)**	Prospective Review	To investigate whether flow cytometric assessment of minimal residual disease can be reliably standardised for multi-centric application	N=413 patients with acute lymphoblastic leukaemia (Centre 1=110, Centre 2=88, Centre 3=61, Centre 4=154) N=395 patients with blood and bone marrow samples received at diagnosis and from follow-up during induction	Flow Cytometry according to a standard protocol	Results from each centre following standard protocol	• Qualitative Concordance of Analyses of Exchanged List-Mode Data • Quantitative Concordance of Analyses of Exchanged List-Mode Data • Concordance of Risk Estimates upon Analyses of Exchanged List-Mode Data • Reproducibility in Inter-Laboratory Sample Exchange • Agreement of MRD Results from independent patient cohorts

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
				treatment: PB at day 8, 15, 22, and 33; BM at day 15, 33 and 78).			
11	**Norgaard et al (2005)**	Retrospective Study	To examine the data quality and quantifying the impact of any misclassification of the diagnoses on the survival estimates	N=1159	Danish Cancer Registry (DCR)	North Jutland Hospital Discharge Registry	• Degree of completeness • Positive Predictive Value • Survival
12	**Proctor et al (2011)**	Retrospective Study	A large scale assessment of expert central review in a UK regional cancer network and the impact of discordant diagnoses on patient management as well as the financial and educational implications of providing a centralised service.	N=1949	Expert Review	Initial Diagnosis	• Concordance
13	**Rane et al (2014)**	Retrospective Study	To evaluate the ability and interobserver variability of pathologists with varying levels of experience and with an interest in lymphomas to diagnose Burkitt Lymphoma in a resource limited set up.	N=25	Consensus Diagnosis	Initial Independent Assessment	• Initial Independent Assessment • Interobserver variation in morphological features • Parameters used to differentiate between classic CL, atypical BL and B-cell lymphoma intermediate between Burkitt's and DLBL • Consensus Diagnosis • Concordance with consensus diagnosis • Effect of tissue fixation, age group and provision of additional information on revision of diagnoses

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
							• Accuracy of pathologists • Sensitivity and Specificity to diagnose Burkitt Lymphoma
14	**Siebert et al (2001)**	Retropsective Study	To compare diagnoses made at a community and an academic centre to evaluate the reproducibility of the revised European-American Classification	N=188	Review of community hospital assessments at an academic centre	lymphoid neoplasms subtyped according to revised European-American classification criteria at a community hospital	• Concordance
15	**Stevens et al (2012)**	Retrospective Study	To observe concordance and discrepancies between local findings and the specialist opinion.	N=125	Central Review	Regional/Community Hospital Review	• Pathology • Staging • Therapy
16	**Strobbe et al (2014)**	Retrospective Study	To investigate whether implementation of an expert panel led to better quality of initial diagnoses by comparing the rate of discordant diagnoses after the panel was established compared with discordance rate 5 years later To evaluate whether lymphoma types with high discordance rate could be identified	N=161 referred to the expert panel N=183 reviewed at a later date	Expert Panel review	Initial Diagnosis	• Discordance rate in 2000-2001 • Discordance rate in 2005-2006

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
17	**Van Blerk et al (2003)**	Retrospective Study	To report first experiences from Belgian national external quality assessment scheme (EQAS)	N=17	External quality assessment review	N/A	• Stability • Intralaboratory reproducibility • Homogeneity • Interlaboratory reproducibility • Single vs. Dual Platform • Influence of Gating strategy • CD4+,CD3+ and CD8+CD3+ cells versus total CD4 and CD8 cells • Abnormal Samples
18	**Van de Schans et al (2013)**	Retrospective Study	To evaluate the value of an expert pathology panel and report discordance rates between the diagnosis of initial pathologists and the expert panel and the effect on survival	N=344	Expert review of diagnosis	Initial Diagnosis	• Discordance Rate
19	**Zhang et al (2007)**	Retrospective Study	To compare similarities and differences in results from participating laboratories and to identify variables which could potentially affect test results to discern variables important in test standardisation	N=38 laboratories	Quantitative testing for BCR-ABL1	Results from different participating laboratories	• Test accuracy at different dilutions

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 expert review ranged from 6%-60%. Revision of one type of lymphoma to another type was the most common source of discordance ,ranging from 6.5%-23% (2 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 rate of discordance between an initial diagnosis and review diagnosis ranging from 17.8% to 55%.

Low quality evidence from one retrospective study (Engel-Nitz et al, 2014) which compared diagnostic outcomes between specialist haematology laboratories and other commercial laboratories and 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). It reported the overall data completeness was 91.5% [95% CI, 89.6%-93.1%] and that 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 compared to those with 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) reported a poor rate of concordance between the pathologists for independent diagnosis (κ0.168, SE±0.018) and a direct correlation between level of experience and diagnosis.Expert lymphoma pathologists showed marginally higher concordance rates and general pathologists the lowest (κ0.373 versus κ0.138). For consensus diagnosis the level of agreement between pathologists for revised diagnosis was very high (κ0.835, SE±0.021) and revision of diagnosis was highest among general pathologists. The concordance of independent diagnosis and consensus diagnosis was low (κ=0.259, SE±0.039; median=0.207; range=0.131-0.667) and increased with increasing experience of diagnosing lymphoma.

Low quality evidence from a retrospective study including 25 cases of Burkitt Lymphoma reviewed by 10 pathologists (Rane et al) reported 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).

Low quality evidence from two retrospective studies (Matasar et al 2012 and Strobbe et al, 2014) showed that the rates of discordance between initial and review diagnoses were found to have dropped between 2001 and 2005, but with 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 and Strobbe et al, 2014 reported a drop in discordance rate of lymphoma diagnoses from 14% to 9% (p=0.06) following the setting 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.

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Evidence Tables

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td colspan="6">Bowen et al (2014) USA</td></tr>
<tr>
<td>Retrospective Study

Laboratory Setting

January 2009 – December 2010</td>
<td>To determine the rate of revised diagnosis and subsequent impact on therapy following a second review</td>
<td>N=1010

N=683 (67.6%) mandatory reviews
N=327 (32.4%) outside consultations

N=142 (14%) referred from academic centres
N=868 (86%) referred from non-academic centres

Exclusions
Myeloid neoplasms
Acute lymphoblastic leukaemia
Plasma cell myeloma
Staging bone marrows for non-haematological malignancies
Cases sent without a primary diagnosis

Inclusions
Lymph Nodes and extranodal tissues that were reactive or benign</td>
<td>Second Review Diagnosis</td>
<td>Primary referral diagnosis</td>
<td>Diagnostic Discrepancies

• Second review resulted in no change to diagnosis in 83% of cases
• In 17% of cases second review resulted in a changed or modified diagnosis
  ○ 14.8% were considered major discrepancies and 12.9% resulted in significant changes to therapy
  ○ 2.2% were considered minor discrepancies and so were grouped with the agreement cases
• Overall agreement was 85.2% when considering only major discrepancies
• The largest category of discrepant cases was one in which diagnosis was revised from one type of lymphoma to another (6.5%) with change from one type of B-NHL to another B-NHL being the most common revision within this group (4.3%)
• 3% of grading discrepancies occurred in Follicular Lymphoma with most diagnoses changing from low grade to high grade on second review
• 2.8% of discrepancies occurred in benign entities originally diagnosed as lymphoma or vice versa.
• Imprecise or unclear diagnoses occurred in 2.1% of discordant cases
• There was a significantly higher rate of discordance in diagnoses from non-academic centres compared with academic centres (15.8% versus 8.5%, p=0.022)
• There were similar rates of discordance between referral cases and consultation cases (15% versus 13.5%, p=0.42)
• Excision biopsies (61.9%) had a significantly higher rate of discordance compared to other biopsy types (needle core, punch biopsy, shave biopsy) (17.9% versus 9.6%, p=0.0003)
• Biopsy site (lymph nodes (52.1%), bone marrow (14.3%), soft tissue (8.5%), gastrointestinal tract (6.3%), skin (5.8%)) was not a significant factor affecting disagreement rate (p=0.20).
• Cases requiring additional investigative studies (51.5%) had a significantly higher rate of revised diagnosis compared to ones not requiring additional studies (20.6% versus 8.6%, p<0.0001).

Comments
Cases were divided into two groups – ‘mandatory reviews’ and ‘outside consultations’

Mandatory Reviews: patient referral to NLSG for clinical management

Outside Consultation: pathology slides and materials sent for a second opinion

Quality Assessment
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Low Risk of Bias</td></tr>
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</table>
</td></tr>
<tr><td colspan="6">Chang et al (2014)</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

2003-2011</td><td>To review the final diagnoses made by general pathologists and analyse the discrepancies between referral and review diagnosis</td><td>N=395 (406 specimens)

Cases transferred for treatment or for second opinion were excluded</td><td>Expert Review</td><td>Initial Diagnosis</td><td>Diagnostic Discrepancies

• Turnaround time was 2.3 days (0-19 days)
• 95% of cases sent for review were haematological cases and 5% were non-haematological lesions
• Pathology review resulted in major revisions in 55% of cases, minor revisions in 5% of cases and insignificant revision or agreement in 40% of cases
• The major discrepancy category (52%) was the most common group consisted of ambiguous and non-diagnostic reports and the more common lymphoma types were diffuse large B cell lymphoma, marginal zone lymphoma and follicular lymphoma
• In Group 2, the revision of lymphoma typing (23%), the most common entities were diffuse large B cell lymphoma, Hodgkin Lymphoma and plasmacytoma/myeloma
• Group 3 represented cases from malignant to benign diagnosis (n=32, 14.4%)
• Group 4 was the easily missed lymphomas (4%), group 5 consisted of haematologic tumours revised as non-haematologic tumours (5%) and group 6 was non-lymphoma tumours revised as lymphomas (1%)
• Review diagnosis results in 259 cases of lymphoma (72% B-cell and Hodgkin lymphoma, 28% T/natural killer cell lymphomas)
• Comparison between referral and review diagnosis showed a lymphoma concordance rate of 39% (101/259) in total, 41% (77/187) for B cell lymphoma and 33% (24/72) for T/NK cell lymphomas respectively.

Comment
Major discrepancies – those that would alter management

Minor discrepancies – those that would not fundamentally alter management although a different diagnosis was given

Non-diagnostic reports – diagnosis not given by referral diagnosis

Ambiguous original reports – diagnosis not sufficiently specific to generate a treatment plan</td></tr>
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<tr><td colspan="6">Engel Nitz et al (2014) USA</td></tr>
<tr>
<td>Retrospective Study

Laboratory Setting

July 2005 – June 2011</td>
<td>To compare diagnostic changes, patterns of additional testing, treatment decisions and health care costs for patients with suspected haematological malignancies/conditions whose diagnostic tests were managed by specialty haematology laboratories and other commercial laboratories.</td>
<td>Initial laboratory population N=34,904 – patients with non-haematological cancer or any other non-haematological condition on bone marrow biopsy claims were excluded from analysis.

N=24,664 patients

Genoptix N=1,387
Large Labs N=4,162
Other Controls (community hospital labs) N=19,115

Academic labs that sponsor haematopathology fellowships were excluded due to the likelihood of a higher percentage of referral cases.

Patients with suspected haematological malignancies/conditions who had a bone marrow procedure (biopsy/aspirate) INDEX DATE

Patients were grouped according to diagnosis – Myelodysplastic Syndrome, myeloproliferative neoplasm, Chronic</td>
<td>Initial interim diagnosis (based on date of first non-laboratory claim with a diagnosis of haematological malignancy/disease in the primary position at least 3 days after and <1 year post-index date

Laboratory tests in the 30 days post biopsy were identified</td>
<td>Final Diagnosis</td>
<td>

Diagnostic Uncertainty following initial diagnostic uncertainty (using 2 definitions comparing haematological diagnosis between initial interim and final diagnoses)
Stability of Diagnosis (at least 1 haematological condition that was the same between the two time points, excluding disease progression or haematological signs/symptoms)
Number of tests performed
Repeat bone marrow studies
Time to final diagnosis
Changes in chemotherapy in the 60 days post-biopsy
Testing Costs
All cause health care costs

Baseline Characteristics

Patients in other laboratories were younger compared with Genoptix and Large lab patients (p<0.001) and were more likely to be enrolled in Medicare advantage plans (p<0.001)
Genoptix patients were more likely to be located in the south
Patients in the ‘other laboratory’ cohort were more likely to have had chemotherapy or radiotherapy.

Diagnostic Characteristics

Patients in the Genoptix cohort were more likely to undergo more complex diagnostic testing during the initial 30 day testing period.
Patients in the other lab cohort were less likely to undergo complex diagnostic testing and when done, these tests were more likely to be performed at a different lab type.

<table>
<tr><th></th><th>Cytogenetics/FISH</th><th>Molecular Diagnostics</th></tr>
<tr><td>Genoptix</td><td>95.96%</td><td>26.03%</td></tr>
<tr><td>Large laboratory</td><td>80.78%</td><td>14.27%</td></tr>
<tr><td>Other laboratory</td><td>51.68%</td><td>9.31%</td></tr>
</table>

The number of tests varied across the 1 year follow-up period though the majority of patients received 1 bone marrow biopsy
The large lab cohort had the fewest total test and average time to final diagnosis ranged from 36 days for Genoptix to 41 days for the other lab cohort.
Median time to final diagnosis was roughly 2 weeks. The Cox proportional hazard ratio of reaching a final diagnosis by any point in the initial 30 days testing period were 1.002 (p=0.0029) for the Genoptix Cohort and 0.95 (p=0.0002) for the large lab cohort (other lab cohort as the reference group).
At any point in the 30 day testing period, the Genoptix cohort had a 23% higher hazard of having reached a final diagnosis compared with the other lab cohort (HR=1.23, p=0.0007) and the large lab cohort had a 10% higher hazard (HR=1.10, p=0.005) compared with the other lab cohort.
Fewer patients in the Genoptix cohort underwent repeat marrow biopsies, with difference remaining after adjustment for type of haematological malignancy and other characteristics

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<tr><td></td><td></td><td>Lymphoid Leukaemia, non-Hodgkin lymphoma, multiple myeloma, other haematological cancer, non-cancer haematological condition</td><td></td><td></td><td>
<table>
<tr><th></th><th>Repeat Marrow Biopsy</th><th>Odds Ratio</th><th>P value</th></tr>
<tr><td>Genoptix</td><td>9.59%</td><td>0.307 (0.255-0.371)</td><td>P<0.001</td></tr>
<tr><td>Large laboratory</td><td>17.11%</td><td>0.563 (0.514-0.617)</td><td>P<0.001</td></tr>
<tr><td>Other laboratory</td><td>28.16%</td><td colspan="2">Reference Group</td></tr>
</table>
Stability of initial diagnosis varied across the cohorts
<table>
<tr><th></th><th>Unstable Diagnoses</th><th>Odds Ratio</th><th>P value</th></tr>
<tr><td>Genoptix</td><td>6.16%</td><td>0.87 (0.68-1.10)</td><td>0.2427</td></tr>
<tr><td>Large laboratory</td><td>8.04%</td><td>0.99 (0.87-1.13)</td><td>0.9014</td></tr>
<tr><td>Other laboratory</td><td>9.73%</td><td colspan="2">Reference Group</td></tr>
</table>
The percentage of diagnoses changes was lower in the Geneoptix cohort
<table>
<tr><th></th><th>Change in Diagnosis</th><th>Odds Ratio</th><th>P Value</th></tr>
<tr><td>Genoptix</td><td>7.88%</td><td>0.82 (0.72-0.94)</td><td>0.004</td></tr>
<tr><td>Large laboratory</td><td>11.19%</td><td>0.94 (0.87-1.02)</td><td>0.1256</td></tr>
<tr><td>Other laboratory</td><td>14.08%</td><td colspan="2">Reference Group</td></tr>
</table>
Comments
Length of follow up: First appearance was followed up for 1 year post index date

Genoptix - a specialised haematopathology lab which designed a specific diagnostic workflow to address the main concerns associated with diagnostic testing in the community oncology setting (tests ordered, sampling error, and interpretation/integration errors).
</td></tr>
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Low Risk of Bias</td></tr>
<tr><td>Diagnostic service models – are they comparable to what is in the PICO?</td><td>Unclear - there was not enough information reported in the study to determine whether the comparisons were those outlined in the PICO. Personal communication from the author provided more detail which suggested that the comparisons were more closely matched to those of interest than was first though, however some of the additional information provided also suggested there were some differences between the comparisons which meant that this study did not completely address the PICO.</td></tr>
<tr><td>Reference standard tests – did all patients receive the same tests to get the definitive diagnosis.</td><td>Unclear

Unclear risk of Bias</td></tr>
<tr><td>Blinding – are expert pathologists blinded to the initial diagnosis information</td><td>No

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<tr><td>Health care setting – is it applicable to the UK?</td><td>Unclear

Unclear Risk of Bias</td></tr>
</table></td></tr>
<tr><td colspan="6">Gundlapalli et al (2009) USA</td></tr>
<tr><td>Survey</td><td>To address the hypotheses that clinical providers perceive composite laboratory reports to be important for the care of complex</td><td>N=10 clinical staff

Clinical staff involved in the Myeloma program and who routinely accessed the patient labs</td><td>Survery and interview</td><td>None</td><td>End User Survey
• Team members spent an average of 18 minutes per patient gathering lab data and an average of 4 minutes per patients on protein immunology labs.
• 6/10 responders reported being familiar with or having used the ‘trend’ or ‘graph’ feature of the EMR to view serial labs with numeric results
• All providers reported accessing free text reports of serum protein electrophoresis and immune fixation electrophoresis because it was the only way to identify the presence of a myeloma protein, its type and quantitation.</td></tr>
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<tr><td></td><td>patients and that such reports can be generated using laboratory informatics methods</td><td>Average experience was 9 years (range 1-30 years)

All accessed the electronic medical record multiple times per day with the laboratory results screen the most accessed tab.</td><td></td><td></td><td>

7/10 reported accessing and viewing pdf files of actual gels
All 10 reported they would be in favour of a single report with the ability to view serial changes in key myeloma biomarkers
8/10 were willing to collaborate with informatics teams to work up an ideal composite report and were willing to participate in a validation study.
All 10 supported the idea of providing a composite report directly to the patient.
The primary elements identified were that access to and downloading of disparate protein immunology lab data and free text interpretations were challenging and time consuming and the provision of a composite report would be beneficial to patient care and improve work flow.

Data Flow of Laboratory Orders and Results

During 2007, a total of 4699 protein immunology tests were performed on 1450 unique patients, these tests are performed multiple times on accessing and correlation of even the last 3 results of tests reported in free text poses a challenge

Comments:

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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
Herrera et al (2014) USA					
Retrospective Study Laboratory Setting April 2007-June 2012	To evaluate the rate of diagnostic concordance between referring centre diagnoses and expert haematology review for 4 subtypes of T-cell lymphoma	N=89 *Inclusion* Documented pathologic review at a referring centre before expert haematology review Final diagnosis of 1 of the following 4 TCL WHO subtypes; PTCL-NOS, AITL, ALK negative ALCL and ALK positive ALCL *Exclusion* Primary presentation to an NCCN centre so no referring pathology Incomplete or insufficient data for analysis	Review of primary diagnosis at an NCCN centrte	Primary diagnosis at a referring centre	*Concordance between diagnoses* • Overall concordance rate was 44% (n=57 patients with concordant results) and the discordant rate was 24% (n=32 patients with discordant results). • 32% of patients (n=42) were referred for a second opinion with additional biopsy or further work-up suggested • Rates of pathologic discordance were 19% for PTCL-NOS, 33% for AITL, 34% for ALK negative ALCL and 6% for ALK positive ALCL • Discordance rates among patients referred for a second opinion with final diagnosis were 38% for PTCL-NOS, 50% for AITL, 38% for ALK negative ALCL and 7% for ALK positive ALCL • 47% (15/32) of patients were reclassified based on a different interpretation of available data or noncontributary additional studies • 53% (17/32) of patients with discordant results had additional studies performed at the NCCN centre which led to a different diagnosis. • 86% (n=112) of patients had an excision biopsy sample submitted for review by an NCCN centre and no association was observed between biopsy type and pathologic concordance among patients referred with a final diagnosis (p=0.18) or between biopsy type and whether a final diagnosis was rendered at the referring centre (p=0.09). • Additional testing was performed at the referring centre before second opinion referral in 95% of cases (IHC stains=84%; flow cytometry=52%; TCR gene rearrangement testing=36% and FISH=6%). There was no association between pathologic concordance or discordance and the type of additional tests performed (IHC p=0.66, flow cytometry p =0.83, TCR gene rearrangement testing p = 0.5, IHC+flow cytometry p=0.825, IHC+flow cytometry+TCR testing p=0.6). • Additional testing performed in at the NCCN centre included IHC stains (53%), flow cytometry (18%), TCR gene rearrangement (18%) and FISH (6%). • Median number of IHC stains performed at the NCCN centres was 2 (range 0-29) compared with 11 (range 0-35) at the referring centres • Median duration of time spent reviewing a case at the NCCN centre was 5 days (range 1-34 days) • 72% of cases were reviewed by a single pathologist and 28% were referred for intradepartmental consulation compared with 76% and 24% at the referring centres. ***Comments*** Pathological concordance was defined as the same pathological diagnosis at both the referring centre and the NCCN centre when considering all supporting documentation including pathology reports, immunohistochemistry, flow cytometry, fluorescence in-situ hybridization and cytogenetics, T-cell gene rearrangement studies and physician progress notes Review of records was carried out by 3 of the authors to determine concordance

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<tr><td colspan="6">Irving et al (2009) UK</td></tr>
<tr><td>Report

Laboratory Setting</td><td>To show that the standardised protocol has high sensitivity and technical applicability, has good concordance with the gold standard molecular based analysis and is highly reproducible between laboratories across different instrument platforms.</td><td>No details</td><td>Standardised protocol for flow cytometry</td><td>Gold standard molecular technique</td><td>Internal and External quality assurance testing of Flow minimal residual disease
• QA testing consisted of mock MRD sample posted to all 6 network laboratories for analysis and interpretation (n=15 samples prepared by laboratories within the network using fresh material and n=6 provided by the UK National External Quality Assessment Scheme using mock samples prepared with fixed, stabilised material)
• List mode data files of MRD samples acquired in one centre were analysed by all network laboratories to assess gating strategies (n=2)
• Gives a total of 23 quality assessment exercises with 42 separate LAIP analyses

• Interlaboratory correlation coefficient ranged from 0.97 to 0.99
• Interlaboratory agreement on risk category compared to the consensus risk was 100% for 4 laboratories, 90% for one lab and 80% for one lab. One discordant example was attributed to inappropriate gating which was subsequently standardised during group workshops.

Sensitivity and variability of the standardised method
• Sensitivity of the assay was assessed by spiking leukaemic blasts with a known LAIP into normal bone marrow and preparing serial dilutions down to 0.01%. a sensitivity of 0,01% was confirmed for all LAIP combinations tested (CD38, CD45, CD58 and CD66c).
• Interassay variability was assessed using mock MRD replicates analysed using 2 different cytometers. The coefficient variation ranged from 2.2%-4.1%, 3.14%-5.47% and 10.21%-13.13% for 10%, 0.5% and 0.05% MRD mocks respectively.</td></tr>
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Applicability of the standardised method in prospective samples
• 182/206 patients with diagnostic precursor B-lineage ALL had 2 or more sensitive LAIPs for an applicability of 88.3%
• 45/182 (24.7%) of patients were classified high risk at day 28.

Comparison of minimal residual disease as measured by PCR and by flow cytometry
• MRD quantification of bone marrow aspirates was performed by both PCR and flow cytometry in 134 children.
• 90 samples were low risk by both methods, 25 were high risk by both methods, 8 were high risk by flow cytometry but low risk by molecular and 11 were low risk by flow and high risk by molecular.
• Excluding the 90 cases below the threshold of both methods, the percentage of cases in which logPCR and log Flow MRD were within half a log was 47.6% and within one log was 76.2%.
• The risk category concordance was 79% at day 28 and 100% at week 11 for a combined figure of 86%
• In the 25 high risk samples, correlation was high (r=0.76).
• The majority of the discordant samples were around the threshold level and in 8 sample, MRD was detectable by both techniques but did not attain the 0.01% level in both assays.

Comments:

Quality Assessment

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<tr><td>Health care setting – is it applicable to the UK?</td><td>Yes (UK study)

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<tr><td colspan="6">LaCasce et al (2005) USA</td></tr>
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<tr>
<td>Retrospective Study

Laboratory Setting

July 1, 200 and December 31, 2004</td>
<td>To determine the rate of discordance for 5 common B-cell NHL diagnoses in five tertiary centres participating in a large national lymphoma database
The determine whether additional information was obtained at the National Comprehensive Cancer Network (NCCN) centre
To estimate the likely impact of a change in diagnosis on treatment</td>
<td>N=928 patients presented with newly diagnosed NHL

N=731 referred from other centres and had a documented pathologic diagnosis of one of 10 NHL subtypes before presentation at the NCCN

N=66 patients for whom the referring diagnosis and the NCCN diagnosis were discordant

Patients with newly diagnosed NHL (≤90 days from diagnostic biopsy date to first NCCN presentation)
Documented pathologic diagnosis assessed at a referral centre
Final diagnosis of follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Mantle cell lymphoma (MCL), small lymphatic lymphoma (SLL), nodal marginal zone lymphoma (NMZ), extranodal marginal zone lymphoma (EMZ) or splenic marginal zone lymphoma (SMZ)</td>
<td>Pathologic diagnosis from the referral centre was compared with the final WHO diagnosis at the NCCN centres

Etiology of the discordance was investigated along with the potential impact on treatment.

A random sample of concordant cases (10%) were also reviewed</td>
<td>No Details</td>
<td>
Discordance Rates
42/66 patients were considered truly discordant after central and site review and 1 additional pathologically discordant case was identified among the sample of concordant cases reviewed and was included in the analysis

• Overall pathologic discordance rate was 6% (95% 4%-8%)
• Pathologic concordance was highest for DLBCL, FL and MZL
• Final diagnosis with the highest proportion of pathologic discordance was FL3 (13%) though the total number of cases was small (=32)
• Reasons for a change in pathologic diagnosis included: preliminary diagnosis with further evaluation recommended (n=4), different interpretation of the existing data (n=19), one or more additional biopsies performed (n=9), other studies including immunoperoxidasae stains were performed (n=11).
• Treatment category discordance occurred in 5% (95% CI 3%-7%) of cases overall and in 81% (35/43) patients in whom pathology was discordant.
• 2% of patients with DLBCL were assigned a pathological diagnosis at the referral centre which resulted in less aggressive treatment thus missing a chance for cure
• All patients who with FL3 who were pathologically discordant were also treatment discordant with original diagnosis classified as indolent.
• Fine needle aspiration and core biopsy accounted for 9% (n=68) and 19% (n=142) of initial biopsies at referral sites with no statistically significant difference in concordance between those who had FNA or core biopsy or other biopsy types (94%, 93% and 94% respectively, p=0.76)
• Proportions of nodal and extra nodal referrals were 61% (n=473) and 34% (n=258) respectively and there was no statistically significant difference in concordance between nodal and extranodal referral specimen (94% versus 95%, p=0.47)
60% (n=437) of cases had ancillary testing prior to presentation at NCCN but there was no statistically significant difference in concordance between referral specimens with and without ancillary testing (95% versus 93%, p=0.24).
Comments:

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Lester et al (2003)					
Retospective Study Laboratory Setting	To establish the impact of the All Wales Lymphoma Panel review on clinical management decisions	N=99 cases for whom submitted diagnosis was changed as a result of central pathological review	Cases submitted for central review Hypothetical management plan created within MDT using the original submitted diagnosis and other patient information Each patient was presented and discussed as if a new referral and MDT members were not told that the cases used the original diagnoses to minimise bias	Actual management plan received by the patient	*Change in management* • 46/99 (46%) had a change in management as a result of central pathological review • 37/99 (37%) had a submitted diagnosis of a specific non-Hodgkin lymphoma entity reclassified to another NHL entity on review but of these only 6 (16%) resulted in a change in management. • 29/99 (29%) of cases resulted in a change in diagnosis from lymphoma to reactive lymphadenitis and 18/29 (62%) had a change in management as a result. • 13/99 (13%) of original reactive lymphadenitis diagnoses were reclassified as a specific lymphoma entity on review and 10/13 had a change in management as a result. • 7/99 (7%) of cases had a submitted diagnosis of Hodgkin's lymphoma reclassified to a specific NHL entity on review resulting in a change in management for 6/7 cases. • 6/99 (6%) cases with a submitted diagnosis of a specific NHL entity were reclassified to Hodgkin's lymphoma on review resulting in a change in management for 3/6 patients. • In 6/99 (6%) of cases a submitted lymphoma entity diagnosis was reclassified to another non-haematological malignancy on review and resulted in a change in management in 2 cases. • 1/99 (1%) case was reclassified from another specific non-haematological malignancy to a specific lymphoma entity and resulted in a change in management. *Treatment to No Treatment* • 43% of management changes resulted in a 'treatment to no treatment' decision • 22% of management changes resulted in a 'no treatment to treatment' decision with patients receiving oncological treatment in 9/10 cases. • 35% (n=16) patients had a 'change in oncological treatment' as a result of review, with 13/16 patients receiving a change in chemotherapy regimen. Specialist central pathological review impacted on patient management in three key areas: • Inappropriate oncological treatment • Unnecessary oncological treatment • Delay in oncological treatment *Comment* A change in management was diagnosed as: • Treatment to no treatment • No treatment to treatment • Change in oncological treatment

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Low Risk of Bias</td></tr>
</table>
</td></tr>
<tr><td colspan="6">Matasar et al (2012)</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

1 January 2001 to 30 June 2001 and 1 January 2006-30 June 2006</td><td>To test the hypothesis that increased familiarity with the WHO classification of haematological malignancies is associated with a change in frequency of major diagnostic revision at pathology review.</td><td>N=719

Jan 2001-June 2001 N=365
Jan 2006-June 2006 N=354

There was a predominance of white, non-Hispanics and a younger median age when compared with population-based statistics (SEER)</td><td>Diagnosis and review in 2001 using the WHO classification of haematologic al malignancies</td><td>Diagnosis and review in 2006 using the WHO classification of haematological malignancies</td><td>• Agreement between the submitted and review diagnosis (most recent diagnosis was considered the submitted diagnosis)
• Factors associated with the rate of major diagnostic revisions

Agreement between the submitted and review diagnosis (most recent diagnosis was considered the submitted diagnsosis)
Agreement
Minor Discrepancy (would result in a different diagnosis but would not alter management according to NCCN guidelines)
Major Discrepancy (those that would alter management according to guidelines published by the NCCN)

Factors associated with the rate of major diagnostic revisions
Available patient demographic data (age, gender, race and ethnicity)
Clinical features (original diagnosis, type of biopsy, site of biopsy, immunohistochemistry reviewed or carried out at MSKCC, additional biopsy, type of referring lab)

Pathology review resulted in a major revision in 17.8% of cases in 2001 and in 16.4% of cases in 2006 (p=0.6)</td></tr>
</table>

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<tr><td></td><td></td><td>Hodgkin lymphoma was over represented in comparison with population based statistics
T-cell lymphomas increased from 2001 to 2006 which was temporally associated with the development of a focused T-cell lymphoma program giving an imbalance in the distribution of referring diagnoses between the two time periods (p=0.007).</td><td></td><td></td><td>
<table>
<tr><th>Diagnostic Revision</th><th>2001(n=365)</th><th>2006 (n=355)</th><th></th></tr>
<tr><th></th><th>N (%)</th><th>N (%)</th><th>P</th></tr>
<tr><td>Major Diagnostic Revision</td><td></td><td></td><td></td></tr>
<tr><td>MSKCC or other NCI-CCC secondary review</td><td>78 (21.4)</td><td>66 (18.6)</td><td>0.35</td></tr>
<tr><td>MSKCC revision of submitted diagnosis</td><td>65 (17.8)</td><td>58 (16.4)</td><td>0.60</td></tr>
<tr><td>Prior NCI-CCC revision (MSKCC confirmed)</td><td>13 (3.6)</td><td>8 (2.3)</td><td></td></tr>
<tr><td>Minor Diagnostic Revision</td><td></td><td></td><td></td></tr>
<tr><td>MSKCC or other NCI-CCC secondary review</td><td>24 (6.6)</td><td>31 (8.7)</td><td></td></tr>
<tr><td>MSKCC revision of submitted diagnosis</td><td>24 (6.6)</td><td>31 (8.7)</td><td></td></tr>
<tr><td>Prior NCI-CCC revision (MSKCC confirmed)</td><td>0 (0)</td><td>0 (0)</td><td></td></tr>
<tr><td>No Diagnostic Revision</td><td>263 (72.1)</td><td>258 (72.7)</td><td></td></tr>
</table>
<table>
<tr><th>Original Diagnosis</th><th>Revised Diagnosis</th><th>2001, number revised (% of original)</th><th>2006 number revised (% of original)</th></tr>
<tr><td>Benign</td><td>Lymphoma (any)</td><td>3/6 (50)</td><td>1/5 (20)</td></tr>
<tr><td>Lymphoma (any)</td><td>Benign</td><td>1/330 (0.3)</td><td>6/333 (2)</td></tr>
<tr><td>Non-diagnostic/ambiguous</td><td>Diagnostic/definitive</td><td>26/72 (36)</td><td>25/46 (54)</td></tr>
<tr><td>Diagnostic/definitive</td><td>Non-diagnostic/definitive</td><td>13/260 (5)</td><td>12/310 (4)</td></tr>
<tr><td>HL</td><td>NHL</td><td>3/72 (4)</td><td>2/57 (4)</td></tr>
<tr><td>NHL</td><td>HL</td><td>1/251 (0.4)</td><td>1/275 (0.3)</td></tr>
<tr><td>Classical HL</td><td>Nodular Lymphocyte Predominant Hodgkin Lymphoma</td><td>1/69 (1)</td><td>1/51 (2)</td></tr>
<tr><td>T-cell neoplasm</td><td>B-cell neoplasm</td><td>3/22 (14)</td><td>2/43 (5)</td></tr>
<tr><td>Highly aggressive B-cell neoplasm</td><td>Aggressive B-cell neoplasm</td><td>2/5 (40)</td><td>3/7 (43)</td></tr>
<tr><td>Aggressive B-cell neoplasm</td><td>Highly aggressive B-cell neoplasm</td><td>3/92 (6)</td><td>0/93 (0)</td></tr>
<tr><td>Aggressive B-cell neoplasm</td><td>Indolent B-cell neoplasm</td><td>6/92 (6)</td><td>3/93 (3)</td></tr>
</table>
</td></tr>
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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results

Indolent B-cell neoplasm	Aggressive B-cell neoplasm	16/118 (14)	8/118 (7)
Highly aggressive B-cell neoplasm	Highly aggressive B-cell neoplasm	0/5 (0)	1/7 (14)
Aggressive B-cell neoplasm	Aggressive B-cell neoplasm	0/92 (0)	1/93 (1)

Multivariate analysis of relationship between clinical features and major diagnostic revision

Clinical Feature	Adjusted Odds Ratio (95% CI)	Adjusted P value
Biopsy site		
Lymph node	1	0.27
Skin	1.44 (0.76-2.75)	
Other	0.73 (0.44-1.19)	
IHC carried out at MSKCC		
No	1	0.04
Yes	1.58 (1.03-2.41)	
Referring Diagnosis		
B-cell neoplasms	1	
T-cell neoplasms	1.50 (0.76-2.94)	<0.001
Non diagnostic	2.24 (1.11-4.55)	0.03
Hodgkin Lymphoma	0.37 (0.17-0.78)	0.009
Rare Diagnosis	3.52 (1.37-9.09)	0.009
Year of Pathology Review		
2001	1	
2006	0.84 (0.56-1.26)	0.4

Comment:

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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
Norbert-Dworzak et al (2008) Europe (Germany, Italy, Austria)					
Prospective Review Laboratory Setting	To investigate whether flow cytometric assessment of minimal residual disease can be reliably standardised for multi-centric application	N=413 patients with acute lymphoblastic leukaemia (Centre 1=110, Centre 2=88, Centre 3=61, Centre 4=154) N=395 patients with blood and bone marrow samples received at diagnosis and from follow-up during induction treatment: PB at day 8, 15, 22, and 33; BM at day 15, 33 and 78). List Mode Data Exchange N=31 patients were selected for comparisons between centres with a total of 202 samples from 7 time points submitted to all centres for blinded LMD file interpretation.	Flow Cytometry according to a standardised process which included: Standardised SOPs for sample preparation and staining Standardisation of monoclonal antibodies for manufacturer, clone and partly for flurochrome Monoclonal antibodies were strategically assorted to fixed quadruple combinations of those markers which have been proven highest relevance for MRD studies in ALL Quality Control Immunophenotyping at diagnosis	Results from each centre following standard protocol	• Qualitative Concordance of Analyses of Exchanged List-Mode Data • Quantitative Concordance of Analyses of Exchanged List-Mode Data • Concordance of Risk Estimates upon Analyses of Exchanged List-Mode Data • Reproducibility in Inter-Laboratory Sample Exchange • Agreement of MRD Results from independent patient cohorts ***Qualitative Concordance of Analyses of Exchanged List-Mode Data*** • 106/202 (53%) submitted samples were classified as MRD positive and 96 as negative • Observed versus expected agreement was 89%, 97%, 93% and 96% for each of the centres • All four of the centres agreed on MRD status of samples in 76% of cases overall and in 78% of MRD positive and 73% of MRD negative samples. • There was no significant difference between sample series1 (n=15 patients recruited in early 2002) and series 2 (n=16 patients recruited in late 2003). • Agreement by at least 3 of the centres was found in 96% of the total sample cohort • Reasons for discordance included disturbance by normal lymphoid regeneration (n=3) MRD at the limits of detection (n=2) and technical flaws (n=3). • Agreement was best in bone marrow samples from day 15 (86% by four centres) and day 78 (81%). Samples from day 33 had lowest agreement (52%). 3 centres agreed in 100%, 96% and 84% of cases respectively • In analysing peripheral blood samples from days 0, 8, 15 and 33 there was complete agreement between centres in 100%, 83%, 62% and 73% respectively (by 3 centres it was at least 97% at all time points) • According to leukaemia phenotype, agreement was 78% in samples from BCP-ALL and 66% in T-ALL samples (at least 3 centres agreed in 96% and 94% respectively) ***Quantitative Concordance of Analyses of Exchanged List-Mode Data*** • Overall concordance of observed versus expected MRD-values was high (ICC=0.979) (series 1 ICC=0.986 and series 2 ICC=0.975) • There was little variance between centres 1 to 4 regarding their agreement in their observed and expected votes (Centre 1 ICC=0.983; Centre 2 ICC=0.993, Centre 3 ICC=0.997, Centre 4 ICC=0.995) • The variance in the ability to interpret data in relation to sample origin was small ((Centre 1 ICC=0.987; Centre 2 ICC=0.993, Centre 3 ICC=0.922, Centre 4 ICC=0.997) • In MRD positive samples (n=106), correct MRD levels were recorded by centres 1 to 4 in 82%, 93%, 85% and 94% respectively. All centres were in agreement in 67% of samples and at least 3 centres were in agreement in 86% of samples. • Concordance was slightly better between centres for bone marrow samples compared with blood samples with all 4 centres in agreement in 72% of bone marrow samples compared with 56% of blood samples. • Level of agreement declined with the level of MRD, samples positive ≥10% (n=27), ≥1-10% (n=21), ≥0.1-1% (n=33) and <0.1% (n=25) showed agreement in all four centres in 96%, 71%, 64% and 36% respectively. • Cumulatively there were 25 false-negative estimates (6%) among 420 available single values from all positive samples and an additional 22 estimates (5.2%) described the wrong levels of MRD. • Among the 96 negative samples, concordantly negative votes were given in 74% and by at least 3 centres in 97%. There were 24 false positive estimates (6.3%).

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<tr><td></td><td></td><td></td><td>Continued training of study group members</td><td></td><td>
Concordance of Risk Estimates upon Analyses of Exchanged List-Mode Data
• Observed risk estimates matched expected in 79%, 89%, 100% and 93% of centres respectively (based on the double time point risk algorithm) and matched expected in 96%, 89%, 100% and 89% of centres (based on the single time point algorithm (day 15, bone marrow)).

Reproducibility in Inter-Laboratory Sample Exchange
• 63 samples were exchanged between two centres with a positive/negative concordance of 90% (κ=0.81)
• The reproducibility of MRD values including quantitative aspects was high (ICC=0.97 for relative estimates)
• Concordance in the artificial dilution experiments was high between all four centres (ICC=0.98)
• Of 164 MRD values available (from 42 submitted samples) sensitivity was 95.6% and specificity was 90.2%
• MRD-status agreement was 77% (samples with poor agreement was due to insufficient red cell lysis after prolonged transportation or too few sample resulting from tube leakage)

Agreement of MRD Results from independent patient cohorts
• Agreement between the four centres with respect to available MRD results from their locally recruited patient cohorts did not differ significantly at the various time points for blood samples. In bone marrow analysis agreement between the centres differed significantly only at day 15 (p<0.001) and overall agreement was 89%.
• The proportions of patients distributed to each risk group did not differ significantly

Comments:

Quality Assessment

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<tr><td colspan="6">Norgaard et al (2005) Denmark (free, tax-supported health care)</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

January 1994 – December 1999</td><td>To examine the data quality and quantifying the impact of any misclassification of the diagnoses on the survival estimates</td><td>N=1159 patients identified in 2 registries (Danish Cancer Registry (DCR) and North Jutland Hospital Discharge Registry(HDR))

Inclusion
Patients registered for the first time with a haematological malignancy discharge diagnosis during 1994-1999

Exclusion
Patients <15 years
Patients who were registered prior to 1994 with an haematological diagnosis based on ICD-8</td><td>Danish Cancer Registry (DCR)</td><td>North Jutland Hospital Discharge Registry</td><td>

Degree of completeness
Positive Predictive Value
Survival

Degree of Completeness
PPV (defined as the proportion of patients registered with a haematological malignancy in HDR and in DCR
Survival

78.3% (n=908) of patients were found in both registries, 14.4% (n=167) were found in the HDR registry only and 7.3% (n=84) were found in the DCR only

Degree of Completeness and Positive Predictive Value

Completeness overall was 91.5% (95% CI 89.6%-93.1%)
PPV was 84.5% (95% CI 82.2%-86.5%) when using the DCR as reference standard

<table>
<tr><th></th><th colspan="6">Patients Registered</th></tr>
<tr><th></th><th>Both registries (%)</th><th>HDR (%)</th><th>DCR (%)</th><th>Total</th><th>Degree of Completeness</th><th>PPV (95% CI)</th></tr>
<tr><td>All haematological malignancies</td><td>908 (78.3)</td><td>167 (14.4)</td><td>84 (7.3)</td><td>1159</td><td>91.5 (89.6-93.1)</td><td>84.5 (82.2-86.5)</td></tr>
<tr><td>Acute Myeloid Leukaemia</td><td>73 (62.4)</td><td>35 (29.9)</td><td>9 (7.7)</td><td>117</td><td>89 (80.4-94.1)</td><td>67.6 (58.3-75.7)</td></tr>
<tr><td>Hodgkin’s disease</td><td>55 (65.5)</td><td>22 (26.2)</td><td>7 (8.3)</td><td>84</td><td>88.7 (78.5-94.4)</td><td>71.4 (60.5-80.3)</td></tr>
<tr><td>Non-Hodgkin’s lymphoma or chronic lymphocytic leukaemia</td><td>523 (76.6)</td><td>90 (13.2)</td><td>70 (10.3)</td><td>683</td><td>88.2 (85.3-90.6)</td><td>85.3 (82.3-87.9)</td></tr>
<tr><td>Multiple Myeloma</td><td>130 (76)</td><td>28 (16.4)</td><td>13 (7.6)</td><td>171</td><td>90.9 (85.1-94.6)</td><td>82.3 (75.6-87.4)</td></tr>
</table>
Pathological Record Reviews

73.8% of patients registered in DCR only were confirmed as having a correct or most likely correct diagnosis compared with 42.5% for patients registered in HDR only (histopathology or peripheral blood smears).
96/1075 (8.9%) of patients with a haematological malignancy registered in HDR could not be confirmed as actually having a haematological malignancy and HDR missed 62 patients who were confirmed as correctly diagnosed in DCR.
71 patients registered in HDR only, actually had a haematological malignancy
992 patients were registered in DCR as having a haematological malignancy giving an under-notification in DCR by approximately 7%.

Survival
<table>
<tr><th></th><th>Mortality Rate</th><th>95% CI</th></tr>
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<tr><th></th><th>Ratio (MR)</th><th></th></tr>
<tr><td>All haematological malignancies</td><td>0.98</td><td>0.88-1.09</td></tr>
<tr><td>Acute Myeloid Leukaemia</td><td>0.91</td><td>0.67-1.24</td></tr>
<tr><td>Hodgkin’s disease</td><td>1.33</td><td>0.77-2.38</td></tr>
<tr><td>Non-Hodgkin’s lymphoma or chronic lymphocytic leukaemia</td><td>0.98</td><td>0.84-1.14</td></tr>
<tr><td>Multiple Myeloma</td><td>0.87</td><td>0.68-1.12</td></tr>
</table>

In acute myeloid leukaemia and in multiple myeloma HDR overestimated the survival by 10-15% while in Hodgkin’s disease survival was underestimated by 33% compared with DCR.
Survival of patients registered in DCR only was around 20% lower than survival of patients registered in both DCR and HDR
Survival of patients registered in HDR only was around 10% lower than survival of patients registered in both DCR and HDR
Differences in survival were most pronounced in the period immediately following diagnosis

Comments

ICD-9 was never used in Denmark
Reporting to the Danish Cancer Registry became mandatory for all doctors in 1987
Patients recorded in both registries were considered to be correctly diagnosed.

</td></tr>
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Unclear Risk of Bias</td></tr>
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<tr><td colspan="6">Proctor et al (2011) UK</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

2003-2008</td><td>A large scale assessment of expert central review in a UK regional cancer network and the impact of discordant diagnoses on patient management as well as the financial and educational implications of providing a centralised service.</td><td>N=1949 samples sent for expert central review

N=1873 (96.1%) were received with a primary diagnosis

Patient pathology samples sent for central expert review over a 6 year period Patient samples without a primary diagnosis were included but analysed separately</td><td>Expert Review</td><td>Initial Diagnosis</td><td>• Concordance
The overall discordance rate was 27.4% (513/1873) though the rate differed significantly between different diagnoses.

Table: Concordant and Discordant Diagnosis in the 10 most common lymphoid malignancies
<table>
<tr><th></th><th colspan="10">Expert/Final Pathology</th></tr>
<tr><th>Referral Pathology</th><th>DLBL</th><th>FL</th><th>PCN</th><th>cHL</th><th>CLL</th><th>LPL</th><th>Reactive</th><th>MCL</th><th>MZL</th><th>TCL</th></tr>
<tr><td>DLBL</td><td>361*</td><td>7</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td><td>2</td><td>1</td><td>1</td></tr>
<tr><td>FL</td><td>10</td><td>242*</td><td>0</td><td>0</td><td>2</td><td>3</td><td>0</td><td>1</td><td>2</td><td>0</td></tr>
<tr><td>PCN</td><td>0</td><td>0</td><td>187*</td><td>0</td><td>0</td><td>3</td><td>2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>cHL</td><td>0</td><td>1</td><td>0</td><td>172*</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>CLL</td><td>1</td><td>6</td><td>0</td><td>0</td><td>139*</td><td>5</td><td>0</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>LPL</td><td>1</td><td>4</td><td>1</td><td>0</td><td>0</td><td>53*</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Reactive</td><td>1</td><td>4</td><td>0</td><td>1</td><td>0</td><td>2</td><td>33*</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>MCL</td><td>1</td><td>1</td><td>0</td><td>0</td><td>4</td><td>0</td><td>0</td><td>29*</td><td>0</td><td>0</td></tr>
<tr><td>MZL</td><td>2</td><td>7</td><td>0</td><td>0</td><td>1</td><td>0</td><td>1</td><td>0</td><td>24*</td><td>0</td></tr>
<tr><td>TCL</td><td>3</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>61*</td></tr>
<tr><td>Burkitts</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table></td></tr>
</table>

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results

Lymphoma										
Unspecified Lymphoma	47	42	4	4	25	14	2	7	6	6
Low-grade Lymphoma	0	0	0	0	0	1	0	0	0	0
High-grade Lymphoma	63	5	0	0	0	0	0	0	0	0
Normal/no lymphoma	0	1	1	0	1	0	2	1	0	0
Other	0	0	1	1	0	2	1	0	0	1
Total Samples	512	333	195	185	175	88	47	44	37	70
Discordant samples (%)	132 (25.8)	78 (23.4)	7 (3.6)	7 (3.8)	35 (20)	30 (34.1)	8 (17)	15 (34.1)	10 (27)	9 (12.9)
No diagnosis provided (%)	19 (3.7)	13 (3..9)	1 (0.5)	6 (3.2)	1 (0.6)	5 (5.7)	2 (4.3)	0 (0)	3 (8.1)	10 (14.3)

Discordance rates varied significantly over time with 32%discordance in 2003 dropping to between 13% and 15% after 2006.

350/512 discordant diagnoses were assessed to see whether expert panel review would have altered treatment and it was noted that expert panel review would have resulted in a significant change in 11% 9n=39) patients and in 39% (n=136) central review would have led to minimal changes to patients care.
In 50% (n=175) of patients, the primary diagnosis provided insufficient or outdated information and, without central review, would have led to delayed or potentially inappropriate treatment.

Comments
Pathologic discordance was defined as a disagreement between the primary or referred diagnosis and the diagnosis recorded after expert review

Diagnoses not conforming to the WHO system were considered discordant

Primary diagnoses were not considered discordant if they failed to provide additional details relating to grade or subtype

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<tr><td>Health care setting – is it applicable to the UK?</td><td>Yes

Low Risk of Bias</td></tr>
</table></td></tr>
<tr><td colspan="6">Rane et al (2014) India</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

March 2011 – no end date reported</td><td>To evaluate the ability and interobserver variability of pathologists with varying levels of experience and with an interest in lymphomas to diagnose Burkitt Lymphoma in a resource limited set up.</td><td>N=25 cases selected

Diagnosis of Burkitt Lymphoma based either on clinical features, morphological features and immunophenotypes</td><td>Consensus Diagnosis</td><td>Initial Independent Assessment</td><td>• Initial Independent Assessment
• Interobserver variation in morphological features
• Parameters used to differentiate between classic CL, atypical BL and B-cell lymphoma intermediate between Burkitt’s and DLBL
• Consensus Diagnosis
• Concordance with consensus diagnosis
• Effect of tissue fixation, age group and provision of additional information on revision of diagnoses
• Accuracy of pathologists
• Sensitivity and Specificity to diagnose Burkitt Lymphoma

Initial Independent Assessment
• 10 pathologist committed to a diagnoses in all 25 cases while 3 pathologists committed to a diagnosis in 24/25 cases, 1 pathologist committed in 23/25 cases.
• There was poor concordance for independent diagnosis (κ=0.168, SE±0.018)
• Level of experience showed direct correlation with expert lymphoma pathologists showing marginally higher concordance rates (κ=0.373, SE±0.071) and general pathologists showing the lowest (κ=0.138, SE±0.035)

Interobserver variation in morphological features
• There was very low concordance for morphological features tested among all pathologists (κ=0.192, SE±0.05) and concordance for morphological diagnosis was highest among expert lymphoma pathologists (κ=0.356, SE±0.127).
• Highest concordance rate was observed for nuclear contour (κ=0.896, SE±0.110) and was lowest for nuclear</td></tr>
</table>

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					prominence (κ=-0.62, SE±0.124) *Parameters used to differentiate between classic CL, atypical BL and B-cell lymphoma intermediate between Burkitt's and DLBL* • Cross tabulation of morphological and immunohistochemical features against the independent final diagnosis showed that pathologists were least likely to accept deviation from certain features perceived to be characteristics of Burkitt Lymphoma (intermediate cell size, CD10 + MIB-1 labelling of greater than 90% and the greater the deviation the more likely a pathologist was to classify the case as either atypical BL or B cell lymphoma intermediate between Burkitt's and DLBL. *Consensus Diagnosis* • 12/14 pathologists attended the consensus meeting and a consensus was reached in 23/25 cases, unanimously in 19 cases and consensus based (≥8 pathologists in agreement) in 4 cases. • Level of agreement between pathologists for revised diagnosis was very high (κ=0.835, SE±0.021) and was similar across the different groups of pathologists • Revision of diagnosis was highest amongst general pathologists and lowest among lymphoma experts (p=0.121) • Revision was highest for cases originally diagnosed as either atypical BL or B cell lymphoma intermediate between Burkitt's and DLBL. and minimum revision occurred in classic BL (p=0.001). *Concordance with consensus diagnosis* • Concordance of independent diagnosis and consensus diagnosis was low and highly variable (κ=0.259, SE±0.039; median 0.207; range -0.131-0.667). • Concordance with independent diagnosis increased and variability decreased with increasing experience of diagnosing lymphomas • Concordance of the revised diagnosis with consensus diagnosis was high (κ=0.633, SE±0.011, median 0.656) *Effect of tissue fixation, age group and provision of additional information on revision of diagnoses* • No difference was observed in the distribution of fixation and staining scores across the diagnostic categories (p=0.654) • Equal proportions of cases were reclassified in all three grades of fixation: (means Grade 1=54.167±29.167,Grade 2= 47.222±7.217 and Grade 3=50±6.989; p=0.931).C-MYC status, EBER-ISH results and BCL6 IHC results did not affect the frequency of revision of diagnoses • Age of patients (adult versus paediatric) did not affect the rates of revision of diagnosis (mean revision 45.513±6.579% in patients <18 years and 53.472±7.429 in adult patients. *Accuracy of pathologists* • Expert lymphoma pathologists were significantly more likely to make a correct diagnosis compared with both the pathologists with experience (OR=3.14, p=0.012) and the general pathologists (OR=5.3, p=0.00032) and pathologists with experience were more likely to make a correct diagnosis compared with general pathologists though this was not statistically significant (OR=1.69, p=0.062). • Mean change of accuracy by IHC over morphology was 9.698±4.799 and mean change of accuracy by discussion/consensus meeting over that by IHC was 47.464±5.039%.

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<table>
<tr><th>Mean Accuracy</th><th>Morphological diagnosis</th><th>Morphological Diagnosis + IHC</th><th>Revised Diagnosis post consensus meeting</th><th>Burkitt Lymphoma group</th><th>DLBL</th><th>Atypical BL</th><th>B-cell lymphoma intermediate between BL and DLBL</th></tr>
<tr><td>All</td><td>36.79±2.631 %</td><td>45.963±13.825 %</td><td>95.652±1.31 1%</td><td>72.619±7.5 36%</td><td>58.9 28±8 .535 %</td><td>24.186±7 .026%</td><td>35.714±10.16 6%</td></tr>
<tr><td>Expert lymphoma pathologists</td><td>~42%</td><td>66.667±13.825 %</td><td>97.101±2.89 8%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pathologists with lymphoma experience</td><td></td><td>51.087±4.82%</td><td>92.391±2.73 5%</td><td></td><td></td><td></td><td></td></tr>
<tr><td>General Pathologists</td><td>~33%</td><td>34.161±3.727 %</td><td>97.391±1.46 9%</td><td></td><td></td><td></td><td></td></tr>
</table>
Sensitivity and Specificity to diagnose Burkitt Lymphoma

Expert lymphoma pathologists had the highest sensitivity (96.8%) and specificity (94.44%) for the diagnosis of Burkitt Lymphoma (typical and atypical)
General pathologists had a higher sensitivity (78.57% versus 65.63%) compared with pathologists with lymphoma experience, however pathologists with lymphoma experience had much higher specificity (80.56% versus 63.49%).

Comments
The 14 pathologists were divided into three groups:

A1-A3 expert lymphoma pathologists working in diagnostic centres with >500 lymphoma cases/year,
B1-B4 pathologists with experience in lymphomas working in general hospitals with some training in lymphoma
C1-C7 Other pathologists involved in diagnostic surgical pathology

</td></tr>
</table>

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</table></td></tr>
<tr><td colspan="6">Siebert et al (2001) USA</td></tr>
<tr><td>Retropsective Study

Laboratory Setting

July 1995- December 1997</td><td>To compare diagnoses made at a community and an academic centre to evaluate the reproducibility of the revised European-American Classification</td><td>N=188 lymphoid neoplasms subtyped according to revised European-American classification criteria</td><td>Review of community hospital assessments at an academic centre</td><td>lymphoid neoplasms subtyped according to revised European-American classification criteria at a community hospital</td><td>• Concordance
Subtype was concordant for 88.8% of cases (167/188)

Methods used for diagnosing and subtyping
<table>
<tr><th>Method</th><th>Frequency</th><th>Concordant</th><th>Discordant</th></tr>
<tr><td>Morphologic Examination</td><td>7 (3.7)</td><td>7 (3.7)</td><td>0 (0)</td></tr>
<tr><td>Morphologic Examination and paraffin-section immunohistochemical examinations</td><td>49 (26.1)</td><td>41 (21.8)</td><td>8 (4.3)</td></tr>
<tr><td>Morphologic Examination and paraffin-section immunohistochemical examinations and flow cytometry</td><td>57 (30.3)</td><td>48 (25.5)</td><td>9 (4.8)</td></tr>
<tr><td>Morphologic Examination and flow cytometry</td><td>75 (39.9)</td><td>71 (37.8)</td><td>4 (2.1)</td></tr>
<tr><td>Total</td><td>188 (100)</td><td>167 (88.8)</td><td>21 (11.2)</td></tr>
</table>
Additional Data/material provided for academic centre review before diagnosis of 44 cases
<table>
<tr><th>Method</th><th>Frequency</th><th>Concordant</th><th>Discordant</th></tr>
<tr><td>Additional Clinical or Laboratory Data</td><td>10</td><td>7</td><td>3</td></tr>
<tr><td>Paraffin embedded tissue</td><td>18</td><td>13</td><td>5</td></tr>
<tr><td>Flow cytometry histograms</td><td>22</td><td>19</td><td>3</td></tr>
<tr><td>Cytogenetic or molecular test results</td><td>2</td><td>1</td><td>1</td></tr>
</table></td></tr>
</table>

<table>
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Comments
For each case, clinical data, glass slides for morphologic evaluation and immunophenotying data were submitted for blinded review at an academic centre.

Quality Assessment
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<tr><td colspan="6">Stevens et al (2012)</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

January 2006 – May 2010</td><td>To observe concordance and discrepancies between local findings and the specialist opinion.</td><td>N=125 patients visiting the Hodgkin outpatient clinic

Newly diagnosed and previously untreated patients with HL</td><td>Central Review</td><td>Regional/Community Hospital Review</td><td>
Pathology
Staging
Therapy
Pathology
There was agreement in 108/125 (86%) of cases between the pathologists in the referring hospital and the RUN MC; minor discordances were recorded in 12 cases and major discordance was recorded in 5 cases.

<table>
<tr><th></th><th colspan="5">Referring hospital</th></tr>
<tr><th>Central Review</th><th>NScHL</th><th>MCcHL</th><th>LRcHL</th><th>NLPHL</th><th>NOS</th></tr>
<tr><td>NScHL</td><td>75</td><td>3</td><td></td><td></td><td>4</td></tr>
<tr><td>MCcHL</td><td></td><td>10</td><td></td><td></td><td>1</td></tr>
<tr><td>LRcHL</td><td></td><td></td><td>5</td><td>1</td><td></td></tr>
<tr><td>NLPHL</td><td></td><td></td><td>2</td><td>10</td><td></td></tr>
<tr><td>NOS</td><td>1</td><td>1</td><td></td><td></td><td>8</td></tr>
<tr><td>Others</td><td></td><td></td><td>1</td><td>1</td><td></td></tr>
</table>
Staging
The Ann Arbor stage could be attributed to 123/125 cases (98%) of patients at central review and 95/123 (77%) were concordant with regional results.
There were 10 minor discordant and 18 major discordant results; discordant results included downscaling or upscaling after central review.

<table>
<tr><th></th><th colspan="8">Ann Arbor Referring Hospital</th></tr>
<tr><th>Ann Arbor Centralised Revision</th><th>Stage I (favourable)</th><th>Stage I (unfavourable)</th><th>Stage II (favourable)</th><th>Stage II (unfavourable)</th><th>Stage III (good risk)</th><th>Stage III (poor risk)</th><th>Stage IV (good risk)</th><th>Stage IV (poor risk)</th></tr>
<tr><td>Stage I (favourable)</td><td>9</td><td></td><td>2</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Stage I (unfavourable)</td><td></td><td>4</td><td></td><td>2</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Stage II (favourable)</td><td>4</td><td></td><td>21</td><td>1</td><td>1</td><td></td><td></td><td></td></tr>
<tr><td>Stage II (unfavourable)</td><td></td><td>1</td><td>6</td><td>26</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Stage III (good risk)</td><td></td><td></td><td>1</td><td>1</td><td>14</td><td></td><td></td><td></td></tr>
<tr><td>Stage III</td><td></td><td></td><td></td><td>4</td><td></td><td>6</td><td></td><td></td></tr>
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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results

(poor risk)								
Stage IV (good risk)	1		1	1			5	
Stage IV (poor risk)				1		1		10
Missing/Other					1		1	

Therapy
Central treatment advice could be given in 124/125 cases
Regional centres had already defined treatment in 104 cases and treatment advice was concordant in 84/104 (81%) of cases
Central review led to treatment changes in 20/104 (19%) of cases based on either changes in pathology or staging results. Treatment changes included changes to radiotherapy field, changes in the number of ABVD cycles and involved nodes for the IN-RT and other changes including changes in chemotherapy.

	Referring Hospital							
Central Revision	**IF-RT**	**ABVDx 6**	**ABVDx 8**	**ChIVPPx6 -8**	**Other Chemo**	**ABVDx3 + IN-RT**	**ABVD x4 + IN-RT**	**Missing Data**
IF-RT	8					1		
ABVDx6		27				2	3	6
ABVDx8			1					
ChIVPPx6-8				1				1
Other Chemo	1				2			2
ABVDx3 + IN-RT	2	1				22	1	2
ABVD x4 + IN-RT						5	23	7
Missing Data		1						
Other Chemo+RT						1	1	1
Other Treatment							2	1

Comments

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<tr><td colspan="6">Strobbe et al (2014) The Netherlands</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

2000-2001
2005-2006</td><td>To investigate whether implementation of an expert panel led to better quality of initial diagnoses by comparing the rate of discordant diagnoses after the panel was established compared with discordance rate 5 years later

To evaluate whether lymphoma types with high discordance rate could be identified</td><td>N=161 referred to the expert panel
N=183 reviewed at a later date

2000-2001

N=433 patients with a diagnosis of malignant lymphoma

N=89 patients excluded (not possible to retrieve pathology, tissue, diagnosis at autopsy, fine needle aspiration only, patients already sent for consultation, cutaneous lymphoma)</td><td>Expert Panel review</td><td>Initial Diagnosis</td><td>• Discordance rate in 2000-2001
• Discordance rate in 2005-2006

• Overall discordance rate decreased from 14% in 2000-2001 to 9% in 2005-2006 (p=0.06)
• In 2000-2001, the highest rate of discordance was observed for lymphoma with transformation (90%), lymphoma NOS (61%), low grade lymphoma NOS (44%) and follicular lymphoma grade 3 (33%)
• In 2005-2006, the highest rate of discordance was observed for Lymphoma NOS (57%), lymphomas with transformation (56%), follicular lymphoma grade 3 (50%) and nodular lymphocyte predominant Hodgkin lymphoma (50%)
• Despite overall decrease in discordance, 3/4 groups with the highest discordance rates were the same
In 2000-2001, 11% of cases were discordant compared with 16% who were not referred (p=0.2) and in 2005-2006, discordance rate for referred versus non-referred were 10% versus 9% (p=0.8).

Comments
• All seven hospitals in the region agreed to submit histological slides of all new cases of patients with a diagnosis of malignant lymphoma
• Initial diagnosis was made in three pathology laboratories
• Expert panel consisted of three expert haematopathologists (one from each laboratory) so haematopathologists sometimes reviewed their own cases (no information as to whether this was blinded review though reviewers were not blinded to initial diagnosis) but the other two reviewers confirmed/rejected the diagnosis.</td></tr>
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<tr><td></td><td></td><td>N=344 cases included in the analysis

2005-2006

N=473 cases of malignant lymphoma

N=103 cases excluded (not possible to receive pathology tissue, fine needle aspiration only, diagnosed at autopsy, already sent for consultation, cutaneous lymphoma)

N= 370 cases included in the analysis</td><td></td><td></td><td>Quality Assessment

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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
Van Blerk et al (2003)					
Retrospective Study Laboratory Setting January 2000 – November 2001	To report first experiences from Belgian national external quality assessment scheme (EQAS)	N=17 blood samples were sent for evaluation by EQAS N=41 laboratories 61.5% non-university hospitals 25.6% university hospitals 12.9% private laboratories 78.4 % Sample analysis was performed within 24 hours and 96.2% within 48 hours	External Quality assessment Review (an expert laboratory tested both the fresh samples immediately after apherisis and the mailed samples)	N/A	• Stability • Intralaboratory reproducibility • Homogeneity • Interlaboratory reproducibility • Single vs. Dual Platform • Influence of Gating strategy • CD4+,CD3+ and CD8+CD3+ cells versus total CD4 and CD8 cells • Abnormal Samples *Stability* No significant difference in variation was observed over the test period Variability increased with age of sample but stability of control samples appeared satisfactory until day 2. Results between fresh and mailed samples did not differ significantly Results obtained by participants within 24 hours of blood collection and those obtained from specimens processed later *Intralaboratory Reproducibility* Within laboratory variability and relative contribution to total variability was assessed by sending duplicate samples to labs and asking them to analyse them twice. For duplicate measurements, differences ranged between -5.0 and 5.0% for the percentages of lymphocyte subsets and between -0.33 and 0.28 10^9/litre for the absolute counts. Between duplicate measurements or duplicate samples, no significant difference was observed *Homogeneity* The homogeneity of the specimens was demonstrated by the ratios of duplicate samples being practically equal to 1 *Interlaboratory Reproducibility* Between-laboratory CV values for the white blood cell and lymphocyte count ranged between 2.9-5.6% and 3.9-16.2% respectively Overall between laboraotory variability for the percentage of CD3+, CD4+, CD8+ and CD19+ cells was 4.0, 5.0, 13.2 and 16.2% respectively. Median CVs of the absolute values were 12.2, 11.4.16.4 and 16.5% for CD3+, CD4+, CD8+ and CD19+ cells respectively *Single versus dual platform approach* Overall interlaboratory CVs obtained from 2 surveys with single platform approach were 6.6% (range, 3.5-8.8%), 7.4% (range 1.6%-11.8%), 9.1% (range, 2.5-15.3%) and 17% (range, 5.6-34.3%) for the absolute CD3+, CD4+, CD8+ and CD19+ cell counts respectively (6 laboratories) Overall interlaboratory CVs obtained with dual platform approach were 9.3% (range 4.5-11.7%), 10.5% (range 8.3-13%), 11% (range 7.9-13.8% and 15.1% (range 10.5-21.1%) for the absolute CD3+, CD4+, CD8+ and CD19+ cell counts respectively (35 laboratories) No significant difference was observed between the two groups *Influence of gating strategy* There was no significant difference in different gating strategies observed

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					CD4+CD3+ and CD8+CD3+ cells versus total CD4 and CD8 cells The percentage of double-positive CD4+CD3+ cells and CD8+CD3+ cells was significantly lower than the percentage total CD4+ and CD8+ cells for a number of samples. The overall CVs for the percentages of CD4+CD3+ cells and CD8+CD3+ cells for the six surveys were, respectively 4.3 and 7.1% Overall CVs for the absolute numbers of CD4+CD3+ cells and CD8+CD3+ cells were 10.1% and 11.6% respectively Between laboratory variability for the determination of CD4+CD3+ cells and CD8+CD3+ cells was lower than for the measurement of total CD4+ and CD8+ cells The percentage of laboratories which reported measuring total CD4+ and CD8+ cells was 29.3% in January 2000 and dropped to 19.5% by November 2001. *Abnormal Sample* One survey included a specimen with an abnormal proportion of lymphocyte subsets Median values obtained by participating laboratories matched well with the results of the expert laboratory. Between laboratory variability for CD3, CD4 and CD8 was considerable *Comments* Two or three fresh anticoagulated whole blood sample were sent out to laboratories a total of six times for analysis. In two send outs, within laboratory variability and abnormal samples analysis were assessed: • Survey 2: To assess variability within each laboratory (duplicate samples, analysed twice) • Survey 4: To evaluate variability inherent to abnormal samples (samples sent included a sample from a patient suffering from chronic B-lymphocytic leukaemia) Laboratories were required to report • Date of receipt of sample • Date of sample analysis • Type of flow cytometer • Sample preparation technique • Source of antibodies • Gating strategy • Data analysis software
					Comments:

<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td>Quality Assessment
<table>
<tr><th>Question</th><th>Risk of bias (high, low, unclear, NA)</th></tr>
<tr><td>Patient selection – how were patients chosen for the study (e.g. consecutive or random sample)?</td><td>Not reported –

High risk of bias</td></tr>
<tr><td>Are the patients in the study representative of the PICO population</td><td>Yes (haematology patients)

Unclear Risk of Bias</td></tr>
<tr><td>Diagnostic service models – are they comparable to what is in the PICO?</td><td></td></tr>
<tr><td>Reference standard tests – did all patients receive the same tests to get the definitive diagnosis.</td><td>Unclear

Unclear risk of Bias</td></tr>
<tr><td>Blinding – are expert pathologists blinded to the initial diagnosis information</td><td>Unclear

Unclear Risk of Bias</td></tr>
<tr><td>Health care setting – is it applicable to the UK?</td><td>Unclear

Low Risk of Bias</td></tr>
</table></td></tr>
<tr><td colspan="6">Van de Schans et al (2013) The Netherlands</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

January 200 – December 2001</td><td>To evaluate the value of an expert pathology panel and report discordance rates between the diagnosis of initial pathologists and the expert panel and the effect on survival</td><td>N=391 patients diagnosed with primary malignant lymphoma

N=344 patients included

Inclusion
Patients with malignant lymphoma identified through the regional population based cancer registry

Three pathology labs including one academic performed</td><td>Expert review of diagnosis</td><td>Initial Diagnosis</td><td>• Discordance Rate

Rate of discordance

• 47% of all cases were actively referred for expert review with diffuse large B cell lymphoma the most common type to be referred (32%)

• Discordance rate was 14%; κ=0.84, 95% CI, 0.78-0.89)
• Discordance rate differed for patients referred (11%) compared with patients not referred (16%) though this was not statistically significant.
• Discordance rates varied between 11 and 23% for individual laboratories
• Patients with a discordant diagnosis were older (median age was 68 years versus 63 years) and the distribution of NHL subtypes was different; less DLBCL (9 vs. 36%), more LL NOS (9 vs 2%), more FL grade 3 (11 versus 3%), less TCL (0 versus 7%), less HL (4 versus 12%) and more L NOS (23 versus 2%).
• There was 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%].</td></tr>
</table>

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td>the original diagnosis</td><td></td><td></td><td>
Comments:
55% of diagnoses were made in one laboratory which served 3 hospitals

NHL – Non Hodgkin Lymphoma
DLBCL – Diffuse large B cell lymphoma
LL NOS – low grade lymphoma not otherwise specified
FL – Follicular Lymphoma
L NOS – Lymphoma not otherwise specified
TCL – T cell lymphoma

Quality Assessment

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<tr><td colspan="6">Zhang et al (2007)</td></tr>
<tr><td>Retrospective Study

Laboratory Setting

2004-2005</td><td>To compare similarities and differences in results from participating laboratories and to identify variables which could potentially affect test results to discern variables important in test standardisation</td><td>N=38 laboratories

N=38 laboratories participated in the sample exchange and provided results

N=29 labs had results starting from a 10^{-5} dilution
N=40 labs had results starting from a 10^{-4} dilution
N=43 labs had results starting from a 10^{-3} dilution
N=43 labs had results starting from a 10^{-2} dilution
N=42 labs had results starting from a 10^{-1} dilution</td><td>Quantitative testing for BCR-ABL1</td><td>Results from different participating laboratories</td><td>• Test accuracy at different dilutions
Test accuracy at different dilutions (based on log reductions)

<table>
<tr><th></th><th>10^{-5} dilution</th><th>10^{-4} dilution</th><th>10^{-3} dilution</th><th>10^{-2} dilution</th><th>10^{-1} dilution</th></tr>
<tr><td colspan="6">All internal controls</td></tr>
<tr><td>Mean</td><td>4.45</td><td>3.52</td><td>2.58</td><td>1.536</td><td>0.667</td></tr>
<tr><td>SD</td><td>0.609</td><td>0.578</td><td>0.574</td><td>0.584</td><td>0.394</td></tr>
<tr><td>Median</td><td>4.52</td><td>3.56</td><td>2.63</td><td>1.6</td><td>0.605</td></tr>
<tr><td>Minimum</td><td>3.26</td><td>2.18</td><td>1.03</td><td>0.26</td><td>0.14</td></tr>
<tr><td>Maximum</td><td>6.30</td><td>4.71</td><td>3.7</td><td>3.0</td><td>1.70</td></tr>
<tr><td>Range</td><td>3.04</td><td>2.53</td><td>2.67</td><td>2.74</td><td>1.56</td></tr>
<tr><td>N</td><td>29</td><td>40</td><td>43</td><td>43</td><td>42</td></tr>
<tr><td>ABL1 as control</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean</td><td>4.149</td><td>3.06</td><td>2.09</td><td>1.1225</td><td>0.3773</td></tr>
<tr><td>SD</td><td>0.486</td><td>0.385</td><td>0.54</td><td>0.446</td><td>0.3404</td></tr>
<tr><td>Median</td><td>4.1</td><td>3.08</td><td>2.145</td><td>1.01</td><td>0.300</td></tr>
<tr><td>Minimum</td><td>3.26</td><td>2.34</td><td>1.03</td><td>0.5</td><td>0.14</td></tr>
<tr><td>Maximum</td><td>4.8</td><td>3.85</td><td>3.2</td><td>2.2</td><td>1.50</td></tr>
<tr><td>Range</td><td>1.54</td><td>1.51</td><td>2.17</td><td>1.7</td><td>1.36</td></tr>
<tr><td>N</td><td>10</td><td>14</td><td>16</td><td>16</td><td>15</td></tr>
<tr><td colspan="6">GAPDH, BCR, G6PD and B2M as control</td></tr>
<tr><td>Mean</td><td>4.61</td><td>3.77</td><td>2.875</td><td>1.782</td><td>0.8285</td></tr>
<tr><td>SD</td><td>0.616</td><td>0.401</td><td>0.351</td><td>0.427</td><td>0.3279</td></tr>
<tr><td>Median</td><td>4.58</td><td>3.78</td><td>2.8</td><td>1.755</td><td>0.71</td></tr>
<tr><td>Minimum</td><td>3.52</td><td>2.18</td><td>2.3</td><td>0.26</td><td>0.38</td></tr>
<tr><td>Maximum</td><td>6.3</td><td>4.7</td><td>3.7</td><td>3.00</td><td>1.70</td></tr>
<tr><td>Range</td><td>2.78</td><td>2.53</td><td>1.4</td><td>2.74</td><td>1.32</td></tr>
<tr><td>N</td><td>19</td><td>26</td><td>27</td><td>27</td><td>27</td></tr>
</table>

Effect of different variables on reported log reductions at different dilution (p values)
<table>
<tr><th>Dilution</th><th>Extraction Method</th><th>RT Primer</th><th>RT Enzyme</th><th>PCR Kit</th><th>Instrument</th><th>Standard Curve</th><th>Internal Control</th></tr>
<tr><td>10^{-5}</td><td>0.89</td><td>0.41</td><td>0.9</td><td>0.36</td><td>0.66</td><td>0.16</td><td>0.16</td></tr>
<tr><td>10^{-4}</td><td>0.84</td><td>0.52</td><td>0.4</td><td>0.21</td><td>0.75</td><td>0.11</td><td>0.001</td></tr>
<tr><td>10^{-3}</td><td>0.78</td><td>0.6</td><td>0.005</td><td>0.09</td><td>0.61</td><td>0.01</td><td><0.001</td></tr>
<tr><td>10^{-2}</td><td>0.39</td><td>0.42</td><td>0.08</td><td>0.07</td><td>0.48</td><td>0.05</td><td>0.001</td></tr>
<tr><td>10^{-1}</td><td>0.16</td><td>0.32</td><td>0.75</td><td>0.17</td><td>0.02</td><td>0.06</td><td><0.001</td></tr>
</table>

All Internal Controls
Mean and median results were all within 0.5 log of the known dilution (expected value) apart from 10^{-5} where it was 0.55 log</td></tr>
</table>

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					Standard Deviation was 0.6 log at all dilutions except from 10^{-1} where it was 0.4 log ABL1 Mean and median were ~1 log less than the known dilution value apart from 10^{-1} which was within 0.6 log of the expected value RNA Quality and cDNA Synthesis (spectrophotemtry and/or gel electrophoresis) Low yields did not appear to impact results Storage time did not impact sensitivity or accuracy of results (storage times ranged from 1-25 days) cDNA synthesis was done by reverse transcription and type of primers and enzymes used did not affect the sensitivity or accuracy Reagents for Quantitative PCR (Applied Biosystems kit and instruments, Roche quantification kit and light cycler, Ipsogen Fusion Quant kit or homebrew buffers) Different PCR kits and reagents used by the different laboratories did not impact the reported log reduction results Platforms (ABI Prism 7000, ABI Prism 7700, ABI Prism 7900, Roche LightCycler, Bio-Rad icycler) 91% of laboratories were able to amplify transcripts from samples diluted 10^{-4} and 66% were able to amplify transcripts from samples diluted at 10^{-5} irrespective of the platform or reagents used Calculation and use of the standard curve It appears the there it makes no overall difference whether laboratories use diluted RNA, cDNA, plasmid DNA or cell lines for generation of standard curves Internal Controls A number of internal controls including GUSB, ABL1, GAPDH, BCR, G6PD and B2M were used by the different laboratories (G6PD and ABL1 were the most frequent) Laboratories using BCR as their internal control appear to achieve the most accurate and sensitive results Laboratories using ABL1 showed log reduction values that were significantly different from those that used other internal controls in 4/5 dilutions tested.
					Comments: Reproducible results were defined as those that were different by less than 0.5 log in duplicate samples at dilutions as high as 10^{-4} and 10^{-5} and for duplicate samples at lower dilutions, values should be nearly identical. A 3-log reduction in BCR-ABL1 transcripts are consistent with major molecular response and a low incidence of disease progression whereas rising levels of BCR-ABL1 transcripts indicate a loss of response to treatment and may indicate relapse.

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</table></td></tr>
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Excluded Studies

Reference List	Comment
Burger GT, Van Ginneken AM. Computer-based diagnostic support systems in histopathology: what should they do? Studies in Health Technology & Informatics 2001;84(Pt 2):1120-4.	This paper does not relate to haematology
Cook IS, Cook IS. Referrals for second opinion in surgical pathology: implications for management of cancer patients in the UK. Eur J Surg Oncol 2001 September;27(6):589-94.	This paper does not relate to haematology
Standardised reporting of Haematology Laboratory results 3rd edition 1997. NZ J MED LAB SCI 2002;56(2):68-70.	No data (example of a reporting form for lab)
Recommendations for the reporting of lymphoid neoplasms: a report from the Association of Directors of Anatomic and Surgical Pathology. Virchows Arch 2002;441(4):314-9.	This is a discussion paper, lists recommendations but no data
Richards SJ, Jack AS. The development of integrated haematopathology laboratories: a new approach to the diagnosis of leukaemia and lymphoma. Clin Lab Haematol 2003 December;25(6):337-42.	This is an expert review/discussion paper
Jack A. Organisation of neoplastic haematopathology services: a UK perspective. Pathology (Phila) 2005 December;37(6):479-92.	This is an expert review/discussion paper
LaCasce A, Niland J, Kho ME, TerVeer A, Friedberg JW, Rodriguez MA et al. 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 2005;106(11):789A.	This is a conference abstract only
Mohanty SK, Piccoli AL, Devine LJ, Patel AA, William GC, Winters SB et al. Synoptic tool for reporting of hematological and lymphoid neoplasms based on World Health Organization classification and College of American Pathologists checklist. BMC Cancer 2007;7:144.	This paper is not concerned with diagnostics
Perkins SL, Reddy VB, Reichard KK, Thompsen MA, Dunphy CH. Recommended curriculum for teaching hematopathology to subspecialty hematopathology fellows. Am J Clin Pathol 2007 June;127(6):962-76.	This paper is a discussion paper
Briggs C, Guthrie D, Hyde K, Mackie I, Parker N, Popek M et al. Guidelines for point-of-care testing: haematology. Br J Haematol 2008 September;142(6):904-15.	This paper is a list of guidelines
Briggs C, Carter J, LEE SH, Sandhaus L, Simon-Lopez R, Vives Corrons JL. ICSH Guideline for worldwide point-of-care testing in haematology with special reference to the complete blood count. International Journal of Laboratory Hematology 2008	Duplicate

April;30(2):105-16.	
Dworzak MN, Gaipa G, Ratei R, Veltroni M, Schumich A, Maglia O et al. Standardization of flow cytometric minimal residual disease evaluation in acute lymphoblastic leukemia: Multicentric assessment is feasible. Cytometry Part B, Clinical Cytometry 2008 November;74(6):331-40.	This paper is not relevant to the current topic – does not discuss integrated reporting
Hamdani SNR. Second opinion in pathology of lymphoid lesions - An audit. Pakistan Journal of Medical Sciences 2008;24(6):798-802.	This paper is not relevant to the current topic – does not discuss integrated reporting
NE, Owen RG, Bedu-Addo. UK-based real-time lymphoproliferative disorder diagnostic service to improve the management of patients in Ghana. Journal of Hematopathology 2009;2(3):143-9.	This study was about improving diagnosis and management in Ghana
Chun K, Hagemeijer A, Iqbal A, Slovak ML. Implementation of standardized international karyotype scoring practices is needed to provide uniform and systematic evaluation for patients with myelodysplastic syndrome using IPSS criteria: An International Working Group on MDS Cytogenetics Study. Leuk Res 2010;34(2):160-5.	This paper is not relevant to the current topic – does not discuss integrated reporting
Fang CHO. When are diagnostic laboratory tests cost-effective? A systematic review of cost-utility analyses. Value in Health 2010;Conference(var.pagings):A101.	This is a conference abstract only
Hall J, Foucar K. Diagnosing myelodysplastic/myeloproliferative neoplasms: laboratory testing strategies to exclude other disorders. International Journal of Laboratory Hematology 2010;32(6):559-71.	This is a discussion paper/expert review
Siftar Z, Siftar Z, Paro MMK, Sokolic I, Nazor A, Mestric ZF. External quality assessment in clinical cell analysis by flow cytometry. Why is it so important? Coll Antropol 2010 March;34(1):207-17.	This paper is not relevant to the current topic – does not discuss integrated reporting
Stevens WBC. Impact of centralised multidisciplinary expert re-evaluation of diagnostic procedures in patients with newly diagnosed hodgkin lymphoma. Haematologica 2010 October 1;Conference(var.pagings):01.	This is a conference abstract only
Ireland R. Haematological malignancies: the rationale for integrated haematopathology services, key elements of organization and wider contribution to patient care. Histopathology 2011 January;58(1):145-54.	Review article with no data
Jaffe ES. Centralized review offers promise for the clinician, the pathologist, and the patient with newly diagnosed lymphoma. J Clin Oncol 2011 April 10;29(11):1398-9.	This is a discussion paper/expert review

Ogwang MD, Ogwang MD. Accuracy of Burkitt lymphoma diagnosis in constrained pathology settings: importance to epidemiology. ARCH PATHOL LAB MED 2011 April;135(4):445-50.	This paper is not relevant to the current topic – does not discuss integrated reporting
Rogers R. Can we speed up lymphoma fast tracks? Br J Oral Maxillofac Surg 2011 June;Conference(var.pagings):June.	This is a conference abstract only
Roman E. Evaluation of the completeness of national haematological malignancy registration: Comparison of national data with a specialist population-based register. Br J Haematol 2011 April;Conference(var.pagings):April.	This is a conference abstract only
Toptas TS. Microscopic examination of bone marrow aspiration smears: Diagnostic agreement of hematologists and hematopathologists on common hematological diagnoses. Haematologica 2011 June 1;Conference(var.pagings):01.	This is a conference abstract only
British Committee for Standards in Haematology and Royal College of Pathologists. Best Practice in Lymphoma Diagnosis and Reporting - Specific Disease Appendix. 2012.	This is a discussion paper/expert review, Consensus based recommendations not evidence based
Doshi R. Re-audit of central review cases to identify trends in light of the nice iog on haematological cancers. J Pathol 2012 March;Conference(var.pagings):March.	This is a conference abstract only
Engel-Nitz NME. Changes in diagnoses and outcomes for patients of hematopathology specialty and other laboratories. Blood 2012;Conference(var.pagings).	This is a conference abstract only
Finkelstein A. Addenda in pathology reports: Trends and their implications. Am J Clin Pathol 2012;137(4):606-11.	This paper is not relevant to the current topic – does not include integrated reporting
Kohlmann A, Martinelli G, Hofmann WK, Kronnie G, Chiaretti S, Preudhomme C et al. The Interlaboratory Robustness of Next-Generation Sequencing (IRON) Study Phase II: Deep-Sequencing Analyses of Hematological Malignancies Performed by an International Network Involving 26 Laboratories. Blood 2012;120(21).	This is a conference abstract only
Merino A. External quality assessment scheme (EQAS) for blood smear interpreation: Evaluation of the results after one year experience. International Journal of Laboratory Hematology 2012 June;Conference(var.pagings):June.	This is a conference abstract only
National Cancer Action Team and the Royal College of Pathologists. Additional Best Practice Commissioning Guidance for Developing Haematology Diagnostic Services. 2012.	This paper discusses integrated reporting and methods of achieving this but it is a discussion paper.

Orem J, Sandin S, Weibull CE, Odida M, Wabinga H, Mbidde E et al. Agreement between diagnoses of childhood lymphoma assigned in Uganda and by an international reference laboratory. Clinical Epidemiology 2012;4:339-47.	This study examined agreement in diagnosis between a Ugandan lab and a reference lab in the Netherlands
Van Der Walt J. Audit of lymphoma reporting in a regional referral centre. J Pathol 2012 September;Conference(var.pagings):September.	This is a conference abstract only
Westers TM, Westers TM. Standardization of flow cytometry in myelodysplastic syndromes: a report from an international consortium and the European LeukemiaNet Working Group. Leukemia 2012 July;26(7):1730-41.	This is a discussion paper/expert review
Agarwal R, Juneja S. Pitfalls in the diagnosis of haematological malignancies. NZ J MED LAB SCI 2013;67(2):39-44.	This is a discussion paper/expert review
Anliker M, Hammerer-Lercher A, Falkner A, Heiss B, Willenbacher W, Schrezenmeier H et al. Laboratory examination of hematologic diseases in the Interdiscipline Hematologic Competence Center (IHK) of Innsbruck of the Clinic for Hemato-Oncology V of the University Hospital Innsbruck and the Central Laboratory of the University Hospital Innsbruck. Laboratoriumsmedizin-Journal of Laboratory Medicine 2013;37(1):53-63.	Foreign Language
Chan C. Lessons we learn from hematopathology consultation in Taiwan. J Formos Med Assoc 2013;112(12):738-48.	This is a discussion paper/expert review
Cox H, Cox H. Translating biomedical science into clinical practice: Molecular diagnostics and the determination of malignancy. Health: an Interdisciplinary Journal for the Social Study of Health, Illness & Medicine 2013 July;17(4):391-406.	This paper is not relevant to the current topic – does not discuss integrated reporting
Deetz CO, Scott MG, Ladenson JH. Use of a United States-based laboratory as a hematopathology reference center for a developing country: logistics and results. International Journal of Laboratory Hematology 2013 February;35(1):77-81.	This paper was not about integrated reporting but about whether using overseas labs can act as reference labs in developing countries
Fanelli A. One year experience of a qualitative scoring scheme for EQA blood smear interpretation. Biochimica Clinica 2013;Conference(var.pagings):2013.	This is a conference abstract only
Forlenza CJ, Forlenza CJ. Pathology turnaround time in pediatric oncology: a tool to prepare patients and families for the diagnostic waiting period. J Pediatr Hematol Oncol 2013 October;35(7):534-6.	This paper does not relate to haematology
Kohlmann A, Martinelli G, Alikian M, Artusi V, Auber B, Belickova M et al. The Interlaboratory Robustness Of Next-Generation Sequencing (IRON) Study Phase II: Deep-Sequencing Analyses Of Hematological Malignancies	This paper is not relevant to the current topic – does not discuss integrated reporting

Performed In 8,867 Cases By An International Network Involving 27 Laboratories. Blood 2013;122(21).	
N A. External quality assessment scheme (EQAS) for blood smear interpretation: Evaluati on of the results after two years experience. International Journal of Laboratory Hematology 2013 May;Conference(var.pagings):May.	This is a conference abstract only
Rondoni M. Hematologic diagnostic centralized laboratory of a big area enables to acquire actual epidemiologic data of incidence of AML and improves accuracy of diagnosis: Analysis of two years of activity focused on acute myeloid leukemias. Haematologica 2013 October 1;Conference(var.pagings):01.	This is a conference abstract only
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Merino A. External quality assessment scheme (EQAS) for blood smear interpretation: Evaluation of the results after three years experience. International Journal of Laboratory Hematology 2014 June;Conference(var.pagings):June.	This is a conference abstract only
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Cooper MN, de Klerk NH, Greenop KR, Jamieson SE, Anderson, Cooper MN. Statistical adjustment of genotyping error in a case	This paper is not relevant to the current topic – does not discuss integrated reporting
Siddiqui K, Siddiqui K. Development and implementation of a distributed integrated data	This paper is not relevant to the current topic – does not discuss integrated reporting

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.

Review Question

How should level of care be defined and categorised for people with haematological cancers who are having intensive (non-transplant) chemotherapy 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

Background

Most patients who require curative treatment for aggressive haematological malignancies such as acute leukaemia or high-risk myelodysplastic syndrome, receive several cycles of intensive chemotherapy and the protocols used to treat these patients typically lower the blood cell count leading to severe neutropenia resulting in a neutrophil count of less than 0.5 $x10^9$/L. Other toxicities may also be a feature, and older patients and those with co-morbidities are at a higher risk of complications.
Despite improvements in supportive care, these patients are at a high risk of serious and potentially life-threatening infections and other complications.

In recent multicentre UK studies, early mortality following AML induction chemotherapy has been reported as up to 6% and 9% at 30 days and 10% and 15% at 60 days in younger and older patients respectively (Burnett et al Blood 2015; 125, 3878-3885, Burnett et al JCO 2012; 30,3924-31).

Reported induction mortality is also substantial in ALL; 4% in patients <55 and 18% in patients over 55 years (Sive et al BJH 2012;157:463-71). Early mortality in ALL is not improved with the introduction of modern drugs, such as tyrosine kinase inhibitors in Philadelphia positive disease (Fielding AK et al Blood 2014;123, 843-50). Recent data confirm a 2.2% induction death rate in 16-25 year olds treated on paediatric protocols. In 25 – 60 year olds treated on the current NCRI UKALL 14 type schedule, the induction death rate in UKALL 14 currently is 8.5% (personal communication, Dr Clare Rowntree).

Given the high risks of treatments and complexity of patients and speed complications can occur, immediate availability of specialist nursing staff supported initially by medical staff and then by prompt availability) of specialist staff (i.e. consultant/registrar) cover is essential, along with prompt access to other key specialists, especially intensive care. Specialist support services,

especially specialist radiology and laboratory medicine (including transfusion medicine), are also essential on both an emergency and elective basis.

Along with adequate staffing and access to specialist services, the previous 2003 IOG recommended that patients treated on these protocols were nursed for the duration of their neutropenia (14-21 days) in specialist hospital units equipped in single rooms with or without laminar flow or high-efficiency particulate air (HEPA) filtration to reduce the risk of infection. Whereas this became common practice across many NHS units, for a variety of reasons, some patients receive care on an open ward or be allowed home, either through an informal arrangement with ward staff, or, increasingly through the structured delivery of intensive treatment in carefully selected patients (e.g. younger patients with limited co-morbidities) in the ambulatory care setting. However, promptness of clinical review by specialist staff also has to be in place for ambulatory care, where forward planning and policies are of major importance as the patient will have the additional 'lag-phase' of having to self-refer from home or hospital flat before assessment. This has to be balanced against NHS deliverability within working directives and generic/non-specialist hospital at night initiatives etc.

Despite being stipulated by the previous IOG and peer review recommendations, the provision of isolation rooms to protect intensively treated patients against nosocomial infections has proved challenging for NHS units despite rising levels of C. difficile, VRE, MRSA and other antibiotic resistant strains, along with seasonal respiratory viral infections (like influenza) in this population of patients, who are also susceptible to airborne fungal infections.. Although the benefits of isolation are well established in some contexts, it is not clear whether particular levels of protection are more effective in preventing fungal, bacterial and viral infections in severely immunocompromised patients than others. (e.g. standard en-suite rooms compared to more complex laminar flow and HEPA filtration). In any unit, isolation facilities, whether they are simple or complex, are a limited resource. Mandatory NHS isolation policies, designed to protect hospital inpatients as a whole, may impact significantly on bed availability for the intensively treated acute leukaemia patients, particularly during infectious epidemics such as influenza or outbreaks of antibiotic resistant infection. If isolation rooms for this patient population are not available at short notice, chemotherapy treatments may be delayed, or patients looked after in open wards or at home with informal arrangements, all of which may affect survival outcomes.

The standards of care required to deliver chemotherapy to patients with haematological cancer were previously classified according to the complexity of chemotherapy and duration of neutropenia. The 2003 haemato-oncology IOG and subsequent peer review standards stipulated a minimum of five intensive level 2 patients had to be treated per year but the recommendations were imprecise and open to interpretation, with both new and relapsed patients and a number of less intense lymphoma salvage regimens (such as DHAP and ESHAP etc) being potentially included. A further system of classification came from the updated BCSH recommendations. Three levels of care were defined predominantly relating to the facilities and support services required for patient care (BCSH Haematology Task Force, 2009). Whilst there was recognition that some patients may be managed from home, there was no major consideration of delivery of chemotherapy in the ambulatory care setting. Factors such as minimum numbers of patients required per 'level' of care, staff training and competency assessments were not specifically addressed in the BCSH guidelines for the facilities required for the treatment of adults with haematological malignancy (BCSH Haematology Task Force, 2009),

For haematopoietic stem cell transplantation (HSCT), the international FACT-JACIE accreditation standards for transplant programme stipulate minimum numbers for clinical activity. Despite early deaths from intensive induction chemotherapy for acute leukaemia being consistently higher than those associated with autologous stem cell transplantation (where UK adult 100 and 365 day non-

relapse mortality is 2%) and closer to that for allogeneic transplantation (7% at 100 days rising to 16% at 1 year), there is no well defined minimum recommended threshold for unit activity in intensive chemotherapy (reference BSBMT 6th Report to Specialist Commissioners (2015), http://BSBMT.org). Although minimum transplant activity thresholds are not evidence based, there is evidence that implementation of FACT-JACIE standards in haematological practice results in survival benefits for high-risk treatments (Gratwohl A et al Haematologica 2014; 99; 908-15).. There is also a case for having enough patients to perform meaningful analysis of survival outcomes and other audits within any unit undertaking intensive and complex treatments in this high-risk but potentially curable population of cancer patients.

In this IOG update there is a need to review and make clear evidence based recommendations for 24 hour specialist staffing levels and accessibility to isolation facilities, ITU and other support specialities. These are complex facilities and minimum numbers of patients with acute leukaemia and related conditions patients being treated with intensive chemotherapy in an individual unit need consideration in this IOG update. The update takes into account the potential clinical, patient experience and economic impact of intensive chemotherapy treatment in conventional or ambulatory care settings. Age and co-morbidities will also be a necessary consideration.

Levels of Care

A range of different levels of care, corresponding with the variety of diseases treated by haematology services, is required 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*). 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 regular 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. While some patients requiring these regimens may 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) guidelines currently define four levels of care (level 1, 2a, 2b and 3). Level 2b is currently defined as treatment regimens which encompasses those that will predictably cause prolonged periods of neutropenia, 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 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 Burkitt lymphoma or 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 guidelines for level 2b patients. Data for the commonly used salvage regimens (e.g. 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. Consequently these patients may not require the same complex level 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 IOG (2003) and the two versions of the BCSH Guidelines (1995 and 2009) in conjunction with published data relating to toxicity of different regimens with the aim of redefining level 2b and 3 care from the BCSH guidelines and level 2 care from the IOG 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 haematopoietic Stem cell transplantation (HSCT, covering both autologous and allogeneic HSCT procedures).:

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 and Burkitt and lymphoblastic lymphomas (table 1).

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 2).

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 lymphoma would not usually be included in this definition.
Autologous and allogeneic Hematopoietic Stem cell transplantation	Previously referred to as high-dose therapy in IOG 2003. Commissioned centrally through Specialised Commissioning and a centre should meet FACT-JACIE accreditation standards.
Non-intensive chemotherapy	All other chemotherapy not included in the above definitions.

Table 1: Levels of Care

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	Induct 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% <5
			12.5-24 days (without GCSF support) (Ye SG *et al*)	81%>55yrs (Sive *et al, 2012a)*	18% >
	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%

Table 2: Chemotherapy regimens and associated toxicities

Appendix G: Evidence review

Question in PICO format

Population	Intervention	Comparator	Outcomes
Adults and young people (16 years and older) with haematological malignancies and receiving intensive, non-transplant chemotherapy resulting in >7 days of neutropenia of $>0.5 \times 10^9/L$	• Location of chemotherapy delivery (Local hospital, Specialist Centres/Units, Home setting, Community Clinics etc) • Level of in-patient isolation i.e. en-suite (NHS building specifications for isolation i.e. HBN4 or higher NHS/ international isolation specifications for immunocompromised patients, e.g HEPA filtration to protect against nosocomial infection. • Ability to effectively isolate other infectious patients to prevent nosocomial transmission of respiratory viral illnesses (e.g. influenza), Clostridium difficile and resistant organisms (VRE, MRSA, stenotrophomonas and others) • Ambulatory care ,permitting treatment from home or hospital apartments/hotels /Access to 24 hour helpline (part of peer review measure) • Staffing (levels, experience, chemo competency (trained) (medical/nursing/other HC Professionals)) • Centre size/specialism (number of patients treated, specialist expertise available (nutrition, psychological, physio-therapy), including on-site transplant expertise/facility in situations where subsequent transplant is routinely considered, etc) • Access to ICU	Each Other	• Patient Satisfaction • Quality of Life • Survival Outcomes • Treatment related mortality • Treatment delay • ITU admission rates/discharge • Length of stay • Readmission rates • Infection levels (need for prophylactic anti-fungals, antivirals and antibiotics)

Searching and Screening

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1996-Jul 2015	4001	164	15/07/2015
Premedline	Jul 13 2015	462	13	14/07/2015
Embase	1996-Apr 2015	2480	209	15/07/2015
Cochrane Library	Issue , Jul 2015	113	3	20/07/2015
Web of Science (SCI & SSCI) and ISI Proceedings	1900-2015	3742	188	20/07/2015
HMIC	All	7	3	14/07/2015
PscyInfo	1806-Jul 2015	25	3	14/07/2015
CINAHL		1995	31	21/07/2015
Joanna Briggs Institute EBP database	Current to Jul 08 2015	78	3	14/07/2015
OpenGrey		5	0	22/07/2015
HMRN (Haematological Malignancy Research Network)		3	0	22/07/2015
British Committee for Standards in Haematology		35	3	22/07/2015

Total References retrieved (after databases combined, de-duplicated and sifted): 558

Medline search strategy (This search strategy is adapted to each database.)

1. exp Hematologic Neoplasms/
2. ((haematolog* or hematolog* or blood or red cell* or white cell* or lymph* or marrow or platelet*) adj1 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma*)).tw.
3. exp Lymphoma/
4. lymphoma*.tw.
5. (lymph* adj1 (cancer* or neopla* or oncolog* or malignan* or tumo?r*)).tw.
6. hodgkin*.tw.
7. lymphogranulomato*.tw.
8. exp Lymphoma, Non-Hodgkin/
9. (nonhodgkin* or non-hodgkin*).tw.
10. lymphosarcom*.tw.
11. reticulosarcom*.tw.
12. Burkitt Lymphoma/

13. (burkitt* adj (lymphom* or tumo?r* or cancer* or neoplas* or malign*)).tw.
14. brill-symmer*.tw.
15. Sezary Syndrome/
16. sezary.tw.
17. exp Leukemia/
18. (leuk?em* or AML or CLL or CML).tw.
19. exp Neoplasms, Plasma Cell/
20. myelom*.tw.
21. (myelo* adj (cancer* or neopla* or oncolog* or malignan* or tumo?r*)).tw.
22. kahler*.tw.
23. Plasmacytoma/
24. (plasm?cytom* or plasm?zytom*).tw.
25. (plasma cell* adj3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)).tw.
26. Waldenstrom Macroglobulinemia/
27. waldenstrom.tw.
28. exp Bone Marrow Diseases/
29. exp Anemia, Aplastic/
30. (aplast* adj an?em*).tw.
31. exp Myelodysplastic-Myeloproliferative Diseases/
32. exp Myeloproliferative Disorders/
33. exp Myelodysplastic Syndromes/
34. exp Thrombocytopenia/
35. (thrombocytop?eni* or thrombocyth?emi* or poly-cyth?emi* or polycyth?emi* or myelofibros or myelodysplas* or myeloproliferat* or dysmyelopoietic or haematopoetic or hematopoetic).tw.
36. exp Anemia, Refractory/
37. (refractory adj an?em*).tw.
38. (refractory adj cytop?en*).tw.
39. Monoclonal Gammopathy of Undetermined Significance/
40. (monoclonal adj gammopath*).tw.
41. (monoclonal adj immunoglobulin?emia).tw.
42. MGUS.tw.
43. ((oncohaematolog* or oncohematolog*) adj2 (disorder* or disease* or syndrome*)).tw.
44. or/1-42
45. limit 44 to yr="2000 - 2015"
46. exp Antineoplastic Combined Chemotherapy Protocols/st
47. exp Antineoplastic Agents/st
48. Antimetabolites, Antineoplastic/st
49. (chemotherap* adj (regim* or protocol* or combin*)).tw.
50. intensive chemotherap*.tw.
51. (immunochemotherap* or immuno-chemotherap*).tw.
52. polychemotherap*.tw.
53. or/46-52
54. FLAG.tw.
55. Fludarabine/
56. Cytarabine/
57. Granulocyte Colony-Stimulating Factor/
58. 55 and 56 and 57
59. ((fludarabine or fludara) and (cytarabine or "Ara C" or "cytosine arabinoside") and (g-csf or granulocyte colony-stimulating factor)).tw.
60. 54 or 58 or 59

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61. FLAG-IDA.tw.
62. Idarubicin/
63. 58 and 62
64. (idarubicin or zavedos).tw.
65. 59 and 64
66. 61 or 63 or 65
67. DHAP.tw.
68. exp Dexamethasone/
69. Cisplatin/
70. 68 and 69 and 56
71. ((dexamethasone or decadron or oradexon or dexafree or dexsol) and (cytarabine or "Ara C" or "cytosine arabinoside") and (cisplatin or platinol)).tw.
72. 67 or 70 or 71
73. ESHAP.tw.
74. Etoposide/
75. exp Methylprednisolone/
76. 74 and 75 and 56 and 69
77. ((etoposide or VP-16 or etopophos or vepesid) and (cytarabine or "Ara C" or "cytosine arabinoside") and (cisplatin or platinol) and methylprednisolone).tw.
78. 73 or 76 or 77
79. IVE.tw.
80. Ifosfamide/
81. Epirubicin/
82. 80 and 81 and 74
83. ((ifosfamide or mitoxana) and (epirubicin or pharmorubicin) and (cytarabine or "Ara C" or "cytosine arabinoside") and (etoposide or VP-16 or etopophos or vepesid)).tw.
84. 79 or 82 or 83
85. ICE.tw.
86. Carboplatin/
87. 80 and 86 and 74
88. ((ifosfamide or mitoxana) and carboplatin and (etoposide or VP-16 or etopophos or vepesid)).tw.
89. 85 or 87 or 88
90. (mini-BEAM or BEAM).tw.
91. Carmustine/
92. Melphalan/
93. 91 and 74 and 56 and 92
94. ((carmustine or BICNU) and (etoposide or VP-16 or etopophos or vepesid) and (cytarabine or "Ara C" or "cytosine arabinoside") and melphalan).tw.
95. 90 or 93 or 94
96. DT-PACE.tw.
97. Thalidomide/
98. Doxorubicin/
99. Cyclosphamide/
100. 68 and 97 and 69 and 98 and 99 and 74
101. ((dexamethasone or decadron or oradexon or dexafree or dexsol) and (thalidomide or celgene) and (cisplatin or platinol) and (doxorubicin or adriamycin) and cyclophosphamide and (etoposide or VP-16 or etopophos or vepesid)).tw.
102. 96 or 100 or 101
103. CODOX-M IVAC.tw.
104. Vincristine/
105. Methotrexate/

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106. 99 and 104 and 98 and 105 and 74 and 80 and 56
107. (cyclophosphamide and (vincristine or oncovin) and (doxorubicin or adriamycin) and methotrexate and (etoposide or VP-16 or etopophos or vepesid) and (ifosfamide or mitoxana) and (cytarabine or "Ara C" or "cytosine arabinoside")).tw.
108. 103 or 106 or 107
109. DA.tw.
110. Daunorubicin/
111. 56 and 110
112. (daunorubicin and (cytarabine or "Ara C" or "cytosine arabinoside")).tw.
113. 109 or 111 or 112
114. ADE.tw.
115. 56 and 110 and 74
116. ((cytarabine or "Ara C" or "cytosine arabinoside") and daunorubicin and (etoposide or VP-16 or etopophos or vepesid)).tw.
117. 114 or 115 or 116
118. (FLAG or FLAG-IDA or DHAP or ESHAP or IVE or ICE or BEAM or mini-BEAM or DT-PACE or CODOX-M IVAC or DA or ADE).ps.
119. 53 or 60 or 66 or 72 or 78 or 84 or 89 or 95 or 102 or 108 or 113 or 117
120. rituximab.tw.
121. 119 and 120
122. 119 or 121
123. exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
124. leuk?emi*.tw.
125. (akut$ or acut$).tw.
126. 124 and 125
127. 123 or 126
128. Induction Chemotherapy/
129. Consolidation Chemotherapy/
130. (chemotherap* adj2 (induction or consolidat* or intensi*)).tw.
131. or/128-130
132. 127 and 131
133. 122 or 132
134. 45 and 133
135. exp Health Services/ma, st, ut
136. models, organizational/
137. exp Health Resources/og, st, ut
138. exp "Delivery of Health Care"/ma, mt, og, st, ut
139. Health Services Accessibility/og, st
140. Patient-Centered Care/ma, mt, og, st, ut
141. patient care plan*.tw.
142. Health Facilities/ma, st, ut
143. exp Health Facility Size/ma, og, st, sd
144. Health Manpower/
145. Specialization/
146. "Delivery of Health Care, Integrated"/
147. ("model* of care" or "level* of care" or "care model*" or "standard* of care" or "care standard*").tw.
148. ("care coordination" or "care co-ordination").tw.
149. (specialist* or expert* or expertise).tw.
150. Centralized Hospital Services/

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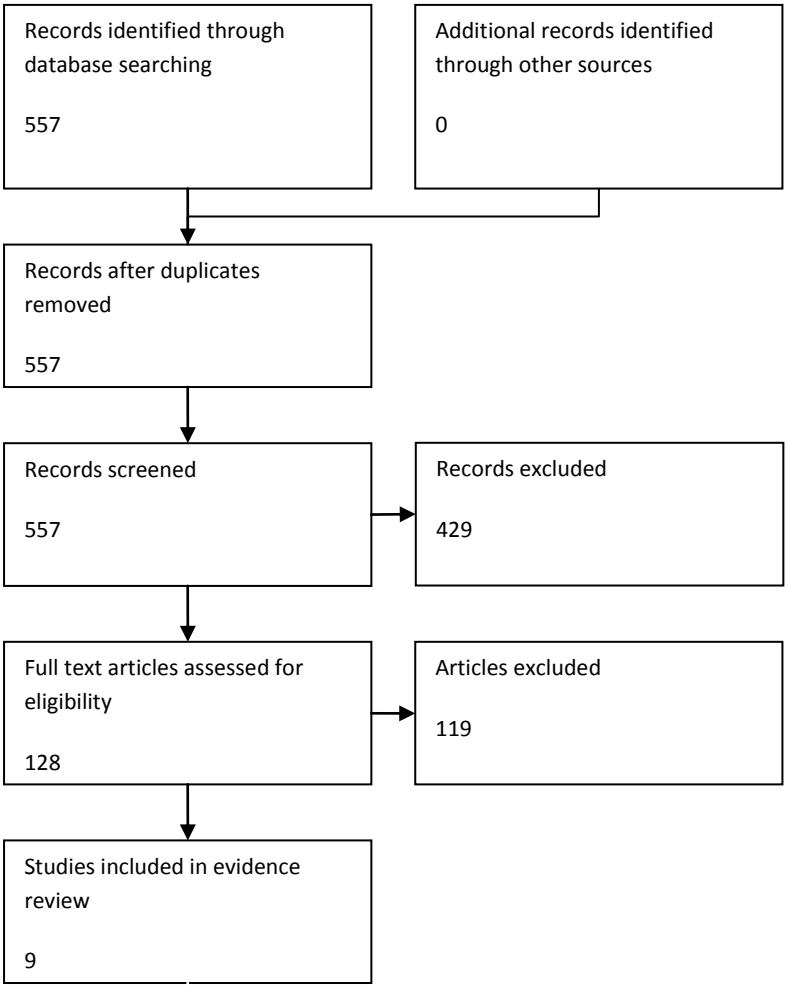
151. ((integrat* adj3 healthcare) or (integrat* adj3 health care) or (integrat* adj3 service*) or (integrat* adj3 care*)).tw.
152. ((integrat$ adj3 provision) or (integrat$ adj3 organisation$)).tw.
153. (supercentre* or supercenter* or "super centre*" or "super center*").tw.
154. exp Regional Health Planning/
155. ((local adj hospital*) or facility* or centre* or center* or service* or clinic* or unit* or site*).tw.
156. ((outreach or satellite*) adj (healthcare or health care or care or service* or centre* or center* or clinic* or unit* or department* or facilit* or site*)).tw.
157. co-locat*.tw.
158. Cancer Care Facilities/
159. Oncology Service, Hospital/
160. Medical Oncology/ma, og, st
161. Ancillary Services, Hospital/
162. (support* adj (service* or facilit* or unit* or department* or on-site)).tw.
163. ((haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog* or oncolog*) adj2 (service* or facilit* or unit* or department* or on-site)).tw.
164. outpatients/
165. ambulatory care facilities/
166. exp Ambulatory Care/ma, st, ut
167. (ambulatory care or ambulatory health care or ambulatory healthcare).tw.
168. (ambulatory service* or ambulatory health service*).tw.
169. Outpatient Clinics, Hospital/
170. (outpatient* or out-patient*).tw.
171. Day Care/ma, og, st, ut
172. (day adj (care or case* or unit* or facilit*)).tw.
173. Hospital Shared Services/
174. shared care.tw.
175. exp Hospitalization/
176. ((hospital* or inpatient* or in-patient* or patient*) adj (admission* or admitted or readmission* or re-admission* or readmitted or re-admitted)).tw.
177. Patient Isolation/
178. (patient* adj2 isolat*).tw.
179. Hemodialysis Units, Hospital/
180. exp Emergency Medical Services/ma, og, st, ut
181. (emergenc* adj (healthcare or health care or care or service* or centre* or center* or clinic* or unit* or department* or facilit* or site*)).tw.
182. Intensive Care Units/
183. exp Critical Care/ma, og, st, ut
184. (critical care or intensive care or high dependency or ICU or HDU).tw.
185. (intensive therapy unit or ITU).tw.
186. exp health personnel/
187. staff*.tw.
188. (haematologist* or hematologist* or haemato-oncologist* or hemato-oncologist* or oncologist*).tw.
189. Nursing Services/
190. Oncology Nursing/
191. (nurs* adj2 (haematolog* or hematolog* or haemato-oncolog* or hemato-oncolog*)).tw.
192. Nurse's Role/
193. Clinical Nursing Research/
194. Inservice Training/og, st
195. Pharmacies/ma, og, st, ut

196. exp Pharmaceutical Services/
197. Pharmacists/
198. exp Home Care Services/
199. (home adj2 (care or nursing or service*)).tw.
200. exp Community Health Services/
201. (communit* adj2 (care or nursing or service* or clinic*1 or unit* or centre* or center*)).tw.
202. Social Support/
203. Palliative Care/ma, og, st, ut
204. Catheterization, Central Venous/st, ut
205. (prophyla* adj2 (anti-fungal* or antiviral* or antibiotic*)).tw.
206. Catheter-Related Infections/pc
207. Bacterial Infections/pc
208. Bacteremia/pc
209. Cross Infection/pc
210. exp Infection Control/mt, og, st
211. Environment, Controlled/
212. *Filtration/
213. HEPA filtration.tw.
214. high efficiency particulate air filtration.tw.
215. (air adj2 (filtration or filter*)).tw.
216. or/135-215
217. 134 and 216

Screening Results



Reasons for Exclusion
Expert Reviews
Abstract Only
No Comparators
Treatment Comparisons not relevant to PICO
Population not relevant to PICO
Included in a systematic review

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n=1)
Randomized controlled trial (n=1)
Prospective cross sectional study (n=0)
Case Series Studies (n=7)
Qualitative Study (n=0)

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 impacted 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.

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
1	**Bakshi et al (2009)**	Retrospective Analysis	To assess the outcomes of high dose cytosine arabinoside consolidation cycles versus inpatient in paediatric AML patients	N=30	Outpatient Chemotherapy	Inpatient Chemotherapy	• Mortality • Morbidity • Antifungal use
2	**Hutter et al (2009)**	Retrospective cohort control	To assess thecorrelation between improvement of room comfort conditions in patients with newly diagnosed AML on a haematological waard and the incidence of invasive pulmonary aspergillosis	N=63	Post Room Renovation • 2 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	Pre Room Renovation • 2 patients per room • 6 patients sharing a toilet placed outside the room • Washing basin inside the room • Shower accross the hospital corridor • No ventilation system, air filtration or room pressurisatio n • No false ceilings	• Incidence of invasive pulmonary aspergillosis
3	**Lehrnbecher et al (2012)**	Retrospective Study	To assess institutional recommendations	N=336 centres in 27 countries	Recommendations on restrictions	Each other	• Variation in recommendations for social contact, exposure to

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
			regarding restrictions of social contacts, pates and food and instructions on wearing face masks in public for children with standard risk ALL and any risk AML during intensive chemotherapy				pets, food and the use of face masks in public • Restriction scores by location and centre size
4	**Luthi et al (2012)**	Retrospective study	N=17	To evaluate the safety, feasibility and costs of home care for the administation of intensive chemotherapy	Chemotherapy in the home care setting	Inpatient chemotherapy	• Feasibility • Safety • Quality of Life • Satisfaction of patients and relatives
5	**Schlesinger et al (2009)**	Systematic review and meta analysis	To quantify the evidence for infection control interventions among high risk cancer patients and haematopeitic stem cell recipients	N=40 studies	Infection control interventions Protective Isolation	No intervention Placebo Other interventions	• All cause mortality at 30 days, 100 days, and the longest follow-up in each study • Rate of infection • Type of infection • Length of hospital stay • Length of febrile period • Infection related mortality • Bacterial and fingal colonisation • Antibiotic and actifungal treatment
6	**Sive et al (2012)**	Audit	To present the experience in managing patients receiving intensive chemotherapy and HSCT protocols on daycare basis with full nursing and medical support while staying in a hotel within	N=668	Hotel Based Outpatient Care		• Admissions

Study		Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes
			walking distance of the hospital				
7	**Sopko et al (2012)**	Retrospective Case series	To investigate the safety and feasibility of home care following consolidation chemotherapy	N=45	Home care after consolidation chemotherapy	Inpatient care after consolidation chemotherapy	• Discharge Rates • Mortality
8	**Stevens et al (2005)**	Randomised cross over trial	To compare two models of health care delivery for children with ALL	N=29	Home Chemotherapy	Hospital Chemotherapy	• Quality of life (child) • Effect on parental care givers • Adverse effects • Cost
9	**Stevens et al (2004)**	Prospective descriptive study, nested in a randomised cross over trial	To evaluate quality of life, nature and incidence of adverse effects, parental caregiver burden and direct and indirect costs of a home chemotherapy program for children with cancer	N=33 (health practitioners)	Home Chemotherapy	Hospital Chemotherapy	• Perceived family benefits • Human Resources and service delivery implications • Hospital health practitioners perspective • Community Health practitoners perspective

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); 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); 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); 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); 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).

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).

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 (2 patients per room, 6 patients sharing a toilet placed outside the room, wash basin inside the room, shower across the hospital corridor, no ventilation system, air filtration or room pressurisation, no false ceilings) stayed 3 days longer compared with those treated on the newly renovated ward (2 patients per room, separate bath 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 aspergillus (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); 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); there were 1443 admissions to the Ambulatory Care Unit (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).

Very low quality evidence (grade table 2) from one retrospective analysis of 30 patients (Bakshi et al, 2009); 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); 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 (Bakshi et al, 2009); 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 (Bakshi et al, 2009); 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

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 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 POQOLS measures when they switched from home based treatment to hospital based treatment with an average change of 5.2 while standard care patients experienced an improvement in QoL when they switched to home based treatment with an average score of -10.5 (p=0.023)
Patients in the home-based group had significantly higher scores for factor 2 (emotional distress) measures compared with the hospital treatment group (pair wise comparison at the end of each 6 months phase p=0.043).

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 seemed 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 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 and87% 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), 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.

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

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)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 coordinated.

> *"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 tests carried out, 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); 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.

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); 2 clinic nurses and 3 paediatric oncologists reported no change in their workload; 5 clinic nurses and 1 physician reported an increase due to the increased volume of paperwork and 3 clinic nurses reported a decrease. 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) thing.

> *"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); home treatment required 1 physician visit and 2 nurse visits per day accounted 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 9 cases and needle disconnection from the port of the catheter occurred in 2 cases

2 major pump failures were reported resulting in one overnight hospitalisation and a 4 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 do 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 facemasks, 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.

Grade Tables

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

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 days**[1]	**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 days**[1]	**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

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]	studies: RR=0.75 (0.68-0.83)
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: RR=0.66 (0.56-0.79)
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 low**[3,4,5]	
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 studies[6])	**very low**[3,4,]	
Number of antibiotic days	**Study population**	**RR 0.81**	0	**very**	

Appendix G: Evidence review

Follow-up: 3-36 months		(0.75 to 0.85)[2,7]	(3 studies[6])	**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

Grade Table 1: 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 (Bakshi et al, 2009)	N/R	N/R	N/R	30	**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.		(1 study)		
Transfusions (Bakshi et al, 2009)	**Study population** Median of 1 (0-4) unit of packed red blood cells | Median of 2 (0-5) units of packed red blood cells Median of 1 (0-13) platelet transfusions | Median of 2 (0-12) platelet transfusions	N/R	0 (1 study)	**very low**[1]	
Antibiotic Use (Bakshi et al, 2009)	**Study population** 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)	N/R	0 (1 study)	**very low**[1]	
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** See evidence statements and evidence tables for detailed results	N/R	0 (1 study)	**very low**[1]	

Impact on practitioners (Stevens et al, 2004)	See evidence statements and evidence tables for detailed results	N/R	0 (1 study)	**very low**[1]	Paediatric 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					

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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.

Evidence Tables

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
Bakshi et al (2009) USA,					
Retrospective Analysis **July 2003-July 2007**	To assess the outcomes of high dose cytosine arabinoside consolidation cycles versus inpatient in paediatric AML patients	N=30 patients received 90 HIDAC cycles • Median Age was 8 years (1.5-15) • 23 patients ha standard daunorubicin and cytosine arabinoside • 7 patients received daunorubcin, cytosine arabinoside and etopside as induction • 21/90 cycles were administered as inpatients and 69 as outpatient	Outpatient Chemotherapy	Inpatient Chemotherapy	• Mortality • Morbidity • Antifungal use • Median number of blood investigations (complete blood counts/liver function tests/renal function tests) was significantly lower in the outpatient group. • 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. • A median of 1 (0-13) platelet transfusions were administered at the outpatient clinic and 2 (0-12) in the inpatient setting • 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. • There was no significant difference between inpatient and outpatient mortality. • Febrile neutropenia was recorded in 66/90 cycles; 50 in the outpatient group and 16 in the inpatient group. • 16/50 outpatients and 10/16 inpatients required second line antibiotics ($p=0.03$) and mean duration of antibiotic administration was significantly lower in the outpatient group ($p=0.04$). • There was significantly more use of therapeutic antifungals in the inpatient group compared with the outpatient group. ***Comments*** ***Study Quality*** Not randomised Outpatient chemotherapy was administered to patients who could not get an inpatient bed in time to avoid treatment delays (possible selection bias)

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					Comments Only results from round 2 randomisation are relevant to this topic Patients were randomised to round 1 intensive chemotherapy and if they reached complete remission were eligible for round 2 randomisation between ambulatory and intensive postremission therapy with stratification by centres, AML type and round 1 treatment group.
					Study Quality Only patients with complete remission in after round 1 treatment were put forward for round 2 randomisation
Hutter et al (2009) Germany **Follow-up= 8 years**					
Retrospective cohort control **November 2000 (renovation happened in October 2006)**	To assess thecorrelation between improvement of room comfort conditions in patients with newly diagnosed AML on a haematological waard and the incidence of invasive pulmonary aspergillosis	N=63 N=28 patients after renovation works N=35 patients before renovation works	Post Room Renovation 2 patients per room Separate restroom in each room equipped with toilet, wash basin and shower No ventilation system, air filtration or room pressurisation No false ceilings	Pre Room Renovation 3 patients per room 6 patients sharing a toilet placed outside patients room Washing bowl inside patients room Showering involved crossing the hospital corridor	Incidence of invasive pulmonary aspergillosis Patients treated before renovation stayed 3 days longer compared with the treated on the newly renovated ward. There was no significant difference in median time of aplasia which was 1.0 longer (18.5 versus 19.5 days) in the pre-renovation cohort (p=0.69). 39% of pre-renovation patients and 34% of post-renovation patients developed an invasive pulmonary aspergillis (p=0.79) with diagnosis usually determined on CT scan. Patients in the post-renovation cohort received more CT scans (64% versus 54%) 2 patients in the pre-renovation group died during initial AML treatment versus 4 in the post-renovation group. Average *Aspergillus fumigates* was 7 (0-28) CFU/m^3 pre-renovation and was 19 (0-106) CFU/m^3 post-renovation. Aspergillus air concentration was measured 11 times from November 2002 until the ward closed and 9 times after the new ward opened and cumulative concentration of fungal spores was 75 (2-273) CFU/m^3 in the rooms pre-renovation compared with 209 (67-299) CFU/m^3 post renovation
					Comments

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>No ventilation system, air filtration or room pressurisation
No false ceilings</td><td>Study Quality

Not biased
Small sample</td></tr>
<tr><td colspan="6">Lehrnbecher et al (2012), Multiple countries including UK</td></tr>
<tr><td>Retrospective Study</td><td>To assess institutional recommendations regarding restrictions of social contacts, pates and food and instructions on wearing face masks in public for children with standard risk ALL and any risk AML during intensive chemotherapy</td><td>N=336 centres in 27 countries</td><td>Recommendations on restrictions</td><td>Each other</td><td>• Variation in recommendations for social contact, exposure to pets, food and the use of face masks in public
• Restriction scores by location and centre size

N=336 centres in 27 countries (1-76 institutions per country) responded to the survey.
Overall response rate for the study was 61% (range per country was 34%-100%)
21 centres in the UK were approached of which 16 responded constituting 4.8% of the total centres responding to the survey.
The majority of centres had fewer than 20 newly diagnosed patients with ALL and fewer than 5 patients newly diagnosed with AML per year.
<table>
<tr><th></th><th>No. of newly diagnosed patients</th><th>No. of centres (%)</th></tr>
<tr><td>ALL</td><td><10</td><td>120 centres (36%)</td></tr>
<tr><td></td><td>10-19</td><td>112 centres (33%)</td></tr>
<tr><td></td><td>20-40</td><td>73 centres (22%)</td></tr>
<tr><td></td><td>>40</td><td>31 centres (5%)</td></tr>
<tr><td>AML</td><td><5</td><td>231 centres (68%)</td></tr>
<tr><td></td><td>5-10</td><td>26 centres (8%)</td></tr>
<tr><td></td><td>>10</td><td>79 centres (24%)</td></tr>
</table>
107 centres (32%) had written protocols for non-pharmacological anti-infective approaches and n=64 (64%) had a general agreement without a written policy.</td></tr>
</table>

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
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.

Social Contact
Most centres do not allow children with AML to visit indoor public place, attend daycare or kindergarten or attend school while recommendations for patients with ALL varied considerably.
Restrictions mostly related to neutropenia (58%) and to chemotherapy regimens.
The health of surrounding people was a pre-condition for reduced restrictions in 16% of centres.

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%).

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%).

Face Masks
9% (n=30) institutions recommended children with ALL wear face masks in public while 34% (n=114) recommend 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.

Restriction scores in Europe were significantly higher than in USA, suggesting greater restrictions

<table>
<tr><th></th><th colspan="3">Social Restrictions (Max score, 12)</th><th colspan="3">Pet Restrictions (max score 10)</th><th colspan="3">Food Restrictions (Max score 10)</th></tr>
<tr><th></th><th>USA/Canada</th><th>Europe</th><th>P</th><th>USA/Canada</th><th>Europe</th><th>P</th><th>USA/Canada</th><th>Europe</th><th>P</th></tr>
<tr><td>ALL</td><td>5 (0-12)</td><td>7 (0-12)</td><td><0.001</td><td>3 (0-8)</td><td>5 (0-10)</td><td>0.06</td><td>6 (0-13)</td><td>10 (0-16)</td><td><0.001</td></tr>
<tr><td>AML</td><td>8 (0-12)</td><td>9 (0-12)</td><td>0.04</td><td>4 (0-10)</td><td>5 (0-10)</td><td>0.02</td><td>8 (0-16)</td><td>11 (0-16)</td><td><0.001</td></tr>
<tr><td>P</td><td><0.001</td><td>).007</td><td></td><td>0.007</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Restriction scores did not differ by centre size

<table>
<tr><th></th><th colspan="3">Median Score (range)</th></tr>
<tr><th>New patients per year</th><th>Social Restrictions (max score 12)</th><th>Pet Restrictions (max score 10)</th><th>Food restrictions (max score 16)</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>ALL</td><td></td><td></td><td></td></tr>
<tr><td><10</td><td>7 (0-12)</td><td>5 (0-10)</td><td>9 (0-16)</td></tr>
<tr><td>10-19</td><td>6 (0-12)</td><td>4 (0-10)</td><td>10 (0-16)</td></tr>
<tr><td>20-40</td><td>6 (0-10)</td><td>6 (0-10)</td><td>8 (0-16)</td></tr>
<tr><td>>40</td><td>6 (0-10)</td><td>4 (0-10)</td><td>11 (0-16)</td></tr>
<tr><td>p</td><td>0.42</td><td>0.59</td><td>0.39</td></tr>
<tr><td>AML</td><td></td><td></td><td></td></tr>
<tr><td><5</td><td>9 (0-12)</td><td>5 (0-10)</td><td>10 (0-16)</td></tr>
<tr><td>5-10</td><td>9 (0-12)</td><td>5 (0-10)</td><td>12 (0-16)</td></tr>
<tr><td>>10</td><td>9(0-12)</td><td>4.5 (0-10)</td><td>10.5 (0-16)</td></tr>
</table>
Comments
Each question received a score of 2 for always restricted, 1 for sometimes restricted and 0 for no restrictions.

Study Quality
</td></tr>
<tr><td colspan="6">Luthi et al (2012), Switzerland</td></tr>
<tr><td>Retrospective study

November 1998-April 2001</td><td>N=17

Inclusion
16 years or older
Assigned to a relevant intensive chemotherapy treatment
Fitted with a central venous catheter
Live within 30km of the hospital
Relative consenting to be a care giver for the study duration</td><td>To evaluate the safety, feasibility and costs of home care for the administation of intensive chemotherapy</td><td>Chemotherapy in the home care setting</td><td>Inpatient chemotherapy

A subgroup of patients (n=7) received the same chemotherapy regimen at home and in the inpatient setting. These patients had already been treated in hospital and agreed to their next treatment being at home</td><td>

Feasibility
Safety
Quality of Life
Satisfaction of patients and relatives

Feasibility
1 physician visit and 2 nurse visits per day accounted 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 9 cases and needle disconnection from the port of the catheter occurred in 2 cases
2 major pump failures were reported resulting in one overnight hospitalisation and a 4 day hospitalisation.

Safety
3 patients experienced medical complications; heart failure, angina attack and an allergic reaction to BCNU. All complications were treated at home and no hospitalisation was required
Grade 1-2 nausea and vomiting occurred during 36% of chemotherapy cycles are were dealt with at home
There were no requests for hospitalisation during home care from patients or carers
There were 8 unplanned hospital admissions following the home care period, 5 for febrile neutropenia, 2 for fever without documented infection and one for pneumonia.

Quality of Life</td></tr>
</table>

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					79% (73/92) questionnaires were returned completed. Mean FLIC score was 115.5±20.8 on day 1 of treatment (37 questionnaires) and remained stable until last day of treatment (114±21.1; 36 questionnaires). Questionnaires from 5 patients could be compared for home care and inpatient care (8 questionnaires; 37 chemotherapy cycles) and there was no difference in overall FLIC score or the seven individual FLIC categories. WHO performance status was 0 for 50% of patients on day 1 and remained stable at 0 in 28% of patients during chemotherapy and increased to one in 65% and 2 in 27% patients respectively. *Satisfaction of patients and relatives* 70% of patients returned questionnaires (32 questionnaires on 46 treatment cycles) 31 cases reported to be 'very satisfied' with home care and one case reported being 'satisfied' None of the patients showed a preference for inpatient care for 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 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 87% did not record any anxiety during home care treatment The main patient reported disadvantages were feelings of dependency on a relative (19%) and or being a burden (6%) Other concerns related to potential technical problems of the pump and side effects of chemotherapy Relative returned 29 questionnaires (63%) and all were in favour of home care and 97% were in favour of home care for next treatment (1 did not answer the question) 90% of relatives reported better tolerance to treatment (fewer side effects, less distress) as advantages of home care. 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%)
					Comments
					Study Quality Recall bias Small sample size

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td colspan="6">Schlesinger et al (2009)

Long enough to record the period covering engraftment after HSCT, neutropenia resolution and/or attainment of complete remission

Ranged from 100 days to 3 years</td></tr>
<tr><td>Systematic review and meta analysis</td><td>To quantify the evidence for infection control interventions among high risk cancer patients and haematopeitic stem cell recipients</td><td>Cancer patients in the hospital or ambulatory setting who were receiving chemotherapy for solid tumours, haematological malignancies and/or HSCT recipients.

N=40 studies

N=26 assessed protective isolation (14 randomised)
N=11 assessed outpatient versus inpatient care (non-randomised)
N=3 assessed unique interventions such as footwear exchange, Shinki bioclean rooms and a neutropenic diet

29 studies included patients with acute leukaemia
6 studies included other haematological cancers
2 studies included breast cancer patients undergoing HSCT
1 study included patients with aplastic anaemia
1 study included</td><td>Infection control interventions

Protective Isolation</td><td>No intervention

Placebo

Other interventions</td><td>• All cause mortality at 30 days, 100 days, and the longest follow-up in each study
• Rate of infection
• Type of infection
• Length of hospital stay
• Length of febrile period
• Infection related mortality
• Bacterial and fingal colonisation
• Antibiotic and actifungal treatment
• Adverse Events

All cause Mortality
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); 100 days (RR=0.79, 95% CI, 0.73-0.87) and at the longest available follow-up (RR=0.86, 95% CI 0.81-0.91).
No significant heterogeneity was observed when combining randomised and non-randomised studies (I^2=14.8%)

<table>
<tr><td>Protective environment/prophylactic antibiotics</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>30 day follow-up</td><td>9 studies
N=838 patients

RR=0.66 (0.49-0.87)</td><td>6 studies
N=5442

RR=0.57 (0.45-0.71)</td><td>15 studies
N=6280

RR=0.6 (0.5-0.72)</td></tr>
<tr><td>Any closest to 100 day follow-up</td><td>12 studies
N=1015 patients

RR=0.79 (0.73-0.87)</td><td>8 studies
N=5877 patients

RR=0.8 (0.72-0.88)</td><td>21 studies
N=6892 patients

RR=0.79 (0.73-0.87)</td></tr>
<tr><td>Longest follow-up</td><td>8 studies
N=691 patients

RR=0.84 (0.77-0.93)</td><td>5 studies
N=5382 patients

RR=0.87 (0.81-0.93)</td><td>13 studies
N=6073 patients

RR=0.86 (0.81-0.91)</td></tr>
<tr><td>PEPA versus no preventative measures</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any closest to 100 day follow-up</td><td>8 studies
N=538

RR=0.69 (0.56-0.84)</td><td>4 studies
N=512

RR=0.61 (0.43-0.85)</td><td>12 studies
N=1050

RR=0.66 (0.55-0.79)</td></tr>
<tr><td>Air Quality Control and Barrier Isolation</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td>patients high risk patients with sarcoma undergoing intensive chemotherapy</td><td></td><td></td><td>
<table>
<tr><td>Any closest to 100 day follow-up</td><td>8 studies
N=484

RR=0.86 (0.67-1.10)</td><td>2 studies
N=387

RR=1.20 (0.78-1.86)</td><td>10 studies
N=961

RR=0.93 (0.75-1.15)</td></tr>
<tr><td>Air Quality Control Alone</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any closest to 100 day follow-up</td><td>2 studies
N=66

RR=0.88 (0.58-1.33)</td><td>3 studies
N=5154

RR=0.81 (0.73-0.91)</td><td>5 studies
N=5220

RR=0.81-0.91)</td></tr>
<tr><td>Barrier Isolation Alone</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any closest to 100 day follow-up</td><td>2 studies
N=68

RR=1.25 (0.66-2.38)</td><td></td><td></td></tr>
<tr><td>Endogenous Flora Suppression</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any closest to 100 day follow-up</td><td>3 studies
N=155

RR=0.8 (0.56-1.16)</td><td>1 study
N=99

RR=1.11 (0.56-2.18)</td><td>3 studies
N=254

RR=0.88 (0.63-1.21)</td></tr>
</table>

Any clinically and/or microbiologically documented infection
Protective isolation significantly reduced the occurrence of any clinically and/or microbiologically documented infection when considering all studies together, studies assessing PEPA and studies assessing air quality control and barrier isolation. No significant difference was observed when assessing barrier isolation alone.

<table>
<tr><td>Protective environment/prophylactic antibiotics</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>11 studies
N=859

RR=0.61 (0.52-0.71)</td><td>9 studies
N=1045

RR=0.92 (0.79-1.06)</td><td>20 studied
N=1904

RR=0.75 (0.68-0.83)</td></tr>
<tr><td>PEPA versus no preventative measures</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>7 studies
N=439

RR=0.52 (0.42-.64)</td><td>6 studies
N=601

RR=0.75 (0.60-0.95)</td><td>13 studies
N=1040

RR=0.62 (0.53-0.76)</td></tr>
<tr><td>Air Quality Control and Barrier Isolation</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>7 studies
N=478

RR=0.71 (0.6-0.85)</td><td>2 studies
N=387

RR=0.35 (0.23-0.55)</td><td>9 studies
N=865

RR=0.61 (0.51-0.72)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study Type/Setting</th><th>Aim</th><th>Population</th><th>Intervention</th><th>Comaprison</th><th>Outcomes and results</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Air Quality Control Alone</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>1 study
N=21

RR=0.91 (0.43-1.90)</td><td>3 studies
N=249

RR=1.54 (1.25-1.89)</td><td>4 studies
N=270

RR=1.48 (1.21-1.80)</td></tr>
<tr><td>Barrier Isolation Alone</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>2 studies
N=74

RR=1.64 90.93-2.89)</td><td></td><td></td></tr>
<tr><td>Endogenous Flora Suppression</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Any clinically and/or microbiologically documented infection</td><td>3 studies
N=136

RR=0.89 (0.72-1.10)</td><td>2 studies
N=228

RR=0.97 (0.65-1.46)</td><td>5 studies
N=364

RR=0.92 90.75-1.14)</td></tr>
</table>
Infection related mortality, bacteraemia, respiratory tract infections
Protective isolation resulted in significant reductions in infection related mortality, bacteraemia, and respiratory tract infections.
No significant benefit of protective isolation (all studies used air quality control) was observed in relation to mould infections nor was the need for systemic antifungal treatment reduced (RR=1.02, 95% CI 0.88-1.18).
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).
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).
Duration of hospital stay was shorter with protective isolation in 2 of 5 studies and was longer or similar length in the remaining 3 studies.
Discontinuation of the intervention was reported in 2-42% of patients as a result of psychological intolerance (usually occurring in older or sicker patients).
<table>
<tr><td>Protective environment/prophylactic antibiotics</td><td>Randomised</td><td>Non-randomised</td><td>All</td></tr>
<tr><td>Bacteraemia</td><td>9 studies
N=683

RR=0.48 (0.35-0.66)</td><td>6 studies
N=860

RR=0.79 (0.63-0.98)</td><td>15 studies
N=0.66 (0.55-0.79)

RR=0.66 (0.55-0.79)</td></tr>
<tr><td>Infections per 100 patient days</td><td>10 studies
N=36610

RR=0.59 (0.49-0.70)</td><td>4 studies
N=29821

RR=0.39 (0.27-0.55)</td><td>14 studies
N=66428

RR=0.53 (0.45-0.63)</td></tr>
</table>
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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results

Gram positive infections	10 studies N=966 RR=0.55 (0.4-0.76)	7 studies N=515 RR= 0.76 (0.62-0.91)	17 studies N=1481 RR=0.66 (0.56-0.79)
Gram negative infections	12 studies N=1136 RR=0.49 (0.40-0.62)	7 studies N=515 RR=0.70 (0.54-0.91)	19 studies N=1651 RR=0.55 (0.46-0.66)
Candida Infections	9 studies N=726 RR=0.31 (0.19-0.52)	6 studies N=5740 RR=0.84 (0.67-1.05)	15 studies N=6466 RR=0.69 (0.56-0.85)
Fungal Infections	6 studies N=388 RR=0.84 (0.33-2.14)	3 studies N=591 RR=0.42 (0.08-2.10)	9 studies N=979 RR=0.69 (0.31-1.53)
Infection related mortality	10 studies N=889 RR=0.54 (0.4-0.73)	6 studies N=860 RR=1.33 (0.89-1.99)	16 studies N=1749 RR=0.74 (0.59-0.93)
Respiratory Infection	10 studies N=776 RR=0.45 (0.32-0.63)	6 studies N=723 RR=0.77 (0.46-1.28)	16 studies N=1499 RR=0.53 (0.40-0.70)
Intervention discontinuation	5 studies N=394 RR=1.54 (0.93-2.56)	3 studies N=470 RR=57.0 (8.86-366)	8 studies N=864 RR=4.34 (2.78-6.76)

Neutropenic Care in the outpatient setting
11 non-randomised studies assessed neutropenic care in an outpatient setting (some degree of matching between inpatients and outpatients was used in 6 studies) and all included patients after HSCT.
A common requisite was for an adult caregiver to be available 24 hours and medical and nursing care was provided at home or in the outpatient clinic.
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).
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).

Comments

Study Inclusion Criteria
Prospective comparative studies including individual patient or cluster randomised trials, quasi-randomised trials,

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					controlled clinical trials, prospectively planned or prospective data collection for comparative cohort studies, before-after studies and interrupted time series studies. Studies comparing intervention with placebo, no treatment or another intervention All environmental measures, barrier precautions and other non-pharmacological measures used for prevention of acquisition of infectious agents or diseases. *Exclusions* Non-randomised studies comparing patients with different cancer types or had inherently different treatment protocols (HSCT versus chemotherapy). Studies done in outbreak settings Studies assessing pharmacological interventions such as antimicrobial prophylaxis and mouth rinse preparations unless these interventions were applied together or as a control for the infection control interventions. Children below the age of 15 years were included in 22 studies 3 studies did not specify the age of included patients Older studies used protective environment prophylactic antibiotic (PEPA) methods (use of a special room or plastic tent with built in air filtration device, total barrier isolation and use of non-absorbable antibiotics and other decontamination methods) 10 study groups assessed endogenous flora suppression alone; barrier isolation with endogenous suppression by non-absorbable antibiotics was assessed by six groups; barrier isolation alone in 5 groups, air quality control plus barrier isolation in 3 and air quality control alone was assessed in 1 study.
					Study Quality Not all haematology populations High risk patients
Sive et al (2012)					
Audit **) January 2005 – January 2011**	To present the experience in managing patients receiving intensive chemotherapy and HSCT protocols on daycare basis with full nursing and medical support while staying in a hotel within walking distance of the hospital	N=668 Inclusion • Patients aged 18 and over who consented to receive treatment within the ambulatory care unit and were independent of nursing care in the daily living (on their own or with a	Hotel Based Outpatient Care		• Admissions • Patients were reviewed daily by a dedicated ACU nursing team and clinician and a consultant review was carried out twice a week. • Predicted toxicities were assessed and vital signs (temperature, pulse and blood pressure were monitored) • Reviews were carried out in the ambulatory care unit, not in the hotel room and patients undergoing allogeneic transplant were treated exclusively in a side room to reduce the risk of infection. • Patients were provided with strict guidelines on when to contact the unit, instructed to call if they experienced rigors or a temperature of ≥38 degrees, persistent nausea, vomiting or diarrhoea or any other symptoms of concern • If a patient remained well throughout their ACU stay, they were discharged home while any patients with significant medical complications or who felt unable to cope in the hotel environment were admitted to the ward. *Admission Numbers* • There were 1443 admission to the Ambulatory Care Unit (9126 patient days) during the study period made up of 688 patients from 18-79 years of age. • 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

<table>
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<tr><td></td><td></td><td>companion).
• Good command of written and spoken English (patient or companion)
• Able to follow advice in the event of becoming unwell
• A mobile phone
• Able to self administer oral medications and use a thermometer provided to them
• Mandatory companion for patients with limited mobility or receiving ifosfamide as part of their treatment (though all patients were recommended to have a companion).</td><td></td><td></td><td>by days of use.
• 1203 admissions were specifically for the administration of chemotherapy or HSCT and the for the monitoring period during the neutropenic phase immediately after treatment.
• Duration of stay varied based on treatment length and whether patients stayed in for monitoring during the neutropenic phase
• ESHAP (n=171), miniBEAM (n=57) and all acute myeloid leukaemia (n=80) were the most common regimens
• Autologous and allogeneic HSCT accounted for 368 treatment admissions with a median duration of stay of 9 days (2-25 days). There were 158 BEAM HSCT's , 136 melphalan autografts, 60 RI FMC and 10 BEAM-Campath allografts.
• For some chemotherapy regimens, patients discharged home after treatment stay were readmitted for monitoring during the neutropenic period
• Patients admitted to the ward and subsequently recovered but still requiring neutropenic monitoring were often readmitted to the ACU prior to going home.
• There were 158 monitoring admissions (1120 patient days; mean 7 days per admission) for the more myelosuppressive chemotherapy protocols such as the AML regimens and lymphoma protocols.

Outcomes of ACU stay
• 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.
• From 2008 onwards all allograft patients were admitted electively to the ward by the day of stem cell return regardless of their condition
• 813/1443 (56%) patients were discharged directly home
• 53/630 (9%) patients admitted to the ward were scheduled in advance
• 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.

ACU Episodes by treatment protocol
<table>
<tr><th>Treatment</th><th>Median Patients Age (range)</th><th>Number of ACU episodes</th><th>Total patients days in ACU (% of total)</th><th>Median length of ACU stay (days) (range)</th></tr>
<tr><td>AML intensive chemotherapy</td><td>41 (18-79)</td><td>80</td><td>818 (9%)</td><td>10 (1-30)</td></tr>
<tr><td>DA</td><td>48 (18-71)</td><td>21</td><td>251 (3%)</td><td>12 (3-30)</td></tr>
<tr><td>ADE</td><td>34 (27-39)</td><td>6</td><td>68 (1%)</td><td>14 (4-16)</td></tr>
<tr><td>MACE</td><td>38 (20-64)</td><td>15</td><td>139 (2%)</td><td>9 (4-15)</td></tr>
<tr><td>MiDAC</td><td>46 (20-71)</td><td>15</td><td>181 (2%)</td><td>12 (2-29)</td></tr>
<tr><td>HD AraC</td><td>36 (19-57)</td><td>17</td><td>137 (2%)</td><td>5 (1-16)</td></tr>
<tr><td>Other AML regimens</td><td>41 (20-79)</td><td>6</td><td>42 (<1%)</td><td>8 (2-5)</td></tr>
<tr><td>ALL intensive chemotherapy</td><td>26 (19-48)</td><td>36</td><td>253 (3%)</td><td>5 (2-42)</td></tr>
<tr><td>UKALL 2003 trial</td><td>19 (19-26)</td><td>17</td><td>70 (1%)</td><td>5 (2-19)</td></tr>
</table>
</td></tr>
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Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results

protocol				
UKALL12 trial protocol	27 (21-48)	19	183 (2%)	5 (2-42)
ATRA regimens	48 (40-53)	15	70 (1%)	8 (3-6)
Azacytidine	61 (32-62)	13	70 (1%)	5 (2-7)
ESHAP	44 (18-65)	171	961 (11%)	5 (2-15)
MiniBEAM	41 (18-63)	57	416 (5%)	6 (2-22)
CODOX-M/IVAC	35 (19-59)	21	185 (2%)	9 (3-15)
Other haematology chemotherapy	51 (19-74)	43	212 (2%)	4 (2-14)
Sarcoma Chemotherapy	24 (19-61)	379	1467 (16%)	4 (1-8)
Doxorubicin	45 (20-54)	10	35 (<1%)	4 (2-5)
Doxorubicin/Cisplatin	33 (26-54)	10	32 (<1%)	3 (2-5)
Doxorubicin/ifosfamide	34 (23-57)	42	153 (2%)	4 (2-5)
Etoposide/ifosfamide	29 (19-53)	63	293 (3%)	5 (2-7)
Ifosfamide	42 (21-61)	28	91 (1%)	3 (2-4)
MAP	24 (20-43)	116	535 (6%)	4 (2-8)
VAI	27 (20-46)	66	172 (2%)	3 (1-6)
VDC	24 (20-31)	17	54 (1%)	3 (1-5)
VIDE	22 (20-28)	18	63 (1%)	3 (2-6)
Other sarcoma chemotherapy	37 (24-61)	9	39 (<1%)	5 (2-6)
Other oncology chemotherapy	29 (23-46)	20	87 (1%)	4 (1-12)
RI FMC allograft	50 (25-63)	60	651 (7%)	9 (3-25)
RI BEAM-Campath allograft	36 (22-54)	10	72 91%)	8 (4-9)
Melphalan autograft	59 (32-70)	136	853(9%)	6 (2-12)
BEAM autograft	50 (18-69)	158	1444 (16%)	9 (3-18)
Other transplants	37 (21-45)	4	18 (<1%)	5 (3-6)
Monitoring	42 (18-71)	157	11071107 (12%)	6 (2-43)
Miscellaneous	38 (19-78)	83	442 (5%)	3 (1-25)

Comments
Chemotherapy regimens were the same as those given in the inpatient setting and all protocols and other medications were reviewed by a pharmacist.
Patients received medication counselling and a written reminder chart by the pharmacist
Supportive care and antimicrobial prophylaxis were given as required and according to the same protocols as ward based patients.

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					Study Quality
Sopko et al (2012)					
Retrospective Case series	To investigate the safety and feasibility of home care following consolidation chemotherapy	N=45	Home care after consolidation chemotherapy	Inpatient care after consolidation chemotherapy	• Discharge Rates • Mortality N=41 patients were discharged from hospital (73.2%) and the remaining 15 stayed in hospital. 17 patients required ambulatory management only while 24 patients required re-hospitalisation, primarily due to febrile neutropenia. In 36 febrile episodes the 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). 10 outpatients (43.5%) responded to initial therapy for febrile episodes compared with 2(16.7%) patients in the inpatient group. *Mortality* There were 2 (4.8%) deaths in the outpatients group compared with 1 (6.6%) death in the inpatient group
					Comments Patients who went home had to check their vital parameters daily, avoid obviously sick people, avoid places with large numbers of people, eat only fresh and well cooked meals, visit the clinic weekly and contact the clinic if there were any changes in clinical status. Change in clinical status resulted in patients being immediately admitted to clinic and a complete laboratory and clinical check performed Patients re-admitted to hospital and patients who remained in hospital were treated and managed in the same way Patients were usually discharged after several days of non-febrile period and when clinical and laboratory signs of infection were gone.

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					Study Quality This was a patient choice study. All patients offered the choice to go home after consolidation treatment or to stay in hospital were considered fit to go home therefore there is a high risk of selection bias with patients who choosing to go home likely to be different in some way to those who choose to remain in hospital.
Stevens et al (2005), Canada					
Randomised cross over trial	To compare two models of health care delivery for children with ALL	N=50 eligible N=29 agreed to take part Reasons for refusal included parents who preferred to bring their child to hospital for treatment, preferred to keep them at home or provided no reason. *Inclusions* Children attending the oncology outpatient clinic of the study setting for cancer treatment Aged 2-16 years Diagnosed with ALL in the year prior to enrolment Treated on a standard high risk ALL protocol by a paediatric oncologist Cared for at home by parents Spoke and read English or had an interpreter available	Home Chemotherapy	Hospital Chemotherapy	• Quality of life (child) • Effect on parental care givers • Adverse effects • Cost Phase 1 data were collected at Time 1 (baseline prior to randomisation); time 2 (3 months after start of phase 1); and time 3 (6 months after start/end of phase 1) Phase 2 data were collected at time 4 (3 months after start of phase 2) and time 5 (6 months after start/end of phase 2) N=23 children completed both home and hospital phases of the study There was no significant difference in baseline characteristics between the groups at the time of randomisation 24/29 patients who began the study were at the maintenance phase of their chemotherapy protocol *Quality of Life* • 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 POQOLS measure when they switched from home based treatment to hospital based treatment with an average change of 5.2. • Standard care patients experienced an improvement in QoL when they switched to home based treatment with an average score of -10.5 • The difference between the groups was significant (p=0.023) • There was no significant difference between the groups in relation to factor 2 (emotional distress) of factor 3 (reaction to current medical treatment) measures (p=0.95 and p=0.39 respectively). • Patients in the home based group had significantly higher scores for factor 2 (emotional distress) measures compared with the hospital treatment group (pairwise comparison at the end of each 6 months phase p=0.043). • There was no significant difference in factor 3 measures (p=0.061) • In a long term comparison (end of each 6 month phase), values of factor 1 measures did not differ with sites of chemotherapy administration. • There was no significant difference between the groups in CBCL (child behaviour checklist) scores at any of the follow-up periods *Burden Of Care* No evidence of an effect of the location of chemotherapy administration was observed on the parental burden of care (assessed using the caregiving burden scale).

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
		Resided in the greater metropolitan area *Exclusions* Children with other major congenital illnesses Children who did not have a patent central venous catheter for the administration of medications			***Comments*** • Baseline data was collected prior to randomisation • The two phase cross-over design allow the children serve as their own controls • Children were randomly assigned by the study site manager to either hospital (standard care) or home (treatment) chemotherapy for phase 1 (6 months) and children transferred to the other treatment group at 6 months for phase 2. ***Study Quality***
Stevens et al (2004), Canada					
Prospective descriptive study, nested in a randomised cross over trial	To evaluate quality of life, nature and incidence of adverse effects, parental caregiver burden and direct and indirect costs of a home chemotherapy program for children with cancer	N=33 health practitioners which included nurses, paediatric oncologists, administrators/unit managers, laboratory and pharmacy personnel *Inclusion* Aged 2-16 years Diagnosed with Acute Lymphoblastic Leukaemia for <1 year Treated on a hospital-based leukaemia protocol for newly diagnosed patients with high risk ALL Cared for by a paediatric oncologist and by parents at home in the greater metropolitan area of Toronto	Home Chemotherapy	Hospital Chemotherapy	• Perceived family benefits • Human Resources and service delivery implications • Hospital health practitioners perspective • Community Health practitoners perspective *Perceived Family Benefits* All practitioners claimed that the programme had a positive impact on daily life and psychological well-being of children and families particularly in relation to disruption and psychological stress. Health practitioners reported 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 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."* *Human Resources and Service Delivery Implications* Home chemotherapy was supported by both groups (home/hospital treatment) and by all types of health practitioners and they suggested ways in which the service could be improved to ensure a successful and safe healthcare delivery service. The advantages conferred by consistency in personnel and practice were emphasised by hospital based practitioners.

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					Children in the hospital setting were seen by the same practitioner which helped 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] Both groups considered it to be important 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. 4 home care nurses took part in a 3 day educational session on chemotherapy administration and reported that they found the course extremely valuable. All health practitioners were of the opinion that practice standards should be similar for nurses administrating chemotherapy regardless of setting. 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 work completed, 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. Some suggestions were put forward to streamline and refine the communication process with many responders suggesting one central person to liaise between the hospital and community. 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. Health practitioners felt that it was important that identifying eligibility criteria was important and thought that this should include families having a flexible schedule to accommodate treatment times, be familiar with the process of receiving chemotherapy and the types of chemotherapy, have the ability to handle change, to be housed in safe and clean living conditions, have high levels of compliance and be comfortable with healthcare delivered in the home. *"Not every family wants to have their home environment invaded with hospital equipment; they want to keep*

Study Type/Setting	Aim	Population	Intervention	Comaprison	Outcomes and results
					that a safe place." [community nurse] *Hospital Health Practitioners* 2 clinic nurses and 3 paediatric oncologists reported no change in their workload ; 5 clinic nurses and 1 physician reported an increase due to the increased volume of paperwork and 3 clinic nurses reported a decrease. 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) thing. *"You look forward to their visits, I do anyways. Because the communication of how they're really doing and how things are going is fort of broken down, there's a gap because you don't see them every two weeks."* [hospital clinic nurse] 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. 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]
					Comments Individual, moderately structures interviews with open-ended questions about the strengths and limitations of providing home chemotherapy to children, resource, training and education implications, extending the program and impact on the health practitioners' role. Interviews were between 20-90 minutes long depending on time available and information provided and was conducted by experienced interviewers.
					Study Quality

Appendix 1: Ambulatory Care Data

Ambulatory Care Data provided by UCHL (personal communication Barbara von Barsewisch) and Sheffield (personal communication John Snowdon)

Acute Myeloid Leukaemia /Acute Promyelocytic Myeloid Leukaemia

AML/APML (London)				
	No of Patients	**No. of Admissions***	**Days in ACU**	**Care Episode (days)**
2011	17	27	168	416
2012	20	35	277	685
2013	13	19	207	421
2014	21	43	444	555
2015	11	14	99	157
Total	72	138	1195	2234
AML/APML (Sheffield)				
	No of Patients	**No of Admissions***	**Days in ACU**	**Care Episode (days)**
2011	3	1	63	94
2012	5	4	42	93
2013	13	5	258	326
2014	12	8	148	276
2015	4	4	24	85
Total	37	22	535	874
Combined Total	**109**	**160**	**1730**	**3117**
Average bed days saved per patient was 16				
London data included planned and unplanned admissions while Sheffield data included only unplanned admissions				

Acute Lymphoblastic Leukaemia

ALL (London)				
	No of Patients	**No of Admissions***	**Days in ACU**	**Care Episode (days)**
2011	45	15	367	372
2012	35	8	266	323
2013	23	8	324	348
2014	13	2	86	160
2015 (end March)	3	0	44	48
Total	119	33	1087	1251
ALL (Sheffield)				
	No of Patients	**No of Admissions***	**Days in ACU**	**Care Episode (days)**
2011	0	-	-	-
2012	0	-	-	-
2013	3	3	15	73
2014	3	3	15	66
2015	6	5	64	145
Total	12	11	94	284
Combined Total	**131**	**44**	**1181**	**1535**

Average bed days saved per patient was 9
London data included planned and unplanned admissions while Sheffield data included only unplanned admissions

Burkitt Lymphoma

Burkitt Lymphoma (London)				
	No of Patients	**No of Admissions***	**Days in ACU**	**Care Episode (days)**
2011	6	7	44	147
2012	3	10	81	163
2013	5	8	95	215
2014	3	9	61	91
2015	1	1	11	11
Total	18	35	292	627
Average bed days saved per patient was 16				
London data included planned and unplanned admissions				

Salvage Treatment

Salvage (London)				
	No of Patients	**No of Admissions**	**Days in ACU**	**Care Episode (days)**
2011	0	-	-	-
2012	0	-	-	-
2013	0	-	-	-
2014	26	3	160	
2015	18	0	106	
Total	44	3	266	
Salvage (Sheffield)				
	Total No of Patients (Patients undergoing 1st treatment)	**Total No of Admissions (Patients undergoing 1st treatment)**	**Total Days in ACU (Patients undergoing 1st treatment)**	**Total Care Episode (days) (Patients undergoing 1st treatment)**
2011	0	-	-	-
2012	1	1	0	4
2013	6 (4)	0 (0)	24 (17)	24 (17)
2014	16 (5)	1	56 (14)	58 (16)
2015	19 (7)	3 (2)	47 (13)	67 (20)
Total	42 (17)	5 (2)	127 (44)	153 (53)

Autologous Transplant

Autos (London)				
	No of Patients	**No of Admissions**	**Days in ACU**	**Care Episode (days)**
2011	68	61	483	
2012	77	69	586	
2013	71	69	586	
2014	102	94	964	
2015	35	31	287	
Total	353	324	2906	
Autos (Sheffield)				
	No of Patients	**No of Admissions**	**Days in ACU**	**Care Episode (days)**
2011	6	6	62	139
2012	11	9	120	231
2013	25	17	250	506
2014	17	15	179	337
2015	31	26*	257*	453*
Total	90	73	868	1666

Allogeneic Transplant

Allos (London)				
	No of Patients	**No of Admissions**	**Days in ACU**	**Care Episode (days)**
2011	34	34 (7)	227	-
2012	23	23 (8)	170	-
2013	38	37 (33)	402	-
2014	42	35 (33)	538	-
2015	4	4(4)	55	-
Total	141	133 (85)	1392	-

Excluded Studies

Study	Included/Excluded
Allan DS, Allan DS. Outpatient supportive care following chemotherapy for acute myeloblastic leukemia. Leukemia & Lymphoma 2001 July;42(3):339-46.	Not relevant to PICO – Does not describe/compare services
Oren I. Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. Am J Hematol 2001 April;66(4):257-62.	Included in a systematic review (Eckmanns et al, 2006/Schlesinger et al, 2009)
Kroschinsky F, Kroschinsky F, Weise M, Illmer T, Haenel M, Bornhaeuser M et al. Outcome and prognostic features of intensive care unit treatment in patients with hematological malignancies. Intensive Care Med 2002 September;28(9):1294-300.	Not relevant to PICO (population, critically ill patients)
Low J, Smith A, George S, Roderick P, Davis C. How many patients with haematological malignancy need the facilities offered by a district general hospital? J Public Health Med 2002 September;24(3):196-9.	Not relevant to PICO
Rabe CM. Outcome of Patients With Acute Myeloid Leukemia and Pulmonary Infiltrates Requiring Invasive Mechanical Ventilation - A Retrospective Analysis. J Crit Care 2004;19(1):29-35.	Not relevant to PICO – Does not describe/compare services
Sekeres MAS. Decision-making and quality of life in older adults with acute myeloid leukemia or advanced myelodysplastic syndrome. Leukemia 2004;18(4):809-16.	Not relevant to PICO – Does not describe/compare services
Colombo A, Colombo A, Solberg B, Vanderhoeft E, Ramsay G, Schouten H. Measurement of nursing care time of specific interventions on a hematology-oncology unit related to diagnostic categories. Cancer Nurs 2005 November;28(6):476-80.	Not relevant to PICO – Does not describe/compare services
Moller T, Moller T. Patient education--a strategy for prevention of infections caused by permanent central venous catheters in patients with haematological malignancies: a randomized clinical trial. J Hosp Infect 2005 December;61(4):330-41.	Not relevant to PICO – Does not describe/compare services
van Tiel FH, Harbers MM, Kessels AG, Schouten HC., van Tiel FH. Home care versus hospital care of patients with hematological malignancies and chemotherapy-induced cytopenia. [Review] [31 refs]. Ann Oncol 2005 February;16(2):195-205.	Not relevant to PICO (population/transplant patients)
Cherif H, Cherif H, Johansson E, Bjorkholm M, Kalin M. The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. Haematologica 2006 February;91(2):215-22.	Not relevant to PICO – Does not describe/compare services
Hallbook HG. Treatment outcome in young adults and children > 10 year of age with acute lymphoblastic leukemia in Sweden: A comparison between a	Not relevant to PICO (comparison)

pediatric protocol and an adult protocol. Cancer 2006;107(7):1551-61.	
Reece D, Reece D. Bortezomib in multiple myeloma and lymphoma: a systematic review and clinical practice guideline. Current Oncology 2006 October;13(5):160-72.	This is a treatment comparison – not relevant to PICO
Savoie ML, Nevil TJ, Song KW, Forrest DL, Hogge DE, Nantel SH et al. Shifting to outpatient management of acute myeloid leukemia: a prospective experience. Ann Oncol 2006 May;17(5):763-8.	Non-comparative/describes outpatient care)
Gardin C, Turlure P, Fagot T, Thomas X, Terre C, Contentin N et al. Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: Results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. Blood 2007;109(12):5129-35.	Not relevant to PICO – Population not relevant
Pinquart M, Pinquart M, Hoffken K, Silbereisen R. Social support and survival in patients with acute myeloid leukaemia. Support Care Cancer 2007 January;15(1):81-7.	Not relevant to PICO – Does not describe/compare services
Dini G, Banov L, Dini S. Where should adolescents with ALL be treated? Bone Marrow Transplant 2008;42:S35-S39.	Review Article/No data
Muhlbacher AC, Lincke HJ, Nubling M. Evaluating patients' preferences for multiple myeloma therapy, a Discrete-Choice-Experiment. Psychosocial Medicine 2008;5:Doc10.	Not relevant to PICO – Does not describe/compare services
Aksoy S, Dizdar O, Hayran M, Harputluoglu H. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. Leukemia & Lymphoma 2009;50(3):357-65.	This is a treatment comparison study and therefore not relevant to the PICO.
Cohen ACD. Cost burden analysis of ineffective induction chemotherapy in elderly patients with AML. Blood 2009;Conference(var.pagings).	This is an abstract only
Gruschkus SKD. Impact of disease progression on healthcare cost and resource utilization among follicular NHL patients treated within the us oncology network. Blood 2009;Conference(var.pagings).	This is an abstract only
Lin TFA. Routine hospitalization after AML chemotherapy may not improve outcomes. Pediatric Blood and Cancer 2009;Conference(var.pagings):723.	This is an abstract only
Maschmeyer G, Neuburger S, Fritz L, Bohme A, Penack O, Schwerdtfeger R et al. A prospective, randomised study on the use of well-fitting masks for prevention of invasive aspergillosis in high-risk patients. Ann Oncol 2009 September;20(9):1560-4.	Not relevant to PICO – Does not describe/compare services
Miura YT. Safety and effectiveness of rehabilitation for elderly patients with hematological malignancies who received intensive chemotherapies. European Journal of Cancer, Supplement 2009;Conference(var.pagings):219.	This is an abstract only

Paessens BS. The burden of chemotherapy induced toxicity in routine hospital care. Support Care Cancer 2009;Conference(var.pagings):947.	This is an abstract only
Vokurka S, Bystricka, Vokurka S, Bystricka E, Visokaiova M, Scudlova J. Once-versus twice-weekly changing of central venous catheter occlusive dressing in intensive chemotherapy patients: results of a randomized multicenter study. Medical Science Monitor 2009 March;15(3):CR107-CR110.	Not relevant to PICO – Does not describe/compare services
Beed M, Levitt M, Bokhari SW. Intensive care management of patients with haematological malignancy. Continuing Education in Anaesthesia, Critical Care & Pain 2010 December;10(6):167-71.	Not relevant to PICO – Does not describe/compare services
Bejanyan N, Bejanyan N. Impact of weekend admissions on quality of care and outcomes in patients with acute myeloid leukemia. Cancer 2010 August 1;116(15):3614-20.	Not relevant to PICO – Does not describe/compare services
Braga P, Carvalho S, Gomes M, Guerra L, Lucio P, Marques H et al. Economic Analysis of Rituximab in Combination with Cyclophosphamide, Vincristine and Prednisolone in the Treatment of Patients with Advanced Follicular Lymphoma in Portugal. Acta Med Port 2010;23(6):1025-34.	Foreign Language/No translation
British Committee for Standards in Haematology. Facilities for the Treatment of Adults with Haematological Malignancies – 'Levels of Care'. 2010.	Report for information
British Committee for Standards in Haematology. Guidelines for supportive care in Myeloma. 2010.	Review article/No data
Coutsouvelis J, Coutsouvelis J, Corallo CE, Dooley M. Implementation of a pharmacist-initiated pharmaceutical handover for oncology and haematology patients being transferred to critical care units. Support Care Cancer 2010 July;18(7):811-6.	Not relevant to PICO – Does not describe/compare services
Kanat O, Kanat O, Ozet A, Ataergin S, Arpaci F, Kuzhan O et al. Modified outpatient dexamethazone, cytarabine and cisplatin regimen may lead to high response rates and low toxicity in lymphoma. Medical Principles & Practice 2010;19(5):344-7.	Not relevant to PICO – Does not describe/compare services
Kusick KY. Fluoroquinolone prophylaxis in adult acute myeloid leukemia (AML) patients undergoing consolidation chemotherapy. Journal of Oncology Pharmacy Practice 2010;Conference(var.pagings):14-5.	This is an abstract only
Lengline E. Early admission to the intensive care unit in high risk acute myeloid leukemia (AML) patients. Intensive Care Med 2010 September;Conference(var.pagings):September.	This is an abstract only
Matthey F. Facilities for the treatment of adults with haematological malignancies - 'Levels of Care': BCSH Haemato-Oncology Task Force 2009. Hematology 2010;15(2):63-9.	Review article/No data
Moller T, Nielsen OJ, Welinder P, Dunweber A, Hjerming M, Moser C et al. Safe and feasible outpatient treatment following induction and consolidation chemotherapy for patients with acute leukaemia. Eur J Haematol 2010	No details on the difference between the

April;84(4):316-22.	inpatient/outpatient service
Moller TA. Hematologic patients' clinical and psychosocial experiences with implanted long-term central venous catheter: Self-management versus professionally controlled care. Cancer Nurs 2010;33(6):426-35.	Not relevant to PICO – Does not describe/compare services
Sulis MLF. Infection control practices during induction chemotherapy for acute lymphoblastic leukemia: Results of a survey from the dana-farber cancer institute all Consortium. Pediatric Blood and Cancer 2010;Conference(var.pagings):956.	This is an abstract only
Walter RBL. Early discharge and outpatient management of adult patients following intensive induction chemotherapy for MDS and Non-APL AML: A pilot study. Blood 2010;Conference(var.pagings).	This is an abstract only
Compaci G, Compaci G, Ysebaert L, Oberic L, Derumeaux H, Laurent G. Effectiveness of telephone support during chemotherapy in patients with diffuse large B cell lymphoma: the Ambulatory Medical Assistance (AMA) experience. Int J Nurs Stud 2011 August;48(8):926-32.	Not relevant to PICO – Does not describe/compare services
Lee YMRADiNBMiN, Lang DRADiNB, Tho PCRADiNO. Title The experience of being a neutropenic cancer patient in an acute care isolation room: a systematic review of qualitative evidence. The JBI Library of Systematic Reviews 2011;9(12):400-16.	Not relevant to PICO – Does not describe/compare services
Mauro MJC. A survey of current practices in the management of chronic myeloid leukemia (CML). J Clin Oncol 2011;Conference(var.pagings).	This is an abstract only
Muhlbacher AC, Nubling M. Analysis of physicians' perspectives versus patients' preferences: direct assessment and discrete choice experiments in the therapy of multiple myeloma. European Journal of Health Economics 2011 June;12(3):193-203.	Not relevant to PICO – Does not describe/compare services
Paul M, et al. Infections in hematogical cancer patients: The contribution of systematic reviews and meta-analyses. Acta Haematol 2011;125(1-2):80-90.	Not relevant to PICO Identified a reference to order: Robenshok et al (2007) Antifungal prophylaxis in cancer patients after chemotherapy of haematopoietic stem cell transplantation: a systematic review Journal of Clinical Oncology 25;5471-5489
Phillips B, Phillips B, Richards M, Boys R, Hodgkin M, Kinsey S. A home-based maintenance therapy program for acute lymphoblastic leukemia-practical and safe? J Pediatr Hematol Oncol 2011 August;33(6):433-6.	Not relevant to PICO – Does not describe/compare services

Valgus JM, Valgus JM. Integration of a clinical pharmacist into the hematology-oncology clinics at an academic medical center. Am J Health Syst Pharm 2011 April 1;68(7):613-9.	Not relevant to PICO – Does not describe/compare services
Walter RB, Lee SJ, Gardner KM, Chai X, Shannon-Dorcy K, Appelbaum FR et al. Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study. Haematologica 2011 June;96(6):914-7.	Not relevant to PICO – Does not describe/compare services
Bohme A, Bohme A, Atta J, Mousset S, Ehlken B, Shlaen M et al. Antifungal management and resource use in patients with acute myeloid leukaemia after chemotherapy--retrospective analysis of changes over 3 yr in a German hospital. Eur J Haematol 2012 January;88(1):68-77.	
Calderon CF. Patterns of infection in patients with myeloid malignancies receiving 5-azacytidine: Identification of candidates for antifungal prophylaxis. Blood 2012;Conference(var.pagings).	This is an abstract only
Cluzeau TD. Dose-intensity impacts on survival of adolescents and young adults with acute lymphoblastic leukemia treated in adult departments by a pediatric protocol (FRALLE 2000BT). Blood 2012;Conference(var.pagings).	This is an abstract only
Ferro RAZ. Early discharge and out patient management after AML induction chemotherapy: Determinants of safety. Blood 2012;Conference(var.pagings).	This is an abstract only
Gomez AJC, Lopez-Guillermo A, Dominguez AR, Salar A, Moreno CV, Rubio-Terres C. Cost-Effectiveness Analysis of Maintenance Therapy with Rituximab in Patients with Follicular Lymphoma Responding to Induction Therapy at the First Line. Revista Espanola de Salud Publica 2012;86(2):163-76.	Foreign language/No translation
Lee JH, Joo Y-DK. Induction chemotherapy in patients with acute myeloid leukemia. Ann Oncol 2012 October;Conference(var.pagings):October.	This is an abstract only
Kersten MJM. At home treatment after high dose chemotherapy is safe and feasible, and leads to significant cost savings. Haematologica 2012 June 1;Conference(var.pagings):01.	This is an abstract only
Klimm B, Brillant C, Skoetz N, MÃ¼ller H, Engert A, Borchmann P. The Effect of Specialized Cancer Treatment Centers on Treatment Efficacy in Hodgkin's Lymphoma. Deutsches Aerzteblatt International 2012 December 24;109(51-52):893-9.	Not relevant to PICO – Does not describe/compare services
Mank AS. At home treatment after high-dose chemotherapy and autologous stem cell transplantation is safe and feasible. Evaluation of 4 years of ambulatory care from a medical, nursing, patient and financial perspective. Bone Marrow Transplant 2012 April;Conference(var.pagings):April.	This is an abstract only
Muwakkit S, Al-Aridi C, Samra A, Saab R, Mahfouz RA, Farra C et al. Implementation of an intensive risk-stratified treatment protocol for children and adolescents with acute lymphoblastic leukemia in Lebanon. Am J Hematol	Not relevant to PICO – Does not describe/compare services

2012 July;87(7):678-83.	
Shanafelt TD, Kay NE, Rabe KG, Inwards DJ, Zent CS, Leis JF et al. Hematologist/Oncologist Disease-Specific Expertise and Survival: Lessons from Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL). Cancer 2012;118(7):1827-37.	Not relevant to PICO – Does not describe/compare services
Sung LA. Effectiveness of supportive care measurements to reduce infections during induction for children with acute myeloid leukemia: A report from the children's oncology group. Blood 2012;Conference(var.pagings).	This is an abstract only
Allart P, Allart P, Soubeyran P, Cousson-Gelie F. Are psychosocial factors associated with quality of life in patients with haematological cancer? A critical review of the literature. [Review]. Psychooncology 2013 February;22(2):241-9.	Not relevant to PICO – Does not describe/compare services
Berrueco RR. Prospective surveillance study of blood stream infections associated with central venous access devices (port-type) in children with acute leukemia: An intervention program. J Pediatr Hematol Oncol 2013;35(5):e194-e199.	Not relevant to PICO – Does not describe/compare services
De Rosa FGM. Epidemiology of bloodstream infections in patients with acute myeloid leukemia undergoing levofloxacin prophylaxis. BMC Infectious Diseases 2013;13(1).	Not relevant to PICO – Does not describe/compare services
Glotzbecker BE, Yolin-Raley DS, DeAngelo DJ, Stone RM, Soiffer RJ, Alyea EP et al. Impact of physician assistants on the outcomes of patients with acute myelogenous leukemia receiving chemotherapy in an academic medical center. Journal of oncology practice/American Society of Clinical Oncology 2013 September;9(5):e228-e233.	Not relevant to PICO – Does not describe/compare services
Jarden M, Jarden M, Adamsen L, Kjeldsen L, Birgens H, Tolver A et al. The emerging role of exercise and health counseling in patients with acute leukemia undergoing chemotherapy during outpatient management. Leuk Res 2013 February;37(2):155-61.	Not relevant to PICO – Does not describe/compare services
Martell MP, Atenafu EG, Minden MD, Schuh AC, Yee KWL, Schimmer AD et al. Treatment of elderly patients with acute lymphoblastic leukaemia using a paediatric-based protocol. Br J Haematol 2013;163(4):458-64.	Not relevant to PICO – Does not describe/compare services
Saini L, Saini L, Rostein C, Atenafu E. Ambulatory consolidation chemotherapy for acute myeloid leukemia with antibacterial prophylaxis is associated with frequent bacteremia and the emergence of fluoroquinolone resistant E. Coli. BMC Infectious Diseases 2013;13:284.	Not relevant to PICO – Does not describe/compare services
Smith BK-B, I. Estimates of burden of disease associated with management of acute myeloid leukemia in UK and US. Haematologica 2013 June 1;Conference(var.pagings):01.	This is a poster presentation

Sung LA. Effectiveness of supportive care measures to reduce infections in pediatric AML: A report from the Children's Oncology Group. Blood 2013;121(18):3573-7.	Only some of the data (discharge data) would be relevant and not enough information in detailed
Tuglular TT. Real life experience of anti-fungal prophylaxis with posaconazole in patients with acute leukemia at a single center lacking hepa-filter. Haematologica 2013 June 1;Conference(var.pagings):01.	This is an abstract only
Xhaard A, Xhaard A, Epelboin L, Schnell D, Vincent F, Levy V et al. Outcomes in critically ill chronic lymphocytic leukemia patients. Support Care Cancer 2013 July;21(7):1885-91.	Not relevant to PICO – Does not describe/compare services
Calefi KAC, da Rocha V, Nabhan S, Maftum M, Kalinke L, de FÃ¡tima Mantovani M. THE QUALITY OF LIFE OF PATIENTS WITH HEMATOLOGICAL NEOPLASIA UNDERGOING CHEMOTHERAPY. Revista Mineira de Enfermagem 2014 January;18(1):48-53.	Not relevant to PICO – Does not describe/compare services
Clinton-Mcharg TC. Anxiety and depression among haematological cancer patients attending treatment centres: Prevalence and predictors. J Affect Disord 2014 August 20;165(pp 176-181):20.	Not relevant to PICO – Does not describe/compare services
Esfahani A, Esfahani A, Ghoreishi Z, Abedi Miran M, Sanaat Z, Ostadrahimi A et al. Nutritional assessment of patients with acute leukemia during induction chemotherapy: association with hospital outcomes. Leukemia & Lymphoma 2014 August;55(8):1743-50.	Not relevant to PICO – Does not describe/compare services
Fu JB, Fu JB. Frequency and reasons for return to the primary acute care service among patients with lymphoma undergoing inpatient rehabilitation. Pm & R 2014 July;6(7):629-34.	Not relevant to PICO – Does not describe/compare services
Gaya AR. At-home management of adult patients following consolidation chemotherapy for acute myeloid leukemia. Blood 2014;Conference(var.pagings).	This is an abstract only
Guillemette A, Guillemette A, Langlois H, Voisine M, Merger D, Therrien R et al. Impact and appreciation of two methods aiming at reducing hazardous drug environmental contamination: The centralization of the priming of IV tubing in the pharmacy and use of a closed-system transfer device. Journal of Oncology Pharmacy Practice 2014 December;20(6):426-32.	Not relevant to PICO (comparison)
Hamsar HK. Role of nursing care in management of relapsed hodgkin lymphoma patients during high dose chemotherapy and autologous stem cell transplant-single center experience from pakistan. Pediatric Blood and Cancer 2014 December;Conference(var.pagings):December.	This is an abstract only
Inaba HG. Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia. Cancer 2014;120(13):1985-92.	Not relevant to PICO – Does not describe/compare services
Inoue S, Khan, Inoue S, Khan I, Mushtaq R, Carson D et al. Postinduction Supportive Care of Pediatric Acute Myelocytic Leukemia: Should Patients be	Not relevant to PICO – Does not describe/compare

Kept in the Hospital? Leukemia Research and Treatment 2014;2014:592379.	services
Orme LM, Babl FE, Barnes C, Barnett P, Donath S, Ashley DM. Outpatient versus inpatient IV antibiotic management for pediatric oncology patients with low risk febrile neutropenia: A randomised trial. Pediatric Blood & Cancer 2014;61(8):1427-33.	Not relevant to PICO – Does not describe/compare services
Osborne TR, Osborne TR. Understanding what matters most to people with multiple myeloma: a qualitative study of views on quality of life. BMC cancer 2014;14:496.	Not relevant to PICO – Does not describe/compare services
Parakh S. Outcomes of haematology/oncology patients admitted to intensive care unit at The Canberra Hospital. Internal Medicine Journal 2014 November;44(11):1087-94.	Not all haematology (55%)/Non-comparative
Raghavendra M, Raghavendra M. Management of neutropenic fever during a transition from traditional hematology/oncology service to hospitalist care. WMJ 2014 April;113(2):53-8.	Not relevant to PICO – Does not describe/compare services
Schenkel BN. Patient-reported experiences with treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL): Results of a quantitative survey. Blood 2014;Conference(var.pagings).	This is an abstract only
Seif AE, Fisher BT, Li, Seif AE, Fisher B. Patient and hospital factors associated with induction mortality in acute lymphoblastic leukemia. Pediatric Blood & Cancer 2014 May;61(5):846-52.	Not relevant to PICO – Does not describe/compare services
van der Poel MW, Mulder WJ, Ossenkoppele GJ, Maartense E, Wijermans, van der Poel MWM. Comorbidity and treatment decision-making in elderly non-Hodgkin's lymphoma patients: a survey among haematologists. Neth J Med 2014 April;72(3):165-9.	Not relevant to PICO – Does not describe/compare services
Vazquez F, I. Prognostic factors and outcomes of haematological patients with ICU admission during the 100 first days of auto HSCT. Bone Marrow Transplant 2014 March;Conference(var.pagings):March.	This is an abstract only
Waight CC, Waight CC. Authorising bortezomib treatment prior to reviewing haematology results: a step toward home administration. Journal of Oncology Pharmacy Practice 2014 October;20(5):351-5.	Not relevant to PICO – Does not describe/compare services
Algrin C, Algrin C, Faguer S, Lemiale V, Lengline E, Boutboul D et al. Outcomes after intensive care unit admission of patients with newly diagnosed lymphoma. Leukemia & Lymphoma 2015 May;56(5):1240-5.	Not relevant to PICO – Does not describe/compare services
Arthurs G, Simpson J, Brown A, Kyaw O, Shyrier S, Concert CM. The effectiveness of therapeutic patient education on adherence to oral anti-cancer medicines in adult cancer patients in ambulatory care settings: a systematic review. The JBI Library of Systematic Reviews 2015;13(5):244-92.	This study was not haematology patients.
Bryant ALD. Use of ED and hospital services for patients with acute leukemia after induction therapy: One year follow-up. Leuk Res 2015;39(4):406-10.	Not relevant to PICO – Does not describe/compare

	services
Delpeuch A, Delpeuch A, Leveque D, Gourieux B, Herbrecht R. Impact of clinical pharmacy services in a hematology/oncology inpatient setting. Anticancer Res 2015 January;35(1):457-60.	Not relevant to PICO – Does not describe/compare services
Jansen F, Jansen F, van Uden-Kraan C. Cancer survivors' perceived need for supportive care and their attitude towards self-management and eHealth. Support Care Cancer 2015 June;23(6):1679-88.	Not relevant to PICO – Does not describe/compare services
Kavookjian J, Wittayanukorn S. Interventions for adherence with oral chemotherapy in hematological malignancies: A systematic review. Research in Social and Administrative Pharmacy 2015 May;11(3):303-14.	This review is concerned with the impact of patient education rather than service provision/access therefore the comparisons and outcomes are not relevant. None of the individual studies in this review were identified in the searches.
Ko HF, Tsui SS, Tse JW, Kwong WY, Chan OY, Wong GC. et al. Improving the emergency department management of post-chemotherapy sepsis in haematological malignancy patients. Hong Kong Medical Journal 2015 February;21(1):10-5.	Not relevant to PICO – Does not describe/compare services
Kugler E.Levi. The association of central venous catheter placement timing with infection rates in patients with acute leukemia. Leuk Res 2015;39(3):311-3.	Not relevant to PICO – Does not describe/compare services
Maymani HA. Time from hospital admission to induction chemotherapy adversely affects outcomes in patients with acute myeloid leukemia. J Investig Med 2015;Conference(var.pagings):682-3.	This is an abstract only
McGrath P. Overcoming the distance barrier in relation to treatment for haematology patients: Queensland findings. Aust Health Rev 2015 January 15.	Not relevant to PICO – Does not describe/compare services
Pfeil AM, Pfeil AM. Trends in incidence and medical resource utilisation in patients with chronic lymphocytic leukaemia: insights from the UK Clinical Practice Research Datalink (CPRD). Ann Hematol 2015 March;94(3):421-9.	Not relevant to PICO – Does not describe/compare services
Vives S, Oriol A, Piernas S, Brunet S, Clapes V, Guardia R et al. Feasibility and efficacy of outpatient therapy with intermediate dose cytarabine, fludarabine and idarubicin for patients with acute myeloid leukaemia aged 70 or older. Eur J Haematol 2015 February 17.	Not relevant to PICO – Does not describe/compare services

Wise, M., Barnes, R., Baudouin, S., Howell, D., Lyttelton, M., Marks, D., Morris, E., Parry-Jones, N., and British Committee for Standards in Haematology. Guidelines on the management and admission to intensive care of critically ill adult patients wiht haematological malignancy in the UK. British Committee for Standards in Haematology; 2015.	Not relevant to PICO – Does not describe/compare services